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Review

Human matrix metalloproteinases: An ubiquitarian class of enzymes involved in several pathological processes

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ABSTRACT

Human matrix metalloproteinases (MMPs) belong to the M10 family of the MA clan of endopeptidases. They are ubiquitarian enzymes, structurally characterized by an active site where a Zn^{2+} atom, coordinated by three histidines, plays the catalytic role, assisted by a glutamic acid as a general base. Various MMPs display different domain composition, which is very important for macromolecular substrates recognition. Substrate specificity is very different among MMPs, being often associated to their cellular compartmentalization and/or cellular type where they are expressed. An extensive review of the different MMPs structural and functional features is integrated with their pathological role in several types of diseases, spanning from cancer to cardiovascular diseases and to neurodegeneration. It emerges a very complex and crucial role played by these enzymes in many physiological and pathological processes.

Contents

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1. Introduction

The term metallo-proteases encompasses esopeptidase and endopeptidase involved in many biological processes, such as morphogenesis, metabolism of biologically active peptides and hormones, development, regulation of cell cycle, cell proliferation, migration, adhesion and antibiotics metabolism (Nagase, 2001). In the MEROPS database, metallo-protease families are grouped into 14 different clans, namely MA, MC, MD, ME, MJ, MK, MM, MO, MP (these requiring only one catalytic metal ion) and MF, MG, MH, MQ (these containing two metal ions acting co-catalytically). The divalent metal ion contained in the active site is in the vast majority of cases a zinc ion, but cobalt, manganese or nickel are also represented. In humans, the majority of metalloproteinases are zinc metallo-endopeptidases distributed in: clan MA (*i.e.*, M3, M10, M12, M13, M41, M43 and M48 families), clan ME (*i.e.*, M16 family), clan MJ (*i.e.*, M19 and M38 families), clan MK (*i.e.*, M22 family), clan MM (*i.e.*, M50 family). Further, there are three families, namely M49, M76 and M79, which have not been assigned yet to a specific clan. Human metallo-peptidases play important roles in a variety of biological processes and the unbalance of their activity and expression is often at the basis of diseases like cancer, neurodegeneration, inflammation, arthritis, cardiovascular diseases. For this reason, they have been historically represented an intriguing drug targets, even though their therapeutical inhibition have raised many questions, since (i) the activity of these enzymes is pleiotropic so that their inhibition could negatively modulate some cellular functions; (ii) a large number of inhibitors are not selective for a single enzyme (Nagase, 2001). For a detailed properties of a single enzyme, it is possible to refer to the "Handbook of Proteolytic enzymes" (Barret et al., 2004).

This chapter will focus on human matrix metalloproteases, grouped as M10 family. In particular, in the first part this review briefly summarizes other families of MA clan, while in the second part attention will be concentrated on the present knowledge of members of M10 family, with a major focus on their biological functions and involvement in human diseases.

1.1. An overview of human zinc metalloprotease grouped as clan MA

Clan MA is the main clan of metalloproteinases and it is characterized by the "HEXXH" zinc-binding motif with two histidines acting as ligands of the catalytic Zn^{2+} and the glutamate as the general basis. Proto-typical proteases with this motif are: neurolysin (M3), matrix metalloproteinases (MMP, subfamily A of family M10). Here, we furnish a brief overview of this human family, discussing only representative examples of their functions.

1.1.1. M3 family

Human proteins included in M3 family are the soluble metallopeptidases neurolysin and thimet oligopeptidase (TOP), which reveal similar biological and biochemical features, and mitochondrial-processing-peptidase (MIP) (Table 1) (see for review Shrimpton et al., 2002; Ferro et al., 2004). Although neurolysin and TOP are well characterized biochemically, their physiopathological role has yet to be established. Both peptidases seem to play important roles in reproduction, nociception and cardiovascular homeostasis (Ferro et al., 2004). In particular, several studies indicate an involvement of neurolysin and TOP in neurotensin degradation (by exerting a broad range of endocrine and cardiovascular effect, such as hypotension, analgesia and hypothermia) and in bradykinin degradation, postulating a direct involvement in blood pressure regulation (Chabry et al., 1990; Checler et al., 1995; Davis et al., 1992; Genden and Molineaux, 1991; Kadonosono et al., 2007; Norman et al., 2003). Additionally TOP inactivates opioids and the gonadotrophin-releasing hormone, suggesting a putative role in the modulation of nociception and reproductive physiology (Cyr et al., 2010; Kest et al., 1991; Shrimpton et al., 2002).

Table 1
Association of family grouped as clan MA with human diseases.

Family	Subfamily	Human proteins	Pathology association	References
M3		TOP, neurolysin, MIP	Cancer[a]; Schizophrenia[b]; Alzheimer's disease[c]; Mithocondrial Disease[d]	[a]Paschoalin et al. (2007); [b]Widerlöv et al. (1982); [c]Pollio et al. (2008); [d]Gakh et al. (2002)
M12	A	Astacins	Roles in ECM formation and morphogenesis[a]; Antifibrotic-target[a]; Renal failure[b]; Diabetic nephropahty[c]	[a]Hopkins et al. (2007); [b]Li et al. (2008); [c]Oneda et al. (2008)
	B	ADAMs	Cancer[a]; Inflammation[b]; Allergic response[c]; Down Syndrome[d]; Rheumathoid arthritis[e]; Multiple sclerosis[f]; Asthma[g]; Alzheimer's disease[h]; Psoriasis[i]; Atherosclerosis[j]	[a]Valkovskaya et al. (2007), Roy et al. (2004), Borrell-Pages et al. (2003), Wildeboer et al. (2006); [b]Schulz et al. (2008); [c]Weskamp et al. (2006), Lemieux et al. (2007); [d]Laigaard et al. (2003); [e]Charbonneau et al. (2007); [f]Plumb et al. (2006); [g]Van Eerdewegh et al. (2002); [h]Bernstein et al. (2003); [i]Lesueur et al. (2007); [j]Papaspyridonos et al. (2006)
		ADAMTS	Arthritis[a]; Atherosclerosis[b]; Thrombotic Thrombocytopenic Purpura[c]; Ehler–Danlos syndrome type 7C[d]; Cancer[e]	[a]Song et al. (2007), Stanton et al. (2005), Luan et al. (2008); [b]Jonsson-Rylander et al. (2005), Wågsäter et al. (2008), Moriguchi-Goto et al. (2009); [c]Moake (2004), Shenkman (2006); [d]Colige et al. (2004); [e]Dunn et al. (2006), Rocks et al. (2008)
M13		Neprilysin, PEX, KELL, ECE1–ECE2, ECEL1	Inflammation[a]; Systemic-Sclerosis[b]; Rheumatoid arthritis[c]; Intestinal and respiratory infections[d]; Cardiometabolic-risk[e]; Cancer[f]; Alzheimer's Disease[g]; Atherosclerosis[h]; X-linked hypophosphatemic rickets[i]	[a]Turner and Nalivaeva (2006); [b]Matucci-Cerinic et al. (1999); [c]Sreedharan et al. (1990); [d]Koehne et al. (1998), Hwang et al. (1993); [e]Standeven et al. (2011); [f]Sumitomo et al. (2005); [g]Hersh and Rodgers (2008), Eckman et al. (2003); [h]Ihling et al. (2004); [i]Sabbagh et al. (2000)
M41		Paraplegin, AFG3L2	Hereditary Spastic Paraplegia[a]; Autosomal-dominant Spinocerebellum Ataxia 28[b]	[a]Koppen et al. (2007); [b]Di Bella et al. (2010)
M43		Pappalysin 1 and 2	Down Syndrome-marker[a]; Atherosclerosis marker[b]; Pre-eclampsia[c]	[a]Van Heesch et al. (2010); [b]Consuegra-Sanchez et al. (2009b); [c]Carty et al. (2008)
M48	A	Farnesylated-protein converting enzyme 1	Hutchinson–Gilford Progeria Syndrome[a]; Mandibuloacral Dysplasia[b]; Restrictive Dermopathy[c]	[a]Capell et al. (2007); [b]Agarwal et al. (2003a,b); [c]Capell and Collins (2006)

1.1.2. M12 family

Human members of M12 family are classified in two subfamilies, A and B, which include astacins, ADAM and ADAMTS proteases, respectively (see for review Edwards et al., 2008; Klein and Bischoff, 2011; Mochizuki and Okada, 2007; Murphy, 2008; Tousseyn et al., 2006; Van Goor et al., 2009).

ADAM (a disintegrin and metalloprotease) proteases are type 1 transmembrane proteins, defined by a modular structure encompassing (i) a prodomain, whose removal in the trans-Golgi network by pro-protein convertases is a key step in protease activation (with the exception of ADAM8 and ADAM28, which are activated by an autocatalytic cleavage), (ii) a Zn-binding domain, (iii) a disintegrin domain implicated in ADAMs–integrin interaction, (iv) a cysteine-rich domain which can interact with ECM proteins like fibronectin (as in the case of ADAM13) and also binds to syndecan cell surface proteoglycans (as for ADAM12), (v) a epidermal growth factor (EGF)-like domain, (vi) a transmembrane and (vii) a cytoplasmatic tail that acts as binding site for SH3-domain containing proteins (Gaultier et al., 2002; Howard et al., 2000; Lum et al., 1998; Schlomann et al., 2002; Seals and Courtneidge, 2003; Thodeti et al., 2003; White, 2003; White et al., 2005). Only half of known ADAMs are enzymatically active, since some of them lack one or more critical catalytic residues (Van Goor et al., 2009). ADAM biological functions have been generally linked to fertility, cell adhesion and fusion, cell fate determination in nervous system, aspects of immunity (Edwards et al., 2008). Several data support the roles of at least three ADAMs in the fertilization process; in particular, ADAM2 (fertilin β) and ADAM3 (cyritestin) knockout mice show reduced spermatozoon binding to oolemma and also poor adherence to the zona pellucida, while ADAM1-deficient mice show reduced egg migration from uterus to the oviduct (Cho et al., 1998; Nishimura et al., 2001, 2004). ADAM1 and ADAM3 are apparently non functional in humans, since their absence does not impair fertility because it is presumably compensated by other enzymes, such ADAM21 and ADAM30 (Grzmil et al., 2001; Jury et al., 1997). One of the major ADAM functions is the ectodomain shedding of a broad spectrum of transmembrane proteins substrates, including epidermal growth factor (EGFR) ligands, tumor necrosis factor α (TNF-α), cell adhesion molecules like CD44 and cadherins (Blobel, 2005; Nagano et al., 2004; Reiss et al., 2005). Although several ADAMs have sheddase function, the archetypal activity is shown by ADAM17 (known as TNF-α-converting-enzyme, TACE), which is involved in immune and inflammatory response trough activation of TNF-α and plays a relevant role in the development via EGFR activation (Blobel, 2005). ADAM10 is the main ADAM sheddase involved in Regulated Membrane Proteolysis (RIP), the latter being defined as a pathway characterized by an ectodomain shedding on transmembrane protein followed by a cleavage within membrane itself, with critical role in Notch/Delta and Eph/ephrin signaling (Edwards et al., 2008; Saftig and Hartmann, 2005). In this context, ADAMs seem to be involved in neurogenesis, axon extension, adipogenesis and lung, heart and pancreas morphogenesis (Tousseyn et al., 2006; Van Goor et al., 2009).

Furthermore, ADAM family has been implicated in a number of human diseases, such as cancer, asthma, infection and inflammation, neurodegeneration, thus representing attractive targets for novel therapies (Mochizuki and Okada, 2007) (Table 1). As a matter of fact, several ADAMs have been associated with cancer development and progression; for example ADAM12 is upregulated in hematologic, breast and gastric malignancies (Carl-McGrath et al., 2005; Lendeckel et al., 2005; Wu et al., 1997) and ADAM10 is highly expressed in pheochromocytoma and neuroblastoma (Yavari et al., 1998). ADAMs involvement in tumor biology can be explained by different mechanisms, since (i) ADAMs (*i.e.*, ADAM9) could cleave ECM components, such as laminin, and promote cell invasion, similarly to MMPs; (ii) the shedding of adhesion molecules could affect cell adhesion to vasculature; (iii) the shedding of growth factors and their receptors may alter cell growth, as documented for ADAM17 and TNF-α in breast cancer (Kenny and Bissell, 2007; Mazzocca et al., 2005; Tousseyn et al., 2006). The shedding of adhesion molecules directly links ADAMs with inflammatory response, being involved in leukocyte recruitment (Garton et al., 2006; Hafezi-Moghadam and Ley, 1999; Schulz et al., 2008). Linkage studies have also demonstrated that ADAM33 is a candidate asthma-susceptibility locus, even though its function in asthma is unknown (Van Eerdewegh et al., 2002). Interestingly, the identification of ADAM9, ADAM10 and ADAM17 as α-secretases, involved in non-amyloidogenic processing of β-amyloid precursor protein (APP), highlights a new therapeutical approach for Alzheimer's disease based on the modulation of ADAMs functional profile (Fahrenholz and Postina, 2006; Kojro and Fahrenholz, 2005).

ADAMTS (a disintegrin and metalloprotease with thrombospondin motif) are a group of proteins closely related to ADAMs (see for a review Apte et al., 2009; Jones and Riley, 2005; Li and Liu, 2010; Porter et al., 2005; Salter et al., 2010; Shiomi et al., 2010; Tortorella et al., 2009; Wagstaff et al., 2011).

Unlike ADAMs, ADAMTS are secreted proteins and possess: (i) a thrombospondin type-like (TS) repeat between the disintegrin-like and the cysteine-rich domain; (ii) several thrombospondin-like repeats in the C-terminal region, which seem to be important to bind ECM components (Apte, 2009; Hashimoto et al., 2004; Kuno et al., 2000). These enzymes play roles in development, angiogenesis and coagulation and their dysregulation have been implicated in many disease processes, such as inflammation, cancer, arthritis and atherosclerosis (Li and Lu, 2010) (Table 1). ADAMTS13 has been identified as the von Willebrand factor (VWF)-cleaving protease, whose substrate is a carrier protein for clotting factor VIII, which mediates platelet adhesion to areas of vascular damage (Fujikawa et al., 2001; Levy et al., 2001; Sadler et al., 2000). ADAMTS13 deficiency, determined by anti-ADAMTS13 autoantibody formation or gene mutations, can lead to thrombotic thrombocytopenic purpura (TPP), a condition characterized by microvascular thrombosis with renal failure, anemia and neurological disorder (Levy et al., 2001; Furlan, 1996). In addition, members of this family (such as ADAMTS1 and ADAMTS8) show a powerful angioinhibitory activity, since they suppress fibroblast growth factor-2 and vascular endothelial growth factor (VEGF)-mediated angiogenic effect on endothelial cells (Vazquez et al., 1999). Mutations in ADAMTS1 have been also associated with an increased risk of coronary artery disease and ADAMTS4, ADAMTS7 and ADAMTS8 have been implicated in atherosclerotic plaque formation (Moriguchi-Goto et al., 2009; Sabatine et al., 2008; Wågsäter et al., 2008). A subgroup of ADAMTS, also referred as "aggrecanases" (*i.e.*, ADAMTS4 and ADAMTS5), have been involved in the degradation of the aggrecan, which forms a major component of cartilage and plays a key role in protecting collagen from degradation (Malfait et al., 2002; Pratta et al., 2003). In this context, several recent discoveries have connected ADAMTS to arthritic disease, rendering these enzymes an important target in arthritis treatment (Li and Liu, 2010).

Astacins family includes several hundred protein detected in species ranging from hydra to humans (for a review see Ge and Greenspan, 2006; Hopkins et al., 2007; Sterchi et al., 2008).

In humans, there are six astacin genes, including two meprins, three bone morphogenetic protein1 (BMP1)/Tolloid like (TLD) proteases and one ovastacin (Sterchi et al., 2008) (Table 1). *BMP1* was shown to provide the procollagen C-protease activity involved in the cleavage of C-propeptide from collagen I–III (Kessler et al., 1996; Li et al., 1996). It has then become the prototype of a small subgroup of the astacin family with a similar protein domain architecture, which includes Tolloid-like 1 and Tolloid-like 2. These enzymes play a key role in ECM formation and development through the processing of a variety of precursor proteins in mature functional form (such as procollagen V, VII, XI and laminin 5) and the activation of a subset of transforming growth factor-β (TGF-β) proteins. The multiple roles of BMP1/TLD-related proteins in collagen fibrillogenesis render them interesting anti-fibrotic targets and their inhibition represents a possible approach for the treatment of muscular dystrophies (Hopkins et al., 2007; Wolfman et al., 2003). *Meprin proteins* are distinguished from other astacins since they include a transmembrane domain and have been discovered only in vertebrates. Meprin subunits α and β cleave a variety of biologically active peptides; in particular, we want to point out gastrin and cholecystokin on one side (which are substrates for meprin β) and substance P and many cytokines on the other side (which are substrates for meprin α, see Sterchi et al., 2008). Meprins are expressed abundantly in epithelial cells of kidney, intestine and skin and recently a number of studies indicate their potential functions in pathological conditions, such as acute and chronic renal failures, diabetic nephropathy, colon carcinoma (Bylander et al., 2008; Lottaz et al., 1999; Red Eagle et al., 2005).

1.1.3. M13 family

M13 family is group of neutral endopeptidases including neprilysin (NEP), endothelin-converting enzyme (ECE1), endothelin-converting-enzyme-like 1 (ECEL1), the erythrocyte surface antigen KELL and the PHEX gene product (for a review see Kiryu-Seo and Kiyama, 2004; Lee et al., 2000; Turner, 2003; Turner and Nalivaeva, 2006). They are involved in a great number of biological processes, such as neurotransmission, reproduction, cancer progression, control of blood pressure; therefore, they are considered potential therapeutic targets in cardiovascular and inflammatory disorders (Bland et al., 2008; Turner et al., 2001) (Table 1). M13 enzymes display a short N-terminal cytoplasmic domain, a single transmembrane helix

and a C-terminal extracellular domain containing the active site and they are generally selective inhibited by Streptomyces product phosphoramidon (Emoto and Yanagisawa, 1995; Turner and Nalivaeva, 2006).

NEP involvement in the inactivation of a variety of physiologically active peptides (such as enkephalin, substance P, bradykinin, oxytocin, neurotensin, bombesin, atrial-natriuretic-peptide (ATR) and β-amyloid) reflects its broader spectrum of physiopathological functions. It is now accepted that NEP functions in the turn off of neuropeptide signals (as for enkephalins) in a fashion similar to acetylcholinesterase at cholinergic synapses. It is located on pre- and post-synaptic membranes and on axonal membrane, where it inactivates the neuropeptide release, acting after their interaction with respective receptors (Matsas et al., 1983; Roques et al., 1980; Turner, 2003). Similarly to angiotensin-converting-enzyme (ACE), NEP inactivates ATR and thus enhances vasodilatation and natriuresis. NEP/ACE inhibitors, the so called "vasopeptidase inhibitors", are considered a novel therapeutic approach in hypertension, heart and renal disease treatment (Bralet and Schwartz, 2001; Kenny and Stephenson, 1988). Recently, a third class of inhibitors, also including the ECE inhibitor, has been developed: the dual and triple inhibitors, in addition to their ability to effectively lower blood pressure in hypertensive patients, also display antinflammatory and antifibrotic activities. However, this therapy is not free of concerns, since clinical data suggest that the incidence of angioedema may increase with vasopeptidase inhibition (Campbell, 2003; Daull et al., 2007; Quaschning, 2005). Possible NEP implication in cancer mechanism has been postulated on the basis of the NEP identity with the common acute lymphoblastic leukemia antigen CD10, a leukemia associated antigen expressed in lymphoid precursors and germinal B cells, and of an alteration of its expression and activity in a variety of malignancies (Carrel et al., 1983; Tran-Paterson et al., 1989). In particular, NEP plays a pivotal role in the development and progression of androgen-independent-prostate cancer (PC) (Osman et al., 2004; Papandreou et al., 1998; Usmani et al., 2000), since its substrates, such as bombesin and endothelin-1, are implicated at various stages of PC (Albrecht et al., 2004; Freedland et al., 2003). In recent years, NEP has also emerged as an important tumor suppressor gene product and its biological role has been not only related to its enzymatic function, but also to a direct protein–protein interaction (Sumitomo et al., 2005). For example, NEP cytoplasmic tail directly associates with the tumor suppressor PTEN, leading to a negative regulation of downstream cell growth and cell survival pathways, thereby regulating Akt/PKB signaling (Sumitomo et al., 2004). *In vitro* and *in vivo* evidences show NEP involvement in β-amyloid (βA) catabolism and NEP is now considered one of the most important proteases targeting βA in the extracellular space, raising the concept of its use as therapeutic target for Alzheimer's disease (Hersh and Rodgers, 2008; Iwata et al., 2000; Kanemitsu et al., 2003).

NEP homologue *ECE1* has been also characterized as an Aβ-degrading enzyme that appears to act intracellularly, thus limiting the amount of Aβ available for secretion (Eckman et al., 2001, 2003; Shirotani et al., 2001). ECE1 is also known to catalyze the final step in the biosynthesis of the potent endogenous vasoconstrictor peptide, endothelin-1, which acts in a paracrine fashion to regulate vascular tone (Matsumura et al., 1990; Xu et al., 1994). Since the upregulation of ET-1/ECE1 is present at different stages of atherosclerotic plaque evolution, it has been also suggested as a target in atherosclerosis therapy (Ihling et al., 2001, 2004). A number of other peptides are cleaved *in vitro* by ECE1, such as substance P, neurotensin and bradykinin, even though is not clear whether these peptides are its physiological substrates (Turner et al., 2001). Despite the structural similarities between *ECEL1*, ECE and NEP, ECEL1 does not cleave ECE and NEP substrates and its physiological function and substrate specificity remain unknown (Kiryu-Seo et al., 2000; Turner et al., 2001). ECEL1, specifically expressed in neurons of the central and peripheral nervous system since early developmental stages, seems to play an important role in neuronal development (Nagata et al., 2006). ECEL1 expression has been also highly associated with nerve injury in CNS and PNS, since peripheral and optic nerve transections induce ECEL1 expression in nerve-injured neurons (Kato et al., 2002; Kiryu-Seo et al., 2000).

Mutations in the *PHEX* gene have been identified as responsible for X-linked hypophosphatemic rickets (XLH), the most common form of inherited rickets characterized by growth retardation and rachitic and osteomalacic bone disease (Sabbagh et al., 2000; Tenenhouse, 1999). Although no endogenous substrates for PEX protein have been identified, it has been suggested that PEX could inactivate paracrine or autocrine factors involved in bone and teeth mineralization and/or circulating factors which mediate renal phosphate reabsorption and vitamin D metabolism (Lipman et al., 1998; Tenenhouse, 1999).

Kell protein is a component of the highly polymorphic Kell/XK complex, expressing over 25 antigens, that can induce severe reactions in mismatched blood-transfused patients and severe fetal anemia in sensitized mothers (Lee et al., 2000). The physiological functions of Kell and XK have not been fully elucidated, but Kell is a zinc endopeptidase with endothelin-3-converting enzyme activity and XK has the structural characteristics of a membrane transporter (Redman et al., 1999; Sha et al., 2006).

1.1.4. M41 family

M41family includes paraplegin and its homologous AFGR3L2 (Table 1) (for a review see Rugarli and Langer, 2006; Salinas et al., 2008). *Paraplegin* is part of the mitochondrial AAA + protein complex which forms cylindrical hexamers on the inner mitochondrial membrane. It is implicated in the cleavage of the mitochondrial targeting sequence, in ribosome maturation, in the degradation of proteins misfolded after mitochondrial membrane transport and antioxidant defense (Esser et al., 2002; Karlberg et al., 2009; Koppen et al., 2007; Nolden et al., 2005). Mutations in paraplegin gene (SPG7) bring about around 5% of autosomal recessive hereditary spastic paraplegia (HSP), an heterogeneous group of conditions characterized by the presence of lower limb plastic and weakness (Rugarli and Langer, 2006; Salinas et al., 2008). HSP-related mutations in SPG7-gene are associated to axonal degeneration and correlate with the onset of motor impairment (Ferreirinha et al., 2004). Recent investigations show that also *AFGR3L2*, which forms supercomplex with paraplegin on the inner mitochondrial membrane,

is essential for axonal development (Maltecca et al., 2008). Interestingly, genetic and functional data demonstrate that missense mutations of AFGR3L2 lead to dominant hereditary spinocerebellar ataxia type 28 (SCA28), which is a neurological disorder characterized by cerebellar dysfunction related to Purkinje cell degeneration (Di Bella et al., 2010). This result highlights the emerging concept of mitochondrial quality control machinery in protecting human cerebellum from neurodegeneration (Di Bella et al., 2010).

1.1.5. M43 family

Pappalysin family includes the pregnancy-associated plasma protein-A (PAPPA) and pregnancy-associated plasma protein-E (PAPPA2) (Table 1) (for a review see Boldt and Conover, 2007; Conover, 2010; Consuegra-Sanchez et al., 2009a; Kirkegaard et al., 2010). *PAPPA*, originally isolated as one of the proteins synthesized in the placenta, circulating at high concentrations in pregnant women, is commonly used as biochemical marker in the screening of Down's syndrome during first-trimester of pregnancy (Lin et al., 1974; Van Heesch et al., 2010; Wald et al., 1999). PAPPA seems to be a critical determinant of growth and development through the proteolysis of insulin-growth-factor-binding proteins (IGFBPs), which bind IGFI and IGFII, thus preventing their interaction with IGF receptors (Oxvig, 2001). PAPPA-mediated IGFBP cleavage "releases" IGF for receptor activation, modulating the local availability of IGF (Byun et al., 2001; Durham et al., 1994; Laursen et al., 2000). Emerging preclinical, clinical and histopathological evidences sustain that PAPPA may serve as a marker of cardiovascular risk, reflecting the atherosclerotic plaque instability (Bayes-Genis et al., 2001; Lund et al., 2003; Consuegra-Sanchez et al., 2009a). In this context, it has been proposed that cell-associated PAPPA, enhancing local IGF actions, could amplify atherosclerosis plaque formation (Conover, 2010). Little is known on PAPPA1 homologue, *PAPPA2*, even though in a recent study the analysis of tissue expression patterns and biological consequences of KO gene indicate distinct physiological roles for PAPP-A2 and PAPP-A in mice (Conover et al., 2011).

1.1.6. M48 family

Farnesylated-protein converting enzyme 1, also known as ZMPSTE24, is a membrane protease with seven predicted membrane spans (for a review see Barrowman and Michaelis, 2009; Liu and Zhou, 2008; Young et al., 2006). It performs a critical step in the processing of prelamin A in lamin A, a nuclear intermediate filament which provides nuclear structure and participates to heterochromatin organization and cell cycle control, removing the farnesyl tail of prelamin A (Mattout et al., 2006; Ramirez et al., 2007). ZMPSTE24 is associated directly and indirectly to human progeroid disorders (Capell and Collins, 2006; Young et al., 2005). The failure of prelamin A cleavage by ZMPSTE24 due to the absence of the cleavage site results in one form of laminopathy, Hutchinson–Gilford Progeria Syndrome (HGPS), which appear to mimick accelerated aging, being characterized by bone abnormalities, slow growth and atherosclerosis (Capell et al., 2007). Mutations in ZMPSTE24 gene also induce two secondary laminopathies, Restrictive Dermopathy (RD) and Mandibuloacral Dysplasia (MD) (Capell and Collins, 2006). RD generally results in death in uterus, since it is associated to total loss of ZMPSTE24 function, while MD is a mild condition with one partially active ZMPSTE24 allele, characterized by skeletal abnormalities, such as hypoplasia of mandible, cutaneous atrophy and progeroid feature (Agarwal et al., 2003a,b; Ahmad et al., 2010; Denecke et al., 2006; Lombardi et al., 2008; Miyoshi et al., 2008).

2. M10 family

M10 family includes human Zn-endopeptidases known as "Matrix metalloproteinases" (MMPs) (see Table 2), which are involved in a great variety of physiopathological processes like skeletal growth and remodeling, wound healing, cancer, arthritis and multiple sclerosis (Bafetti et al., 1998; Hirose et al., 1992; Matrisian et al., 1986; Vu et al., 1998; Wysocki et al., 1993; Nagase and Woessner, 1999; Sternlicht and Werb, 2001; Vu and Werb, 2000; Opdenakker et al., 2003; Fingleton, 2007).

Since MMPs are able to degrade basement membranes and extracellular matrix components (see Table 3), they have traditionally been viewed as effectors of late stage of cancer evolution. However, MMPs also have an important regulatory role, as they can modulate cytokine and chemokine activity by proteolytic processing (McQuibban et al., 2000; Opdenakker et al., 2001; Schönbeck et al., 1998; Van den Steen et al., 2000).

Up to now, at least 24 MMPs have been found to be expressed in human tissues. MMPs share high protein sequence homology and have defined domain structure; thus, according to their structural properties can be divided into eight groups, namely: (1) minimal domain-MMPs (*i.e.*, MMP-7 and MMP-26), (2) simple hemopexin-containing domain MMPs (*i.e.*, MMP-1, MMP-8, MMP-13, MMP-18, MMP-10, MMP-12, MMP-19, MMP-20 and MMP-27), (3) gelatin-binding MMPs (*i.e.*, MMP-2 and MMP-9), (4) furin-activated secreted MMPs (*i.e.*, MMP-11 and MMP-28), (5) vitronectin-like insert MMP (*i.e.*, MMP-21), (6) type I transmembrane MMPs (*i.e.*, MMP-14, MMP-15, MMP-16 and MMP-24), (7) glycosylphosphatidylinositol-anchor linked MMPs (*i.e.*, MMP-17 and MMP-25), (8) type II transmembrane MMPs (*i.e.*, MMP-23A and MMP-23B) (see Fig. 1 and Table 2).

According to their substrate specificity and structural organization, MMPs are usually also classified into five main subgroups, which will be used in this work, namely:

(i) Collagenases (*i.e.*, MMP-1, MMP-8 and MMP-13), which are able to preferentially cleave fibrillar collagen, recognizing the substrate through the haemopexin-like domain (Gioia et al., 2002; Hirose et al., 1993; Murphy et al., 1992).

Table 2
Domain structure and classification of human MMPs.

MMP group	MMP subgroup	MMP	Alternative name
Simple hemopexin-containing MMPs			
	Collagenases	MMP-1	Interstitial collagenase
		MMP-8	Neutrophil collagenase
		MMP-13	Collagenase-3
	Stromelysines	MMP-3	Stromelysin-1 (transin-1)
		MMP-10	Stromelysin-2
	Other MMPs	MMP-12	Macrophage metalloelastase
		MMP-19	RASI-1
		MMP-20	Enamelysin
		MMP-27	None
Gelatin-binding MMPs			
	Gelatinases	MMP-2	Gelatinase-A
		MMP-9	Gelatinase-B
Furin-activated secreted MMPs			
		MMP-11	Stromelysin-3
		MMP-28	Epilysin
Vitronectin-like insert MMPs			
		MMP-21	None
Minimal domain MMPs			
	Matrylisins	MMP-7	Matrilysin-1 (Pump-1)
		MMP-26	Matrilysin-2 (endometase)
Type I-transmembrane MMPs			
	MTs-MMPs	MT1-MMP	MMP-14
		MT2-MMP	MMP-15
		MT3-MMP	MMP-16
		MT5-MMP	MMP-24
GPI-linked MMPs			
	MTs-MMPs	MT4-MMP	MMP-17
		MT6-MMP	MMP-25 (leucolysin)
Type II-transmembrane MMPs			
	MTs-MMPs	MMP-23A	Femalysin
		MMP-23B	None

(ii) Gelatinases (*i.e.*, MMP-2 and MMP-9), which are able to enzymatically process various substrates of the extracellular matrix (ECM), such as collagen I and collagen IV. Beside the haemopexin-like domain, gelatinases are characterized by the presence of a "collagen binding domain" (CBD), located in their catalytic domain. CBD is made of three fibronectin II-like repeats and represents the preferential binding domain for fibrillar collagen I (Steffensen et al., 1995).
(iii) Stromelysins (*i.e.*, MMP-3, MMP-10 and MMP-11), which are able to hydrolyse collagen IV, but do not cleave fibrillar collagen I (Nagase and Woessner, 1999).
(iv) Matrilysins (*i.e.*, MMP-7 and MMP-26), which lack the haemopexin-like domain and are able to process collagen IV but not collagen I (Marchenko et al., 2001; Wilson and Matrisian, 1996).
(v) Membrane-type I (MT-MMPs) (*i.e.*, MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-25), which contain at the C-terminal an additional domain, represented by an intermembrane region, completed by a short cytoplasmic tail. Only MMP-14 and MMP-16 has been shown to be able to cleave fibrillar collagen I (Ohuchi et al., 1997; Sabeh et al., 2009).

Finally, there are few MMPs, such as metalloelastase (MMP-12), RASI-1 (MMP-19), MMP-21 and MMP-28, which cannot be included in any of the above mentioned classes, and which will be treated separately.

In view of the MMP involvement in several pathological processes (see Table 4), the development of powerful and selective inhibitors might represents an important therapeutic goal, this being especially relevant for cancer therapy (Konstantinopoulos et al., 2008; Martin and Matrisian, 2007). However, recent failures in cancer clinical trials of MMP inhibitors (Coussens et al., 2002) have raised a question on MMPs druggability, mostly because of their multiple and often contradictory role in cancer disease (Overall and Kleifeld, 2006a; Fingleton, 2007).

In spite of these problematic aspects, the relevance of the physiopathological role of MMPs is unquestionable, keeping unaltered their importance as potential druggable targets, even though a better knowledge is needed to understand which (and when) a MMP is actually involved in a specific pathological process (Overall and Kleifeld, 2006a).

2.1. Structural aspects

Sequence comparison of MMPs reveals consistent similarities in their domain organization (Fig. 1), which is usually made by: (i) the pre-peptide involved in the pro-enzyme secretion process, (ii) the auto-inhibitory pro-domain, (iii) the

Table 3
MMPs macromolecular substrates.

MMP group	MMP	Substrates	
		Matrix substrates	Bioactive substrates
Simple hemopexin containing MMPs	MMP-1	Collagens I, II, III, VII,VIII, X; gelatin; aggrecan; link protein; entactin; tenascin; perlecan	α2-M; α-PI; α1-antichymotrypsin; IGFBP-2, 3, 5; proIL-1β; CTGF
	MMP-8	Collagens I, II, III, V, VII, VIII, X; Fn; entactin; tenascin; gelatin; aggrecan; link protein	α-PI
	MMP-13	Collagens I, II, III, IV, VII, IX, X, XIV; aggrecan; gelatin; Fn; tenascin; osteonectin; Ln; perlecan	CTGF; ProTGF-β; MCP-3; α1-antichymotrypsin; plasminogen
	MMP-3	Aggrecan; decorin; gelatin; Fn; Ln; collagens III, IV, V, IX, X, XI; tenascin; link protein; perlecan; osteonectin; entactin	IGFBP-3; proIL-1β; HB-EGF; CTGF; E-cadherin; α1-antichymotrypsin; α1-PI; α2-M; plasminogen; uPA; pro-MMP-1, 7, 8, 9, 13
	MMP-10	Aggrecan; Ln; Fn; gelatin; collagens III, IV, V, IX, X, XI; tenascin; link protein;	Pro-1, 8, 10
	MMP-12	Elastin; aggrecan; Fn; collagen IV; gelatin; vitronectin; entactin; osteonectin; Ln; nidogen	Plasminogen; apoliprotein(a)
	MMP-19	Collagen IV; gelatin; Fn; tenascin; aggrecan; enatctin; COMP; Ln; nidogen	IGFBP-3; proIL-1β; HB-EGF; CTGF; E-cadherin; α1-antichymotrypsin; α1-PI; α2-M; plasminogen; uPA; pro-MMP-1, 7, 8, 9, 13
	MMP-20	Amelogenin; aggrecan; gelatin; COMP	Unknown
	MMP-27	Unknown	Unknown
	MMP-2	Gelatin; collagens I, IV, V, VII, X, XI, XIV; Ln; Fn; elastin;aggrecan; osteonectin; link protein	ProTGF-β; FGF receptor I; MCP-3; IGFBP-5; proIL-1β; galectin-3; plasminogen
	MMP-9	Gelatin; collagens I, III, IV, V, VII, X, XII; elastin; entactin; aggrecan; Fn; link protein; vitronectin; N-telopeptide of collagen I	ProTGF-β; IL-2 receptor a; Kit-L; IGFBP-3; proIL-1β; ICAM-1; α1-PI; galectin-3; plasminogen
	MMP-11	Fn; Ln; aggrecan; gelatins	α1-PI; α2-M; IGFBP-1
	MMP-28	Unknown	Casein
Vitronectin-like insert MMPs	MMP-21	Unknown	Unknown
Minimal domain MMPs	MMP-7	Aggrecan; gelatin; Fn; Ln; elastin; entactin; collagens, III, IV, V, IX, X, XI; tenascin; decorin; link protein; vitronectin	Proα-defensin; Fas-L; β4 integrin; E-cadherin; proTNF-α; CTGF; HB-EGF; RANKL; IGFBP-3; plasminogen
	MMP-26	Gelatin; collagen IV; Fn; fibrinogen; vitronectin	pro-MMP-9; α1-PI
Type I-transmembrane MMPs	MT1-MMP	Collagen I, II, III; gelatin; aggrecan; Fn; Ln; fibrin; vitronectin; entactin; proteoglycans; Ln-5	Pro-MMP-2; Pro-MMP-13; CD44; MCP-3; tissue transglutaminase
	MT2-MMP	Fn; tenascin; nidogen; aggrecan; entactin; collagen; gelatin; perlecan; Ln; vitronectin	Pro-MMP-2; tissue transglutaminase
	MT3-MMP	Collagen III; aggrecan; gelatin; Fn; vitronectin.	Pro-MMP-2; tissue transglutaminase
	MT5-MMP	Gelatin;fibronectin; vitronectin; collagen, aggrecan; PG	Pro-MMP-2
GPI-linked MMPs	MT4-MMP	Gelatin; fibrinogen	Unknown
	MT6-MMP	Gelatin; collagen IV; fibrin; Fn; Ln	ProMMP-2
Type II-transmembrane MMPs	MMP-23A	Unknown	Unknown
	MMP-23B	Gelatin	Unknown

catalytic domain and (iv) the C-terminal haemopexin-like domain often involved in the recognition/positioning of substrates (Fig. 1).

The pro-domain, composed of about 80 residues, extends from the N-terminus to the catalytic domain and it is responsible for the enzyme latency. A cysteine sulphydryl group present in the N-terminal pro-domain (*i.e.*, "Cys-switch": Pro-Arg-Cys-Gly-X-Pro-Asp) interacts with the Zn^{2+} ion and blocks the active site. The pro-domain of some MMPs shows a recognition sequence for furin-like serine proteinases, which is needed for the pro-domain cleavage and, consequently, for the MMPs activation (Skiles et al., 2001).

All MMPs structures contain in the active site the common sequence motif His-Glu-X-Gly-His-X-X-Gly-X-X-His, where three His residues coordinate the catalytic Zn^{2+} ion (Bode et al., 1999) (Fig. 2).

The overall topology of the MMP catalytic domain is spherical, with (i) the catalytic Zn^{2+} ion coordinated by three His residues, (ii) a structural Zn^{2+}coordinated by three His and one Asp residues, and (iii) at least two structural calcium atoms octahedrally coordinated, which stabilize the whole architecture (Borkakoti, 2000).

In unliganded MMPs, the catalytic zinc residing in its center is coordinated by three imidazole $N_{\varepsilon 2}$ atoms of the three His and by a fixed water molecule, which lies at a hydrogen bond distance to the carboxylate group of the catalytic Glu residue, conserved in all MMPs (see Fig. 2). Conversely, in the case of MMP complexes with bidentate inhibitors (*i.e.*, those with an hydroxamic acid function) this water is replaced by two oxygen atoms, which together with the three imidazoles bind the

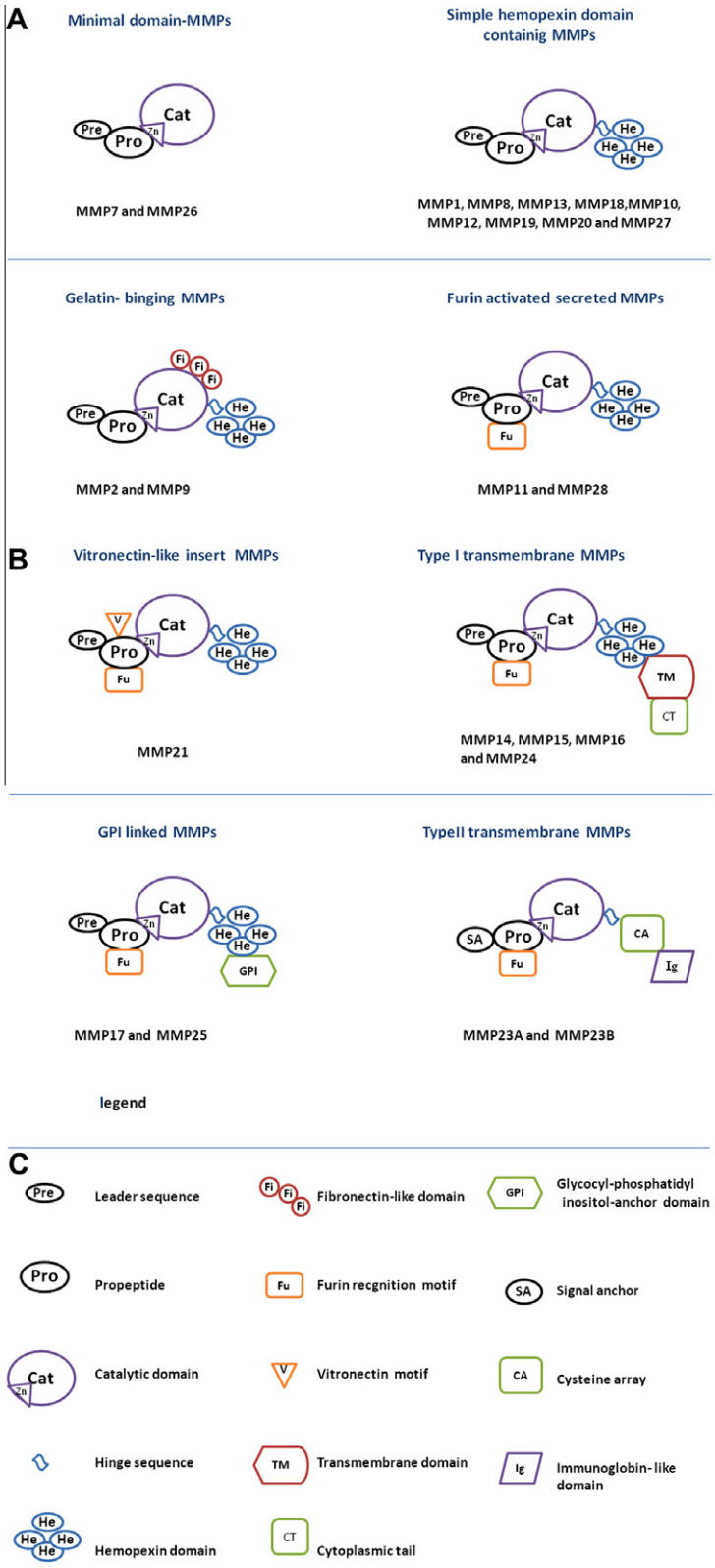

Fig. 1. Classification of human MMPs. Human MMPs are classified according to their domain composition into eight groups. Each MMP is illustrated in the latent zymogen form with the catalytic zinc (Zn) binding to the cystein of the prodomain.

Table 4
Involvement of different MMPs in various pathological processes.

System	Disease	MMP
Cardiovascular		
	Aortic aneurysm	MMP-1 MMP-2 MMP-3 MMP-7 MMP-8 MMP-9 MMP-12 MMP-13 MMP-14
	Atherosclerosis	MMP-1 MMP-2 MMP-3 MMP-8 MMP-9 MMP-10 MMP-11 MMP-12 MMP-13 MMP-14
	Myocardial infarction	MMP-2 MMP-3 MMP-7 MMP-9 MMP-13 MMP-14
	Left ventricular hypertrophy	MMP-1 MMP-7 MMP-13 MMP-14
	Stroke	MMP-2 MMP-3 MMP-9 MMP-12 MMP-13 MMP-14
Nervous		
	Alzheimer	MMP-1 MMP-2 MMP-9 MMP-24
	Blood–brain barrier (BBB) disruption	MMP-2 MMP-7 MMP-9 MMP-14
	Brain injury	MMP-7 MMP-13
	Encephalomyelitis	MMP-8 MMP-9 MMP-12 MMP-25
	HIV-dementia	MMP-7
	Intracerebral hemorrhage (ICH)	MMP-12
	Meningitis	MMP-8 MMP-12
	Multiple sclerosis	MMP-2 MMP-7 MMP-9 MMP-12 MMP-19 MMP-25
	Parkinson	MMP-3
	Spinal chord injury	MMP-12
	Vascular dementia	MMP-1
Joint and muscular		
	Dupuytren	MMP-7
	Inflammatory myopathies	MMP-7
	Medial collateral ligament (MCL) injury	MMP-12
	Osteoarthritis (OA)	MMP-1 MMP-2 MMP-3 MMP-7 MMP-8 MMP-9 MMP-13 MMP-14 MMP-16 MMP-17
	Polymyositis	MMP-9
	Rheumatoid arthritis (RA)	MMP-1 MMP-2 MMP-3 MMP-8 MMP-9 MMP-12 MMP-13 MMP-14 MMP-19
Respiratory		
	Acute respiratory distress syndrome (ARDS)	MMP-3
	Asthma	MMP-1 MMP-8 MMP-9 MMP-12 MMP-25
	Emphysema/chronic obstructive pulmonary (COP)	MMP-1 MMP-8 MMP-9 MMP-12 MMP-14 MMP-25
	Idiopatic pulmonary fibrosis (IPF)	MMP-1 MMP-7 MMP-12
	Lung fibrosis	MMP-1 MMP-7 MMP-8 MMP-12
Digestive		
	Liver fibrosis	MMP-1 MMP-8 MMP-12 MMP-13 MMP-15
	Liver cirrhosis	MMP-8 MMP-9 MMP
Infectious diseases		
	Helicobacter pylori	MMP-1
	Mycobacterium tuberculosis	MMP-1 MMP-7
	Schistosoma mansoni	MMP-12
Autoimmune diseases		
	Autoimmune inner ear	MMP-9
	Bullosus pemphigoid	MMP-9
	C-protein induced myocarditis	MMP-9
	Lupus erythematosus	MMP-2 MMP-9
	Sjögren Syndrome	MMP-9
Other diseases		
	Diabetic nephropathy	MMP-24
	Endometriosis	MMP-1 MMP-2 MMP-3 MMP-7 MMP-13 MMP-24
	Periodontal inflammation	MMP-2 MMP-8 MMP-9 MMP-13 MMP-25
Wound healing		
		MMP-1 MMP-2 MMP-3 MMP-8 MMP-9 MMP-10 MMP-11 MMP-13 MMP-14 MMP-28

catalytic Zn^{2+} ion in a trigonal–bipyramidal (pentacoordinate) manner. Additionally, a conserved Met residue, forming a "Met-turn", contributes to protect the catalytic zinc (Bode et al., 1999).

The catalytic domain is connected to the haemopexin-like domain by a segment, called linker (see Fig. 1) or hinge region (Maskos, 2005). This connecting linker might fulfill important functional roles rather than simply acting as physical spacer, since it turns out to be important for the enzyme stability and for the substrate degradation (Overall and Butler, 2007), this being especially true for the collagenase family (Tsukada and Pourmotabbed, 2002).

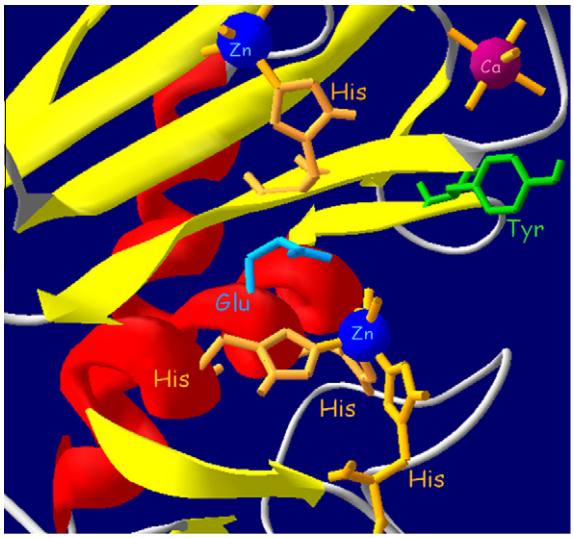

Fig. 2. Ribbon representation of the catalytic site of a MMP (in particular of MMP-8). In orange are the three histidines (His197, His201, His207 in MMP-8), coordinating the catalytic Zn^{2+} atom (blue sphere), and in blue the glutamate residue (Glu198 in MMP-8) involved in the proton shuttle catalytic mechanism. The magenta sphere is a structural Ca^{2+} atom, in green is a tyrosyl residue (Tyr189 in MMP-8) and in orange is a histidyl residue (His162 in MMP-8), which coordinates a structural Zn^{2+} atom (blue sphere). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The active site cleft consists of several recognition pockets, half of which are located on the right side of the catalytic Zn^{2+} ion (called primed side, with pockets named Sn' and $n = 1, 2, \ldots n$) and the rest on the left side of the catalytic Zn^{2+} ion (called unprimed side, with pockets named Sn and $n = 1, 2, \ldots n$). By analogy P1′, referring to substrate and/or inhibitor, shows a generic chemical group able to fit into the S1′ pocket.

Usually, the most important recognition site (at least for small synthetic substrates and inhibitors) is the primary hydrophobic S_1' pocket, which is characterized by a variable length amino acid composition and conformation (according to the different MMPs), followed by shallow S2′ and S3′ pockets, which are primarily exposed to the solvent. For all MMPs, the size and shape of the S1′ specific pocket critically regulates the ligand binding selectivity, such that MMPs generally fall in two classes (Borkakoti, 2000; Skiles et al., 2001, 2004):

1. those with a large and open S1′ pocket, such as MMP-2, MMP-3, MMP-8, MMP-9, MMP-12 and MMP-13;
2. those with a small S1′ pocket, such as MMP-1 and MMP-7.

In MMPs belonging to the first class, the S1′ pocket is preformed, wide and more able to accommodate large P1′ groups. Conversely, in MMPs belonging to the second class the S1′ pocket is smaller and not preformed, since it is occluded by either Arg^{214} or Tyr^{214}, respectively (Skiles et al., 2001). Although large P1′ groups are not excluded to be recognized by the so-called small S1′ pocket, their binding requires an induced-fit open conformation, as observed in MMP-1 (see below).

The haemopexin-like *C*-terminal domain is composed of four β-sheets, each forming a blade of the four-bladed β-propeller structure (Bode et al., 1999). On the other hand, MMP-7 and MMP-26 are lacking the haemopexin domain, while MMP-23 has an immunoglobulin-like domain replacing the haemopexin repeat (Skiles et al., 2001).

Further, MMP-2 and MMP-9 show an additional domain, called fibronectin-like domain (see Fig. 1), which is inserted within the catalytic region and involved in collagen recognition (Skiles et al., 2001).

Moreover, some MT-MMPs contain either a membrane anchor (such as MMP-17 and MMP-25, which are anchored to the membrane through a C-terminal glycosylphosphatidylinositol moiety, and MMP-23, which is anchored to the membrane at the N-terminus) or a cytoplasmic domain at the C-terminus (such as MMP-14, MMP-15, MMP-16 and MMP-24) (Skiles et al., 2001).

The growing availability of MMP 3D structures has contributed to develop and speed up the drug design process, which can now exploit realistic molecular modeling procedures (Aureli et al., 2008; Pirard, 2007).

2.1.1. Natural MMPs inhibitors

Primary function of MMPs is tissue growth and remodeling by selective proteolytic degradation. Therefore, in order to avoid uncontrolled ECM turnover, inflammation, cell growth and migration, under physiological conditions, the activity of matrix metalloproteinases is accurately regulated at the levels of transcription, zymogen activation and inhibition by endogenous inhibitors.

Tissue inhibitors of metalloproteinases (TIMPs) are natural MMPs endogenous inhibitors involved in MMP-mediated ECM turnover, tissue remodeling and cellular behavior (Bourboulia and Stetler-Stevenson, 2010; Brew and Nagase, 2010).

In humans four different TIMPs have been found, namely TIMP-1, TIMP-2, TIMP-3 and TIMP-4, which share about 40% homology in sequencer (see Table 5). All mammalian TIMPs show two distinct domains, a C-terminal domain with about 65 residues and a N-terminal domain of about 125 amino acid residues. Each of their N- and C-terminal domains contains six conserved cysteine residues that form three disulfide loops. The N-terminal region binds the MMP catalytic domain and inhibits MMP activity; in particular, the TIMP inhibition mechanism is due to a bidentate coordination of the metal ion in MMPs by the N-terminal α-amino group, thus impairing the hydrolase activity. Even though TIMP-3 is unique among human (and mammalian) TIMPs in inhibiting also several members of the ADAM and ADAMTS families and all TIMPs show a relatively low affinity for the membrane-type MMPs (*i.e.*, MMP-14, MMP-16, MMP-24 as well as MMP-19), most of TIMPs are, under physiological conditions, broad-spectrum inhibitors, although some differences in specificity can be observed.

Furthermore, the TIMP C-terminal region interacts with pro-MMP-2 and pro-MMP-9 C-terminal hemopexin domain to stabilize the pro-enzyme. The interaction of TIMP-2 with pro-MMP-2 is part of the pro-MMP-2 activation mechanism which is observed on cell membrane surface where both membrane-type-1 MMP (MT1-MMP or MMP-14) and TIMPs play a key role in MMP-2 autolytic cleavage and activation (Itoh et al., 2001).

It should be underlined that, although TIMPs were originally characterized as MMP inhibitors, their activities only partially arise from metalloproteinase inhibition: in fact, they have various biological activities, including the modulation of cell proliferation, cell migration and invasion, anti-angiogenesis, anti- and pro-apoptosis and synaptic plasticity (Stetler-Stevenson, 2008).

2.2. General mechanistic aspects

MMPs catalyze the cleavage of a peptide bond by a mechanism which is similar to that reported for serine and cysteine proteinases, although different groups accomplish the electrophilic attack. In MMPs, the catalytic Zn^{2+} ion is coordinated by the three His residues; in the absence of a substrate or an inhibitor, a water molecule (*i.e.*, the catalytic water) is coordinated by the Zn^{2+} ion as a fourth ligand, being entrapped between the metal and the catalytic Glu residue belonging to the His-Glu-Xxx-Xxx-His-Xxx-Xxx-Gly-Xxx-Xxx-His motif (see Fig. 2). In all MMPs, the carbonyl group of the scissile peptide bond points towards the catalytic Zn^{2+} ion and therefore it can be polarized (Fig. 2). The peptide hydrolysis is assisted also by the relatively high pK_a of the carboxyl group of the catalytic Glu residue (see Fig. 2), which becomes protonated at neutral pH, increasing the hydroxyl character of the catalytic water molecule (Stocker and Bode, 1995). This feature facilitates the nucleophilic attack of the water molecule on the carbonyl carbon atom of the scissile peptide bond, which has a carbocationic character due to the polarization induced by the Zn^{2+} ion. This reaction gives rise to the tetrahedral intermediate, stabilized by both the Zn^{2+} ion and a carbonyl group of a nearby peptide bond, leading to the cleavage of the scissile peptide bond when a second residue (usually a residue of His, which decreases its pK_a) donates a hydrogen atom to the nitrogen atom of the imido portion of the peptide bond (Harrison et al., 1992). This sequence of events is confirmed by the dramatic reduction of the MMP activity following the Glu residue mutation (Cha and Auld, 1997). A consequence of this protonation/deprotonation sequence of events is a complex pH-dependence of the enzymatic mechanism, which has been investigated in several MMPs (Fasciglione et al., 2000; Stack and Gray, 1990); in particular, site-directed mutagenesis has allowed to identify in MMP-3 the crucial role of His^{224} as a proton donor (Holman et al., 1999; Johnson et al., 2000).

A large fraction of functional studies on the enzymatic activity by MMPs has been carried out employing synthetic fluorogenic peptidic substrates (Stack and Gray, 1989; Weingarten et al., 1985). These peptides were usually based on the amino acid sequences of natural substrates, such as collagens, aiming to identify the substrate specificity pocket (see Nagase and Fields (1996) for a review). Although a comprehensive overview of all these studies is off the scope for this review, it is important to underline that this approach turned out to be very useful for the identification of the substrate recognition and the cleavage process in the immediate environment of the active site. In this respect, as an example of the relevant informations obtained, we can mention that (i) in the case of the two collagenases MMP-1 and MMP-8 the residue in position P'_1 has been shown to play a crucial discriminatory effect, since an aromatic residue in this position renders the synthetic peptide a much better substrate for MMP-8 with respect to MMP-1 (Fields et al., 1987); (ii) in the case of the two gelatinases MMP-2 and MMP-9 a substrate selectivity (in favor of MMP-2, see Chen et al., 2002) could be only achieved by the simultaneous presence of a rather hydrophobic residue in the P'_1 position and a positively charged residue (*e.g.*, Arg) in the P_2 position.

Further, investigations on the cleavage of structured synthetic substrates, derived from short triple-helical collagen-like peptides (Ottl et al., 2000), have clearly shown that the thermal stability of triple-helical synthetic substrates is a crucial aspect of the catalytic and recognition mechanism of MMP (Minond et al., 2006).

Table 5
Properties of human TIMPS.

Property	TIMP1	TIMP2	TIMP3	TIMP4
No. of residues	184	194	188	194
Approximated M_r	21	22	22	22
MMP inhibition	Weak for MMP-14, -16, -19, -24	All	All	Most
Pro-MMP interaction	Pro-MMP-9	Pro-MMP-2	Pro-MMP-2 and Pro-MMP-9	Pro-MMP-2

Although these investigations indeed have been of the utmost importance for (i) the definition of the mechanistic steps of the proteolytic action by MMPs, (ii) the characterization of protonating groups pK_as involved in the peptide bond cleavage (Fasciglione et al., 2000; Stack and Gray, 1990) and (iii) the identification of substrate recognition pockets in the close proximity of the active site, this information is not enough to account for the MMPs enzymatic activity toward macromolecular substrates. As an example of this, proteolytic cleavage of triple-helical collagen I-like peptides by collagenases is much more efficient than for stromelysins (*e.g.*, MMP-3, see Nagase and Fields, 1996), but this difference did not explain the inability of MMP-3 to process macromolecular collagen I. Thus, functional observations on natural macromolecular substrates, such as collagens, clearly indicated that additional domains (though not directly involved in the enzymatic cleavage chemistry) are very important for substrate recognition and the enzymatic activity on macromolecules (Chung et al., 2000; Gioia et al., 2002; Murphy et al., 1992).

2.3. Macromolecular substrates

In the last years, evidence has been emerging that when MMPs interact with macromolecular substrates the correct active-site positioning is achieved through the interaction of exosites of MMPs with the substrates (Chung et al., 2000; Gioia et al., 2002; Murphy et al., 1992). Exosites are binding sites topologically distinct from the catalytic site (where the substrate cleavage process takes place), they can be located also in additional domains of the MMPs, playing a crucial role in the dynamic unfolding of inaccessible regions of substrates (otherwise uncleavable).

The enzymatic activity of several MMPs on different natural substrates, such as collagen I, II and IV has been investigated by several groups (Gioia et al., 2002, 2007; Patterson et al., 2001; Tam et al., 2002, 2004; Xu et al., 2004a), unraveling various functional features, which imply an important role of different domains in the macromolecular substrate proteolytic processing. Notably, MMP cleavage of bioactive substrates is temperature-dependent (Fasciglione et al., 2000; Gioia et al., 2002; Salsas-Escat et al., 2010), as also supported by the experiments on triple-helical synthetic substrates (Minond et al., 2006). Therefore, in order to derive useful informations for "*in vivo*" studies we think that 37 °C should be the best experimental temperature to employ.

Collagen I is the major component of the extracellular matrix (ECM), consisting in its monomeric form of a triple helix formed by two α-1 chains and one α-2 chain (Prockop and Kivirikko, 1995). Collagenolytic MMPs bind native collagen I via their exosites and these interactions allow to accommodate the individual collagen α chain into the active site cleft of the enzyme for the cleavage process, since the intact triple helix cannot enter the active site. In the case of collagenases (*i.e.*, MMP-1, MMP-8 and MMP-13) and of MT-MMPs (such as MMP-14) the haemopexin-like C-terminal domain is important for collagen I binding (Gioia et al., 2007; Tam et al., 2004), such that its removal (leaving only the catalytic domain) brings about an altered collagen I cleavage process (Gioia et al., 2002; Murphy et al., 1992). However, as pointed out recently, this occurrence seems to be evident only at 37 °C (likely due to the kinetic activation process) (Salsas-Escat et al., 2010). Further, the binding affinity can be either closely similar for the two chains (as in MMP-8, see Gioia et al., 2007) or somewhat higher for the α-2 chain (as in MMP-1 and MMP-13, see Chung et al., 2004; Coletta et al., unpublished results). On the other hand, the haemopexin-like domain does not seem to play a relevant role in substrate recognition by gelatinases, since its removal does not alter appreciably the collagen I binding (Patterson et al., 2001), whereas substrate recognition for these MMPs occurs preferentially through the fibronectin-like domain (Tam et al., 2004). On the other hand, the haemopexin-like domain of gelatinases (and in particular of MMP-2) appears to be connected instead to the lateral mobility of the enzyme along the collagen fibril surface (Collier et al., 2001). Unlike the haemopexin-like domain of collagenases (see above), the fibronectin-like domain of gelatinases shows a much higher affinity for the α-1 chain (Gioia et al., 2007; Tam et al., 2004), clearly indicating that the structural bases for the interaction of the two types of MMPs with collagen I are different, likely involving different regions of the substrate molecule. In addition, while the interaction of the haemopexin-like domain does not bring about gross conformational changes of the triple helix of collagen I (Marini et al., 2000; Tam et al., 2004), fibronectin-like domain binding induces a substantial unwinding of the triple helix (Gioia et al., 2007; Tam et al., 2004). At 37 °C these features result in a dramatically different enzymatic mechanism between collagenases and gelatinases (in particular MMP-2) for collagen I (Gioia et al., 2007), which leads for collagenases to a specific cleavage site (giving rise to the formation of two fragments), corresponding to about 1/4 and 3/4 of the collagen chain length, (Mallya et al., 1990), while for gelatinases a widespread multiple fragmentation of the collagen molecule takes place (Gioia et al., 2007).

It is very important to point out that the interaction of MMPs and macromolecular substrates occurs *in vivo* in different districts and in different environmental conditions (see Table 3). Thus, during inflammation or cancer evolution pH of tissues changes quite drastically, bringing about either acidification and/or alkalinization. This may have important consequences for the interaction and the enzymatic properties of MMPs toward macromolecular substrates, as it has been observed in the case of collagen I (Gioia et al., 2010), putting in evidence as the change of pH may induce increase or decrease of the activity of different MMPs classes.

An additional structural element, which comes into play only for macromolecular substrates, is represented by the linker region, which does not affect the collagen recognition process, but the enzymatic cleavage process (Tsukada and Pourmotabbed, 2002). This feature indeed suggests that after the substrate recognition by collagenases through the haemopexin-like domain the enzymatic activity requires a flexible linker region to correctly position the catalytic domain onto the substrate cleavage site. This requirement seems also confirmed by the fact that the unability of MMP-3 to enzymatically process

collagen I can be bypassed by substituting the region at the edge between the catalytic domain and the linker region with MMP-1 amino acid sequence (Chung et al., 2000).

Also in the case of collagen IV (the major component of the basement membrane) (Kühn, 1995) the role of MMPs additional domains (beside the catalytic one) seems to be very important, since binding of substrate by gelatinases indeed occurs via the interaction of the substrate with the fibronectin-like domain (Monaco et al., 2006).

In the case of macromolecular substrates an additional aspect should be taken into account; thus, unlike a synthetic substrate, a macromolecule can be processed simultaneously by more than one type of enzyme at distinct topological sites. This point may have very important consequences, as it has been shown in the case of collagen IV when it is enzymatically attacked by MMP-2 and MMP-9, which are two of the most efficient enzymes on this macromolecular substrate. In this case, for instance, the interaction site has been shown to be different and allosterically modulated (Gioia et al., 2009), such that the interaction of MMP-2 with its fibronectin-like domain brings about a dramatic increase of the MMP-9 action on the same molecule, a feature likely related to an enzyme-linked conformational change of collagen IV.

In conclusion, the functional modulation of MMPs with macromolecular substrates (as it occurs *in vivo* in cells and tissues) is very complex and can lead to paradoxical results. In the rest of the review we will deal with an overview of the pathological processes in which MMPs are involved. However, for the sake of clarity it must be pointed out that the investigation on and the roles of different MMPs varies very much from enzyme to enzyme, rendering very difficult a purely systematic report of the role of different MMPs. Although we have divided the review on various chapters corresponding to the classification reported above, many crossing points among different chapters will be unavoidable.

3. Collagenases

The name of this class of MMPs refers to the capability of its components to enzymatically process native collagen molecules without unwinding the triple helical assembly of the substrate. Their structural arrangement in the active enzyme is made by a catalytic domain (where the catalytic Zn^{2+} is present and the proteolytic cleavage takes place) and a hemopexin-like domain, made by a typical four-blade propeller structure; they are connected by an intermediate hinge region, which seems to play a relevant role in modulating the interplay between the catalytic and hemopexin-like domain (Tsukada and Pourmotabbed, 2002). In collagenases usually the hemopexin-like domain plays an important role in substrate recognition and correct positioning of the MMP molecule on the macromolecular substrate (Gioia et al., 2002), even though also collagenases devoid of the hemopexin-like domain are able to cleave collagen I at the primary site (Salsas-Escat et al., 2010). Thus, collagenases can degrade fibrillar collagens in their triple-helical structural assembly, bringing about the formation of thermally unstable molecules, which unwind to form gelatin to be then degraded by other proteases. The first cleavage step of type I fibrillar collagen occurs between Gly775/Ile776 residues of the α1(I) chain and between Gly/Leu of the α2(I) chain, both corresponding to about three quarters of the distance from the NH_2-terminus; after the first cleavage by collagenases we obtain the 3/4 and 1/4 fragments of the whole collagen I molecule (Mallya et al., 1990; Salsas-Escat et al., 2010).

There are three enzymes historically belonging to this class, namely (i) MMP-1 or fibroblast collagenase, (ii) MMP-8 or neutrophil collagenase, and (iii) MMP-13 or collagenase-3 (see Table 2). They are structurally similar, displaying also similar functional enzymatic properties (Nagase and Woessner, 1999), even though some slight differences can be detected for substrate specificity (Aureli et al., 2008).

Their physiological role seems to be the remodeling of the collagenous component of the extracellular matrix (ECM), thus being also involved in the wound healing process (see Table 4). As a matter of fact, wound tissues in humans and in experimental animals overexpress multiple MMPs, including mostly the three collagenases (*i.e.*, MMP-1, MMP-8 and MMP-13, see Gill and Parks, 2008), even though some specific role can attributed to each of them (see below). Furthermore, since collagen is the predominant ECM deposit in fibrotic organs, collagenases are believed to be the main proteases responsible for the resolution of fibrosis and restoration of the normal ECM environment.

Alterations of the structure and composition of cardiomyocyte and noncardiomyocyte compartments of the myocardium appear to play a central role in the pathogenesis of heart failure (HF) associated with a number of cardiac diseases (see Table 4). Among these alterations, changes in the quantity and quality of the extracellular matrix, including the collagen network, have been characterized that induce remodeling of the myocardium and ultimately deteriorate left ventricular (LV) function and facilitate the development of HF (Lopez et al., 2010).

A very important role is played by collagenases in the atherosclerotic process, an inflammatory process that affects the vessel wall of large and medium-sized arteries, which is the primary cause of heart disease in the Western world. MMP-8 and MMP-13 collagenases are believed to be ultimately responsible for plaque destabilization and rupture as the play physiological role in the control of collagen degradation in blood vessels; conversely, MMP-1 plays a protective role in human atherosclerosis (Galis et al., 1995). In addition, all collagenases seem involved in abdominal aortic aneurysm (AAA), which is characterized by degradation of extracellular matrix, chronic inflammatory cell infiltration and extensive neovascularization (Choke et al., 2005).

MMP-1 and MMP-13 collagenases are predominantly involved in arthritic diseases. Accumulated lines of evidence have demonstrated that all collagenases are also responsible for the degradation of type II collagen (a major fibrillar collagen in the cartilage), whereas aggrecan (a major proteoglycan in the cartilage) is mostly degraded by MMP-8 and MMP-13 (Okada,

2009). Thus, cartilage is principally degraded by MMP-1 and MMP-13 collagenases, whereas MMP-8 shows a protective role in arthritis.

All three MMP collagenases play a role in liver fibrosis processes. Different diseases of the respiratory system are often associated with aberrant tissue remodeling by MMP-1 and MMP-8 but not by MMP-13.

Although several MMPs play a crucial role in tumor invasion and building of metastatic formations because of their ability to degrade extracellular matrix proteins, collagenases do not seem to play especially relevant roles in tumorigenesis. A variety of human neoplastic diseases have been examined for their ability to produce collagenolytic enzymes in culture, and some types of tumors of epithelial origin demonstrated a very high level of collagenolytic activity, while neoplastic diseases of mesenchymal origin, non neoplastic tissues, and other types of epithelial tumors only seldom produced collagenases. MMP-1 plays a role in initiating tumorigenesis by degrading the stroma and releasing growth factors. MMP-8 can promote tumor growth, but it also plays an anti-metastatic role in cancer. On the other hand, since MMP-13 is able to degrade basement membrane components, indeed it promotes tumor invasion and progression. MMP-13 high levels of expression in breast cancer make it a candidate as a potential tumor marker for breast cancer diagnosis. Nevertheless, MMP-1 and MMP-8 are candidates as potential markers for atypical ductal hyperplasia, respectively (Chang et al., 2009; Poola et al., 2005).

Hereafter, the three collagenases structural–functional features and their specific roles in pathological processes will be reviewed.

3.1. MMP-1

MMP-1 is also known as collagenase-1, fibroblast collagenase and interstitial collagenase. As many other MMPs, MMP-1 is undetectable in normal resting tissues, although *in vitro* is produced by a wide variety of normal cells, such as fibroblasts, macrophages, endothelial and epithelial cells. MMP-1 is mainly expressed *in vivo* during physiological and pathological tissue remodeling, suggesting a broad-based role in biology (Woessner and Nagase, 2000).

MMP-1 is synthesized as a single polypeptide and is secreted as a proenzyme. It comprises a major unglycosylated form of 57 kDa, and a minor glycosylated species of 61 kDa.

In normal adult tissues the levels of MMP-1 are usually low. By contrast, its expression is elevated when the system faces a disturbance, such as wound healing, repair, or remodeling processes as occur in several pathological conditions (Brinckerhoff and Matrisian, 2002).

The expression of collagenase-1 is transcriptionally regulated by growth factors, hormones, and cytokines, and the proteolytic activity is accurately controlled through activators and inhibitors, such as α-macroglobulins and tissue inhibitors of metalloproteinases (TIMPs) (Woessner and Nagase, 2000).

3.1.1. Biological function

Beside the enzymatic processing of collagen I, reported above and common to other collagenases, other matrix molecules are substrates for MMP-1, including aggrecan, versican, perlecan, casein, nidogen, serpins, and tenascin-C (McCawley and Matrisian, 2001). Therefore, MMP-1 should play a pivotal role in the physiological remodeling of extracellular matrix. Notably, MMP-1 may regulate the function of biologically active molecules by releasing them from ECM stores; for example, through degradation of perlecan MMP-1 can release bound FGF (Whitelock et al., 1996).

In the last years it has become evident that MMP-1 is also able to cleave cell surface molecules and other non-matrix substrates. Some of them comprise antichymotrypsin, antitrypsin, insulin-growth factor binding protein (IGFBP)-3, IGFBP-5, IL-Iβ, L-selectin, ovostatin, tumor necrosis factor-α and stromal cell-derived factor-1 (McCawley and Matrisian, 2001). This wide variety of substrates assigns MMP-1 as a multifunctional molecule (see Table 3). For example, MMP-1 may participate in the regulation of insulin-like growth factor (IGF) for its ability to degrade IGFBPs which bind IGF with high affinity. Likewise, MMP-1 appears to play a pivotal role in epithelial morphogenesis which depends on specific movement of epithelial cells. Thus, keratinocyte migration on collagen-1 requires specific cleavage of the collagen molecule by collagenase (Pilcher et al., 1997).

The creation of knock-out mice that are null for specific genes has been useful in attributing functions to a number of MMP family members (see Table 6). Nevertheless, this approach has not been possible in the case of MMP-1, since the human enzyme does not have a clear-cut ortholog in the adult mouse. Interestingly, the mouse ortholog (McolA) for human MMP-1 shows only 58% amino-acid identity and is distantly related, suggesting a rapid evolution in one or both lineages (Balbin et al., 2001).

3.1.2. Neoplastic diseases

MMP-1 is up-regulated in a wide variety of advanced cancers, and in nearly all instances, a significant negative correlation between its expression and survival has been found (Brinckerhoff et al., 2000). Animal studies have suggested that overexpression of MMP-1 protein has a role in initiating mammary tumorigenesis by degrading stroma and releasing growth factors and other mitogens for epithelial cells (Duffy et al., 2000; Hojilla et al., 2003).

Single-nucleotide polymorphisms (SNPs) of MMP-1 seems to increase cancer risk of digestive tract tumors (Langers et al., 2011) and recently a −1607 1G-to-2G MMP-1 polymorphism has been associated with susceptibility to both development and progression of lung cancer (Liu et al., 2011).

Table 6
Phenotypes of MMP knock-out mice.

MMP	Knock-out mice	Phenotype	Effect on tumor development
MMP-1	None		
MMP-2	*Mmp2*$^{-/-}$	Reduced angiogenesis Reduced hepatocyte apoptosis and necrosis in TNF-induced hepatitis Increased immune-complex-induced arthritis Reduced functional recovery from spinal-cord injury Delayed mammary gland differentiation Increased allergen-induced asphyxiation Reduced intraluminal leukocytes	Reduced pancreatic carcinogenesis Decreased tumor growth Deficient vascular architecture and altered angiogenesis in cerebral tumors
MMP-3	*Mmp3*$^{-/-}$	Accelerated mammary gland adipogenesis Resistance to contact dermatitis Decreased immune-complex-induced lung injury Reduced hepatocyte apoptosis and necrosis in TNF-induced hepatitis Impaired ex vivo herniated disc resorption Reduced neutrophil counts Delayed incisional wound healing	
MMP-7	*Mmp7*$^{-/-}$	Increased MMP-8 levels Decreased MMP-13 levels Defective innate intestinal immunity Impaired tracheal wound repair Impaired migration of neutrophils Defective prostate involution Impaired ex vivo herniated disc resorption Lack of activated antimicrobial peptides Decreased reorganization of cell functions	Reduced intestinal adenoma formation Attenuation of cardiac hypertension and hypertrophy
MMP-8	*Mmp8*$^{-/-}$	Defective inflammatory response ApoE$^{-/-}$ developed smaller lesions with increased collagen deposition in atherosclerotic plaques More resistant to autoimmune encephalomyelitis Differenet evolution of wound healing process Protection against TNF-induced lethal hepatitis	Increased skin carcinogenesis in mice
MMP-9	*Mmp9*$^{-/-}$	Defect in endochondral bone formation Resistance to bullosus pemphigoid Resistance to aortic aneurysms Prolonged contact dermatitis Abnormal embryonic implantation Delayed apoptosis of hypertrophic chondrocytes at the skeletal growth plates Deficient vascularization Diminished neutrophil infiltrate in glomerular nephritis Reduced respiratory failure and lung enlargement induced by IL-13, increased BAL leukocyte numbers Protection from cardiac rupture after infarction Lack of alveolar brochiolization in fibrosis Increased BAL-cell recruitment after allergic challenge Decreased lung injury by immune complexes Decreased immune-complex-induced arthritis Resistance to experimental autoimmune encephalitis Aggressive form of a systemic autoimmune lymphoproliferative syndrome	Reduced skin carcinogenesis Reduced pancreatic carcinogenesis Reduced experimental metastasis
MMP-10	None		
MMP-11	*Mmp11*$^{-/-}$	Accelerated neointima formation after vessel injury Increased fat excess and adipogenesis	Reduced mammary carcinogenesis Decreased tumor cell survival and growth Increased number of metastasis
MMP-12	*Mmp12*$^{-/-}$	Reduced elastinolytic capacity of macrophages Reduced macrophage recruitment into aneurysmall lesions to migrate through matrix Resistance to cigarette-smoke-induced emphysema Reduced $CaCl_2$-induced aortic aneurysm Reduced atherosclerotic lesions	
MMP-13	*Mmp13*$^{-/-}$	Abnormal skeletal growth plate development Resistance to osteoarthritic cartilage erosion Reduced liver fibrosis induced by cholestasis	

(*continued on next page*)

Table 6 (*continued*)

MMP	Knock-out mice	Phenotype	Effect on tumor development
MMP-14	*Mmp14*$^{-/-}$	Severe abnormalities in bone and connective tissue formation Altered remodeling of atherosclerotic lesion Resistance to aortic aneurysm formation Abnormal space-temporal modulation of growth plate development Defective angiogenesis Premature death Spontaneous retarded lung alveolar development and diminished surface area	
MMP-15	None		
MMP-16	None		
MMP-17	None		
MMP-19	*Mmp19*$^{-/-}$	Spontaneous adipocyte hypertrophy	Increased early angiogenetic response and tumor invasiveness Decreased clinical carcinogenesis
MMP-21	None		
MMP-23A	None		
MMP-23B	None		
MMP-24	*Mt5-Mmp*$^{-/-}$	Decreased nerve-fiber sprouting and neural invasion	
MMP-25	None		
MMP-26	None		
MMP-27	None		
MMP-28	None		

In breast cancer expression levels of MMP-1 have been found altered, suggesting some role for this collagenase (Köhrmann et al., 2009). Finally, since MMP-1 is one of the most highly upregulated mRNAs in atypical ductal hyperplasia cancer (ADHC), MMP-1 could potentially be used as a diagnostic marker for screening atypical ductal hyperplasia (ADH) and non-ADH benign tissues and identifying patients with lesions that may develop into cancer (Poola et al., 2005).

3.1.3. Non-neoplastic diseases

3.1.3.1. Diseases of the cardiovascular system. MMP-1 is able to degrade insulin-like growth factor-binding proteins (IGFBPs) and the effect of its inhibition was investigated in cardiac hypertrophy induced by beta-adrenergic stimulation (Miura et al., 2003). Moreover, reduction of MMP-1 activity by the MMP inhibitor SI-27 induces a regression in the myocyte hypertrophy and the suppression of IGFBP-3 degradation.

Further, using a transgenic mouse model expressing human MMP-1 in cardiomyocytes, Kim and coworkers demonstrated that a direct disruption of the ECM of the heart results in loss of collagen and a deterioration of systolic and diastolic function, mimicking the progression of human heart failure (Kim et al., 2000).

3.1.3.1.1. Atherosclerosis. MMP-1 was detected in the macrophages, smooth muscle cells and endothelial cells of the atheroma (Galis and Khatri, 2002). Transgenic overexpression of human MMP-1 in macrophages of ApoE knockout mice surprisingly resulted in less advanced atherosclerosis, suggesting that MMP-1 has a protective role in human atherosclerosis, probably through tissue repair (Lemaitre et al., 2001).

3.1.3.1.2. Aneurysm. MMP-1 over-expression within AAA wall has been observed in association with infiltrates and neovascularization (Knox et al., 1997) in luminal endothelial cells (EC), aortic medial smooth muscle cells (SMC) and SMC of mature neovessels (Reeps et al., 2009).

3.1.3.2. Diseases of the nervous system. It has been reported that MMP-1 genotypes (MMP-1 2G2G, and MMP-1 1G2G) were significantly and independently associated with vascular dementia (VAD). MMP-1 2G2G genotype is also associated with increased risk of Alzheimer disease (AD). Interestingly, the odds of VAD and AD was further increased in persons concomitantly carrying more than one MMP gene variation, compared to individuals that only had one high-risk genotype (Flex et al., 2006).

3.1.3.3. Diseases of joints and muscular system. In arthritic disease, it has been demonstrated a correlation between the increase in MMP-1 and collagen degradation suggesting that cleavage of cartilage collagen is directly related to the activity of this enzyme (Vincenti and Brinckerhoff, 2002). Cartilage destruction correlates with the concentration of MMP-1 and can be blocked by broad-range MMP inhibitors in a dose-dependent manner (Neidhart et al., 2003).

3.1.3.3.1. Joint diseases. (a) Osteoarthritis (OA). In human OA cartilage, MMP-1 is overexpressed by chondrocytes (Okada, 2009), likely playing a direct role in collagen degradation because of its collagenolytic activity.

(b) Rheumatoid arthritis (RA). The mechanism of articular cartilage destruction by proteinases is more complex in RA than OA, and composed of three pathways: destruction from the surface of the articular cartilage by proteinases present in the synovial fluid, destruction through direct contact of proteolytic synovium and/or pannus tissue to the articular cartilage and intrinsic destruction by proteinases derived from chondrocytes (Okada, 2009). Rheumatoid synovial tissue exhibits the overproduction of all collagenases together with TIMP-1, 2 and 3 (Okada, 2009). They are secreted into the synovial fluid in the joint cavity, and they are believed to degrade the cartilage from the surface based on the imbalance between MMP and TIMP in favor of MMP (Yoshihara et al., 2000). Rheumatoid synovium is highly proteolytic and chondrocytes in RA also express MMP-1, previous findings indicated that several closely linked single-nucleotide polymorphisms (SNPs) in the MMP-1 loci have an important role in determining its circulating levels in RA (Chen et al., in press).

3.1.3.4. Wound healing. During human skin wound healing, MMP-1 released by keratinocytes is critical for re-epithelialization by promoting cell migration through binding to integrin and type I collagen (Dumin et al., 2001).

3.1.3.5. Diseases of the respiratory system.

3.1.3.5.1. Emphysema/chronic obstructive pulmonary disease. The understanding of the pathogenesis of emphysema in patients deficient in α1-antitrypsin provided the initial idea that a proteinase/antiproteinase imbalance was responsible for the disease (Lomas and Mahadeva, 2002). Since neutrophil elastase is inhibited by α1-antitrypsin, excess elastase activity was thought to be responsible for the destruction of the lung leading to emphysema. However, the development of emphysema in MMP-1 transgenic mice expanded the original concept of a trypsin/antitrypsin unbalance to a proteinase/antiproteinase imbalance theory (D'Armiento et al., 1992). Indeed, bronchoalveolar lavage (BAL) fluid from patients with emphysema contains more MMP-1 compared to fluid from healthy volunteers, and this is associated with increased secretion of active MMP-1 (Finlay et al., 1997). Moreover, immunohistochemistry on emphysematous lung tissue has shown that MMP-1 is expressed in epithelial cells, especially type II pneumocytes. Increased MMP-1 expression in the epithelial cells of smokers may result from a prolonged activation of the ERK mitogen-activated protein kinase pathway (Mercer et al., 2004). These data suggest that inflammatory cells may not be exclusively responsible for lung tissue destruction, but that MMP-1 expression in epithelial cells can cause emphysema (Imai et al., 2001).

3.1.3.5.2. Interstitial pulmonary fibrosis. In human lung fibrosis, studies on gene and protein expression have unexpectedly shown a strong up-regulation of MMP-1 (Selman et al., 2000; Zuo et al., 2002). A paradox emerges as excessive accumulation of collagens is associated with over-expression of the cleaving enzyme not with the absence of it, as it might have been expected. Although there is no a clear explanation for this paradox, the location of the enzyme in the fibrotic lung may partially explain it. Thus, although MMP-1 was highly expressed in fibrotic lung tissue, the localization of the enzyme was noticed mainly in reactive alveolar epithelial cells (Selman et al., 2000). Furthermore, the so called fibroblast-type collagenase was virtually absent in fibroblasts from the interstitial fibrotic areas where collagens are being deposited. The role of epithelial MMP-1 is presently unknown but it might be related with cell migration as occurs with keratinocytes (Pilcher et al., 1997).

In chronic progressive fibrotic lung diseases, there are evidences that MMP-1 may be exploited as a marker, since MMP-1 and MMP-7 over-expression in the lung microenvironment allows to distinguish idiopathic pulmonary fibrosis (IPF) from other chronic lung diseases (Rosas et al., 2008).

3.1.3.5.3. Bronchial asthma. The reasons for enhanced deposition of extracellular matrix in the airways of asthmatic patients and the subsequent consequences on lung function are uncertain (Todorova et al., 2010). MMP-1 has been shown to be upregulated in patients' sputum (Rajah et al., 1996).

3.1.3.5.4. Tuberculosis. Elkington and coworkers have shown that MMP-1 is highly upregulated in tuberculosis (Elkington et al., 2011), leading to the degradation of the major lung ECM components, such as type I collagen and elastin. MMP-1 expression in epithelial cells in culture is driven by a monocyte-dependent network. *Mycobacterium tuberculosis* therefore drives a matrix degrading phenotype by both a direct infection of macrophages and an intercellular network that increases MMP secretion by epithelial cells. Elkington and coworkers provide evidence that *M. tuberculosis* drives the expression of MMP-1, which in turn promotes the collagen breakdown that leads to alveolar destruction in TB. These findings identify putative therapeutic targets for the prevention of TB (Elkington et al., 2011).

3.1.3.6. Diseases of the digestive system. The opposite process to the destructive degradation observed in arthritis occurs in fibrotic disorders that are characterized by exaggerated extracellular matrix accumulation. Here, at least theoretically, fibrillar collagen deposition in the scarring tissue might be partially related to a decreased collagenolytic activity (Iredale et al., 1998; Ruiz et al., 2003). These findings open new therapeutic avenues for fibrotic disorders, including gene therapy. In this context, it has been shown that gene delivery of human MMP-1, with transient over-expression of the enzyme in the liver attenuated established experimental hepatic fibrosis (Iimuro et al., 2003). However, analysis of the expression of MMP-1 in fibrotic disorders has given contradictory results, and the possibility of inhibition should be considered carefully.

Helicobacter pylori has been shown to induce MMP-1 expression in gastric epithelial cells, contributing to tissue destruction of the gastric mucosa (Krueger et al., 2006).

3.2. MMP-8

One of the most intriguing MMPs, MMP-8, also known as collagenase-2 or neutrophil collagenase, was long thought to be expressed solely in neutrophil precursors during late myeloid maturation. However, it has become evident that MMP-8 can be expressed in a wide range of cells (*e.g.*, maturing neutrophils, peripheral neutrophils, macrophages, plasma cells, T cells, bronchial epithelial cells, oral epithelial cells, corneal epithelial cells, colon mucosal cells, keratinocytes, endothelial cells, fibroblasts, colon myofibroblasts, smooth muscle cells, chondrocytes, mainly in the course of different inflammatory conditions). Many studies report that MMP-8 is indeed associated with a wide range of inflammatory disorders, as well as cancer progression.

Apart from the PMN-derived full-length MMP-8 (80 kDa) and its 75-kDa activated form devoid of the prodomain, several other MMP-8 species with a much smaller molecular weight (40–60 kDa) have been identified. These forms are poorly glycosylated compared to PMN-derived MMP-8 (Bergmann et al., 1998; Devarajan et al., 1991; Hanemaaijer et al., 1997; Kiili et al., 2002). Further experiments revealed that this high degree of glycosylation of PMN-derived MMP-8 is associated with the storage of the enzyme in the intracellular granules of those neutrophils. This explains why poorly glycosylated MMP-8, which is produced by other cell types, is not retained within the cell but is promptly secreted in the extracellular compartment after synthesis (Hasty et al., 1990; Smith et al., 1994). Owen and coworkers have described a PMN membrane-bound MMP-8 form (Owen et al., 2004). Membrane-associated MMP-8 appears to be more stable and more resistant to TIMP inhibition than the soluble secreted form.

The conformation of the N-terminal portions (consequences of pro enzyme activation) is of extreme importance to the regulation of MMP-8 proteolytic activity. In fact two different forms of the MMP-8 result from activation alternately cleavage at two cleavage sites, leaving either Met-80 or Phe-79 as the N-terminal residue (Reinemer et al., 1994). The latter form is 'superactivated', as Phe-79 as forms a salt bridge with a Asp-232 and thereby prevents the N-terminal sequence from transient or other interference with active site. The result is a 3-fold increase in activity compared with activation cleavage at Met-80 (Knäuper et al., 1993). This feature is retained also for macromolecular substrates, such as collagen I (Gioia et al., 2002).

3.2.1. Biological substrates

Once activated, MMP-8 can cleave a wide range of substrates (see Table 3). Besides being an efficient collagen degrading protease (collagen type I > type III > type II), MMP-8 also cleaves a wide range of non-collagenous substrates, such as serine protease inhibitors and several chemokines. This allows MMP-8 to influence the biological activities of many of these substrates, since cleavage can either lead to their inactivation (Van den Steen et al., 2003a) or to an increase in their biological activities (Van den Steen et al., 2003b). MMP-8 is a potent collagenolytic enzyme that is involved in the pathogenesis of several inflammatory conditions.

3.2.2. Neoplastic diseases

Several studies support the notion that MMP-8 promotes tumor growth and metastasis and identify MMP-8 as a marker for tumor progression. For example, MMP-8 is expressed in head and neck squamous cell carcinomas (Moilanen et al., 2002), and patient serum levels correlate positively with the tumor stage (Kuropkat et al., 2004). In ovarian cancers, its expression level was found to be correlated with tumor grade and stage, as well as with poor prognosis (Stadlmann et al., 2003; Stenman et al., 2003). These data, which indicate that MMP-8 blockade might be beneficial for cancer patients, support the use of MMP-8 inhibitors in therapy. On the other hand, recent findings indicate that inhibiting MMP-8 could be counterproductive and might promote initial tumor formation and tumor spreading. Experimental carcinogenesis experiments revealed that MMP-8 deficient male mice are more prone to developing carcinogen-induced skin tumors (Balbin et al., 2003). The same study also revealed that the fibrosarcomas derived from MMP-8 deficient animals were more aggressive than fibrosarcomas isolated from wild-type animals (Balbin et al., 2003).

Additionally, MMP-8 expression levels were negatively correlated with the metastatic potential of tumor cell lines derived from breast tumors (Agarwal et al., 2003a,b). Furthermore, MMP-8 provides a protective effect in the metastatic process, decreasing the metastatic potential of breast cancer cells when it is over-expressed (Decock et al., 2008). Similarly, MMP-8 expression in the squamous cell carcinoma of the tongue is correlated with improved survival of patients and it is proposed that this protective action is probably correlated with the role of estrogen in the growth of tongue squamous cell carcinomas (Ardi et al., 2007; Korpi et al., 2008). A direct anti-metastatic role for MMP-8 was confirmed by Montel and coworkers, who observed that overexpressing MMP-8 in breast cancer cell lines leads to a decrease in metastasis, whereas knocking-down of MMP-8 using ribozyme technology results in increased metastasis (Montel et al., 2004).

3.2.3. Non neoplastic diseases

3.2.3.1. Diseases of the cardiovascular system. An increasing amount of clinical data supports the notion that MMP-8 is involved in the development of atherosclerosis, being ultimately responsible for plaque destabilization and rupture (Galis et al., 1995). Thus, MMP-8 can be found in atherosclerotic lesions, specifically in macrophages, smooth muscle cells and endothelial cells, and rupture prone plaques clearly displayed increased MMP-8 expression compared to stable plaques (Herman et al., 2001). Further studies have shown that vulnerable plaques also had an increased amount of activated MMP-8 (Molloy et al., 2004), and that patients with vulnerable plaques had higher MMP-8 plasma levels than patients with stable

plaques (Turu et al., 2006). However, studies using genetically modified mice have revealed a more complex role of MMP-8 in atherosclerosis (see Table 6). apolipoprotein-E (ApoE) deficient mice develop atherosclerotic lesions similar to those observed in humans, although they do not spontaneously rupture or erode. Deficiency of MMP-8 in ApoE-null mice resulted in smaller lesions with increased collagen deposition (Laxton et al., 2009), and absence of MMP-13 (see below) led to thinner and less aligned collagen fibers in the plaque (Deguchi et al., 2005).

Although the levels of MMP-8 in biopsies from patients with abdominal aortic aneurysms (AAA) were higher than in normal aortas, there was no significant correlation between MMP-8 concentrations and AAA size (Wilson et al., 2005). A possible direct role for MMP-8 in AAA was tested in an experimental animal model. The study revealed that although neutrophil depletion, which was accompanied by a decrease in MMP-8, could diminish the probability for AAA formation, MMP-8 deficiency by itself could not affect the process, indicating that MMP-8 might be useful as a marker rather than as a target for AAA treatment (Eliason et al., 2005).

Among matrix-unrelated effects of MMPs, MMP-8 plays a very important role in the control of inflammation through chemokine cleavage (McQuibban et al., 2000; Page-McCaw et al., 2007). Of particular interest is the MMP-8 proteolytic activity on angiotensin (Ang) I (Mallat, 2009). The control of blood pressure is achieved through the modulation of Ang I cleavage by MMP-8 (Van Lint and Libert, 2006). Rupture of atherosclerotic plaques with subsequent thrombus formation is the most significant mechanism underlying clinically important ischemic events. Specific localization of elevated mRNA, protein, and activity levels of MMP-8 within atherosclerotic lesions, particularly at the shoulder regions of the fibrous cap, implies that MMP-8 plays a role in fibrous cap weakening by degrading extracellular matrix components, such as interstitial collagens. Raised intra-plaque levels of active MMP-8 were observed in patients with plaques showing histological evidence of rupture (Cheng et al., 2009). Interestingly, angiotensin II (ATII)-mediated hypertension promotes a "stable" fibrotic phenotype by inducing severe intra-plaque hemorrhages, characterized by increased degradation of interstitial collagen I via an MMP-mediated (MMP-8 and MMP-13) mechanism (Cheng et al., 2009).

3.2.3.2. Diseases of the nervous system. Both human and animal studies indicate that MMP-8 is involved in several inflammatory diseases of the central nervous system (CNS). MMP-8 was found to be up-regulated in the spinal cord of animals with experimental autoimmune encephalomyelitis (EAE) (Nygardas and Hinkkanen, 2002). A later study found a significant correlation between the expression of MMP-8 and the severity of symptoms. This study also revealed that granulocytes, and to a lesser extent macrophages and T cells, are the originating cell type (Toft-Hansen et al., 2004). Lopez-Otin and coworkers report that MMP-8$^{-/-}$mice are more resistant to EAE than their wild-type counterparts, showing a marked reduction in CNS-infiltration cells and demyelinating lesions (Folgueras et al., 2008).

Finally, MMP-8 was found to be up-regulated in the cortex of animals with experimental bacterial meningitis (BM) (Leib et al., 2000). In line with these data, significantly higher levels of MMP-8 were found in the cerebrospinal fluid of human patients suffering from BM (Leppert et al., 2000).

3.2.3.3. Diseases of joints and muscular system. Osteoarthritis (OA) is a chronic disease of synovial joints. Although the etiology and pathogenesis of OA are poorly understood, it has been well established that degradation of the extracellular matrix (ECM) in articular cartilage is a major cause of joint destruction. Cartilage degradation is mediated by matrix metalloproteinases (MMPs), principally MMP-1, MMP-3, and MMP-13 (Klatt et al., 2009). However, in human OA cartilage, MMP-8 is overexpressed by chondrocytes similarly to MMP-1 (Okada, 2009).

Several findings suggest that MMP-8 has a role in rheumatoid arthritis (RA) pathogenesis. It is expressed in serum and synovial fluid from patients with RA. Fibroblast-like synoviocyte cultures from RA patients produce MMP-8 after TNF-α stimulation (Tchetverikov et al., 2003; Hanemaaijer et al., 1997). In addition, MMP-8 regulates the activity of several chemokines implicated in RA (Van den Steen et al., 2003a,b; Balbin et al., 2003). In addition, MMP-8 protect against inflammatory synovitis and bone erosion in the K/BxN serum-transfer arthritis model. Its protective role in arthritis derived from the ability of this metalloprotease to induce changes in a series of inflammatory mediators namely, IL-1, pentraxin-3, and prokineticin receptor 2 in arthritic mice joints (Garcia et al., 2010).

The mechanism of articular cartilage destruction by proteinases is more complex in RA than OA, and composed of three pathways: destruction from the surface of the articular cartilage by proteinases present in the synovial fluid, destruction through direct contact of proteolytic synovium and/or pannus tissue to the articular cartilage and intrinsic destruction by proteinases derived from chondrocytes (Okada, 2009). Rheumatoid synovial tissue exhibits the over-production of MMP-8 together with TIMPs (Okada, 2009).

3.2.3.4. Wound healing. MMP-8 is upregulated in tissue remodeling processes (Balbin et al., 1998). However, activated MMP-8 is more prominent in chronic than in healing wounds (Nwomeh et al., 1999), a difference that was linked to the large number of neutrophils present in chronic wounds (Impola et al., 2005). Using MMP-8 knockout mice (see Table 6), Balbin and coworkers showed that MMP-8 indeed influences the process of wound healing, because the inflammatory reaction after a subcutaneous injection of a carcinogen evolves differently in MMP-8 deficient animals (Balbin et al., 1998). Thus, MMP-8 deficient mice initially display a neutrophil influx that is more diffuse, as compared to their wild-type counterparts; further, these animals are also unable to clear out the neutrophils present, resulting in an abnormally sustained inflammatory response (Balbin et al., 2003).

Wound tissues in humans and in experimental animals over-express all collagenolytic MMPs including MMP-8. An increased neutrophil accumulation was found, however, during wound healing in mice lacking MMP-8 (Gutierrez-Fernandez et al., 2007). This collagenase expectedly plays a role in the complex process of wound healing that includes acute inflammatory reaction, regeneration of parenchyma cells, cell migration and proliferation, angiogenesis, contraction and tissue remodeling (Gill and Parks, 2008). As indicated by the sustained presence of PMNs in MMP-8 knock-out animals during the process of wound healing, MMP-8 can also influence the immune response in the course of a chronic inflammation. Mice lacking MMP-8 show a delayed wound healing due to a persistent inflammatory infiltrates (see Table 6). Additionally, a decrease of collagen deposition has been observed in the wounds of these animals (Gutierrez-Fernandez et al., 2007). These studies indicate that MMP-8 can influence neutrophil recruitment during an acute inflammatory response, but at the same time it can help to resolve the inflammation at a later stage, as shown by the sustained number of neutrophils in MMP-8 deficient animals during the course of a chronic inflammation. A very recent work demonstrates that exceeding physiological levels of the proteinase MMP-8 can result in a decreased collagen content, leading to impaired wound healing (Danielsen et al., 2011).

3.2.3.5. Diseases of the respiratory system. Clinical data from asthma patients suggest that levels of activated MMP-8 in bronchoalveolar lavage fluid (BALF) are an indicator of disease severity and are correlated with airway obstruction (Prikk et al., 2002). Also, MMP-8-deficient mice developed more severe inflammation than wild type mice in an allergen-induced airway inflammation model and showed more neutrophils in the bronchoalveolar lavage fluid (Gueders et al., 2005). Using an ovalbumin-sensitized (OVA) mouse model of asthma, Gueders and coworkers studied the role of MMP-8 during allergen-induced lung inflammation. Prevalence of neutrophils and eosinophils after allergen-induced bronchial inflammation was greater in MMP-8-deficient mice than in wild-type mice (Gueders et al., 2005). Interestingly, these animals also displayed increased IL-4, increased anti-OVA-specific IgEs, and enhanced Th2 recruitment, indicating that MMP-8 absence promotes a Th2 profile.

The progression of pulmonary emphysema, which is characterized by loss of lung elasticity and enlargement of alveolar airspaces, is also associated with MMP-8 presence. Whereas MMP-8 levels are significantly increased in BALF from patients with subclinical emphysema (Betsuyaku et al., 1999), levels of MMP-8 in the sputum of patients with emphysema correlate negatively with lung function if the patients have developed chronic obstructive pulmonary disease (COPD) (Culpitt et al., 2005). Finally, MMP-8 levels in BALF also correlate with the severity of bronchiectasis, a disease characterized by a permanent dilation of the bronchi due to chronic inflammation, leading to irreparable deformation of bronchial wall components (Sepper et al., 1995). Other studies identified activated epithelial cells (as well as infiltrating neutrophils and macrophages) as the cell types responsible for the de novo MMP-8 expression in the course of this pathology (Prikk et al., 2001; Zheng et al., 2002).

However, high MMP-8 levels, originating mostly from accumulated PMNs, are also often correlated with the degree of fibrosis. In patients suffering from cystic fibrosis (CF), MMP-8 levels correlate with PMN counts (Ratjen et al., 2002) and in patients with a more advanced CF disease state there is also correlation with disease severity (Power et al., 1994). High levels of neutrophils and accompanying MMP-8 also correlate with the fibrotic state in patients suffering from hypersensitivity pneumonitis (Pardo et al., 2000). Other groups have shown that MMP-8 is down-regulated during the course of lung fibrosis (Ruiz et al., 2003), which could be attributed to increased levels of TGF-β, being associated to a decrease of MMP-8 expression (Moilanen et al., 2002; Palosaari et al., 2000). These data indicate that a shift from highly regulated MMP-8 expression to exaggerated, mainly PMN-driven, MMP-8 release might trigger the pathogenesis of fibrosis by disturbing the delicate balance that exists in matrix turnover.

The accumulation of collagen fibers in the lung interstitium is a form of abnormal repair in some respiratory diseases. Lung fibrosis can be secondary to an injury which leads to chronic inflammation. In this context, knocked-down experiments have demonstrated that the absence of MMP-8 results in antifibrotic effects by increasing IL-10 levels (Garcia-Prieto et al., 2010).

3.2.3.6. Diseases of the digestive system. Liver fibrosis develops as a result of chronic liver wound repair following diverse insults. The ultimate outcome of liver fibrosis is the formation of hepatocyte nodules encapsulated by a fibrillar scar matrix. In the liver, hepatic stellate cells and Kupffer cells are thought to be the main source of MMPs (Arthur, 2000). Infiltrated neutrophils produce MMP-8, which can contribute to the remodeling process. In liver fibrosis, hepatic stellate cells are converted to myofibroblastic cells and produce fibrillar collagens in the space of Disse.

Van Lint and colleagues showed that MMP-8-deficient mice were protected against TNF-induced lethal hepatitis (Van Lint et al., 2005). Livers of knockout mice did not show the massive influx of neutrophils seen in wild type mice, probably due to the functional link between MMP-8 and lipopolysaccharide-induced CXC chemokine, a PMN chemokine. Their work suggests that MMP-8 is involved in lipopolysaccharide-induced CXC chemokine release and, in turn, in neutrophil recruitment during inflammation. Likewise, the pivotal role of MMP-8 in lipopolysaccharide-induced CXC chemokine, CXCL5 and CXCL8 activation was reported (Tester et al., 2007).

The role of MMP-8 in regulating an innate immune response has been confirmed by several recent studies. One study showed that indeed MMP-8 affects the acute recruitment of neutrophils in a model of TNF/GalN-induced liver inflammation, in which animals develop a neutrophil-dependent lethal hepatitis. Livers of MMP-8 deficient animals did not show the characteristic massive neutrophil influx observed in wild-type animals, which enhanced survival (Van Lint and Libert, 2006). Surprisingly, MMP-8 deficiency increased neutrophil recruitment in the lung in response to intratracheal LPS administration

(Owen et al., 2004). This indicates that the influence of MMP-8 on neutrophil migration is complex, and might depend on the stimulus, tissue and timeframe.

Reperfusion injury of the liver is believed to share similar mechanisms as seen in the brain, heart and lungs with regard to MMPs (Viappiani et al., 2006). Stimuli induced by cytokines and reactive oxygen species due to ischemic–reperfusion injury cause a release of MMP-8 from infiltrated neutrophils. This enzyme acts as inducer of cell apoptosis and ECM remodeling.

Because collagen is the predominant ECM deposit in fibrotic organs, collagenases are believed to be the main proteases responsible for the resolution of fibrosis and restoration of a natural ECM environment. It has been shown that repair after a cholestatic liver injury indeed correlates with MMP-8 activity (Harty et al., 2005). Furthermore, Siller-Lopez and coworkers showed in a very elegant fashion that adenoviral delivery of MMP-8 improves the recovery from liver cirrhosis in rats (Siller-Lopez et al., 2004). The increased liver cell proliferation, seen after adenoviral MMP-8 delivery (Siller-Lopez et al., 2004), indicates that MMP-8 also contributes to tissue regeneration itself, possibly by releasing ECM associated growth factors, such as HGF (Schuppan et al., 1998).

Gene therapy with MMP-8 displays improvement in liver cirrhosis, since MMP-8 regulates the degradation of excessive matrix deposition (Siller-Lopez et al., 2004). A very recent study using a combinatorial gene therapy strategy (*i.e.*, Adenovirus-MMP-8 plus Adenovirus-human plasminogen activator) proved the therapeutical effect of MMP-8 on liver fibrosis regression, demonstrating that MMP-8 gene insertion improves neuroanatomical and neurochemical conditions in hepatic encephalopathy (Galvez-Gastelum et al., 2011).

3.3. MMP-13

MMP-13, also known as collagenase-3, is expressed in hypertrophic chondrocytes and osteoblasts during human fetal development (Johansson et al., 1997a; Ståhle-Bäckdahl et al., 1997). Increased levels of MMP-13 have been associated not only with arthritis and tumors, but also with other pathologies, including adult periodontitis (Kiili et al., 2002), ocular surface diseases (Li de et al., 2003), chronic ulcers (Vaalamo et al., 1997), and chronic inflammation of oral mucosal epithelium (Uitto et al., 1998) (see Table 4).

3.3.1. Biological function

There is little or no expression of MMP-13 in normal adult tissues, but the enzyme is expressed in diseases where there is a need for tissue repair or remodeling. The very restricted distribution of MMP-13 in normal tissues, coupled with its ability to degrade type II collagen and other extracellular matrix components (see Table 3), make this enzyme an interesting pharmaceutical target in a number of diseases (see below).

MMP-13 preferentially hydrolyzes type II collagen, the major collagen type of cartilage. This enzyme is 5–10 times more efficient than MMP-1 at cleaving this collagen type II but is five times less active on types I and III collagens (Knäuper et al., 1996). In contrast, MMP-1 preferentially cleaves type III collagen and MMP-8 type I collagen. MMP-13 is also active on other matrix components such as types IV, IX, X, and XIV collagens, and gelatin, fibronectin, and aggrecan (Billinghurst et al., 1997; Fosang et al., 1996; Freije et al., 1994; Knäuper et al., 1997; Mitchell et al., 1996). It is noteworthy that the gelatinolytic activity of MMP-13 is about 44 times greater than that of MMP-1. Other works have broadened the list of molecules which are susceptible to digestion by MMP-13 to include connective tissue growth factor (CTGF) and fibrinogen.

Hashimoto and colleagues have found that MMP-13 could restore the angiogenic properties of one isoform (namely VEGF165) of the vascular endothelial growth factor (VEGF) by cleaving CTGF and releasing VEGF165 from the CTGF/VEGF165 complex (Hashimoto et al., 2002). This property may be important for VEGF-induced angiogenesis in arthritic tissues: the cleavage of the CTGF/VEGF165 complex by the MMPs produced in the diseased joint could result in synovial membrane pannus invasion of the cartilage.

Fibrinogen is a glycoprotein that participates in both the cellular and the fluid phases of blood clot formation. It has been shown that MMP-13 interacts with the clotting system by proteolytically processing fibrinogen and also by inactivating factor XII (Hiller et al., 2000).

3.3.2. Neoplastic diseases

MMP-13 was originally found in breast carcinoma, but it is now associated with other types of human cancer, such as chondrosarcomas (Uria et al., 1998), gastric cancer (Elnemr et al., 2003), basal cell carcinomas (Hattori et al., 2003), and squamous cell carcinomas of the head and neck, larynx, vulva, and epithelium of the skin (Airola et al., 1997; Cazorla et al., 1998; Johansson et al., 1997b, 1999). An extensive overview of MMP-13 expression in malignant tumors has been recently published (Pendas et al., 2000). Because of its ability to degrade the components of the basement membrane, MMP-13 promotes tumor invasion and progression; thus, MMP-13 expression enhances invasion of human squamous cell carcinomas (Ala-aho et al., 2002a) and of human fibrosarcoma HT-1080 cells (Ala-Aho et al., 2002b). Some factors relevant to tumor progression are also regulators of MMP-13 expression, such as endostatin, a 20-kDa collagen XVIII fragment, which inhibits *in vivo* tumor growth. Nyberg and colleagues suggested that this factor's inhibitory activity on human tongue carcinoma cell invasion occurs by blocking the activation and catalytic activity of some MMP, including MMP-13 (Nyberg et al., 2003). Another factor, named relaxin, appears to enhance the invasiveness of some breast cancer cell lines by up-regulating MMP-13 mRNA expression in these tissues (Binder et al., 2002). Tumor hypoxia is a factor which contributes to the progression of a more malignant

phenotype. Koong and coworkers analyzed the changes induced by hypoxia in cell lines derived from squamous cell carcinomas and found that MMP-13 was among the induced genes (Koong et al., 2000).

Glioblastoma, the most malignant type of primary brain tumor, has been shown to contain a small population of cancer stem cells, whose highly invasive potential depends on MMP-13 enzymatic activity (Inoue et al., 2010).

Dynamic reciprocal interactions between a tumor and its microenvironment affects both the establishment and progression of metastases. These interactions are in part mediated through proteolytic sculpting of the microenvironment, particularly by the matrix metalloproteinases (MMPs), with both tumors and stroma contributing to the proteolytic milieu. The influence of breast cancer metastases on the bone microenvironment that is executed via the induction of osteoblast MMP-13 with potential to enhance metastases growth is reported (Morrison et al., 2011).

A recent paper reports that MMP-13 is over-expressed in breast cancer tissue and confirmed to be a secreted protein by Western blot analysis. The high expression level of MMP-13 was also measured by immunohistochemical staining suggesting that MMP-13 has potential to be a new tumor marker for breast cancer diagnosis (Chang et al., 2009).

3.3.3. Non-neoplastic diseases

3.3.3.1. Diseases of the cardiovascular system.

3.3.3.1.1. Remodeling of the myocardium. The communication and chemical gradient between the endothelium to myocyte and among different myocytes is very important in maintaining the function of the organ, such as the heart. Extracellular matrix (ECM) connects the myocyte to myocyte, and to the endothelial cells (Henderson and Tyagi, 2006). A cause–effect relationship has been established between matrix metalloproteinases (MMPs) and left ventricular (LV) myocardial remodeling through the use of pharmacologic MMP inhibitors (Chapman et al., 2003). There is a disconnection/uncoupling between cardiomyocytes and endothelial cells by MMP-mediated collagen breaks (Henderson et al., 2007a). MMP-13 expression and collagen synthesis/degradation may play a role in pressure-overload induced cardiac remodeling (Henderson et al., 2007b).

3.3.3.1.2. Atherosclerosis. An enhanced expression of MMP-13 mRNA has been detected in aortas of apolipoprotein E-deficient mice with advanced atherosclerosis (Jeng et al., 1999). Yoon and colleagues reported a similar link between atherosclerosis and MMP-13 (Yoon et al., 2002). These authors discovered two polymorphisms in the MMP-13 promoter associated with atherosclerosis in the abdominal aorta of young black males. One polymorphism was associated with the PEA-3 site, but the mechanism for the polymorphism's action remains unknown.

Interstitial fibers of collagen type I in the plaque can be degraded by MMP-13 (Cheng et al., 2009) and recent studies demonstrated that MMP-13 regulates collagen content in the atheroma artery walls. Pharmacological MMP-13 inhibition yields collagen accumulation in plaques (a feature associated in humans with resistance to rupture), even in established plaques (Quillard et al., 2011).

3.3.3.1.3. Aneurysm. In human abdominal aortic aneurysms, which are lesions with the potential to rupture (Choke et al., 2005), MMP-13 is the most expressed MMP (Tromp et al., 2004). Moreover, there are differences in sex for collagen regulation during rodent experimental abdominal aortic aneurysm formation. Some studies suggest that alterations in extracellular matrix collagen turnover may be responsible for altered abdominal aortic aneurysm formation between sexes, proving that a decrease in types I and III collagen with a concurrent increase in MMP-13 in males compared with females (Cho et al., 2010).

Angiotensin II (ATII)-mediated hypertension increases the risk for acute coronary events, which may be induced by augmented collagen degradation. Interstitial fibers of collagen type I in the plaque can be degraded by MMP-13 specifically. Indeed high MMP-8 levels have been correlated with ruptured plaques in patients. Angiotensin II (ATII)-mediated hypertension increases the risk for acute coronary events, which may be caused by augmented collagen degradation.

3.3.3.2. Diseases of the nervous system. Neurovascular perturbations occurring after stroke lead to blood–brain barrier leakage, edema, hemorrhage, leukocyte infiltration, and progressive inflammatory reactions to brain injury over hours or even days after the initial stroke. Brain endothelium, astrocytes, neurons, and inflammatory-activated cells, such as neutrophils, may release MMP-13. High levels of MMP-9 and MMP-13 are involved in infarct growth in spite of thrombolytic therapy suggesting its ultra-early role in brain injury.

The use of specific brain biomarkers might aid stroke diagnosis and that approach might permit rapid referral of stroke patients to hospitals with acute treatments. It has been recently described that MMP-13 may be a promising marker of stroke outcome, as it exerts an ultra-early role in brain injury and it is very well correlated with infarct expansion evaluated by Diffusion-Weighted Image (DWI) MRI and have the potential to drive triage for thrombolysis therapy (Montaner, 2009). Synthesized MMP inhibitors and several compounds used for stroke secondary prevention, such as anti-inflammatory drugs, might decrease MMPs and improve the acute treatment of human brain ischemia without compromising the beneficial effects of matrix plasticity during stroke recovery (Morancho et al., 2010). MMPs are involved in tissue destruction produced by the neuroinflammatory response that follows ischemic stroke. In particular, within the neuroinflammatory response, high levels of MMP-13 is involved in brain tissue damage despite thrombolytic therapy, suggesting its ultra-early role in brain injury (Rosell et al., 2005).

3.3.3.3. Diseases of joints and muscular system.

3.3.3.3.1. Joint diseases. MMP-13 is expressed by chondrocytes and synovial cells in human OA and RA and is thought to play a critical role in cartilage destruction. The recent development of a MMP-13 knockout mouse has documented the important role played by this enzyme in cartilage formation and further studies under pathological conditions should reveal the function of this enzyme in the progress of the disease (Takaishi et al., 2008) (see Table 6). Several *in vitro* studies have demonstrated the importance of MMP-13 in human arthritis (Bau et al., 2002; Billinghurst et al., 1997; Mitchell et al., 1996; Reboul et al., 1996). *In vivo* studies with animal models have confirmed the role of MMP-13 in osteoarthritis (OA) progression. In one of these studies, Otterness and coworkers injected active human recombinant MMP-13 intra-articularly into the knee joint of hamsters (Otterness et al., 2000). Collagen cleavage was limited to a thin superficial band at the cartilage surface, probably because of the strong binding of the hemopexin-domain for collagen and gelatin. The injection of MMP-13 led to cartilage collagen damage with the release of measurable collagen fragments. In another study, Neuhold and coworkers showed that the expression of a constitutively active human MMP-13 into hyaline cartilages and joints of transgenic mice resulted in erosion of the articular cartilage with excessive cleavage of type II collagen, loss of proteoglycan, and synovial hyperplasia, which are changes similar to those observed in human OA (Neuhold et al., 2001). Immunohistochemistry and in situ hybridization methodologies have been used to localize MMP-13 in normal and OA cartilage, and variable results have been obtained. Shlopov and colleagues showed that chondrocytes from areas surrounding OA lesions expressed more MMP-13 than the cells located further from the lesion (Shlopov et al., 1997). At the protein level, Moldovan and coworkers found that the MMP-13 protein was preferentially localized in the lower intermediary and deep layers (deep zone) of human OA cartilage (Moldovan et al., 1997), while Tetlow and colleagues associated the presence of MMP-13 at the superficial cartilage zone characterized by fibrillations and degenerative matrix changes (Tetlow and Woolley, 1998, 2001). Freemont and coworkers used in situ zymography to demonstrate that the distribution and amount of collagen II degrading activity varied with the extent of cartilage damage, being greatest in the deep zone and in cartilage lesions, and that MMP-13 mRNA expression distributed in parallel with the collagenase activity (Freemont et al., 1999). The MMP-13 localization in diseased cartilage is in the deep zone where type II collagen fibers are largest and chondrocytes are most able to reconstitute extracellular matrix (Fernandes et al., 1998).

Collagen II can modulate the gene expression profile of primary human chondrocytes inducing pro-inflammatory cytokines and MMP-13; thus, one way of inducing MMP-13 is by interleukin-1β via inflammatory signaling cascades, such as the MAPK and NFκB cascade (Klatt et al., 2009).

Others works showed that OA chondrocytes and synovial fibroblasts have impaired the receptor-mediated removal of MMP-13, a mechanism that may lead to enhanced local degradation of cartilage (Barmina et al., 1999; Walling et al., 1998). Internalization of MMP-13 is mediated by a 170-kDa receptor both in rodent cells and in human chondrocytes (Walling et al., 2003). As mentioned above, MMP-13 is expressed in RA, an arthritic disease characterized by chronic inflammation and cartilage destruction. In this disease, MMP-13 has been detected in some synovial membranes (Konttinen et al., 1999a,b; Lindy et al., 1997; Petrow et al., 2002; Tetlow and Woolley, 1998; Wernicke et al., 1996; Westhoff et al., 1999), and its expression correlated with elevated levels of systemic markers of inflammation, including erythrocyte sedimentation rate and C-reactive protein. In these diseased synovial membranes, MMP-13 was localized at the lining and sublining layers and also at the membrane/cartilage interface (Konttinen et al., 1999b; Lindy et al., 1997; Petrow et al., 2002; Westhoff et al., 1999).

The employment of an highly selective non-competitive inhibitor of MMP-13 (Johnson et al., 2007) significantly reduced the cartilage erosion in animal models of RA (Jüngel et al., 2010). The chondroprotective effects of micro-RNA inhibition of the MMP-13 expression was proved in human cartilage explants *in vitro* and through the development of inflammatory arthritis in mouse model *in vivo* (Akhtar et al., 2010).

3.3.3.4. Wound healing. Physiological wound repair is a highly regulated, complex process, which leads to formation of new tissue after injury. Proteolytic degradation of extracellular matrix is a crucial step in the healing of incisional skin wounds. Thus, healing of skin wounds is delayed by treatment with the broad-spectrum metalloproteinase (MP) inhibitor Galardin. Several matrix metallo proteinases (MMPs), including MMP-13, are expressed in the leading-edge keratinocytes of skin wounds (Juncker-Jensen and Lund, 2011). In mouse wound healing, MMP-13 plays a key role in keratinocyte migration, angiogenesis through digestion of connective tissue growth factor and contraction by activation of latent TGF-β (Hattori et al., 2009). However, the healing process is not perfect and healing impairments can occur. Delayed healing and formation of chronic wounds has been linked to the excessive production of proteolytic enzymes leading to reduced amounts of growth factors and successive destruction of the extracellular matrix. It has been implied that there is an alteration in the normal control mechanisms regulating the levels of these enzymes. The study presented provides data on the concentration of proteases and cytokines in wound fluid from chronic when compared with acute wounds. Levels of proteases such as MMP-13 is found to be profoundly elevated in chronic when compared with acute wound fluids (Wiegand et al., 2010).

3.3.3.5. Diseases of the digestive system. Liver fibrosis develops as a result of chronic liver wound repair following diverse insults. The ultimate outcome of liver fibrosis is the formation of hepatocyte nodules encapsulated by a fibrillar scar matrix. In the liver, hepatic stellate cells and Kupffer cells are thought to be the main source of MMPs (Arthur, 2000). Hepatocytes produce MMP-13 upon injury and loss of MMP-13 has lead to attenuation of fibrosis in a mouse model of liver disease (Uchinami et al., 2006).

A newly designed hyaluronic acid (HA)-shielded gene delivery system for systemic administration of plasmid DNA encoding MMP-13 is a promising therapeutic antifibrotic strategy. In fact, the enhanced expression of MMP-13 reduces collagen deposition and ameliorates liver fibrosis in mice. Moreover, the serum levels of aspartate transaminase were reduced to levels approaching those in untreated normal mice (Kim et al., 2011a).

4. Gelatinases

Gelatinases is a class of MMPs historically defined according to their affinity for denatured collagen (*i.e.*, gelatin). This class includes two members, namely (i) gelatinase A or MMP-2 (72 and 62 kDa for the pro-enzyme and the active enzyme, respectively); (ii) gelatinase B or MMP-9 (92–85-82 kDa for the pro-enzyme, the intermediate form and active enzyme, respectively) (see Table 2).

The domain composition shares with other MMPs the presence of a pro-peptide, a highly conserved N-terminal catalytic domain and a C-terminal hemopexin-like domain; however, unlike other MMPs, there is a peculiar additional exosite, inserted in the catalytic domain, which is called Collagen Binding Domain (CBD) (Nagase and Woessner, 1999) (see Fig. 1).

Gelatinases are deeply involved both in inflammatory processes and in tumor progression, being considered for long time one of the most important antitumoral target (Overall and Lopez-Otin, 2002). However, this potentiality has been recently questioned, drastically reducing its attraction as a pharmaceutical target.

In the last decades, concomitantly to the identification of novel substrates and physiopathological processes (see Tables 3 and 4), gelatinases have been identified as involved in several non-neoplastic pathologies (Rogriduez et al., 2009).

As a matter of fact, it is widely recognized that gelatinases participate to the aetiology of a plethora of pathologies and mainly in cardiovascular and auto-immune diseases which, taken altogether, represent a leading cause of mortality and morbility in Western countries. More specifically, in the case of cardiovascular diseases, gelatinases participate both to the genesis of the atherosclerotic lesions and to the acute event (*i.e.* stroke or myocardial infarction), which follows the fibrous cap rupture, whereas in the case of auto-immune diseases gelatinases are involved both in the generation of remnant epitopes and in the modulation of cross-talking between immune system compartments.

In conclusion, MMP-2 and MMP-9 role is supported by several *in vivo* and *in vitro* evidences, even though they follow distinct and even opposite patterns, consistently with the notion that MMP-9 has a pro-inflammatory property, whereas MMP-2 has a pro-homeostatic one (Ram et al., 2006; Van den Steen et al., 2002). As a matter of the fact, MMP-9 takes part on the onset of a wider panel of pathologies (Sanchez et al., 2005).

4.1. MMP-2

4.1.1. Structural peculiarities

Crystallographic analysis of pro-MMP-2 and of pro-MMP-2 in complex with TIMP-2 have been solved, furnishing deep insights on the structure and on the activation mechanism (Morgunova et al., 1999, 2002). The S1 site (notation according to Schechter and Berger, 1967) in the catalytic cleft is deep and recognizes the classic substrate motif $PXXXH_{Hy}$, consistently with the notion that hydrophobic residues are likely to adapt in the S1 site and proline in the S3 site (Chen et al., 2003). Three other conserved motifs have been identified: they are the $L/IXXX_{Hy}$, the $X_{Hy}SXL$ and the $HXXX_{Hy}$, which, reasonably, account for the enzyme specificity (Chen et al., 2003). On the other hand, substrate specificity of MMP-2 *versus* the highly related MMP-9 is mainly determined by a glutamine (Gln412) residue in the S2 site: hence, targets are mainly discriminated for residues in P2 position (Chen et al., 2003; Nagase and Fields, 1996).

The CBD is composed by three type II fibronectin-like tandem modules with closely similar conformation (Morgunova et al., 1999). The fibronectin-like modules folds separately from the rest of the molecule and display peculiar sequence motifs, including four disulfide bonded cysteines and four aromatic residues which envisage a fixed conformation for the overall domain (Trexler et al., 2003). The CBD has a substantial area of contact with the catalytic domain, mainly involving the second FnII domain. That FnII domain binds preferentially to synthetic peptides with a high proportion of aromatic residues and no acidic side chains, and, being a major structural determinant of MMP-2, represents an intriguing pharmacological target (Briknarova et al., 1999; Trexler et al., 2003). The CBD is the main domain involved in substrates recognition (Gioia et al., 2007; Monaco et al., 2006; Patterson et al., 2001); as a matter of fact, MMP-2 mutants lacking the CBD lose their ability to bind to gelatin (Murphy et al., 1994; Xu et al., 2007). Therefore, the CBD-mediated recognition of specific binding sites is essential to drive the correct positioning of the catalytic domain to the adjacent cleavage site.

Differently from other MMPs, the hemopexin-like domain contribution to substrate recognition is minimal, whereas it is essential for the partial unwinding of substrates facilitating the access to hindered cleavage sites as in the case of collagen IV (Bode, 1995; Gioia et al., 2009; Monaco et al., 2006).

The propeptide domain displays a three-helix fold structure and the cystein of the conserved cystein-switch motif is the fourth ligand of the catalytic Zn^{2+} ion in the inactive enzyme (Morgunova et al., 2002). The activation mechanisms of MMP-2 has been described in detail. The pro-domain displacement occurs in presence of TIMP-2 and MT1-MMP at the cell surface, even though alternative mechanisms involving the MT2-MMP, thrombin and uPAR have been proposed (Koo et al., 2010; Morrison et al., 2001; Nishida et al., 2008; Visse and Nagase, 2003). The first model proposes that the C-terminal domain of a TIMP-2 molecule bound to a cell surface MT1-MMP acts as a receptor for the hemopexin-like domain of pro-MMP-2:

a second MT1-MMP then cleaves the pro-peptide releasing an intermediate MMP-2 which is fully activated by another soluble MMP-2.

4.1.2. Biological aspects

MMP-2 is constitutively expressed in almost all human tissues and mainly by fibroblasts, endothelial and epithelial cells. The enzyme is detectable at significant serum concentration in physiological condition: its activity has been, insofar, linked to homeostatic functions (Van den Steen et al., 2002). MMP-2 expression is inducible by stimuli to a lesser extent with respect to other proteases, reflecting the absence of promoter elements for specific transcriptional factors activated under inflammatory conditions (Xu et al., 2004b).

The MMP-2 activity is tightly regulated by TIMPs; in particular, TIMP-2, TIMP-3 and TIMP-4 (see Table 5) display relevant affinity for the MMP-2 and their adequate secretion is required for a balanced MMP-2/TIMP ratio. Intriguingly, MMP-2 can further undergo PKC-dependent phosphorylation: this recent observation opens important perspectives about MMP-2 interaction with substrates (Sariahmetoglu et al., 2007).

MMP-2, also known as type IV collagenase, cleaves a vast repertoire of substrates, including cytokines, growth factors, receptors or binding factors (see Table 3). Therefore, the biological activity of the enzyme is associated to a plethora of physio-pathological processes and mainly: (i) neoplastic diseases (ii) cardiovascular diseases (iii) auto-immune diseases.

4.1.3. Neoplastic diseases

4.1.3.1. Epidemiological aspects. The identification as leading ECM degrading protease and the up-regulation in almost all cancers had historically linked MMP-2 to tumorigenesis and in particular to invasiveness and dissemination (Björklund and Koivunen, 2005; Fingleton, 2006; Liotta et al., 1980). Several attempts have been carried out to design specific inhibitors. Unfortunately they all failed in their therapeutic purpose: the redundancies of biological activities and the daedalian network of molecular interactions that have been, at least partially, unveiled likely accounts for the unsuccessful approach (Gioia et al., 2009; McCawley and Matrisian, 2001; Sato and Takino, 2010).

Even though MMP-2 is weakly inducible, it is aberrantly up-regulated in the tumor microenvironment and serum concentration is, then, dramatically high (Colotti et al., 2007): this last aspect has been addressed for the MMP-2 screening as a relevant diagnostic and prognostic marker (Patel et al., 2011). Epidemiologic studies suggest MMP-2 quantification as prognostic marker in patients with colorectal cancer, ovarian cancer and thyroid cancer (Kwon et al., 2011; Rajoria et al., 2011). Up-regulated levels of gelatinase A are observed in patients with breast, gastric, bone and melanoma tumors (Daniele et al., 2010; Gerstein et al., 2009; Kushlinsky et al., 2010; Nikkola et al., 2005; Ranogajec et al., in press; Stankovic et al., 2010). Furthermore, MMP-2 strongly contributes to prostate carcinogenesis (Littlepage et al., 2010) and in the vast majority of cases MMP-2 up-regulation is associated to poor prognosis (Offersen et al., 2010; Zhong et al., 2008). MMP-2 and cancer further registers a validation from genetic and epigenetic factors, since polymorphisms (SNPs) in the MMP-2 gene directly correlates with the pathology (Chaudhary et al., 2010; Kang et al., 2011; Scherf et al., 2010).

4.1.3.2. Tumorigenesis. In vivo and *in vitro* experimental models have revealed multiple and overlapping mechanisms through which MMP-2 contributes to tumorigenesis. However, unlike MMP-9 (see Section 4.1), there is no evidence about the unequivocal association of MMP-2 to a specific phase of the tumor development. MMP-2, consistently with the broad spectrum of targets, behaves as a multifunctional enzyme able to modulate the initial as well as the advanced phases of the pathology (Björklund and Koivunen, 2005). In the early phases MMP-2 is crucial in creating a favorable microenvironment for cancer cells growth and contributes to the epithelial–mesenchimal transition (EMT), as demonstrated for renal tubular epithelial cells and breast epithelial cells (Bourboulia and Stetler-Stevenson, 2010; Kim et al., 2011b, 2007). The acquisition of a mesenchimal phenotype is a hallmark of cancer cells, which lose their tissue-specific morphology in favor of a un-differentiated phenotype suitable for migration and invasiveness (Min et al., 2008; Tang et al., 2011). The transition requires the proteolytic shedding of adhesion molecules, such as cadherin and integrin, and a profound rearrangement of the cytoskeleton, which allows malignant cell to detach from the original tissue. These are all processes directly or indirectly linked to MMP-2 activity (Aresu et al., 2011; Ribeiro et al., 2010).

Tumor growth is sustained through multiple mechanisms. MMP-2 solubilizes TGF-β by degrading decorin and is further able to process the inactive precursor of the cytokine (Imai et al., 1997; Yu and Stamenkovic, 2000); TGF-β, while carrying homeostatic and pro-apoptotic stimuli in physiological condition, is a positive regulator of tumor progression favoring a more invasive phenotype (Munger et al., 1999; Yu and Stamenkovic, 2000). In turn, TGF-β induces MMP-2 gene transcription, creating a vicious cycle which definitely promotes tumor growth (Binker et al., 2011; Kim et al., 2007). MMP-2 activates a plethora of cytokines, growth factors and further inactivates adhesion molecules, as TNF-α, MCP-3 (McQuibban et al., 2000), IGF, β-dystroglycan and FGFR (Fowlkes et al., 1994; Bozzi et al., 2009), modulating tumor cells metabolism, immune responses, receptor turnover (Levi et al., 1996) and cell resistance to apoptotis (Gondi et al., 2009). As matter of the fact, glioma cells treated with anti-MMP-2 siRNA trigger apoptosis (Badiga et al., 2011). IGF-BPs bind IGF, limiting its mitogenic activity: MMP-2 cleaves IGF-BPs enhancing IGF availability (Fowlkles et al., 1994). Further, MMP-2 inhibition stimulates autophagy-associated cell death in cancer cells (Jo et al., 2011).

The source of MMP-2 are malignant, stromal and immune cells which surround the neoplastic lesion (Coussens et al., 2000; Egeblad and Werb, 2002). The involvement of MMP-2 in the pathological tumorigenic process stems from its

dysregulation due to release by malignant cells of molecules which trigger secretion of MMP-2 from their not-malignant neighbors (Himelstein et al., 1994; Du et al., 2008). As an example, we can refer to EMMPRIN, a class of glycoprotein secreted by tumor cells, which stimulates MMP-2 expression by fibroblasts (Biswas et al., 2010). Nonetheless, factors accounting for the unbalanced regulation of the enzyme are continuously identified; this is the case of the L1CAM adhesion molecule in a model of lung metastasis and of an E3 uniquitin ligase (c-Cbl) (Hauser et al., 2011; Lee and Tsygankov, 2010; Song et al., 2010).

The aberrant activity of MMP-2 originates also from the unbalanced activation of pro-MMP-2 (Sims et al., 2011); several evidences put the emphasis on the upstream over-expression or dys-regulated compartmentalization of MMP-2 activating enzymes (Sato and Takino, 2010). In this respect, novel *in vivo* mechanisms of pro-MMP-2 activation by macromolecules highly up-regulated in almost all tumors have been identified as for the HSP-90 and ATP-dependent activation the pro-MMP-2 at the cell membrane (Walsh et al., 2011).

The contribution of MMP-2 to invasiveness includes different aspects, namely (i) degradation of BM component (such as collagen IV, laminin and fibronectin) which assists cells migration to the bloodstream (Björklund and Koivunen, 2005), even though recent discoveries about amoeboid movement of cancer cells question the BM breakdown; (ii) release of bio-active factors; and (iii) exposition of hidden adhesion sites that drive cell motility (Reichel et al., 2008).

A precise spatial and chronological dys-regulation of MMP-2 is another important pre-requisite for efficient invasiveness (Stefanidakis and Koivunen, 2006). MMP-2 is often concentrated at the leading edge of migrating cells invadopodia in association with the vitronectin receptor alphaV beta3 integrin (Brooks et al., 1996). The complex occurs between the C-terminal hemopexin like domain of the enzyme and a integrin site distinct from the RGD binding site (Stetler-Stevenson, 1999). This feature allows the cells to keep unaltered the ability to adhere to ECM molecules, taking in the same time advantage of a highly targeted proteolytical activity.

4.1.3.3. Angiogenesis. MMP-2 contribution to angiogenesis is supported by evidences mainly on MMP-2 knock out mice (see Table 6), which show deficient vascular architecture and altered angiogenesis in the microenvironment of cerebral tumors. Modulation of VEGF availability and pericytes homeostasis should represent key aspects (Badiga et al., 2011; Du et al., 2008; Itoh et al., 1999; Rojiani et al., 2010). Even though molecular mechanisms are still elusive, the previously mentioned compartmentalization of MMP-2 at the leading edge of invadopodia seems to be a pre-requisite for efficient angiogenesis, facilitating endothelial cell invasion and migration and, thus, the realization of the pre-metastatic niche (Brooks et al., 1996; Chetty et al., 2008, 2010; Erler et al., 2009).

On the other hand, it is widely known that by cleaving the collagen IV NC1 domain MMP-2 generates fragments with anti-tumoral properties, such as arrestin, canstatin and tumstatin, whereas cleavage of laminin-5 exposes cryptic pro-migratory binding sites (Giannelli et al., 1997).

4.1.4. Non neoplastic diseases

4.1.4.1. Disease of the cardiovascular system.

4.1.4.1.1. Atherosclerosis. Atherosclerosis is a pathological thickness of artery wall due to fatty acids and cholesterol deposition (Caceres et al., 2010). An early event in the onset of the disease is the altered permeability of the endothelial layer to LDL and fatty acids which then are loaded in the sub-endothelial space (Hansson, 2005). The chemical modification of these macromolecules, such as oxidization, triggers inflammation with recruitment of monocytes/macrophages which invade the atherosclerotic lesion (Libby, 2002). Foam cells, a peculiar histological marker of the disease, are macrophages which uptake oxidized LDL (Shashkin et al., 2005). In the advanced stage, a fibrous cap, made up by smooth muscle cells and ECM components, surrounds the lesion: its rupture generally triggers the thrombus-mediated life-threatening acute event.

Gelatinase A is generally constitutively expressed in almost all human tissues and is weakly inducible. Anyway, in the inflammatory context of atherosclerotic lesion the enzyme is particularly abundant.

Experimental models on mice have highlighted its role in atherosclerosis progression, whereas epidemiological investigations in patients reveal that genetic variants of MMP-2 gene and in particular of the promoter region facilitate the onset of the disease (Fiotti et al., 2010; Volcik et al., 2010; Wågsäter et al., 2011).

MMP-2 expression strongly correlates with plaque rupture, by both degrading components of the fibrous cap and modulating the bioavailability of cytokines that contribute to plaque instability, as in the case of TNF-α (Heo et al., 2011; Kaneko et al., 2011).

Furthermore, MMP-2 plays a pivotal role in smooth muscle cells migration, an event which occurs at an advanced stage of the disease and has a strong impact on the formation of the fibrous cap itself (Butoi Dragomir et al., 2011; Jung et al., 2010). Nonetheless, MMP-2 source is just represented by these cells which secrete the enzyme in response to stimuli present in the atherosclerotic lesion (Kodali et al., 2006). As an example, several factors, such as thrombospondin and angiotensin, which promote atherosclerosis progression positively modulate MMP-2 expression by smooth muscle cells. ROS and oxidized LDL further induce gelatinase A secretion (Lee et al., 2003; Luchtefeld et al., 2005).

Notably, oxidized LDL can modify metabolisms and the proteomical pattern of cells surrounding atherosclerotic lesion and should further contribute to the epigenetic modification of MMP-2 gene which ultimately lead to up-regulation of the enzyme (Chen et al., 2011a).

4.1.4.1.2. Stroke. In the central nervous system MMP-2 is normally expressed by neurons, microglia and astrocytes and presumably drives physiological remodeling of BBB (Del Zoppo et al., 2007). It is worth pointing out that MMP-2 is up-regulated within 1 h after stroke (Del Zoppo et al., 2007) and that local hyperthermia and flogistic stimuli enhance the MMP-2 content. This condition leads to an increased degradation of basement membrane components, in particular collagen IV and laminin (Alam et al., 2011). Moreover, MMP-2 should contribute to the activation of glial cells, facilitating the consequent immune modulation that sustains flogosis (Nakaji et al., 2006).

The correlation of MMP-2 with stroke is also reinforced by genetic evidences, namely (i) specific MMP-2 variants correlate with stroke and disease outcome (Manso et al., 2010), (ii) the enhanced toxicity for endothelial cells and the increased risk of BBB breakdown observed in some patients can originate from the MMP-2 dependent proteolytical shedding of a toxic soluble variant of Aβ-peptide (Hernandez-Guillamon et al., 2010).

4.1.4.1.3. Myocardial infarction. The outcome of myocardial infarction (MI) closely depends on a adequate ventricular architecture remodeling. The process is mainly driven by the deposition of ECM macromolecules in a tightly regulated manner in order to prevent stiffness and/or other pathological conditions that often impairs myocardial viscoelasticity ending up with a heart failure (Mountain et al., 2007). The role of MMP-2 in cardiac tissue encompasses critical steps in heart and cardiovascular system development during embryogenesis: nonetheless, the enzyme is well represented in pathological conditions that require ECM remodeling and restoration of cardiomyocytes homeostasis (Linask et al., 2005).

MMP-2 is a key player in the recovery phases after MI: its appearance follows a defined pattern, being maximally induced within the first 3 days (Secchiero et al., 2010). MMP-2 is mainly secreted by endothelial cells in response to cytokines and EMMPRIN, which are the typical inflammatory stimuli in the infarcted myocardium (Nie et al., 2009). IL-1β should be the main MMP-2 inducer in the post-infarction area, but also TNF-α has a major relevance (Bujak et al., 2008; Herrmann et al., 2011; Zitta et al., 2010).

The activity of MMP-2 deals with two different aspects. It is necessary to prevent fibrosis, promoting ECM molecules breakdown and this aspect is further reinforced by the evidence that mesenchimal stem cells stimulate secretion of MMP-2 and delay fibrosis (Giricz et al., 2006; Mias et al., 2009). However, recently reported evidence indicates that MMP-2 activity could trigger the pathological tenascin-C deposition upon fibronectin degradation, suggesting that a MMP-2 inhibition therapeutical strategy should improve the MI outcome (Ma et al., 2011).

4.1.4.2. Diseases of the nervous system. Multiple sclerosis is characterized, from an histological point of view, by focal lesions with a dense infiltrate of macrophages and lymphocytes which massively attack myelin of brain and spinal cord axons. Therefore, the disease is determined by progressive and disseminated destruction of myelin layer.

The involvement of MMP-2 on these pathologies is not particularly significant, at least on the basis of the up to now reported evidences.

Experimental findings illustrate an elevated concentration of MMP-2 in serum of patients with MS, SLE, and a putative correlation between SNPs in MMP-2 gene and disease onset, but the molecular rationale is mys-leading even though myelin basic protein indeed can be *in vitro* degraded by MMP-2 and early axonal injury might be induced by the enzyme (Avolio et al., 2003; Benesova et al., 2008, 2009; Chang et al., 2008; Comabella et al., 2009; Diaz-Sanchez et al., 2006; Fainardi et al., 2009; Shiryaev et al., 2009a).

4.1.4.3. Diseases of joints and muscular system. Rheumatoid arthritis is a chronic muscolo-skeletal disease of the synovial lining. The progress of the disease after the antigenic stimulus evolves through an acute inflammation which rapidly becomes chronic: the consequent proliferative erosive synovitis brings about bone and cartilage destruction inducing severe pain and inability.

Diagnostic markers of the disease are the rheumatoid factor and anti-citrullinated antibodies: the first one is an antibody that binds the Fc portion of the IgG, promoting the formation of immune-complexes, whereas anti-citrulline antibodies recognize proteins which expose the post-translationally modified aminoacidic residue (Van Vollenhoven, 2011).

The inflammatory condition leads to the formation of a "pannus", an aberrant layer of fibrotic or granulated tissue deposited by fibroblasts and immune cells lining the lesion. The "pannus", in turn, stimulates the expression and secretion of pro-inflammatory cytokines, such as IL-1β, TNF-α and MCP-1 by chondrocytes, macrophages and other cells type that complete the vicious cycle by triggering the expression of several bone and cartilage-degrading proteases (Wang et al., 2010a). Hence, many enzymes are over-represented in this context including MMP-2 and MMP-9 (see below), whose high serum concentrations are commonly detectable in patients with RA (Chang et al., 2008; Kim et al., 2011b; Yang et al., 2008).

MMP-2 contribution to rheumatoid arthritis is illustrated by several experimental findings on animal models and gets stronger evidence from the elevated levels in the serum and in the synovial fluid of patients at an advanced stage of the disease (Chang et al., 2008; Goldbach-Mansky et al., 2000). Even though MMP-2 is a matrix degrading enzyme and ECM remodeling is a key pathological event in the onset and progression of RA, many evidences concur in defining a suppressive role of the enzyme, consistently with the notion that it displays a systemic pro-homeostatic function.

The idea of a suppressive role for MMP-2 originates from animal models: the most relevant evidence comes from genetically modified MMP-$2^{-/-}$ and MMP-$9^{-/-}$ mice where the gelatinase A ablation results in a dramatic increase of circulating autoantibodies (Itoh et al., 2002).

Subsequently, other experimental findings have casted light on a differential regulation of gelatinases in the progression of the disease, which reinforce the hypothesis of the elevated concentration of MMP-2 as a consequence of the effort in down-regulating the inflammatory stimulus.

However, the involvement of MMP-2 in the progression of the disease cannot be ruled out, since it is otherwise evident that MMP-2 up-regulation stimulated by TLRs pathways in synovial tissue modulates endothelial cells migration and new vessel formation, a pre-requisite for subsequent flogosis onset and joint destruction while the ECM degrading activity further promotes cartilage and bone breakdown (Saber et al., 2011; Sacre et al., 2007). Elevated levels of the enzyme are determined by cytokines stimulation of macrophages and, mainly, of synovial fibroblasts, the main source of the enzyme.

MMP-2 expression is triggered by macrophages migration inhibitory factor and other cytokines or soluble factors, such as IL-1β and cyclophillin A, which stimulate the expression of the glycoprotein EMMPRIN (CD147) on the cell surface of macrophages, thus inducing MMPs expression (Ahmed et al., 2006; Pakozdi et al., 2006; Zhou et al., 2008; Zhu et al., 2006).

Nonetheless, the ability of MMP-2, once secreted, to degrade and inactivate cyto- and chemokines may account for its protective role in the molecular basis of RA aetiology.

4.2. MMP-9

4.2.1. Structural peculiarities

MMP-9 (gelatinase B) (92–85-82 kDa for the pro-enzyme, the intermediate form and the active enzyme, respectively) domain composition has an high homology degree with that of the related MMP-2 with the exception of a type V collagen-like extensively O-glycosylated linker domain (see Fig. 1) (OG-domain) (Elkins et al., 2002). Insights on MMP-9 structure come out from resolution of mutants lacking the hemopexin and the type V collagen domains since their presence impairs crystals formation. Anyway, overall MMP-9 structure has been deduced using atomic force microscopy combined with small angle X-rays scattering and analytical ultracentrifugation (Rosenblum et al., 2007a).

The catalytic domains of MMP-2 and MMP-9 share the same structural organization; however, the S1 site is particularly deep in MMP-9 and the main difference with the gelatinase A concerns the presence of a Asp410 instead of a Glu in the S2 subsite (Chen et al., 2003).

The Collagen Binding Domain (CBD) is located at one terminus of the catalytic domain and it shares with MMP-2 the presence of conserved cysteines and aromatic residues which limit domain flexibility. The CBD of MMP-9 has a different orientation with respect to the catalytic site and no interaction occurs between these domains (Rosenblum et al., 2007b).

The hallmark of MMP-9 structure is the unusually long linker domain (54 residues) which displays a particularly high content in Ser and Thr residues with a variable pattern of O and N-glycosylation (Van den Steen et al., 2002). The domain is inserted between the catalytic and the hemopexin-like domain, rendering very unlikely their tight interaction, and confers an extraordinary flexibility to the enzyme (Rosenblum et al., 2007a; Overall and Butler, 2007). This feature has suggested the intriguing ''inchworm model'' of MMP-9 movement along collagen fibrils, which furnish an explanation for those still obscure aspects concerning MMPs interaction with large ECM substrate (Overall and Butler, 2007). The OG domain further participates in the MMP-9 dimerization and regulates the trafficking in the intracellular compartments and the secretion (Van den Steen et al., 2006).

The hemopexin-like domain carries out substrate binding functions together with the CBD. Furthermore PEX domain should be involved in MMP-9 homodimerization. Differently from MMP-2, MMP-9 physiologically exists as monomer, dimers or associated to the transport protein lipocalin (Van den Steen et al., 2002): each conformation is generally represented in tissues and they can be released by the same cell type in association to a specific MMP-9 biological activity (Bolignano et al., 2010; Dufour et al., 2010). As for MMP-2, the hemopexin-like domain can be targeted by TIMPs and in particular by TIMP-1 and TIMP-4.

The pro-domain has the classic α-helix composition and the Cys-99 of the conserved cysteine switch motif is the fourth ligand of the Zn^{2+} atom in the enzymatic pro-form. Displacement of the pro-peptide is *in vivo* exerted by many soluble proteases, mostly by MMP-3, MMP-2, MMP-7, MMP-13 and other soluble proteases, such as kallikrein or trypsin or uPA (Van den Steen et al., 2002). Studies on the stepwise activation of pro-MMP-9 by kallikrein have recently suggested a novel mechanism which replaces the cysteine-switch dogma based on the mere degradation of the propeptide domain. The model proposes that the dissociation of Cys-99 from the Zn^{2+} atom is early driven by protein–protein interaction, while the proteolytical cleavage of the propeptide occurs only at a later stage (Kotra et al., 2001; Rosenblum et al., 2007b).

4.2.2. Biological aspects

Substrate specificity of MMP-9 clearly overlaps with that of MMP-2, even though with different affinities (see Table 3): basement membrane components are mainly targeted, but cytokines, growth factors, receptors are highly represented (Björklund and Koivunen, 2005) (see Table 3). MMP-9 is physiologically expressed by a limited cohort of cell types, mainly immune cells, and it is highly inducible (Van den Steen et al., 2002). Therefore its distribution is spatially and chronologically defined, making it a prototypical target in inflammatory events: hence, the proteolytical breakdown of substrates often occurs in association to anti-homeostatic conditions (Van den Steen et al., 2002). Consistently with the identification of *cis*-acting promoter elements, transcriptional activation of MMP-9 is regulated by a multitude of factors which render highly complex the plethora of stimuli that finely tune its biological activity (Lauricella-Lefebvre et al., 1993; Munaut et al., 1999). MMP-9 is induced by adhesion molecules, mainly activated integrins, cytokines and growth factors (Beliveau et al.,

2010; Zhao and Benveniste, 2008). As an example, cell binding to vitronectin or fibronectin trigger MMP-9 expression, IL-1β, TNF-α or TGF-β induce MMP-9 in a autocrine and paracrine fashion, EGF release or the aberrant activation of the EGFR result in over-expression of MMP-9 (Coulson-Thomas et al., 2010; Ehrenfeld et al., 2011; Ikari et al., 2011; Lin et al., 2009; Yu and Stamenkovic, 2000).

Several molecular pathways, once activated, regulate MMP-9 expression: MMP-9 is controlled by the Raf/MEK/ERK cascade and the transcription factors SLUG and NF-κB induce MMP-9 expression (Beliveau et al., 2010; Sun et al., 2008; Moon et al., 2007). Furthermore, the transcriptional stability is maintained through the p38 MAPK/MAPK2 signaling and, interestingly tissue transglutaminase 2 is reported to promote MMP-9 expression (Cai et al., 2011; Kumar et al., 2010; Li et al., 2011).

The homeostasis of the vast majority of the previously mentioned factors that induce MMP-9 expression is compromised in malignancies; as a matter of the fact, MMP-9 is over-represented in almost all human cancer (Egeblad and Werb, 2002).

MMP-9 involvement is further described for cardiovascular, respiratory and auto-immune diseases (*e.g.*, Systemic Lupus Erythematosus, Sjögren's syndrome, Multiple Sclerosis, Rheumatoid Arthritis, polymyositis, asthma, chronic obstructive pulmonary disease, C protein-induced myocarditis, lupus nephritis, auto-immune inner ear disease and bullosus pemphigoid) (Du et al., 2008; Fenton et al., 2009; Hulkkonen et al., 2004; Ito et al., 2009; Ma et al., 2010; Matsumoto et al., 2009; Noseworthy et al., 2000; Pathak et al., 2011). In some cases, the molecular mechanisms underlying its pathogenic activity have been described in detail: therefore, the discussion of MMP-9 role in human pathologies will be limited to those more represented in literature (see Table 4).

4.2.3. Neoplastic diseases

4.2.3.1. Epidemiological aspects. MMP-9 and tumorigenesis is a long standing association which have extensively stimulated research over the past decades (Björklund and Koivunen, 2005; Deryugina and Quigley, 2006). Experimental models, mostly based on MMP-9 knock out mice, have provided unequivocable evidences about the pivotal role played by the enzyme in tumor growth, invasiveness and angiogenesis (Egeblad and Werb, 2002; Fingleton, 2006; Itoh et al., 1999; Wielockx et al., 2001): nonetheless, there is compelling evidence that biology of the enzyme is otherwise complex and a final convincing picture is far from being formulated. In this respect, many findings envisage anti-tumoral properties for MMP-9, as in the case of breast cancer regression in a MMP-9 deficient mouse model (Bendrik et al., 2008). Such a complex biology of the enzyme is further highlighted by the description of a anti-proliferative effects in prostate cancer cells and in colitis associated cancer (Biswas et al., 2010; Garg et al., 2010).

In accordance to the tissue-specific distribution of the enzyme, MMP-9 level in serum is almost undetectable under physiological conditions: therefore, the diagnostic and prognostic value of MMP-9 quantification appears even more significant (Turpeenniemi-Hujanen, 2005). A large number of epidemiological studies illustrate that MMP-9 concentration is abnormal in serum from patients with melanoma, gastric cancer, breast cancer, bladder cancer, colorectal cancer, brain cancer, pancreatic cancer and prostate (Chu et al., in press; Daniele et al., 2010; Jensen et al., 2010; Joergensen et al., 2010; Littlepage et al., 2010; Liu et al., 2010; Nikkola et al., 2005; Offersen et al., 2010; Ranogajec et al., in press; Buhmeida et al., 2009). Elevated MMP-9 concentrations are generally associated to poor prognosis.

4.2.3.2. Tumorigenesis. MMP-9 has been historically identified as a basement membrane degrading protease, due to its high affinity for collagen IV. Hence, pathogenicity had been initially limited to tumor invasiveness: it was anyway clear that MMP-9 contribution was much broader. Matrisian and colleagues have first demonstrated that tumor cells over-expressing TIMP-1, once injected in the chorioallantoic membrane of chicken, invade the host tissue but fail to proliferate: this statement clearly indicated that the biological role of MMPs, and in particular of MMP-9 which is preferentially targeted by TIMP-1, was not strictly dependent on cancer cell invasion, but rather in tumor growth (Chambers and Matrisian, 1997; Khokha et al., 1992). MMP-9 was then shown to modulate the bioavailability of growth factors and to disrupt cell–cell contacts, dramatically affecting cell proliferation and survival. In this respect, the MMP-9 dependent release of TGF-β is a key aspect (Yu and Stamenkovic, 2000); similarly, MMP-9 shedding of the membrane component of HB-EGF lead to increased concentration of the soluble EGF. Both these factors display positive properties for tumor growth and contribute to the epithelial–mesenchimal transition (Aresu et al., 2011; Ongusaha et al., 2004; Wu et al., 2011a). MMP-9 cleaves nexin-1 and adhesion molecules, such as the β-subunit of dystroglycan (Xu et al., 2010; Bozzi et al., 2009), enhancing tumor detachment from the primary site and tumor invasiveness. Furthermore, MMP-9 degrades collagen IV and other basement membrane components and exposes cryptic binding sites for cell migration or releases hidden bio-active factors (Schenk and Quaranta, 2003; Stetler-Stevenson and Yu, 2001). Nonetheless, progress in MMP-9 research are currently revealing that MMP-9 biology is even more complex and that its pathogenic activity takes advantage of many undefined aspects, including interaction with enzymes which share the same tissue localization (Gioia et al., 2009). Interestingly, the MMP-9 source are not exclusively cancer cells, but also inflammatory cells (Coussens et al., 2000; Egeblad and Werb, 2002). In particular, polymorphonucleated cells (PMN), which store elevated concentrations of MMP-9 in their mature granules, provide a consistent reservoir of MMP-9 (Ardi et al., 2007). This statement is further reinforced by the evidence that PMN secrete MMP-9 devoid of TIMP-1, which can be readily activated (Egeblad and Werb, 2002; Du et al., 2008); on the other hand, fibroblasts and endothelial contribute to a much lesser extent.

Attention has recently focussed on the definition of the "tumor niche", a specific anatomical microenvironment adapt for cancer cells growth (Coulson-Thomas et al., 2010; Kaplan et al., 2006). In this context, MMP-9 contributes by controlling cell division and by conferring resistance to apoptosis and to immune surveillance. Mitotic phases are accompanied by a highly

conserved and dynamic distribution of the enzyme as from studies in neuroblastoma cells and in macrophages (Sans-Fons et al., 2010; Ganji et al., 2011). Furthermore, MMP-9 affects apoptosis by degrading apoptotic molecules, as the Kit-ligand, hence promoting cells survival (Meyer et al., 2005). In addition, MMP-9 shedding of ICAM-1 confers protection to NK and T-cell mediated cytotoxicity (Fiore et al., 2002).

Another aspect carefully examined concerns the MMP-9 compartmentalization, which further implies intriguing therapeutical strategies (Ezhiralasan et al., 2009). MMP-9 activity is highly compartmentalized in invadopodia, the leading edge of invading cells. The enzyme interacts with trans-membrane glycoprotein, such as the heparan sulfate proteoglycan (CD44) and integrins (Yu and Stamenkovic, 2000). It is important to outline that such a localization is not a specific cancer cell property, since it is widely observed also in endothelial and immune cells (Mäkelä et al., 1998; Partridge et al., 1997); it is otherwise evident that tumor cells fail to balance this process (Björklund and Koivunen, 2005). The association of MMP-9 and CD44, whose cell membrane distribution is diffusely dys-regulated in cancer, promote growth and survival by optimizing the TGF-β activation (Bourguignon et al., 1998).

The interaction between integrin and MMP-9 deserves a more extended comment: it has been previously reported that integrin activation induces MMP-9 expression upon binding to those ECM macromolecules displaying the RGD sequence. MMP-9 in turn can readily activate integrin promoting cell motility. Invadopodia of tumor cells show strong MMP-9 gelatinolytic activity and down-regulation of MMP-9 expression results in decreased invasion and decreased integrin expression on the cell surface (Lagarrigue et al., 2010; Veeravalli et al., 2010).

It is now evident that these molecules interact through the C-terminal hemopexin-like domain of the enzyme: this aspect is a challenging task in the comprehension of the molecular mechanisms underlying MMP-9 activity (Radjabi et al., 2008). The precise localization allows the cells to help proteolysis; thus, integrins do not lose their ability in recognizing its ECM partner, even when MMP-9 is bound, and MMP-9 might provide the helping hand in the amoeboid movement exposing the hidden binding sites, since the RGD sequence is often cryptic. Additionally, the hemopexin-like domain alone can act as a functional ligand for $\alpha_{iv}\beta_1$ integrin, inducing intracellular signals which promote cell survival (Redondo-Muñoz et al., 2008). The existence of intracellular signals triggered upon binding of MMP-9 hemopexin-like domain with receptors is further highlighted by evidences on leukemia B cell survival (Muñoz et al., 2010). The administration of the hemopexin-like domain has been confirmed to disrupt angiogenesis and to delay the growth of glioblastoma in xenograft mice (Ezhilarasan et al., 2009).

4.2.3.3. Angiogenesis. Beside the involvement in tumor growth and in invasiveness, as above discussed, MMP-9 exclusively contributes to a critical step of tumorigenesis: the so called "angiogenic switch". The first evidence was obtained in the Rip1-Tag2 Mice (Bergers et al., 2000). Vascular endothelial growth factor (VEGF), the main stimulus for endothelial cells activation and for new vessel formation, is normally sequestered in the ECM (Ferrara et al., 2003). MMP-9 was identified as the main enzyme involved in VEGF release from the natural reservoir. In the last decade the role of MMP-9 in angiogenesis has represented an important matter of debate: experimental models both *in vivo* and *in vitro* have extended the original finding and are now revealing that the enzyme contribute is complex (Ahn and Brown, 2008). Even before originating a metastasis, tumor cells implanted in a mouse model attract VEGF receptor positive pro-inflammatory cells that create a niche wherein tumor cells can proliferate (Kaplan et al., 2005). MMP-9 secreted by these immune cells, by degrading basement membrane and by releasing VEGF and Kit-ligand promote recruitment of a large number of inflammatory cells that ultimately build up the niche and sustain pericytes correct positioning on newly formed blood vessels (Chantrain et al., 2004; Kaplan et al., 2005; Karroum et al., 2010; Zijlstra et al., 2006). Notably, MMP-9 modulates also vasculogenesis, helping the implant of stem cells progenitor of endothelial cells in tumor vasculature (Hiratsuka et al., 2006; Shojaei et al., 2007).

4.2.4. Non neoplastic diseases

4.2.4.1. Disease of the cardiovascular system.

4.2.4.1.1. Atherosclerosis. MMP-9 is over-represented in sera from patients with advanced lesions so that, even in this case, its quantification can be considered a suitable marker for diagnosis and treatment (Jefferis et al., 2010). Furthermore, from a clinical point of view, fragments of collagen III generated by MMP-9 are currently under investigations for their putative diagnostic relevance (Barascuk et al., 2011; Zeng et al., 2005).

Stimuli, such as b-FGF, TGF-β and IL-1β and other soluble cytokines as well as oxidized compounds, indeed trigger MMP-9 expression (Chen et al., in press, 2011a,b; Seizer et al., 2010), whereas conditions that reduce secretion of these pro-inflammatory cytokines affects the MMP-9 content as well (Bhaskar et al., 2011; Sigala et al., 2010). Reactions by-products in the inflammatory context further induce the aberrant activation of proMMP-9 (Bonacci et al., 2011). Notably, neutrophils are not recruited in lesions, hence MMP-9 main source are presumably macrophages (Lusis, 2000).

MMP-9 plays a key role in facilitating the migration of smooth muscle cells into the lesion and then it is presumed to contribute to lesion expansion and fibrous cap formation (Galis et al., 2002; Wågsäter et al., 2011).

The MMP-9 mediated degradation of elastin and other components of the fibrous cap lead to its rupture (Gough et al., 2006; Rodriguez-Feo et al., 2008). Even though the strict association between elevated levels of MMP-9 and increased risk of acute event such as ischemia or stroke has been proved, a pro-fibrotic role of MMP-9 in plaque formation has been further described (Lemaître et al., 2009), which is exerted through an elevated deposition of collagen more than a direct involvement in plaque rupture.

Anyway, the evidence that pharmacological targeting of MMP-9 correlates with plaque stability and reduced incidence of coronary events highlight the role of the enzyme in the pathogenesis of atherosclerosis (Moon et al., 2007; Yamamoto and Takai, 2009).

4.2.4.1.2. Stroke. As previously discussed, the consequence of an atherosclerotic plaque rupture is the thrombus-dependent impaired perfusion of heart and/or brain. The MMP-9 serum concentration is elevated in patients with acute ischemic events and this generally correlates with a poor prognosis, being strictly associated to edema formation (Ramos-Fernandez et al., 2011). In the acute event, microglia cells are stimulated by released pro-inflammatory factors to secrete large amounts of MMP-9, which the contributes to the blood–brain barrier (BBB) breakdown (Chen et al., 2009; Copin et al., 2011; Del Zoppo et al., 2007). Occludin, the main component of astrocytes tight junctions, is targeted by the pathogenic activity of MMP-9 and this event usually ends up in alterations of BBB microvascular permeability (Liu et al., 2009). Interestingly, in a mouse experimental model, the gene therapy to inhibit MMP-9 improves the outcome when administered after acute events (Hu et al., 2010; Tu et al., 2011).

4.2.4.1.3. Myocardial Infarction. The recent identification of elevated levels in serum from patients with myocardial infarction (MI) has opened the perspective of a MMP-9 involvement not merely in the atherosclerotic plaque instability but also in the recovery phases (see also MMP-2) (Zeng et al., 2005). The dys-regulation of the enzyme further stems from the unbalanced MMP-9/TIMP-1 ratio and is generally associated with poor prognosis (Cao et al., 2011; Ghaderian et al., 2010; Hansson et al., 2011).

Two chronologically distinct events lead to MMP-9 increase in the infarctuated tissue: the first one corresponds to the neutrophils recruitment, while the second one, which occurs several days afterwards, is linked to macrophages and lymphocytes crowding in the flogistic microenvironment (Mukherjee et al., in press). A benign clinical outcome of MI strictly depends on the adequate remodeling of ventricular architecture: however, correct myocardial regeneration is often impaired by tenascin-C deposition which directly correlates with the the upstream degradation of fibronectin, readily secreted by fibroblasts and myo-fibroblasts. Fibronectin degradation by MMP-9 leads to the release of fragments unable to inhibit tenascin C accumulation (Ma et al., 2011). Therefore, elevated concentrations of MMP-9 favor the unbalanced distribution of these ECM components, leading to compromised ventricular architecture.

Interestingly, transplantation of mesenchymal stem cells down-regulates the expression of MMPs in fibroblast and this is accompanied by an improved outcome (Wang et al., in press), with ameliorated fibrosis and attenuated inflammation (Oyamada et al., 2011).

In conclusion, it is now recognized that the MMP-9 concentration in MI is a delicate equilibrium as its inhibition prevents ventricular stiffness and ECM remodeling, though impairing the otherwise necessary angiogenesis (Cleutjens and Creemers, 2002; Heymans et al., 1999, 2005; Lindsey et al., 2006).

4.2.4.2. Diseases of the nervous system.

4.2.4.2.1. Multiple sclerosis. Among proteases taking part into the disease onset and progression, MMP-9 has a 3-fold role, since it contributes to (i) the blood–brain barrier breakdown (BBB), (ii) the generation of auto-immune epitopes, and (iii) the modulation of cytokines bio-availability.

Epidemiologic investigations correlate MMP-9 concentration in serum with advanced stages of the disease, hence its quantification could represent an intriguing prognostic factor (Benesova et al., 2009; Glass-Marmor et al., 2009; Rosenberg, 2005). Moreover, studies on gene polymorphism reveal that SNPs on MMP-9 gene can facilitate its involvement in MS (Benesova et al., 2008; Fernandes et al., 2009; Garcia-Montojo et al., 2010; La Russa et al., 2010).

The molecular mechanisms of MMP-9 pathological activity have been deduced mostly through the highly related experimental autoimmune encephalomyelitis (EAE) in mouse model: thus, MMP-9 knock out confers protection against the onset of the disease (Dubois et al., 1999; Opdenakker et al., 2006; Du et al., 2010).

Gelatinase B is mainly expressed by immune cells. The need of cytokine-dependent inducibility of the MMP-9 gene promoter fits well with the dynamic ability of these cells to respond, in a spatially and chronologically defined manner, to autocrine and paracrine stimuli (Van den Steen et al., 2002): therefore, in a context of inflated flogosis, as observed in multiple sclerosis lesions, MMP-9 concentration is predictably aberrant. Nonetheless, therapeutical approaches, such as the administration of IFN-β and quercetin, decrease the MMP-9 expression in monocytes isolated from patients, lowering the MMP-9/TIMP-1 ratio (Bernal et al., 2009; Sternberg et al., 2008; Yen et al., 2010).

A plethora of stimuli concurs to the MMP-9 aberrant activation, namely (a) EMMPRIN, a glycoprotein dys-regulated in the pathology, which promotes secretion from resident or activated microglia cells (Agrawal et al., 2011; Fabriek et al., 2007; Shinto et al., 2011); (b) apoptotic neurons, which secrete MMP-3, the main pro-MMP-9 activator (Kim and Lee, 2005); (c) fibronectin and vitronectin of the basement membrane, which stimulate MMP-9 synthesis by activated microglia cells in a integrin-dependent manner (Milner et al., 2007).

There is compelling evidence that MMP-9 pathogenic activity further includes the modulation of cross-talk between immune system compartments (which hinders remission) and, intriguingly, the generation of auto-immune epitopes. About this last aspect, two proteins have been identified as the main source of auto-immunoreactivity: the small heat shock protein α-B crystallin and the myelin basic protein. They are both degraded by MMP-9 (Shiryaev et al., 2009a; Van Noort and Amor, 1998) and fragments share the immunogenic property (Milward et al., 2008; Shiryaev et al., 2009a). Additionally, the therapeutical administration of not-glycosylated interferon-β has been demonstrated to be detrimental for disease outcome,

since the MMP-9 dependent cleavage of that cytokine form, initially adopted in clinical trials, has been shown to be a further source of auto-antibodies (Nelissen et al., 2003).

As a matter of the fact, the combination of therapies addressed toward a suppression of the immune system activation and the inhibition of MMP-9 activity are promising target for long-term remission of the pathology (Muroski et al., 2008).

4.2.4.2.2. Alzheimer's diseases. Alzheimer's disease is a neurodegenerative process characterized by senile plaques deposition and neurofibrillary tangles. The β-amyloid peptide generated upon dys-regulated shedding of the APP precursor displays a marked tendency to aggregate forming unsoluble complex leading to neurons death (Finder, 2010).

The existence of an *in vivo* degradation of β-amyloid plaques has not been proven yet, but a vast deal of knowledge indicates that MMP-9 could bear this cyto-protective role. In fact, MMP-9 *in vitro* degrades β-amyloid aggregates (Yan et al., 2006). Several *in vivo* reported findings, mostly on animal models, reinforces this observation: increased levels of MMP-9 have been found in the cerebrospinal fluid and in post mortem AD brain; MMP-9 and TIMP-1 co-localize with β-amyloid plaques (Asahina et al., 2001; Lorenzl et al., 2003).

In transgenic mice models (see Table 6), MMP-9 expression is further triggered by neurons upon exposure to Aβ derived peptides and macrophages induces MMP-9 expression to get Aβ clearance (Deb et al., 2003; Guo et al., 2006; Zhao et al., 2009).

Recently, it has been shown that astrocytes and neurons are stimulated by Aβ, in particular the $A\beta_{25-35}$ fragment, to secrete, respectively, MMP-9 and TIMP-1 (Hernandez-Guillamon et al., 2009). This is a relevant aspect since it is otherwise known that un-balanced MMP-9 activity affects viability of neurons (Doi et al., 2009; Gu et al., 2002).

4.2.4.3. Diseases of joints and muscular system. The physical and chemical properties of cartilage are conferred by extracellular matrix proteins, such as collagens. In particular, cartilage is made up by type II collagen: its destruction, as it occurs in RA, is followed by replacement with type I collagen whose different properties compromise joint anatomy. Collagen II is mainly degraded by the neutrophil-secreted MMP-8 and the cleavage takes place with the typical 1/4 and 3/4 pattern (see Section 3.1). MMP-9 does not efficiently cleave the whole molecule, but it displays a high affinity for the 3/4 fragment. The event ends up with the release of remnant epitopes which are the source of the anti-type II collagen auto-antibodies which can be found in RA lesions (Burrage et al., 2006; Van den Steen et al., 2004, 2005).

It is intuitive that gelatinase B contributes to the disease onset by modulating the bio-availability of these soluble factors, sustaining flogosis; as a matter of the fact, MMP-9 distribution in lesions correlates with that of IL-8, a cytokine which in turn triggers secretion of the enzyme from neutrophils (Pelletier et al., 2001).

In the last decade experimental evidences have suggested that the MMP-9 role could not be restricted to inflammation promotion, but should include the generation of remnant epitopes and/or the extracellular activation of ADAMTS-4, the main aggrecan-degrading protease (Nagase and Kashiwagi, 2003; Opdenakker et al., 2006; Van den Steen et al., 1998).

4.2.4.4. Diseases of the respiratory system.

4.2.4.4.1. Asthma. Asthma is a chronic condition characterized by airflow obstruction and bronchospasm triggered by mechanical, antigenic or microbial insult which leads to epithelial layer erosion and, in advanced phases, to injured tissue remodeling (Araujo et al., 2008; Kaminska et al., 2009).

The acute event is followed by deposition of several ECM macromolecules, mainly collagen III by fibroblasts, in airways sub-endothelial space. The balance between accumulation and degradation of these components can variably affect physico-chemical properties of the airway. Several proteases take part into this phenomenon and MMP-9 is the most represented one in pulmonary fluids from patients with asthma (Atkinson and Senior, 2003). Under physiological conditions resident cells in lungs do not express constitutively MMP-9, but the asthmatic process induces its secretion by recruited neutrophils and its release by epithelial, endothelial, fibroblasts, smooth muscle cells and alveolar type II cells (Broide, 2008; Mehra et al., 2010; Sands, in press).

The MMP-9/TIMP-1 ratio is a crucial aspect in disease progression. *In vitro* and *in vivo* studies provide discordant findings: anyway, it appears clear that a too low MMP-9/TIMP-1 ratio results in airways wall thickness and impaired respiratory functions, whereas a too high in an excessive collagen III deposition in the sub-endothelial space and reduced elasticity (Matsumoto et al., 2005; Sands et al., 2009; Swartz et al., 2001; Todorova et al., 2010; Watson et al., 2010).

MMP-9 pathogenic activity is not limited to ECM remodeling: two main aspects deserve some comments. (i) Degradation of claudin and occludin destabilizes the tight junctions, determining epithelial permeability and increased cell anoikis (Vermeer et al., 2009); (ii) modulation of soluble factors bio-availability influence response by other cell types (see Table 3). Interestingly, activation of TGF-β, triggers the fibroblasts-mediated deposition of collagen III and further represents a stimulus for epithelial–mesenchimal transition which drives epithelial cells transformation in myofibroblasts, whose aberrant airways colonization represents an histological marker of chronic asthma (Doerner and Zuraw, 2009; Hoshino et al., 1998).

4.2.4.5. Systemic Lupus Erythematosus. Systemic Lupus Erythematosus is a type III auto-immunity reaction that potentially affects any district of the body, with largely variable clinical and serological manifestations caused by auto-antibodies and complement activation dependent on immune complexes (Hahn, 1998, 2003; Muñoz et al., 2010).

Markers of the disease are in particular represented by (i) auto-antibodies against nuclear proteins (anti-dsDNA) (Hahn, 1998), and (ii) impaired leukocytes apoptosis; this last evidence is accompanied by an insufficient clearance of apoptotic

bodies which, indeed, act as a reservoir of autoantigen in the extracellular compartments (Denny et al., 2006; Emlen et al., 1994).

In the case of Systemic Lupus Erythematosus epigenetic factors seems involved in MMP-9 dys-regulation (see Table 4) since in $CD4^+$ lymphocytes the MMP-9 gene is hypomethylated, reflecting a greater expression of the protease (Jeffries et al., 2011).

Even though MMP-9 proteolytical activity is a major determinant in the generation of auto-immune fragments, its contribution to the onset of the disease is still matter of debate.

Two evidences, reported by the same authors, illustrate the MMP-9 pathogenic activity (Cauwe et al., 2009, 2011). The first one is the identification of several intra-cellular novel substrates, which enlarge the enzyme degradome and could be involved in the development of such a pathology. In this sense, the impaired clearance of apoptotic bodies could represent a dramatic reservoir of autoantigens (Cauwe et al., 2008). On the other hand, recent findings in a mouse experimental model illustrate a protective role of MMP-9 on the onset and the progression of the auto-immune disorder (Cauwe et al., 2011). Mice MMP-9 knock out with a systemic auto-immune lymphoproliferative syndrome, develop a pathology several fold more aggressive than that of the $MMP\text{-}9^{+/+}$ counterpart.

Therefore, the aetiology of SLE is still unclear, but the identification of MMP-9 activity seems to be a pre-requisite for a successful approach to the disease treatment.

4.2.4.6. Bullosus pemphigoid. Bullosus pemphigoid (BP) is an autoimmune skin blistering disease, where antibodies anti-hemidesmosome trans membrane protein B180 (collagen XVII) lead to inflammation and, finally, to dermis–epidermis separation (Kasperkiewicz et al., in press). Mast cells physiologically colonize the connective tissues and, upon activation by antigens and allergenic stimuli, they recruit leukocytes and other cell types which secrete proteases with ECM-degrading properties (Walker et al., in press). It is well known that MMP-9 synergizes with neutrophil elastases in the breakdown of almost all components of the extracellular matrix, a pre-requisite for the two-layers separation (Verraes et al., 2001).

The first evidence of the MMP-9 dominant role in disease progression comes from studies on MMP-9 deficient mice which do not develop BP even when anti-B180 autoantibodies are injected into the dermal–epidermal junction (Liu et al., 1998). Furthermore, elevated concentration of MMP-9 can be *in vivo* detected in serum and in blister fluid of patients (Niimi et al., 2006).

MMP-9 is readily released by neutrophils, but a major contribute comes from other cell types which secrete the enzyme in response to soluble stimuli, mainly IL-1β (Gounni-Abdelilah et al., 2006). The cytokine stimulates the expression of a not yet identified pro-MMP-9 activating protease, and the plasminogen/plasmin system may have a significant role (Liu et al., 2005). An additional mechanism could involve the recently identified Mast cell protease-4, which displays MMP-9 activating properties (Lin et al., 2011a).

5. Stromelysins

The class of stromelysins encompasses three enzymes, namely MMP-3 (stromelysin-1), MMP-10 (stromelysin-2), and MMP-11 (stromelysin-3).

The overall structure includes the catalytic domain, the hemopexin-like domain and the pro-peptide, but significant differences with other soluble MMPs are also found. In particular, MMP-11 exhibits an additional pro-protein convertase recognition sequence, which envisages a peculiar activation mechanisms (Visse and Nagase, 2003).

Although stromelysins have been discovered many years ago, there is a limited knowledge of MMP-10 and MMP-11 biology, whereas more convincing findings are reported for MMP-3, even though several aspects still remain obscure, mainly concerning its pathogenic activity.

Natural substrates have been identified and they are mostly represented by ECM matrix components (see Table 3): in particular, stromelysins share the ability to degrade (although with significantly different affinities among them) types IV and IX collagens, laminin, fibronectin, elastin, and proteoglycans. Additional substrates include cytokines, growth factors and regulatory soluble molecules (Visse and Nagase, 2003).

Each stromelysin has a different physiological distribution in human tissue, hence the types of processes which are modulated are largely variable.

Cancer is a pathology wherein a contribution of the three stromelysins has been described quite extensively, even though with divergent molecular mechanisms (Gill et al., 2004; McCawley et al., 2004; Wilkins-Port et al., 2009). Other pathologies, for which a contribution from at least of one member of this family has been reported, mainly include cardiovascular, degenerative and auto-immune diseases.

5.1. MMP-3

MMP-3 or stromelysin-1 was first described in 1985 as a 51-kDa protein secreted by rabbit fibroblasts.

Stromelysin-1 is synthesized as a pro-enzyme which is activated upon removal of the N-terminal pro-domain by serine proteases trypsin-2 (Moilanen et al., 2003) and matriptase (Jin et al., 2006), yielding a 43-kDa active enzyme. The active enzyme contains a catalytic domain and a C-terminal hemopexin-like domain presumably involved in the macromolecular

substrate recognition (see Fig. 1). The catalytic core is very similar for the pro- and the active enzyme forms and it has a high homology degree with the same domain of fibroblast and neutrophil collagenases, as determined through NMR analysis (Becker et al., 1995; Zhang et al., 2000). The prodomain is a separate folding unit containing three α-helices and an extended portion that lies in the active site of the enzyme.

5.1.1. Biological aspects

Matrix metalloproteinase-3 is expressed by a variety of cells, *e.g.* keratinocytes, fibroblasts and chondrocytes, and it is often released in association with MMP-10 by fibroblastic cells and by normal epithelial cells in culture and *in vivo* (Sternlicht et al., 1999; Visse and Nagase, 2003).

The main physiological role of MMP-3 is the activation of other proMMPs during extracellular matrix turnover (Brinckerhoff et al., 1990; Visse and Nagase, 2003). In fact, stromelysin-1 efficiently activates collagenases, matrilysin, and gelatinase B; in particular, the action of MMP-3 on a partially processed pro-MMP-1 is critical for the generation of fully active MMP-1 (Imai et al., 1995; Murphy et al., 1992; Shapiro et al., 1995). The enzyme differs from collagenases by the inability to cleave type I collagen, anyway it degrades a wide range of ECM proteins, *e.g.*, type IV, V, IX, and X collagens, proteoglycans, gelatin, fibronectin, laminin, and fibrillin-1 (Chin et al., 1985).

Furthermore, MMP-3 cleaves α1-proteinase inhibitor, tumor necrosis factor (TNF)-α precursor, myelin basic protein and interleukin (IL)-1β, inactivating it (see Table 3). Moreover, MMP-3 activates TGF-α which then stimulates MMP-9 expression by macrophages in a COX-2 dependent way (Steenport et al., 2009).

MMP-3 expression is upregulated by interleukin-1β and downregulated by retinoic acid, dexamethasone and progesterone which inhibits also its secretion (Osteen et al., 2003; Saus et al., 1988).

5.1.2. Neoplastic diseases

The previously discussed role as proMMPs-activating enzyme indicates that the unbalanced MMPs, and in particular MMP-9, distribution in solid tumors should be related to MMP-3 enhanced secretion. Nonetheless, although findings on skin tumors and the documented MMP-3-dependent release of angiostatin-like fragments from plasminogen suggest an anti-tumoral activity, a vast deal of knowledge concurs in defining a major role for MMP-3 in tumor progression and angiogenesis (Lijnen et al., 1998; McCawley et al., 2004).

As an example, phenotypically normal mammary epithelial cells *in vivo* form epithelial glandular structures in absence of stromelysin-1, whereas they transform into invasive mesenchymal-like tumors in the presence of the enzyme (Thomasset et al., 1998). Once initiated, tumor progression is not linked to MMP-3 expression anymore. Premalignant changes and malignant conversion in mammary glands regulated by MMP-3 have been reported in transgenic mice and, interestingly, the co-expression of TIMP1 reverts this process (Sternlicht et al., 2000). These findings clearly indicate that MMP-3 influences tumor initiation and alters the neoplastic risk (Sternlicht et al., 1999).

The MMP-3 pathogenic activity results in the modulation of growth factors and of cytokine availability which affect both tumor growth per se and neutrophils and macrophages recruitment that often provide a consistent reservoir of pro-angiogenic molecules. Noteworthy, TGF-β bio-availability is strictly linked to MMP-3 activity and such an association further strengthens the recent suggestion of a MMP-3 involvement in the epithelial–mesenchimal transition (Blavier et al., 2010; Lochter et al., 1997; Maeda et al., 2002).

Another relevant aspect is the ability of MMPs to target substrates that modulate apoptosis of cancer cells, even though molecular mechanisms are still elusive. Anyway, it is known that MMP-3 exerts a pro-apoptotic action on epithelial cells and MMP-3-deficient mice have a lower degree of TNF-α-induced of apoptosis (Wielockx et al., 2001; Witty et al., 1995).

5.1.3. Non-neoplastic diseases

5.1.3.1. Diseases of cardiovascular system.

5.1.3.1.1. Atherosclerosis. The primary cause of heart disease in western countries is atherosclerosis, an inflammatory process that affects the vessel wall of large and medium-sized arteries. Genetic and environmental factors associated to the disease include elevated circulating levels of low-density lipoprotein (LDL) and of very low-density lipoprotein (VLDL), obesity, diabetes, high blood pressure, a high-fat diet and smoking (Libby, 2002). The acute coronary syndrome, including myocardial infarction and stroke, results from the erosion or the rupture of the fibrous cap which surrounds the luminal side of the atherosclerotic lesion, leading to thrombus formation (Libby et al., 2006). Henney and coworkers first observed increased MMP-3 expression in human atherosclerotic plaque where the enzyme might erode the connective tissue, leading to vessel wall fissuring and/or rupture of the plaque itself, and drive the aberrant activation of pro-MMP-9 and other MMPs. Cell-specific stromelysin expression in human atherosclerotic plaques was studied by in situ hybridization and immunocytochemistry (Henney et al., 1991). Stromelysin mRNA transcripts were localized in isolated individual cells, mainly smooth muscle cells, in the plaque cap, intima, and adventitia, but not in the media, and in foam cells (Okamoto et al., 2001). The isolated expression of stromelysin-1 by smooth muscle cells may reflect local connective tissue remodeling associated with plaque growth and formation, whereas the more extensive expression observed in macrophages may be of greater pathological significance, contributing to the destabilization of the extracellular matrix and eventually to plaque rupture (Henney et al., 1991).

On the other hand, different studies suggest an athero-protective role by MMP-3. An investigation on the potential role of stromelysin-1 (MMP-3) in the development and progression of atherosclerotic lesions and aneurysm formation has been undertaken, employing mice with a deficiency of apolipoprotein E (ApoE(−/−):MMP-3(+/+)) or with a combined deficiency

of apoE and MMP-3 (ApoE(−/−):MMP-3(−/−)), which were fed with a cholesterol-rich diet (Silence et al., 2001). Atherosclerotic lesions throughout the thoracic aorta were significantly larger in ApoE(−/−):MMP-3(−/−) than in ApoE(−/−):MMP-3(+/+) mice and contained more fibrillar collagen. MMP-3 depletion was further associated to decreased incidence of abdominal aortas aneurysm. Histological analysis revealed enhanced accumulation of macrophages in atherosclerotic lesions of ApoE(−/−):MMP-3(+/+) mice in association to an increased expression of urokinase-type plasminogen activator (u-PA) and of MMP-3. These findings suggest that plasmin activates the pro-MMP-3 pool released by macrophages and MMP-3 activity may then contribute to a reduction of plaque size by degrading matrix components, but at the same time it can affect artery wall integrity by cleaving elastin (Silence et al., 2001).

A common polymorphism in the promoter sequence (the 5A/6A polymorphism) of the human stromelysin-1 gene associates the enzyme to an increased risk of coronary heart disease progression: *in vitro* experimental evidences indicated that these promoter variants can be recognized with different affinity by nuclear factors, leading to variable transcriptional efficiency of MMP-3 gene (Ye et al., 1996).

5.1.3.1.2. Aneurysm. MMP-3 overexpression has been detected in human abdominal aortic aneurysms (Knox et al., 1997; Thompson et al., 2002). In aneurysm a 40-fold increase in MMP-3 expression and a 200-fold increase in TIMP-3 concentration have been detected. The observation clearly suggests that upregulation of stromelysin-1 (MMP-3) and TIMP-3 may play a significant role in aneurysm genesis, but molecular mechanisms are far from being understood. It seems anyway plausible that an excessive production of stromelysin-1 in the atherosclerotic aorta weakens the aortic wall and brings about additional proteolysis by activating other latent, constitutively expressed metalloproteinases (Choke et al., 2005). The origin of this increased stromelysin-1 expression in certain individuals prone to aneurysm formation is not known, but a combination of genetic and environmental factors may contribute (Carrell et al., 2002).

5.1.3.2. Diseases of the nervous system. Parkinson's disease (PD) is determined by a degeneration of the dopamine-synthesizing cells of the mesostriatal–mesocortical neuronal pathway (Vernier et al., 2004). Dopamin (DA) ergic neurons are particularly vulnerable being exposed to toxic by-products of DA catabolism.

Experimental findings associate MMP-3 to DAergic neurons degeneration: in MMP-3 deficient mice, the number of DAergic neurons in the substantia nigra was considerably higher than that of wild type mice (WT). Cultured mesencephalic neurons from MMP-3 KO showed higher [(3)H]DA uptake capability associated with a greater number of tyrosine hydroxylase-immunopositive neurons and an increased length of average dendritic branches (Kim et al., 2010).

MMP-3 is induced and activated in dopaminergic (DA) cells upon stress conditions. This has important consequences since MMP-3 cleaves α-synuclein *in vitro* and *in vivo* and α-synuclein and MMP-3 co-localize in Lewy bodies (LB), as observed in post-mortem brains of PD patients (Choi et al., 2011). Evidence from *in vitro* investigations suggests that the MMP-3 mediated C-terminal truncation of α-synuclein releases fragments with the tendency to aggregate. These results strongly indicate that MMP-3 digestion of α-synuclein in DA neurons could play a pivotal role in the progression of PD (Choi et al., in press).

5.1.3.3. Diseases of joints and muscular system.

5.1.3.3.1. Joint diseases. Excessive degradation of the cartilage ECM is a feature of two major joint diseases, osteoarthritis (OA) and rheumatoid arthritis (RA). In OA, the most common form of arthritis, an increased production of proteinases by chondrocytes leads to the breakdown of cartilage, while synovitis occasionally develops in early phases of the disease. On the other hand, RA, the most refractory and destructive form of arthritis, is characterized primarily by prominent and persistent synovitis and an expansion of inflammation which leads to cartilage and bone destruction. Articular cartilage breakdown by proteinases follows three mechanisms: (i) destruction from the surface of the articular cartilage by proteinases of the synovial fluid; (ii) destruction through direct contact of proteolytic synovium and/or pannus tissue with the articular cartilage; and (iii) intrinsic destruction by proteinases derived from chondrocytes (Okada, 2009).

In human OA cartilage MMP-3, together with other MMPs, is up-regulated by chondrocytes (Okada, 2009). The pathogenic activity relies on the activation of pro-MMP-1, pro-MMP-7, pro-MMP-8, pro-MMP-9 and pro-MMP-13 and digestion of ECM components, such as aggrecan and type IX collagen (Okada, 2009).

However, in an OA model of MMP-3 deficient mice, accelerated cartilage destruction occurred to a greater extent with respect to wild-type mice (Clements et al., 2003; Mudgett et al., 1998). The molecular mechanisms underlying MMP-3 pathogenic activity are not clear, since aggrecan cleavage could contribute to the generation of remnant epitopes (VDIPEN) (Mudgett et al., 1998; Sandy et al., 1991; Van Meurs et al., 1999).

Synovial fluid from RA patients shows aberrant concentration of MMP-3 and the MMP-3/TIMP ratio is also unbalanced (Okada, 2009; Yoshihara et al., 2000). MMP-3 is further detectable in serum samples from RA patients and is clinically accepted as a biomarker for RA diagnosis, for joint destruction prognosis and for RA treatment monitoring (Yoshihara et al., 2000).

5.1.3.4. Wound healing. Wound tissue in humans overexpresses multiple MMPs including MMP-3. This MMP may play a role in the complex process of wound healing that includes acute inflammatory reaction, regeneration of parenchyma cells, cell migration and proliferation, angiogenesis, contraction and tissue remodeling (Gill and Parks, 2008). As a matter of the fact MMP-3 knock out mice show impaired excisional reepithelization (Madlener et al., 1998).

5.1.3.5. Diseases of the respiratory system. Acute respiratory distress syndrome (ARDS) is induced by an increase in the alveolar-capillary barrier permeability and the subsequent impairment of gas-exchange. The disease can progress to chronic fibrotic lung injury (Ware and Matthay, 2000). Since the alveolar basement membrane is primarily composed of type IV collagen, MMP-3 is likely involved in the extensive ECM remodeling observed in ARDS.

In order to determine the involvement of individual MMPs in the development of lung injury, MMP-3 and MMP-9 knockout mice and wild type mice were acutely injured with immunoglobulin G immune complexes and the intensity of the lung injury compared. In wild type mice upregulation of gelatinase B and stromelysin-1 was observed in the injured lungs. As a consequence, the MMP-3 and MMP-9 deficient mice had less severe lung injury, suggesting that both MMPs are involved in the lung injury pathogenesis. Nonetheless, the activity of MMP-3 and MMP-9 differs for some still obscure molecular aspects that lead to a reduced recruitment of neutrophils exclusively in the MMP-3 deficient mice (Warner et al., 2001a).

5.2. MMP-10

Stromelysin-2 or MMP-10 has been firstly identified in mouse and later in humans (Muller et al., 1988). The structure displays a 82% sequence homology with MMP-3 and it is secreted as a 53-kDa proenzyme (Sirum and Brinckerhoff, 1989). No structural details are available, even though it is postulated that it consists on a pro-domain, a catalytic domain and a hemopexin-like domain.

5.2.1. Biological aspects

MMP-10 digests a number of ECM molecules and participates in pro-MMPs activation, although the catalytic activity toward type IV and type V collagens is quite weak in comparison to that of the related MMP-3 (Murphy et al., 1992; Nagase et al., 2006). Inflammatory stimuli induce its release by synovial fibroblasts, whereas treatment with pro-catabolic elements stimulates expression by articular chondrocytes (Barksby et al., 2006). The physiopathological relevance of MMP-10 has been associated to vascular development, atherothrombosis (Montero et al., 2006; Rodriguez et al., 2008), skin wound healing and cell migration, since it is primarily found at the front of the migrating epithelial 'tongue' (Madlener and Werner, 1997) and it has been observed in migrating enterocytes in inflammatory bowel disease (Salmela et al., 2004; Vaalamo et al., 1998). MMP-10 is *in vitro* capable of processing laminin-5, which should be an additional mechanism through which the enzyme assists cell migration (Krampert et al., 2004). MMP-10 activity at sites of developing bones resorption has been demonstrated by histochemistry and by in situ casein zymography: this observation suggests a role in remodeling events occurring during ossification (Bord et al., 1998).

Elevated concentrations of the enzyme have been further detected in some human tumors in association to aggressiveness: a prognostic relevance for its quantification has also been proposed (Gill et al., 2004).

MMP-10 up-regulation in early phases of skin tumor growth is stimulated by TGF-β and EGF: the resulting high collagenolytic activity correlates with invasiveness (Wilkins-Port et al., 2009). Increased levels of MMP-10 have been also found in lung cancer (Frederick et al., 2008).

5.3. MMP-11

5.3.1. Structural peculiarities and biological aspects

Stromelysin-3 (MMP-11) together with matrilysin (MMP-7) and metalloelastase (MMP-12) is often included in the stromelysin subgroup, although they are structurally less closely related to MMP–3 and MMP-10. MMP-11 was first identified in 1990 in a cDNA library extracted from human breast cancer cells and, though sharing with other MMPs the classic domain composition (see Fig. 1), it deserves some additional comment (Basset et al., 1990). Thus, the 56-kDa pro-MMP-11 is activated in the intracellular compartment by furin and Golgi associated furin-like proteases (Pei and Weiss, 1995) or by paired basic amino acid cleaving enzyme-4 (PACE-4) (Bassi et al., 2000); it is then secreted as a 47-kDa active protease. This intracellular activation was shown to be dependent on a unique furin recognition motif RNRQRKR located at the junction between the pro- and the catalytic domain (Pei and Weiss, 1995). Furthermore, the relatively narrow and peculiar substrate specificity observed for MMP-11 probably stems from a mutation that occurs in the highly conserved methionine turn; thus, where all other MMPs contain an MxP sequence in the Met turn, in MMP-11 the proline is replaced by an alanine. This substitution has a profound effect on the structure of the S1′ selectivity pocket leading to greatly changed substrate specificity (Noel et al., 1995).

The 3D-structure of the catalytic domain of mouse MMP-11 in a complex with a phosphinic peptide inhibitor has been solved (Gall et al., 2001). The S1′ cavity appears as a long channel able to accommodate side chains longer than those present in natural amino acids. This observation fits perfectly with the ability of MMP-11 to cleave with high efficiency substrates containing in their P1′ position unusual amino acid with very long side chains (Gall et al., 2001).

Beside the pro- and mature forms of human MMP-11, several other forms of MMP-11 have been also reported. In an *in vitro* stromal/epithelial cell co-culture model, a 35-kDa protein lacking enzymatic activity was found to be produced by normal pulmonary fibroblasts (Mari et al., 1998). Two forms of 35 and 28 kDa were also observed in human atherosclerotic tissues (Schönbeck et al., 1999).

Matrix metalloproteinase-11 is widely expressed in both normal and pathological remodeling processes, such as embryonic implantation (Lefebvre et al., 1995), placentation, interdigitation, osteogenesis, spinal cord morphogenesis, epithelium

growth, larval tissue resorption (Berry et al., 1998), morphogenesis, menstrual breakdown, post-partum involution, ovulation (Hägglund et al., 1999), post-weaning involution, inflammation, wound healing (Wolf et al., 1992), benign tumor proliferation, and tissue invasion (Rio, 2005; Rouyer et al., 1994; Thewes et al., 1999). In both normal and pathological conditions, MMP-11 is mostly secreted by fibroblasts.

MMP–11 expression is maximal in uterus, placenta, and involuting mammary gland (Visse and Nagase, 2003) and is negatively modulated by progesterone treatment, at least in isolated stromal cells *in vitro* (Osteen et al., 2003). Timing of MMP-11 expression in tissue remodeling is well defined; thus, it is induced at an advanced stage, suggesting that it does not take part into the basement membrane breakdown at early phases, but rather in downstream events when the connective compartment remodeling is suitable for epithelial cells incoming and tissue regeneration. Intriguingly, MMP-11 exhibits an anti-apoptotic function, an unusual feature for a MMP.

Despite the identification of possible *in vitro* substrates for MMP-11 (Matziari et al., 2007), there is lack of convincing evidences that support their *in vivo* cleavage (see Table 3). Identification of the *in vivo* physiological substrates of MMP-11, as well as the development of potent and specific inhibitors for this particular MMP family member would certainly provide valuable information about the physio-pathological roles of MMP-11.

However, several putative substrates mainly include protease inhibitors, such as α_1 proteinase inhibitor and α_2 macroglobulin (see Table 3). Further, MMP-11 has a weak caseinolytic activity and it has been shown to cleave insulin-like growth factor-binding protein-1 (IGF-BP-1) in a carcinoma cell line (Pei et al., 1994). Recent research has demonstrated that, although MMP-11 does not cleave many ECM proteins, degradation of type VI collagen could be physiologically related to adipogenesis inhibition (Motrescu et al., 2008).

5.3.2. Neoplastic diseases

It has been shown that MMP-11, among other MMPs, interacts with stromal components that contribute to malignancy in the early and late stages of human tumors progression (Basset et al., 1997; Coussens and Werb, 1996).

Clinical investigations show that an overexpression of MMP-11 is correlated to a lower survival rate in patients with breast, head, neck or colon cancer (Noel et al., 2000; Muller et al., 1993; Porte et al., 1995). Interestingly, as observed for MMP-9, MMP-11 is not exclusively released by malignant cells, but also by the surrounding mesenchymal cells (Thewes et al., 1999).

In carcinomas, both stromelysin-3 RNA and protein have been specifically detected in fibroblasts surrounding cancer cells. In agreement with this observation, carcinomas with the tendency to progress without inducing a prominent stroma are also those which usually do not express the ST3 gene. ST3 gene expression was also observed in non-invasive carcinomas of the breast, uterus cervix and bladder, where the probability of detecting ST3 RNA and protein positively correlated with invasiveness. Taken all together, these observations further support the hypothesis that ST3 may contribute to tissue-remodeling processes associated with carcinoma progression (Rouyer et al., 1994).

In addition, even though MMP-11 is essential for tumor development, it does not share any function with the other MMPs involved in malignant events. MMP-11 is not able to degrade any major ECM component, it does not modify epithelial cell proliferation or motility, and it does not appear to be a pro-angiogenic or a pro-apoptotic factor (Mari et al., 1998). MMP-11 may either control proteinase activity, survival factor bioavailability, or inflammatory reactions to favor cell survival in an environment initially not adequate for epithelial cell growth. Nonetheless, in MMP-11-deficient mice tumors exhibit higher levels of apoptosis, and implantation of experimental tumors is lower in MMP-11 null mice (Boulay et al., 2001). Therefore, it may be hypothesized that, in addition to proteinases, proteinase inhibitors, and insulin-like growth factor binding proteins (IGF-BPs), MMP-11 may hydrolyze yet uncharacterized specific substrates, and therefore, it could exerts the pathogenic activity through different mechanisms (Rio, 2002).

6. Matrilysins

Matrylisin family includes two enzymes: MMP-7 (also known as Pump-1) and MMP-26 (De Coignac et al., 2000; Quantin et al., 1989). These enzymes display significant sequence similarities with collagenases and stromelysins, even though the domain composition lacks the hemopexin-like domain (see Fig. 1) (Uria and Lopez-Otin, 2000).

A vast deal of knowledge defines a relevant physiopathological role for MMP-7, whereas biological aspects of MMP-26 should be restricted to extracellular matrix turn-over and remodeling in a limited cohort of tissues both in physiological and pathological conditions (Park et al., 2000; Marchenko et al., 2001).

MMP-7 is widely expressed in human tissues and mainly in the epithelial-derived ones. The catalytic activity drives proteolytical breakdown of several extracellular matrix molecules (see Table 3), such as cytokines, growth factors and receptors (Li et al., 2002). MMP-7 biological functions mainly concerns ECM remodeling and immune system modulation. Therefore a un-balanced activity of the enzyme is associated to many human pathological conditions, mostly including cancer and cardiovascular, respiratory and neuronal diseases. In particular, MMP-7 affects almost all phases of tumorigenesis through molecular mechanisms that, at least partially, overlap with that of other soluble MMPs, as widely discussed in the present review (Adachi et al., 1999; Li et al., 2002; Tan et al., 2005). This evidence suggests the existence of not yet identified interactions with other factors that contribute in defining a complex MMP-7 biology.

6.1. MMP-7

6.1.1. Biological aspects

MMP-7 (generally called as matrilysin) was originally described as Pump-1 (putative uterine metalloprotease-1) in 1988 (Muller et al., 1988). The MMP-7 cDNA codes for a protein with significant sequence similarity to collagenases and stromelysins; however, it lacks the hemopexin-like domain (see Fig. 1). Pump-1 expressing COS cells secrete a 28 kDa pro-protein; activation by organomercurials agents, leads to two active Pump-1 species of 21 and 19 kDa (Imai et al., 1995).

MMP-7 has been shown to be constitutively expressed in the ductal and glandular epithelium of normal mammary, peribronchial and parotid glands: it is further represented in liver, pancreas, prostate, and airways (Harrell et al., 2005). As other soluble MMPs, activity of MMP-7 is tightly regulated: in particular GAGs have been reported to be key modulators of MMP-7 autolytic activation, but several other not identified macromolecules should contribute (Ra et al., 2009).

Active MMP-7 cleaves ECM and basement membrane proteins, such as fibronectin, collagen IV, laminin, and particularly elastin, entactin, and cartilage proteoglycan aggregates (see Table 3); in addition, it degrades casein, gelatin, collagen of I, III and V, and can activate collagenases (Quantin et al., 1989). Furthermore, MMP-7 appears to mediate the proteolytic processing of other molecules, playing an important role in ectodomain shedding of cell-surface molecules, such as tumor necrosis factor-α (TNF-α) precursor, Fas ligand (FasL), heparin binding epidermal growth factor (HB-EGF), E-cadherin, and β4-integrin (Ii et al., 2006; Wilson and Matrisian, 1996).

Distribution of MMP-7 in the glandular epithelium is of particular biological relevance. The release in either the apical and/or the basolateral side is linked to different processes: apical MMP-7 activity is associated to proliferation induction (Harrell et al., 2005).

MMP-7 has also an important role in the homeostasis of innate immunity in lungs and intestine, where it proteolytically activates anti-bacterial peptides (*e.g.*, pro-defensins) and mediates release of TNF-α by macrophages (Burke, 2004). Consistently with this role in innate immunity, MMP-7 is induced by microbial products and also by hypoxia (Burke, 2004; Wilson et al., 1999).

The influx of inflammatory cells to sites of injury is largely directed by signals from the epithelium, but how these cells form chemotactic gradients is not known. In MMP-7-null mice, neutrophils remained confined in the interstitium of injured lungs and do not advance into the alveolar space. Impaired transepithelial migration is accompanied by a lack of both shed syndecan-1, a heparan sulfate proteoglycan, and KC, a CXC chemokine, in the alveolar fluid. *In vitro*, MMP-7 cleaves syndecan-1 from the surface of cells; therefore, the matrilysin-mediated shedding of syndecan-1/KC complexes from the mucosal surface addresses neutrophil influx toward sites of injury (Li et al., 2002). Furthermore, since MMP-7 mediates shedding of E-cadherin ectodomain from injured lung epithelium both *in vitro* and *in vivo*, transfection of activated matrilysin in alveolar-like epithelial cells results in shedding of E-cadherin and accelerated cell migration (McGuire et al., 2003).

6.1.2. Neoplastic diseases

6.1.2.1. Epidemiological aspects. The role of MMP-7 in cancer has been well described. The MMP-7 source substantially differs from that of other MMPs, since it is almost exclusively released by cancerous cells (Ii et al., 2006). As with other MMPs, MMP-7 has been identified in a wide range of tumors, and correlates with tumor aggressiveness.

MMP-7 is overexpressed in a variety of epithelial tumors, mesenchymal tumors and in invasive cancers of the digestive tract. Matrilysin expression in carcinoma cells at the invasive front was immuno-histochemically detected in patients with esophageal squamous cell carcinoma (SCC) and was associated to an advanced tumor stage (Yamamoto et al., 1999).

Matrilysin promotes *in vitro* invasiveness of cancer cells of esophagus, stomach, colon, liver and pancreas (Adachi et al., 1999, 2001; Jones et al., 2004; Tan et al., 2005; Yamamoto et al., 1999; Yamamoto et al., 2001).

MMP-7 is particularly overexpressed in early undifferentiated gastric carcinoma where it is considered a predictive factors for invasiveness and metastatization: hence, MMP-7 quantification could be of prognostic relevance (Adachi et al., 2001, 1999; Aihara et al., 2005).

MMP-7 shows a peculiar distribution in human pancreatic adenocarcinomas; its expression is usually compartmentalized at the leading edge of invading cells (Bolon et al., 1997).

In all these cases, a matrilysin-positive carcinoma predicts a significantly shorter survival, since it correlates with primary tumor growth, regional lymph nodes colonization and distant metastasis (Jones et al., 2004; Yamamoto et al., 2001).

Moreover, an interesting observation is that the functional polymorphism in the matrilysin promoter (−181A/G) has been shown to increase susceptibility to esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma, and non-small-cell lung carcinoma (Zhang et al., 2005a).

6.1.2.2. Tumorigenesis. Modulation of soluble molecules availability is a major mechanism through which MMP-7 promotes early tumorigenesis. MMP-7 sheds the ectodomain of HB-EGF precursor (pro-HB-EGF) to yield mature HB-EGF, which, upon bindings to the ErbB4 receptor promotes cellular proliferation and inhibits apoptosis (Yu et al., 2002).

Furthermore, recent epidemiologic studies have focused on a correlation between high levels of circulating insulin-like growth factor (IGF-1) and low levels of IGF binding protein 3 (IGFBP-3) and the consequent risk of developing colon, breast, prostate, and lung cancer. MMP-7 cleaves IGFBP-3, hence playing a crucial role in modulating IGF-I bioavailability. This mechanism may promote tumorigenesis of MMP-7-producing IGF-I-receptor-expressing tumors in both primary and

secondary sites (Miyamoto et al., 2004). ADAM28, a member of the disintegrin and metalloproteinase (ADAM) family (see Section 1.1.2), is also a substrate of MMP-7 and it has been reported that the secreted form of ADAM28, once activated by MMP-7, also digests IGFBP-3 even when complexed with IGF-I or IGF-II (Mochizuki et al., 2004).

MMP-7 further contributes to invasiveness by cleaving ECM substrates and by increasing the activation rate of pro-MMP-2 and pro-MMP-9 (Wang et al., 2005, 2006). The function of adhesiveness-related molecules can be altered by cleavage and subsequent release of their ectodomains. The E-cadherin ectodomain is constitutively shed from the surface of MCF-7 and MDCK cells in culture. Matrilysin cleaves E-cadherin (E-CAD) releasing a 80 kDa soluble E-cadherin fragment (sE-CAD) into the medium. The soluble E-cadherin fragment then inhibits E-cadherin functions in a paracrine way, impairing adhesiveness and promoting tumor cells migration and invasion (Noe et al., 2001).

Another interesting MMP-7-linked pathological phenomenon in advanced prostate tumors is the cancer-induced bone resorption: MMP-7 is produced by osteoclasts at the tumor-bone interface where it cleaves the receptor activator of nuclear factor kappa-B ligand (RANKL) whose soluble form promotes osteoclast activation. MMP-7-deficient mice demonstrated reduced prostate tumor-induced osteolysis and RANKL processing (Lynch et al., 2005).

A relevant mechanism through which MMP-7 affects tumor growth is the modulation of apoptosis. MMP-7 processes the recombinant and the cell-associated Fas ligand (FasL) to soluble FasL which induces apoptosis in epithelial cells (O'Connell et al., 1999; Powell et al., 1999). However, there are contradictory evidences about the association of MMP-7 and Fas-mediated apoptosis which reflect the presence of different cleavage sites which are linked to variable biological effects (Hohlbaum et al., 2000; Schneider et al., 1998; Tanaka et al., 1998; Vargo-Gogola et al., 2002).

6.1.2.3. Angiogenesis. Angiogenesis is a process essential for tumor progression. MMP-7 mRNA and protein are found in vascular endothelial cells in close apposition to matrilysin-positive tumor cells (Nagashima et al., 1997). Furthermore, MMP-7 may accelerate the proliferation of human umbilical vein endothelial cells in a dose-dependent manner *in vitro* (Huo et al., 2002). Moreover, in a murine experimental model, matrilysin-induced angiogenesis was inhibited by the administration of a matrilysin-specific antisense oligonucleotide (Nishizuka et al., 2001).

On the other hand, there is evidence that MMP-7 activity further produces anti-angiogenic factors. In this respect, MMP-7 cleaves human plasminogen releasing an angiostatin-like fragment (Patterson and Sang, 1997). In addition, endostatin, an angiogenesis inhibitor, and neostatin-7, the C-terminal 28-kDa endostatin-spanning proteolytic fragment (Chang et al., 2005), are generated from collagen type XVIII by matrilysin *in vitro* (Heljasvaara et al., 2005) and *in vivo* (Lin et al., 2001). Matrilysin further cleaves a matrix-bound isoform of vascular endothelial growth factor (VEGF), releasing it from its natural reservoir (Lee et al., 2005).

6.1.3. Non-neoplastic diseases

6.1.3.1. Diseases of the cardiovascular system. MMP-7 deletion has been shown to improve survival after myocardial infarction (MI) (Chiao et al., 2010). In particular, MMP-7 is involved in N-cadherin cleavage and in vascular smooth muscle cell (VSMC) apoptosis, leading to fibrous cap thickness and to plaque instability (Williams et al., 2010). Nonetheless, MMP-7 is increased in patients with stable and unstable coronary artery disease (Nilsson et al., 2006).

Furthermore, MMP-7 modulates the transcription of ADAM12, the main protease implicated in cardiac hypertension and hypertrophy (Wang et al., 2009) (see Section 1.1.2): hence, knockdown of MMP-7 results in an attenuation of these pathological conditions.

MMP-7 involvement in hypertension is further mediated by signaling of adrenoreceptors and angiotensin receptors that lead to MMP-7 activation, which, in turn, sheds EGFR ligands (such as HB-EGF), thereby promoting EGFR-dependent vasoconstriction (Hao et al., 2004).

MMP-7 is also associated to histopathological alterations in human aneurysms and dissections of the thoracic ascending aorta; immunohistochemical investigations reveal MMP-7 over-expression in areas of mucoid degeneration within the medial layer. This pathological process correlates with areas of cell disappearance and disruption of extracellular matrix elastic and collagen fibers (Borges et al., 2009).

6.1.3.2. Diseases of the nervous system. In multiple sclerosis (MS) where transmigration of pathogenic T cells across the blood–brain barrier (BBB) is facilitated by the expression of cell adhesion molecules and proteinases that degrade the ECM (Pachter et al., 2003), MMP-7 contributes by cleaving proteins that are essential for blood–brain barrier integrity and immune suppression. Thus, elevated levels of MMP-7 have been reported in human MS patients and in a delayed-type hypersensitivity model for MS (Anthony et al., 1998). MMP-7 may facilitate immune cell access or re-stimulation in perivascular areas, which are critical events in experimental autoimmune encephalomyelitis and multiple sclerosis, and provide a new therapeutic target to treat this disorder (Buhler et al., 2009).

Pathological evidence suggests that alterations of the blood–brain barrier (BBB) may occur in association with human immunodeficiency virus (HIV) dementia (HIVD). Also in this pathological process circulating levels of MMP-7 have been found to correlate with the severity of brain injury in infected subjects (Ragin et al., 2009). In this case, the cerebrospinal fluid (CSF) of patients with HIVD shows increased levels of pro-MMP-7, suggesting that elevated CSF levels of MMP-7 may reflect immune activation within the central nervous system (Conant et al., 1999). In general terms, CSF levels of MMP-7 are often significantly correlated with neural injury in multiple brain regions (Ragin et al., 2011).

Interestingly, it has been reported that MMP-7 activity is linked to disruption of mature synapses in hippocampus: therefore, MMP-7 could be an effector of neuronal loss in each pathological conditions which determine its up-regulation (Bilousova et al., 2006).

6.1.3.3. Diseases of joints and muscular system. Pro-MMP-7 is overexpressed in osteoarthritic (OA) articular cartilage (Okada, 2009). A recent study on human OA cartilage shows that pro-MMP-7 is activated through the interaction with tetraspanin CD151, leading to cartilage destruction and/or chondrocyte cloning (Fujita et al., 2006).

Dupuytren's disease (DD) is a common fibrotic condition of the palmar fascia, leading to the deposition of collagen-rich cords and finger contractions. The expression of MMP-7 is increased in the DD nodule and remains equally expressed in the DD cord (Johnston et al., 2007).

In inflammatory myopathies a MMP-7 over-expression has been demonstrated in areas with high levels of expression for the major-histocompatibility-complex class I (MHC-I) in atrophic and invaded myofibers as well as in CD-8 positive lymphocytes and macrophages (Schoser et al., 2002).

6.1.3.4. Diseases of the respiratory system. Idiopathic pulmonary fibrosis (IPF) is a chronic, usually fatal, disorder characterized by excessive matrix degradation and interstitial and intraalveolar fibrosis leading to dyspnea, impaired oxygen transfer and alveolar collapse (Katzenstein and Myers, 1998). MMP-7 is identified as a potential target for therapy of patients with IPF, since MMP-7 gene is up-regulated, as from micro-array gene analyses (Cosgrove et al., 2002). Furthermore, matrilysin knockout mice were dramatically protected from pulmonary fibrosis in response to intratracheal bleomycin (Zuo et al., 2002).

MMP-7 may also be a modulator of pediatric lung disease; thus, MMP-7 levels are elevated in endotracheal tube aspirates from patients with different respiratory syndromes (ETAs) (Winkler et al., 2003).

A putative involvement of MMP-7 in tuberculosis has been demonstrated as well. Thus, MMP-7 (and MMP-1, see Section 3.1.3.2) gene expression and secretion are potently upregulated by *M. tuberculosis*, and no increase in tissue inhibitor of metalloproteinase expression occurs to oppose their activity. These two MMP can then degrade the major lung ECM components, such as type I collagen and elastin (Elkington et al., 2005).

6.2. MMP-26

6.2.1. Structure

MMP-26 (matrilysin-2, endometase) has been identified in an endometrial tumor (De Coignac et al., 2000). The isolated cDNA encodes a 261 amino acids polypeptide, the smallest MMP identified to date, which contains several structural features of MMPs including the signal sequence, the prodomain involved in enzyme latency, and the catalytic domain with the zinc-binding site (see Fig. 1). However, it lacks the hinge region and the hemopexin-like domain (Uria and Lopez-Otin, 2000). The amino acid sequence of matrilysin-2 also contains a threonine residue adjacent to the Zn-binding site that has been defined as a specific feature of MMP-26 (Uria and Lopez-Otin, 2000). MMP-26 is unique among MMPs, since it is the only known MMP (up to now), which does not have a functional cysteine switch mechanism to maintain the pro-enzyme in its latent conformation. Loss of the cysteine switch is attributed to the presence of a histidine residue N-terminal to the cysteine, a feature that is exclusively observed in MMP-26 (Marchenko and Strongin, 2001; Marchenko et al., 2001).

6.2.2. Biological aspects

MMP-26 hydrolyzes type IV collagen, fibronectin, fibrinogen, and gelatin, but it cannot degrade laminin and elastin (Park et al., 2000); in addition, MMP-26 is able to activate progelatinase B (Uria and Lopez-Otin, 2000). Expression analyses revealed that matrilysin-2 is detected in placenta, in endometrium and uterus, but is widely expressed in a wide range of malignant tumors *in vivo* and *in vitro* (Marchenko et al., 2001; Uria and Lopez-Otin, 2000). These data together with the broad spectrum of proteolytic activity, suggest that matrilysin-2 may play a role in tissue-remodeling events associated to tumor progression.

7. Membrane type-MMPs

The first human MT-MMP (MT1-MMP/MMP-14) (Sato et al., 1994) was cloned by a reverse transcriptase-polymerase chain reaction (RT-PCR) from the RNA of placental tissue. Later on, additional studies, focused on MT-MMPs, led to the discovery of five more members of this family, namely MT2-MMP (MMP-15), MT3-MMP (MMP-16), MT5-MMP (MMP-24) and two additional members, MT4-MMP (MMP-17) and MT6-MMP (MMP-25), which are anchored to the plasma membrane via a glycosylphosphatidylinositol (GPI) domain (Zucker et al., 2003).

7.1. Structure and activation of MT-MMPs

The MT-MMPs contain all protein domains characteristic of MMPs from the N-terminal to the C-terminal extremities, that is a signal peptide, a propeptide, a catalytic domain with the zinc binding site, a hinge region and a C-terminal hemopexin

domain (Sternlicht and Werb, 2001). However, MT-MMPs differ from the other MMPs by the presence of a C-terminal domain rich in hydrophobic residues and involved in their association with the cell membrane (see Fig. 1).

According to the structure of this C-terminal extension, MT-MMPs can be classified into two sub-groups (see Fig. 1 and Table 2): (a) type I transmembrane proteins including MT1-, MT2-, MT3- and MT5-MMP characterized by a long hydrophobic sequence followed by a short cytoplasmic tail and (b) glycosylphosphatidylinositol (GPI)-type MT-MMPs (MT4- and MT6-MMP) containing a short hydrophobic signal anchoring to GPI. This sequence is not followed by a cytoplasmic tail. The cytoplasmic tail of type I transmembrane MT-MMPs is likely participating in numerous cellular events, such as cell signaling, sub-cellular localization, MT-MMP trafficking and dimerization (Gingras et al., 2001; Itoh et al., 2001; Rozanov et al., 2001; Sounni et al., 2004; Uekita et al., 2004; Wang et al., 2004a).

The prodomain of MT-MMPs contains a conserved motif, Tyr42- Gly43-Tyr44-Leu45 that acts as an intramolecular chaperone. It appears essential for adequate protease folding and enzymatic activities (*e.g.*, proMMP-2 activation, substrate degradation and TIMP-2 binding) (Pavlaki et al., 2002). A basic tetrapeptidic sequence Arg108-Arg109-Lys110-Arg111 is inserted between the propeptide and the catalytic domain (see Fig. 1). This furin recognition motif is cleaved by proprotein convertases in the trans Golgi network during the trafficking of MT-MMPs from the endoplasmic reticulum to the plasma membrane (Hotary et al., 2000; Pei and Weiss, 1996; Rozanov et al., 2001; Yana and Weiss, 2000; Zucker et al., 2003). However, the activation of MT-MMPs by a furin-independent alternative pathway has been reported only in some types of cells. This alternative activation pathway depends on an autoproteolytic activation or on the action of non-furin proprotein convertases, or else on other proteases located at the plasma membrane (Cao et al., 1996; Rozanov et al., 2001; Sato et al., 1996; Yana and Seiki, 2002). In addition, an extracellular activation of proMT1-MMP by plasmin has been reported (Okumura et al., 1997). The propeptide is followed by the catalytic domain that contains the consensus zinc-binding motif HEBXHXBGBXH, where X is a variable residue and B is a bulky hydrophobic amino acid. The catalytic domain of MT-MMPs contains a characteristic 8-amino acid insertion between stands *b*II and *b*III named MT-loop. The 3D structure of the complex between the catalytic domain of MT1-MMP and TIMP-2 shows that the MT-loop generates a pocket in the MMP catalytic domain fold that interacts with the AB-loop of TIMP-2 (Fernandez-Catalan et al., 1998). The 3D structure of the complex between the MT3-MMP catalytic domain and a synthetic MMP inhibitor (namely batimastat) reveals similar features, but it shows unique properties, such as a modified MT-specific loop and a closed S1′ pocket, which may be important for the substrate specificity and the efficient proMMP-2 activation (Lang et al., 2004). Although mutations or deletion of MT-loop of MT1-MMP do not affect its catalytic activity towards synthetic substrates, it impairs the enzymatic activation of proMMP-2 (English et al., 2001). Consistently, differences in the MT-loop structure between MT-MMPs are translated in their ability to activate proMMP-2. For example, MT4-MMP and MT6-MMP, which are lacking the MT-loop, are either unable or inefficient in activating proMMP-2 (English et al., 2001). Furthermore, human MT2-MMP is somewhat defective in cell-mediated activation of proMMP-2, whereas mouse MT2-MMP is very efficient in this activity. The replacement of two residues (Pro183 and Glu185) in the MT-loop of the human enzyme by the corresponding ones (Ser183 and Asp185) of mouse MT2-MMP endowed the human enzyme with the capacity of an efficient activation of proMMP-2 (Miyamori et al., 2000).

Finally, MT-MMPs contain a C-terminal hemopexin-like domain that confers some degree of substrate specificity (Cataldo et al., 2003; Egeblad and Werb, 2002; Sounni et al., 2003).

7.2. MT1-MMP (MMP-14)

MMP-14, also referred to as MT1-MMP, which is the prototype membrane type MT-MMP, has been studied in the framework of renal development. This enzyme has intrinsic proteolytic capabilities and can also induce its effects by activating MMP-2 and MMP-13 (Itoh and Seiki, 2006).

7.2.1. Biological features

Although several data defined a role for MT1-MMP in renal development and suggested that its role was the cleavage ECM components in renal basal membranes (BM)s, the mechanisms by which the renal abnormalities occur is unclear. Pericellular cleavage of multiple BM components by MT1-MMP is also important for cell proliferation and migration and plays a critical role in normal kidney development (Riggins et al., 2010).

Numerous ECM components, including collagens I, II and III, fibronectin, vitronectin, laminins 111 and 332, fibrin and proteoglycans are substrates for MT1-MMP (Seiki, 2003). In addition, MT1-MMP can cleave other cell surface proteins, such as CD44 (Kajita et al., 2001), transglutaminase (Belkin et al., 2001), low-density lipoprotein receptor related protein (Rozanov et al., 2004), the integrin αv subunit (Baciu et al., 2003; Deryugina et al., 2002a), and syndecan-1 (Endo et al., 2003). These highly divergent substrates (see Table 3) for MT1-MMP make this enzyme a critical regulator of the pericellular environment and allow it to regulate multiple cellular functions. The physiological importance of MT1-MMP was demonstrated by the multiple abnormalities observed in the MT1-MMP null mice, which die shortly after birth with severe musculoskeletal abnormalities characterized by decreased chondrocyte proliferation and decreased collagenolytic activity (Holmbeck et al., 1999; Zhou et al., 2000). More recent investigations on the musculoskeletal system have shown that reconstitution of MT1-MMP activity in the type II collagen expressing cells of the skeleton in MT1-MMP null mice rescues the diminished chondrocyte proliferation in these mice and ameliorates the severe skeletal dysplasia by enhancing bone formation (Szabova et al., 2009). In addition, these null mice have submandibular gland branching morphogenesis abnormalities (Oblander et al., 2005) as well as defects in lung development (Atkinson et al., 2005; Oblander et al., 2005), angiogenesis (Zhou et al., 2000)

and myeloid cell fusion (Guadamillas et al., 2010). These deficiencies are ascribed to a lack of MT1-MMP catalytic ability, alterations in downstream pro-MMP-2 activation and alterations in cell functions regulated by the MT1-MMP cytoplasmic tail.

7.2.2. Neoplastic diseases

7.2.2.1. Epidemiologic aspects. Numerous studies have reported the expression of MT-MMPs, soluble MMPs activated through a MT-MMP-dependent process and their tissue inhibitors in various tumor types (Polette and Birembaut, 1998; Sato and Seiki, 1996; Seiki, 1999). MT1-MMP is mainly believed to be important for tumor invasion and metastasis. Its over-expression strongly promotes cellular invasion *in vitro* (Gilles et al., 2001; Hotary et al., 2000; Kajita et al., 2001; Sato et al., 1994; Seiki, 2003; Sounni et al., 2002a,b) and experimental metastasis (Habelhah et al., 1999; Shimada et al., 2000; Tsunezuka et al., 1996).

Clinical studies revealed that the expression of MT1-MMP and MMP-2 is associated with poor prognosis in patients with advanced neuroblastoma (Sakakibara et al., 1999), small cell lung cancer (SCLC) (Michael et al., 1999), tongue squamous cell carcinoma (Yoshizaki et al., 2001), head and neck carcinoma (Yoshizaki et al., 1997), bladder cancer (Kanayama et al., 1998), and ovarian cancer (Davidson et al., 2002). Low expression levels of MT1-MMP are considered as favorable survival markers in advanced colorectal carcinoma (Bendardaf et al., 2003). MT1-MMP has been detected in tumor cells and adjacent stromal cells in a variety of human tumors, including breast, cervical, colon, bladder, gastric, glioma, pancreatic, liver, ovarian, prostate and thyroid cancer (Nuttall et al., 2003; Zucker et al., 2003). Studies based on in situ hybridization analysis in lung (Polette et al., 1996) and breast carcinomas (Bisson et al., 2003; Okada et al., 1995) revealed that MT1-MMP mRNA is expressed by stromal cells surrounding tumor cells. Other studies have shown the expression of MT1-MMP in cancer cells rather than stromal cells of human thyroid, brain, head and neck cancer (Zucker et al., 2003).

There is clear evidence that MT1-MMP and MMP-2 are involved at different stages of tumor progression from the initial tumor development, growth and angiogenesis to invasion, metastasis and growth at secondary sites (Seiki et al., 2003; Sounni et al., 2003; Zucker et al., 2003). Many of these insights came from experiments with genetically modified animals or cells (see Table 6). For instances, MMP-14 over-expression in the mammary gland leads to the formation of a mammary carcinoma (Ha et al., 2001). Other studies in experimental cancer models demonstrated that human breast, melanoma and glioma cells transfected with MT1-MMP enhanced MMP-2 activation, invasion and *in vivo* tumor growth (Baramova et al., 1997; Deryugina et al., 2002b; Hotary et al., 2003; Iida et al., 2004; Itoh et al., 1998; Sounni et al., 2002a). It should be pointed out that MT1-MMP over-expression in human breast cancer can induce tumor growth, whereas the over-expression of MMP-2 alone in the absence of MT1-MMP does not promote tumor development in nude mice (Sounni et al., 2002b; Tester et al., 2004). These observations suggest that MT1-MMP may contribute to the neoplastic progression independently of its capacity to activate pro-MMP-2. MT1-MMP is viewed as a tumor-derived growth factor that regulates proliferation by controlling cell geometry within the three-dimensional extracellular matrix. In fact, MMP-14 pericellular proteolysis confers a three-dimensional collagen matrix specific growth advantage. When MT1-MMP transfected cells are grown in gels composed of a mutant collagen that cannot be degraded, proliferation is blocked (Hotary et al., 2003).

MT1-MMP expression profile is likely to vary from one tumor type to another. Gliomas, the most common primary CNS malignancy in adults, is associated with upregulation of several MMPs (Kessenbrock et al., 2010). MT-MMPs appear to play a role of particular relevance for pericellular proteolysis, since MT1-MMP, MT2-MMP, MT5-MMP, and MT6-MMP are upregulated in glioma (Llano et al., 1999; Nuttall et al., 2003; Velasco et al., 2000). MT1-MMP plays a key role in glioma cell ability to spread and migrate on myelin (Paganetti et al., 1988; Amberger et al., 1994; Beliën et al., 1999). TIMP-2 could stimulate invasion through its interaction with MT1-MMP by promoting ERK signaling (Sounni et al., 2010).

Superficial spreading melanoma (SSM) and acral lentiginous melanoma (ALM) showed a moderate expression of MT1-MMP. In metastatic melanoma, MT1-MMP is more intensely expressed (Ohnishi et al., 2001).

7.2.2.2. Tumorigenesis. The role of MT-MMPs as well as other MMPs in cancer metastasis and invasion could not be restricted to the ECM component degradation. Cell invasion is a multistep process involving ECM degradation and cell mobility. While ECM degradation can be orchestrated collectively by MMPs, cell migration is likely predominantly associated with MT1-MMP activity.

The ECM degradation is required for a cancer cell to degrade physical barriers during local expansion and intravasation at nearby blood vessels, extravasation and invasion at a distant location. During invasion, the localization of MMP proteolytic activity on specialized cell surface structures, called invadopodia, is a requisite for cancer cells ability to promote invasion. Invadopodia utilize transmembrane invadopodia-related proteinases, including MMP-14, for cancer cell proliferation: MMPs control proliferation signals through integrins because the shedding of E-cadherin results in β-catenin translocation to the nucleus, leading to cell proliferation. It is worth noting that the inactive pro-form of TGF-β, an important biomolecule in cancer, is proteolytically activated by MMP-14 (Mu et al., 2002).

Through its activity towards cell surface adhesion molecules (CD44, tTG and av integrin) (Belkin et al., 2001; Kajita et al., 2001; Ratnikov et al., 2002) or specific ECM protein such as laminin-5 (Gilles et al., 2001; Koshikawa et al., 2000), MT1-MMP can strongly modulate cell adhesion and cytoskeletal organization leading to cell mobility. The importance of endogenous MT1-MMP in cancer invasion was evidenced by downregulation of MT1-MMP in aggressive cancer cells using RNA silencing technology (Ueda et al., 2003). The specific silencing of MT1-MMP is sufficient to inhibit the invasion of highly invasive fibrosarcoma H1080 cells known to produce high levels of different MMPs.

In carcinoma cancer cells, over-expression of MMP-14 has been also associated with epithelial to mesenchymal transition (EMT), a highly conserved and fundamental process of morphological transition (Egeblad and Werb, 2002; Gilles et al., 1996). In particular, during this event, epithelial cells actively down-regulate cell–cell adhesion systems, lose their polarity, and acquire a mesenchymal phenotype with reduced intercellular interactions and increased migratory capacity (Polyak and Weinberg, 2009).

MT1-MMP shares with MT3-MMP and MT5-MMP the capability of activating MMP-2 and MMP-9 providing a mechanism of control in cancer. These type of activation induce the inactivation of the human metastasis suppressor gene *KiSS-1* produced by cancer cells (Takino et al., 2003).

7.2.2.3. Angiogenesis. The key players of the MMP family that participate in tumor angiogenesis are mainly MMP-2, MMP-9 and MMP-14 (Rundhaug, 2003). Initially, the generation of cryptic peptides via degradation of ECM molecules, such as collagen type IV and laminin-5, promotes the migration of cancer cells (Koshikawa et al., 2000; Xu et al., 2001). Laminin-5 is a major component of the basement membrane, which regulates the function of epithelial cells. Several cancer breast epithelial cell lines constitutively express MT1-MMP and generate a unique fragment derived from the cryptic site of the c2-chain of laminin-5, directly affecting the cellular signal and promoting cell migration (Gilles et al., 2001; Koshikawa et al., 2000).The generation of a fragment from laminin-5 c2-chain by MT1-MMP in human uveal melanoma cells plays critical roles in the vasculogenic mimicry (Seftor et al., 2001).

MT1-MMP may modulate the ability of cancer cells to induce angiogenesis. Tumor cells expressing MT1-MMP grow rapidly and form highly vascularized tumors (Hotary et al., 2003; Sounni et al., 2002b). The proangiogenic activity of MT1-MMP is further supported by the effects of MT1-MMP overexpression on tumorigenicity, growth and vascularization of human melanoma (Maquoi et al., 2004; Sounni et al., 2002b), breast adenocarcinoma (Sounni et al., 2002a) or glioma (Deryugina et al., 2002b) cells transfected with MT1-MMP cDNA. Other studies provided evidence that this MT1-MMP pro-angiogenic effect is mediated at least by an up-regulation of VEGF at both mRNA and protein levels by activation of signaling pathway involving Src type tyrosine kinases (Sounni et al., 2002a, 2004). However, the expression of other angiogenic factors, such as VEGF-B, -C, -D, PlGF, angiopoietin or their receptors VEGF-R1, -R2, neuropilin, Tie-1 and Tie-2 is not affected by MT1-MMP over-expression (Sounni et al., 2004). Such a link between the expression of VEGF and MT1-MMP is further confirmed by immunohistochemical and RT-PCR analysis of human glioma tissue samples (Munaut et al., 2002). Correlation between MT1-MMP and VEGF-A has also been observed in early physiological cartilage formation (Sekiya et al., 2002).

MT-MMPs play important roles in the formation of new blood vessels in both physiological and pathological conditions. The activities of MT1-MMP, MT2-MMP, MT3-MMP and MT5-MMP are essential for microendothelial cell differentiation into tubes in a fibrin gel (Lafleur et al., 2002). TIMP-2 and TIMP-4, but not TIMP-1, are able to inhibit angiogenesis *in vitro* (Lafleur et al., 2002). In the absence of uPA/plasminogen system, MT1-MMP fibrinolytic activity supports the tubule formation of endothelial cells in a fibrin gel (Hiraoka and Furukawa, 1998). In 3D-collagen gel, expressions of MT1-MMP and MT3-MMP are required for MDCK and endothelial cell organization into a tubular network (Haas et al., 1998; Kadono et al., 1998; Kang et al., 2001). Although embryonic vasculogenesis and angiogenesis are normal in MT1-MMP-deficient mice, the formation of secondary ossification centers during bone formation is severely impaired due to defect of angiogenesis (Zhou et al., 2000).

Angiogenesis is severely impaired in an ex vivo assay using cornea issued from MT1-MMP-deficient mice, as compared to wild-type mice (Zhou et al., 2000). Corneal epithelial MT1-MMP displays an antiangiogenic activity, which does not require the catalytic domain (Azar et al., 2010). On the other hand, (MT1-MMP), acts as proangiogenic enzyme, cleaving an antiangiogenic protein named decorin (Mimura et al., 2009).

The control of VEGF bioactivity by MMPs has also been reported. The effects of synthetic MMP inhibitors on the expression of VEGF in MCF7 overexpressing MT1-MMP and in an *in vivo* T-cell lymphoma model, support the role of MT1-MMP in promoting tumor angiogenesis during cancer progression (Arlt et al., 2002; Sounni et al., 2004). MT1-MMP can induce tumor angiogenesis through up-regulation of VEGF expression in human breast carcinoma (Deng et al., 2009).

MMP-14 is a shedding protease for endoglin, a transforming growth factor-β coreceptor with a crucial role in angiogenesis. MMP-14 cleaves endoglin at position 586 close to the transmembrane domain, releasing full-length endoglin extracellular domain. Endoglin inhibits angiogenesis and would therefore be a useful tool to inhibit tumor angiogenesis. In turn, inhibiting MMP-14 might be a therapeutic strategy for pathologic conditions with increased endoglin shedding, such as preeclampsia (Hawinkels et al., 2010).

7.2.2.4. Biomarker role. MT1-MMP is a candidate marker to predict distant metastasis among identified genes. MT1-MMP-positive expression in peripheral blood was associated with incidence of peritoneal dissemination, lymphatic permeation, vascular permeation, and lymphonode metastasis. MT1-MMP-positive expression in bone marrow was also significantly related to the incidence of distant metastasis and peritoneal dissemination (Mimori et al., 2008). MT1-MMP plays an important role in the progression of the laryngeal cancer, and may serve as a reliable marker in estimating invasive and metastatic potency of laryngeal cancer (Sun and Li, 2004).

7.2.3. Non-neoplastic diseases

7.2.3.1. Diseases of the cardiovascular system. A number of studies have shown that MMP-14 is involved in the remodeling of the myocardium in cardiac diseases including myocardial infarction, left ventricular hypertrophy and dilated cardiomyopathy (Spinale, 2007). MMP-14 is elevated during pressure overload hypertrophy (Spinale, 2007).

Several studies indicate that MMP-14 collagenolytic activity contributes to collagen remodeling in the atherosclerotic lesion. Lesions of low-density lipoprotein receptor-deficient mice engrafted with MMP-14 knockout bone marrow contained more interstitial collagen than those receiving wild-type bone marrow (Schneider et al., 2008).

MMP-14 has been detected in human abdominal aortic aneurysms, which are lesions with the potential to rupture (Choke et al., 2005; Thompson et al., 2002), accompanied by a MMP-14 over-expression (Annabi et al., 2002). Elevated transplantation with bone marrow from MMP-14 null mice resulted in a resistance to aortic aneurysm formation, a finding which supports the importance of MT1-MMP/TIMP-2-driven proMMP-2 activation in aneurysm formation (Xiong et al., 2009).

7.2.3.2. Diseases of the nervous system. In the nervous system, relatively high mRNA and protein levels of MMP-14, MMP-15, and MMP-24 and TIMP-1 and TIMP-3 are found in the perinatal rodent central nervous system (CNS) but generally decline with age (Ayoub et al., 2005; Fager and Jaworski, 2000; Jaworski, 2000; Ranasinghe et al., 2009; Rivera et al., 1997; Ulrich et al., 2005; Vaillant et al., 1999).

Cerebral ischemia and hemorrhagy initiates a complex pattern of MMP expression that is important in both the injury and repair. Shortly after the initiation of an ischemic damage in animals, basal lamina disruption is observed (Hamann et al., 1995; Heo et al., 1999). Because MMPs are present in latent forms, mechanisms of activation must be brought into play. With the onset of oxygen deprivation, hypoxia inducible factor-1 (HIF-1) activates genes that are important in adapting the brain to the hypoxic conditions, including genes involved in anaerobic metabolism, angiogenesis, red blood cell production, and growth factor production. Notably, HIF-1 activates the proprotein convertase furin, which activates MMP-14, with the consequent formation of a trimolecular complex between MMP-14, TIMP-2, and pro-MMP-2, followed by the formation of active MMP-2. Thus, the initial phase of BBB disruption is mainly mediated by MMP-14. Ultimately, this combination affects the basal lamina and the tight junction proteins claudin and occludin (Furuse et al., 1998; Hawkins and Davis, 2005). After initial structural changes in tight junction proteins, there is resolution of blood–brain barrier (BBB) opening within several hours in the ischemic/reperfusion suture model (Yang et al., 2007a).

7.2.3.3. Diseases of joints and muscular system. Among the MMPs, MMP-13, MMP-9 and MMP-14 (MTl-MMP) appear to be the most important in regulating cellular migration, ECM protein transformation, ECM degradation and apoptosis in the growth plate (Werb and Chin, 1998). Although normal endochondral ossification is also dependent to a significant extent on the activities of members of the hedgehog protein family, parathyroid hormone-related peptide and parathyroid hormone-related peptide receptor (Kobayashi et al., 2002) as well as specific stress-activated and tyrosine receptor protein kinases (Wang et al., 2004b), ablation of the MT1-MMP (Holmbeck et al., 1999) gene to produce MMP-specific null mice resulted in space-temporal modulation of growth plate development.

Accumulated lines of evidence have demonstrated that collagenolytic MMP (MMP-14) is responsible for the degradation of type II collagen (a major fibrillar collagen in the cartilage). In human osteoarthritis (OA) cartilage, MMP-1, MMP-8, MMP-13 and MMP-14 are overexpressed by chondrocytes (Okada, 2009). Among these MMPs, MMP-14 may play a direct role in collagen degradation because of its collagenolytic activity and common expression in the cartilage. Importantly, MMP-14 potentially has a dual role in collagen degradation through both its collagenolytic activity and activation of pro-MMP-2 and pro-MMP-13.

The mechanism of articular cartilage destruction by proteinases is more complex in rheumatoid arthritis (RA) than OA, and composed of three pathways: destruction from the surface of the articular cartilage by proteinases present in the synovial fluid, destruction through direct contact of proteolytic synovium and/or pannus tissue to the articular cartilage and intrinsic destruction by proteinases derived from chondrocytes (Okada, 2009). Rheumatoid synovial tissue exhibits the overproduction of MMP-1, MMP-3, MMP-8, and MMP-14 together with TIMP-1, TIMP-2 and TIMP-3 (Okada, 2009).

Rheumatoid synovium is highly proteolytic, since it has additional activity generated by the activation of proMMP-2 by MMP-14, This activity was blocked when incubated with BB94, a specific MMP inhibitor (Yamanaka et al., 2000). MT1-MMP is expressed in all rheumatoid synovial tissue. Significant correlation is found between the mRNA expression level of MT1-MMP and the activation ratio of proMMP-2 ($p < 0.01$). In situ hybridization indicated that the hyperplastic lining cells of rheumatoid synovium express MT1-MMP. Immunohistochemistry demonstrated that MT1-MMP was co-localized with MMP-2 and with a tissue inhibitor of metalloproteinase-2, and was mainly located in the rheumatoid synovial lining cells (Yamanaka et al., 2000). Direct contact of this synovium may induce cartilage destruction at the peripheral portion of articular surface (Yamanaka et al., 2000). Chondrocytes in RA also express MMP-1, 13, MT1-MMP and MT3-MMP.

7.2.3.4. Wound healing. Wound tissues in humans and in experimental animals over-express multiple MMP including MMP-14. These MMPs expectedly play a role in the complex process of wound healing that includes acute inflammatory reaction, regeneration of parenchyma cells, cell migration and proliferation, angiogenesis, contraction and tissue remodeling (Gill and Parks, 2008). In particular, MMP-14 may contribute to re-epithelialization (Gill and Parks, 2008).

7.2.3.5. Diseases of the respiratory system. Membrane type 1 matrix metalloproteinase (MT1-MMP) expressed by airway epithelial cells is implicated in bronchial epithelial repair, involving keratinocyte growth factor receptor (KGFR) expression and epithelial cell proliferation after acute airway injury (Atkinson et al., 2007).

Induced mainly by cigarette smoking, chronic obstructive pulmonary disease (COPD) is a global public health problem characterized by progressive difficulty in breathing and increased mucin production. MMP-14 together with MMP-9 activity

increases in COPD sputum; in particular, MMP-14 expression is induced in mucin production in COPD (Deshmukh et al., 2009).

7.3. MT-2 MMP (MMP-15)

7.3.1. Structure and activation

The insertion sequence-2 (IS-2) is functionally important, since transfection of the mouse membrane type-2 matrix metalloproteinase (MT2-MMP) gene into COS-1 cells resulted in the activation of progelatinase A; on the other hand, the same event did not produce any effect on the human gene. In particular, seven amino acid residues of the IS-2 (located between amino acid residues 155 and 271) are not conserved between human and mouse MT2-MMP (Miyamori et al., 2000). However, MT2-MMP has been demonstrated to be able to activate pro-MMP-2 *in vitro* (Sato et al., 1994).

7.3.2. Biological features

MT1-MMP and MT2-MMP are predominantly expressed in human placenta during the first trimester of pregnancy (Bjørn et al., 2000), exerting essential but interchangeable roles in placental vasculogenesis. The fetal portion of the placenta, in particular the labyrinth (LA), displays strong overlapping expression of MT1-MMP and MT2-MMP, which is critical for syncytiotrophoblast formation and for fetal vessels. Both MT1-MMP and MT2-MMP are crucial specifically during development of LA, showing a selective temporal and spatial MMP activity required for the development of the mouse embryo (Szabova et al., 2010). The trophoblast compartment of the placenta comprises various subpopulations with distinct functions. In addition, the first trimester cells of human trophoblast subpopulations-TNF-α stimulate MMP-15 expression (Hiden et al., 2007).

7.3.3. Neoplastic diseases

Although MT2-MMP expression in tumors has been found in cervical, breast, head, prostate, and neck cancer, glioblastoma, melanoma, lung adenocarcinoma and astrocytic cancers (Gilles et al., 1997; Giricz et al., 2010; Kobayashi et al., 2004; Nakada et al., 1999; Nuttall et al., 2003; Polette et al., 1996; Riddick et al., 2005), its expression has not been linked to disease progression (Sato and Seiki, 1996). Cancer experimental models have demonstrated that MT1-MMP is negatively regulated by MT2-MMP (Velasco-Loyden et al., 2004). Such a negative regulation of MT1-MMP may explain the lack of correlation between MT2-MMP expression and the aggressiveness of cancers (Velasco-Loyden et al., 2004).

In hepatocellular carcinomas, MT2-MMP displays a pivotal role in the MMP-2 activation process (Théret et al., 1998). Activation of matrix metalloproteinase-2 (MMP-2) by the membrane-type matrix metalloproteinases (MT-MMPs) has been associated with tumor progression. The MT2-MMP and MT3-MMP are MMP-2 activators in pancreatic tumor cell invasion and the development of the desmoplastic reaction characteristic of pancreatic cancer tissues (Ellenrieder et al., 2000), as well as between MMP-2 activity and MT2-MMP expression ($p = 0.018$). There is also an association between MT1-MMP and MT2-MMP expression in tumor tissues ($p < 0.001$). MMP-2 activity and MT2-MMP expression in tumor tissues are statistically associated with high tumor stage ($p = 0.039$ and $p = 0.014$, respectively), while the MMP-2 activity is associated with an increase in MT2-MMP expression and with lymph node metastasis (Mohammad et al., 2010).

Double immunofluorescence demonstrated a consistent colocalization of MT2-MMP/MMP-2 and MT3-MMP/MMP-2 in the nodular melanoma (NM) and metastatic melanoma cells. The colocalization of MT2,3-MMP and MMP-2 in nodular and metastatic melanoma cells suggests that MT-MMPs and MMP-2 co-operate in the invasive and metastatic process of melanoma cells (Ohnishi et al., 2001).

MT2-MMP is an effector of CXCR4 signaling in glioma cells, and they reveal the novel role of MT2-MMP in modulating tumor growth and metastasis (Zhang et al., 2005b). Significant elevations in the levels of mRNA expression of the matrix metalloproteases (MMPs) membrane type 1-MMP (MT1-MMP), MT2-MMP and MMP-9, as well as of TIMP-2 were detected in the muscle invasive transitional cell carcinoma (TCC) of the bladder (Chaffer et al., 2005).

In the mouse model of endometrial cancer, the commercial drug Avastin, a humanized antibody against vascular endothelial growth factor VEGFA, brings about a down-regulation of MMP-15 transcripts (Davies et al., 2011). The MMP-15 gene is identified as being commonly over-expressed in lung adenocarcinoma (AdC) cells in comparison with noncancerous peripheral lung epithelial cells, type II alveolar cells and bronchiolar epithelial cells. This strongly suggest that the MMP-15 genes could be a novel marker for molecular diagnosis and therapy of lung AdC (Kobayashi et al., 2004). Increased expression of MMP-15 in malignant tissue, as compared to benign prostate tissue, is detected suggesting that MMP-15 gene involved in proteolysis can be a potential prognostic indicator (Riddick et al., 2005).

A crucial step in human breast cancer progression is the acquisition of invasiveness. The expression of matrix metalloproteinases MMP-15, and MMP-17 is up-regulated in the invasive cells. Small interfering RNA-based data demonstrated that MMP-15 and MMP-17 are required for the invasive phenotype of breast cells (Rizki et al., 2008).

7.3.3.1. Angiogenesis. The intensity of immunochemical staining of MT2-MMP was significantly correlated in a positive fashion to the intratumoral angiogenesis of esophageal cancer tissues. In addition, MT2-MMP immunochemical intensities were significantly correlated to tumor size, but not to patient's gender, age, invasion depth, lymphonode metastasis and distant metastasis. Moreover, MT2-MMP levels could not be applied for predicting patients' survival rate, although the H-score cut-off value showed the overall survival rate of patients with low MT2-MMP protein level to be better than those with high MT2-MMP protein level (Chen et al., 2010).

7.3.4. Non neoplastic diseases

7.3.4.1. Diseases of the digestive system. In the inflammation processes of the bile ducts, up-regulation of MMP-15 gene transcription contributes to the pathogenesis of liver tissue during chronic cholangitis disease (Nakken et al., 2007). MMP-15 gene is also significantly up-regulated after hepatic ischemia reperfusion lung injury (Zhao et al., 2009).

7.4. MT3-MMP (MMP-16)

7.4.1. Structure and activation

The structure of the catalytic domain (CD) of MT3-MMP/MMP-16 in complex with the hydroxamic acid inhibitor batimastat exhibits a classical MMP-fold with similarity to MT1-MMP (see Fig. 1 and Table 2). Nevertheless, it also shows unique properties, such as a modified MT-specific loop and a closed S1′ specificity pocket, which might help to design specific inhibitors (Lang et al., 2004).

7.4.2. Biological features

Both MT3-MMP and its transmembrane domainless variant MT3-MMP-del hydrolyze gelatin and casein, indicating their broad substrate specificity. The transfection of rat MT3-MMP-del efficiently converts progelatinase A to the intermediate form but not to the mature one, indicating that the transmembrane domain is important for the complete processing of progelatinase A to maturation. Results of experiments with a synthetic MMP inhibitor suggests that MT3-MMP-del and MT3-MMP are rapidly degraded immediately after maturation. The multiple forms of MMPs including MT3-MMP are involved in the matrix remodeling of blood vessels (Shofuda et al., 1997).

Inhibitor profile and MMP-16 mutant enzyme studies indicate that MT3-MMP is regulated on the cell surface by the autocatalytic processing and the ectodomain shedding (Zhao et al., 2004). MT1-MMP and MT3-MMP can process the membrane-anchored proteoglycan betaglycan (sBG-120) that binds transforming growth factor-β (TGF-β) via its core protein, generating a 90-kDa fragment (sBG-90). Notably, the cleavage appears to be mediated by a protease regulated by TIMP-2 (Velasco-Loyden et al., 2004). Shedding of the transmembrane heparan sulfate proteoglycan syndecan-1 is not only produced by MT3-MMP but also induced by MT1-MMP, whereas other MT-MMPs are not able to carry out this process. Both shedding processes occur through the preferential cleavage of Gly245-Leu246 peptide bond stimulates cell migration (Endo et al., 2003).

Inhibition kinetic studies showed that TIMP-3 (see Table 5) is a high affinity inhibitor of MT3-MMP as compared with MT1-MMP (with a K_i = 0.008 nm for MT3-MMP and a K_i = 0.16 nm for MT1-MMP); conversely, TIMP-2 (see Table 5) is a better inhibitor of MT1-MMP. MT3-MMP requires TIMP-2 to accomplish full pro-MMP-2 activation and this process is enhanced in marimastat pretreated cells, consistent with regulation of active enzyme turnover by synthetic MMP inhibitors. TIMP-3 also enhances the activation of pro-MMP-2 by MT3-MMP but not by MT1-MMP. On the other hand, TIMP-4 cannot support pro-MMP-2 activation with either enzyme (Zhao et al., 2004). Pro-MMP-2 can assemble trimolecular complexes with a catalytic domain of MT3-MMP and TIMP-2 or TIMP-3 suggesting that pro-MMP-2 activation by MT3-MMP involves ternary complex formation on the cell surface. TIMP-3 is a major regulator of MT3-MMP activity and further underscores the unique interactions of TIMPs with MT-MMPs in the control of pericellular proteolysis (Zhao et al., 2004).

MMP-16 plays a roles in cartilaginous embryogenesis as a terminal marker induced by responses to Wnt/beta-catenin signaling. Studies have suggested that continuous Wnt/beta-catenin signaling in nascent cartilaginous skeletal elements blocks chondrocyte hypertrophy and endochondral ossification, whereas signaling starting at later stages stimulates hypertrophy and ossification, indicating that Wnt/beta-catenin roles are developmentally regulated (Tamamura et al., 2005).

7.4.3. Neoplastic diseases

Activation of pro-MMP-2 by the membrane-type matrix metalloproteinases (MT-MMPs) has been associated with tumor progression (Ellenrieder et al., 2000). MT3-MMP has been detected in breast and renal carcinomas, astrocytic tumors and melanoma (Kitagawa et al., 1999; Nakada et al., 1999; Takino et al., 1995; Ueno et al., 1997).

MT1, MT2, and MT3-MMP play an important role in the progression of the laryngeal cancer. Early suppression of the expressions of MT1, MT2, and MT3-MMP may inhibit the invasion and metastases of the laryngeal cancer (Sun and Li, 2004).

MicroRNAs (miRNAs) are a class of endogenous, small non-protein coding single-stranded RNA molecules, which are crucial post-transcriptional regulators of gene expression. Using miRNA microarray, miR-146b was identified as one of the miRNAs that is significantly dysregulated in human glioblastoma tissue. The miR-146b molecule is capable of inhibiting glioma cell migration and invasion by targeting MMP-16, underlying a relevant role by MT3-MMP in this tumor (Xia et al., 2009). A different molecule, named miR-146b-5p, by targeting MMP-16 significantly reduces the migration and invasion by MIA PaCa-2 pancreatic cancer cells. This molecule may be a potential therapeutic target for the pancreatic cancer (Lin et al., 2011b).

MT3-MMP possesses the potential to promote melanoma invasion and proteolysis and the formation of a complex between MT3-MMP and Melanoma chondroitin sulfate proteoglycan (MCSP) may be a crucial step in activating invasion (Lida et al., 2001).

Unlike for other carcinoma, the down-regulation of most MT-MMPs, mainly in epithelial cells. is typical for prostate carcinoma. In malignant tissue samples and their corresponding cell cultures, the expression of most MT-MMPs is down-regulated in comparison to the normal counterparts. There is no correlation between prostate tumor classification data and the MT-MMP expression results (Jung et al., 2003).

Unexpectedly, several cancer progression modulators located upstream of MMP mRNA expression in human breast cancer cells, induce a decrease of MMP-16 mRNA expression, suggesting a signaling at a late stage in MMP-16 mRNA accumulation, such as MMP-16 mRNA stabilization or late mRNA processing (Delassus et al., 2011).

7.4.3.1. Angiogenesis. In the endometrium, angiogenesis is a physiological process, whereas in most adult tissues neovascularization is initiated only during tissue repair or pathological conditions. Pericellular proteolysis by MT-MMPs plays an important role in angiogenesis being required for endothelial cell migration, invasion, and tube formation. MT1-, MT3-, and MT4-MMPs are expressed in human endometrial microvascular endothelial cells (hEMVECs) and foreskin MVECs (hFMVECs). Immunohistochemistry data have shown that the presence of MT3-MMP in endothelial cells of endometrial tissue. In contrast to tube formation by foreskin MVECs (hFMVECs), which largely depends on MT1-MMP, capillary-like tube formation by hEMVECs is, at least in part, regulated by MT3-MMP (Plaisier et al., 2004).

7.4.3.2. Biomarker role. Microarray analysis of renal cell carcinoma showed an over-expression of MMP-16 in metastatic primary tumors, suggesting that MMP-16 is one of the potential biomarker for metastatic clear cell renal cell carcinoma (Sanjmyatav et al., 2011).

7.4.4. Non-neoplastic diseases

7.4.4.1. Diseases of joints and muscular system. Matrix degradation by metalloproteinases is considered a key feature in the loss of articular cartilage seen in many joint diseases. The comparison of the expression of gene of MT-MMP subfamily in normal cartilage and cartilage from patients with osteoarthritis (OA) showed increased expression of MMP-16, which can be a potential specific target to refine the specificity of antiproteolytic therapies (Kevorkian et al., 2004).

However, MT3-MMP expression is elevated in human cartilage at the end-stage osteoarthritis, whereas it is not significantly altered in both osteoarthritis and osteochondrosis cartilage. In addition, gene expression is significantly downregulated by the addition of recombinant human interleukin-1β, oncostatin M, or tumor necrosis factor-α to normal cartilage explants (Garvican et al., 2008).

The expression of MT1-MMP, MT2-MMP, and MT3-MMP, and proMMP-2 production levels and activation ratios are found to be significantly higher in rheumatoid synovium, as compared with normal synovium ($p < 0.01$). supporting a positive correlation between the levels of MT-MMPs and the extent of proMMP-2 activation in rheumatoid synovial tissue (Yamanaka et al., 2000). Similarly to MT1-MMP, MT3-MMP is expressed in all rheumatoid synovial tissue, but the mean expression level of MT3-MMP is approximately 11-fold lower than that of MT1-MMP. In situ zymography of the rheumatoid synovium showed gelatinolytic activity, predominantly in the lining cell layer (Yamanaka et al., 2000).

7.5. MT5-MMP (MMP-24)

7.5.1. Biological features

In contrast to other MT-MMPs, MT5-MMP tends to shed from cell surface as a soluble enzyme, thus envisaging the possibility to work in extracellular matrix remodeling processes both as a cell bound and soluble proteinase (Pei, 1999a).

MT5-MMP can degrade several ECM components, such as inhibitory chondroitin sulfate proteoglycans, thereby promoting neurite outgrowth *in vitro* (Bar-Or et al., 2003; Hayashita-Kinoh et al., 2001; Jaworski, 2000; Wang et al., 1999a). MT5-MMP can degrade purified proteoglycans and gelatin substrates *in vitro* (Wang et al., 1999a) and can also relieve the inhibitory function of proteoglycans during axonal elongation on laminin-coated plates (Hayashita-Kinoh et al., 2001). Moreover, it appears capable of mediating the cleavage of cell-adhesion molecule N-cadherin in heterologous cells (Monea et al., 2006).

MT5-MMP (MMP-24) is mainly expressed in neuronal cells of both central and peripheral nervous systems, although its presence has been also detected in inflammatory cells (Bar-Or et al., 2003; Hayashita-Kinoh et al., 2001; Jaworski, 2000; Llano et al., 1999; Pei, 1999a).

In the cerebellum, its expression was regulated developmentally and is closely associated with dendritic tree formation of Purkinje cells, suggesting that MT5-MMP may contribute to neuronal development (Sekine-Aizawa et al., 2001).

MT5-MMP expression is ubiquitous during the brain development while in adult it is restricted to hippocampus and cerebellum regions, displaying synaptic plasticity (Ross and Fillmore, 2007). More than one human MT5-MMP transcript may exist in the central nervous system (Monea et al., 2006; Ross and Fillmore, 2007).

MMP-24 contributes to synaptogenesis and activity-dependent synaptic remodeling, since AMPA receptor binding protein (ABP) and glutamate receptor interacting protein (GRIP) spatially regulate MT5-MMP localization and hence its degradation of ECM or cell adhesion molecules (Monea et al., 2006).

MMP-24 is an essential mediator of peripheral thermal nociception and inflammatory hyperalgesia, mediating the neuroimmune communication. Lopez-Otin and colleagues have demonstrated that the absence of MT5-MMP induces a cutaneous phenotype of hyperinnervation and a morphological and functional alteration in neuro-immune interactions (Folgueras et al., 2010). In contrast to basal nociception, MMP-24(−/−) mice do not develop thermal hyperalgesia during inflammation, a phenotype that appears associated with alterations in N-cadherin-mediated cell–cell interactions between mast cells and sensory fibers (Folgueras et al., 2010) (see Table 6). Therefore, MT5-MMP plays an essential role of in the development of dermal neuro-immune synapses and may be a target for pain control (Folgueras et al., 2010).

MT5-MMP is expressed by CGRP-containing peptidergic nociceptors in dorsal root ganglia and MMP-24-deficient mice display enhanced sensitivity to noxious thermal stimuli under basal conditions. Consistently, mutant peptidergic sensory neurons hyperinnervate the skin, a phenotype that correlates with changes in the regulated cleavage of the cell–cell adhesion molecule N-cadherin (Fariñas and Lopetz-Otin, 2009).

7.5.2. Neoplastic diseases

MMP-24 gene silencing by RNAi demonstrates that MMP-24 can suppress the invasiveness of ovarian cancer SKOV cells *in vitro*, which may provide a new therapeutic approach of ovarian cancer (Luo et al., 2009).

7.5.3. Non-neoplastic diseases

7.5.3.1. Diseases of the nervous system. MMP-24 is expressed in brain tissue after the development and colocalization with senile plaques in Alzheimer brain indicates possible roles in neuronal remodeling naturally occurring in adulthood and in regulating pathophysiological processes associated with advanced age (Sekine-Aizawa et al., 2001). MT5-MMP expressed in neurons may play a role in axonal growth that contributes to the regulation of neural network formation (Hayashita-Kinoh et al., 2001) and may promote structural remodeling after nerve injury (Komori et al., 2004).

7.5.3.2. Other diseases. The evidence of the overexpression of a MT5-MMP in diabetes suggests a role for this enzyme in the pathogenesis of renal tubular atrophy and end-stage renal disease (Romanic et al., 2001). MT5-MMP expression was localized by immunohistochemistry into the epithelial cells of the proximal and distal tubules, the collecting duct, and the loop of Henle. Furthermore, the tubular epithelial cells that expressed MT5-MMP are associated with tubular atrophy. Because renal tubular atrophy is a significant factor in the pathogenesis of diabetic nephropathy and renal failure, although the molecular mechanisms regulating this process remain unknown, it is hypothesized that the elevated expression of MT5-MMP contributes to the activation of pro-MMP-2, which participates in the remodeling of the proximal and distal tubules as well as in the collecting duct (Romanic et al., 2001).

Along with MMP-1, MMP-2, MMP-3, MMP-7, MMP-13, also MT5-MMP participates into the early phases in endometriotic lesion formation (Nap et al., 2004). Both the gene chip expression and PCR analyses indicated expression of MT5-MMP in normal human endometrium and strongly elevated transcript levels in most peritoneal endometriosis lesions analyzed. Moreover an enhanced MT5-MMP expression in the eutopic endometrium from patients suffering from endometriosis was detected, further supporting a role of MT5-MMP in the formation of endometriosis (Gaetje et al., 2007).

7.6. GPI-MT-MMPs: MT4-MMP (MMP-17) and MT6-MMP (MMP-25)

7.6.1. GPI-MT-MMP structure

The GPI-MT-MMPs subfamily includes MT4-MMP (MMP-17) (Kajita et al., 1999; Puente et al., 1996) and MT6-MMP (MMP-25) (Pei, 1999b; Velasco et al., 2000). The two members of the GPI-MT-MMP subfamily are anchored to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor, which confers these enzymes a unique set of regulatory and functional mechanisms that distinguishes them from the rest of the MMP family (Sohail et al., 2008) (see Fig. 2 and Table 2).

GPI-MT-MMPs are structurally and functionally distant from TM-MT-MMPs. Primary sequence alignment of the catalytic domain of MT4- and MT6-MMP shows they are 56% identical and 77% homologous. However, when compared to the MT1-MMP catalytic domain, MT4-MMP displays only 37% identity (50% similarity) while MT6-MMP possesses 42% identity (58% similarity).

With the exception of the anchoring region, GPI-MT-MMPs share the same basic domain organization of most MMPs, including a signal sequence, a propeptide domain, a zinc-containing catalytic domain, a hinge region (linker 1), and a hemopexin-like domain (see Fig. 1). Both the transmembrane and the GPI-MT-MMPs also contain a RXR/KR motif at the end of the propeptide domain that serves as a recognition site for pro-convertases, such as furin, which cleave the propeptide and activate the MTMMP zymogen (see Fig. 1).

On the other hand, the hemopexin-like domain of the GPI-MT-MMPs is followed by a hydrophilic region (~35–45 amino acids), also called stem (linker 2) region, and by a hydrophobic tail of ~20–23 amino acids. The C-terminal hydrophobic tail of the GPI-MT-MMPs is removed by a transamidase in the endoplasmic reticulum (ER) during incorporation of the GPI anchor, a process that is a unique characteristic of GPI-anchored proteins (Udenfriend and Kodukula, 1995).

7.6.2. MT4-MMP (MMP-17)

MT4-MMP was identified in peripheral blood leukocyte preparations and was first cloned from a human breast carcinoma cDNA library (Puente et al., 1996).

7.6.2.1. Structure. MT4-MMP is displayed on the cell surface as a mixed population of monomeric, dimeric, and oligomeric forms. Sucrose gradient fractionation experiments demonstrated that these forms of MT4-MMP are all present in lipid rafts. Mutational and computational analyses revealed that Cys564, which is present within the stem region, mediates MT4-MMP homodimerization by forming a disulfide bond. Substitution of Cys564 results in a more rapid MT4-MMP turnover, when compared to the wild-type enzyme, consistent with a role for dimerization in protein stability. Expression of MT4-MMP in MDCK cells enhanced cell migration and invasion of Matrigel, a process that requires catalytic activity. However, a serine

substitution at Cys564 did not reduce MT4-MMP-stimulated cell invasion of Matrigel suggesting that homodimerization is not required for this process. Deglycosylation studies also show that MT4-MMP is modified by N-glycosylation (Sohail et al., 2011). Moreover, inhibition of N-glycosylation by tunicamycin diminished the extent of MT4-MMP dimerization, suggesting that N-glycans may confer stability to the dimeric form (Sohail et al., 2011).

7.6.2.2. Biological features. The constitutive expression of MMP-17 mRNA is detected in unstimulated eosinophils, lymphocytes, and monocytes (but not in neutrophils) and its expression is modulated by TNF-α in purified human blood eosinophils Consequently, MT4-MMP may be directly involved in the degradation of extracellular matrix components and/or in the modulation of the activity of other proteins implicated in eosinophil migration and tissue remodeling (Gauthier et al., 2003).

MT4-MMP exhibits minimal or no activity against many ECM proteins (see Table 3). Specifically, soluble MT4-MMP was found to be active only against gelatin, fibrin, and fibrinogen (English et al., 2000; Kolkenbrock et al., 1999; Rozanov et al., 2004; Wang et al., 1999b). As a matter of fact, MT4-MMP has been observed to display ADAM-17-like activity (see Section 1.1.2), since it can behave as a sheddase of tumor necrosis factor (TNF)-α when co-transfected with pro-TNF-α in Cos-7 cells (English et al., 2000). The MT4-MMP catalytic domain alone cleaves α2-macroglobulin (English et al., 2000) and low density lipoprotein receptor related protein (LPR) (Rozanov et al., 2004).

MMP-17 is selectively expressed by distinct subsets of direction-selective retinal ganglion cells, suggesting that it is involved in the molecular mechanisms which regulate the cellular motion in different directions (Kay et al., 2011).

7.6.2.3. Neoplastic diseases. MT4-MMP mRNA is consistently found to be over-expressed in breast cancer tissues (Chabottaux et al., 2006). On the basis of immunochemistry studies the levels of MT4-MMP were observed to be particularly high in metastatic lymphonodes where both tumor and inflammatory cells displayed strong staining (Chabottaux et al., 2006). This is consistent with the reported expression of MT4-MMP in leukocytes (Gauthier et al., 2003; Puente et al., 1996). While human breast cancer tissues express MT4-MMP (Chabottaux et al., 2006; Puente et al., 1996), the expression and function of MT4-MMP in mouse mammary carcinoma are unclear. Over-expression of recombinant MT4-MMP in the breast cancer cell line MDA-MB-231 enhanced subcutaneous tumor growth when inoculated in RAG-1 immunodeficient mice (Chabottaux et al., 2006).

MT4-MMP mRNA expression was also examined in human gliomas (Nuttall et al., 2003) and it was found to decrease with advancing tumor grade. Studies in brain and breast tumors also suggest that the association of MT4-MMP expression with tumor progression may be cancer type specific. Interestingly, functional studies failed to reveal an effect of MT4-MMP overexpression on *in vitro* cell migration and invasion, pro-MMP-2 activation, VEGF production, and angiogenesis (Chabottaux et al., 2006).

7.6.2.4. Non neoplastic diseases.

7.6.2.4.1. Diseases of joints and muscular system. Recently, MMP-17 has been implicated in the activation of one of the key aggrecanases ADAMTS4 (see Section 1.1.2), revealing an association between increased levels of MMP-17 expression and inflammatory processes in areas of osteoarthritis cartilage damage (Clements et al., 2011).

7.6.2.4.2. Inflammation. Expression of MT4- and MT5-MMPs was induced in corneas infected with *Pseudomonas aeruginosa*. Immunohistochemistry showed predominant immunoreactivity of MT4- and MT5-MMPs in the substantia propria. Previous histologic studies have revealed different patterns of inflammatory cell infiltration with an increased number of polymorphonuclear neutrophils (PMNs) during the early stage of inflammation and increased macrophages during the late stage. These results indicate a good correlation between the over-expression of the MT-MMPs in the infected corneas and the inflammatory response, indicating that inflammatory cells, such as macrophages and PMNs, may play a role in the upregulation of MT-MMPs during corneal infection, which in turn can lead to the destruction of corneal tissue (Dong et al., 2001).

7.6.3. MT6-MMP (MMP-25)

MT6-MMP was identified from peripheral blood leukocytes and this MMP was also termed leukolysin due to the high expression of MT6-MMP in leukocytes (Pei, 1999b).

7.6.3.1. Structure. The natural MT6-MMP expressed on the cell surface is a major reduction-sensitive form of MW 120 kDa, likely representing enzyme homodimers held by disulfide bridges. Among the membrane type-MMPs, the stem region of MT6-MMP contains three cysteine residues at positions 530, 532, and 534 which may contribute to the dimerization interface, which provides structural stability to the protein (Zhao et al., 2008). A site-directed mutagenesis study of the Cys residues in the stem region shows that Cys (532) is involved in MT6-MMP dimerization by forming an intermolecular disulfide bond. The mutagenesis data also suggest that Cys (530) and Cys (534) form an intramolecular disulfide bond. Dimerization is not essential for transport of MT6-MMP to the cell surface, partitioning into lipid rafts or cleavage of alpha-1-proteinase inhibitor. However, monomeric forms of MT6-MMP exhibited enhanced autolysis and metalloprotease-dependent degradation (Zhao et al., 2008).

7.6.3.2. Biological features. MT6-MMP seems to function like stromelysin-1 (see Section 5.1.1), being able to cleave type-IV collagen, gelatin, fibronectin and fibrin (English et al., 2001). However, it differs from stromelysin-1 and MT1-MMP, since it is able to cleave laminin-I and cannot activate progelatinase B (see Table 3). MT6-MMP could play a role in cellular

migration and invasion of the extracellular matrix and basement membranes and its activity may be tightly regulated by all members of the TIMP family (English et al., 2001).

The regulation mechanisms, the functional role, and the repertoire of physiologically relevant cleavage targets of MT6-MMP remain largely unknown. A number of extracellular matrix components can be cleaved, including fibronectin, fibrin, gelatin, type IV collagen, and chondroitin and dermatan sulfate proteoglycan (English et al., 2001; Kang et al., 2001). The catalytic domain of MT6-MMP has been reported to cleave galectin-3, urokinase plasminogen activator receptor chondroitin dermatan sulfate proteoglycans and myelin basic protein (Kang et al., 2001; Radichev et al., 2010; Shiryaev et al., 2009b; Sohail et al., 2008).

Polymorphonuclear neutrophils (PMNs) express high levels of MT6-MMP, suggesting that it plays a role in the physiology of human PMNs. It is present in the membrane, granules and nuclear/endoplasmic reticulum/Golgi fractions of PMNs where it is displayed as a disulfide-linked homodimer of 120 kDa. Stimulation of PMNs resulted in secretion of active MT6-MMP into the supernatants. Conversely, membrane-bound MT6-MMP is located in the lipid rafts of resting PMNs and stimulation does not alter this location. In addition, TIMP-2, a natural inhibitor of MT6-MMP, does not co-localize with it in the lipid rafts. Interestingly, living PMNs do not display MT6-MMP on the cell surface. However, induction of apoptosis induces MT6-MMP relocation on PMNs' cell surface (Fortin et al., 2011).

There are conflicting results that point out the potential role of MT6-MMP in the mechanisms of MMP-2 activation (Nie and Pei, 2003; Sohail et al., 2008). Even though MT6-MMP does not stimulate cell migration, it generates however a significant level of gelatinolysis of the fluorescein isothiocyanate-labeled gelatin and exhibits an intrinsic, albeit low, ability to activate MMP-2. Because of its lipid raft localization, cellular MT6-MMP is inefficiently internalized. MT6-MMP is predominantly localized in the cell-to-cell junctions (Radichev et al., 2010).

MMP-25 is also present in the extracts of the developing tendon, suggesting its involvement in fibrillogenesis and matrix assembly (Smith et al., in press).

MMP-25 gene expression is high during the development of mouse secondary palate, wherefore MMP-25 is the only MMP showing a functional role (Brown and Nazarali, 2010).

7.6.3.3. Neoplastic diseases. Elevated MT6-MMP mRNA expression was found in several human cancers including brain (anaplastic astrocytomas and glioblastomas) (Nuttall et al., 2003; Velasco et al., 2000), colon (Velasco et al., 2000), urothelial (Wallard et al., 2006), and prostate (Riddick et al., 2005) cancers. In gliomas, expression of MT6-MMP mRNA was suggested to contribute to the disease progression (Nuttall et al., 2003). However, *in vitro* studies showed no effects of MT6-MMP overexpression on tumor cell migration and invasion, and therefore the precise role of MT6-MMP in colon cancer remains elusive. These findings are similar to those obtained with MT4-MMP in colon cancer cells, in which the protease expression does not confer a migratory and/or invasive phenotype or ability to activate pro-MMP-2 (Sun et al., 2007).

Although more studies are required to unveil the roles of GPI-MT-MMPs in cancer, the data so far obtained suggest that these proteases influence cancer progression by mechanisms that are different from the TM-MT-MMPs. First, GPI-MTMMPs do not act as progelatinase activators; second, their ECM degradation profile appears to be very limited; third, GPI-MT-MMPs do not promote tumor cell migration and invasion; and fourth, their inhibition profile appears unique.

7.6.3.4. Non-neoplastic diseases. MMP-25 plays a significant role in the fragmentation autoimmune multiple sclerosis (MS). MT6-MMP proteolysis of the myelin basic protein (MBP) isoforms generated the highly immunogenic N-terminal MBP peptide which efficiently stimulated the proliferation of the specific T cell clone isolated from mice with experimental autoimmune encephalomyelitis (EAE) (Shiryaev et al., 2009b).

Furthermore, the depletion of dietary antioxidants in asthma may result in upregulation of MMP-25 (Baines et al., 2009).

Among MMP members MMP-8, MMP-9 and MMP-13 play the most prominent role in the pathogenesis of periodontal disease progression (Giannobile, 2008). Like these MMPs, MMP-25 participates into the progression of the periodontal lesion. Expression of MMP-25 is associated with periodontal and peri-implant inflammation. Immunoblot in myeloma cell lysates reveals 29–57-kDa MMP-25, but not in macrophages, and partly active MMP-25 is observed in inflamed gingival crevicular fluid and peri-implant sulcular fluid (Kuula et al., 2008).

7.6.3.4.1. Biomarker role. MMP-25 is a serum marker for atopic asthma or chronic obstructive pulmonary disease (COPD). Among individuals with history of chronic airways inflammation (asthma and COPD) serum MMP-25 is a metabolic marker associated with chronic atopy-associated respiratory inflammation. Common factors may stimulate increased production or release of both MMP-25 from myeloid cells and IgE from lymphoid cells (Blumenthal et al., 2010).

8. Other matrix metalloproteinases

8.1. MMP-12

8.1.1. Structure and function

MMP-12, also called macrophage metalloelastase, is the most active MMP against elastin (Shapiro, 1998). MMP-12 is a 54 kDa proenzyme that is processed into a 45 kDa and then a 22 kDa active forms (Shapiro et al., 1992). The human gene, which is designated human macrophage metalloelastase, produces a 1.8-kb transcript encoding a 470-amino acid protein

that is 64% identical to the mouse protein (Shapiro et al., 1992). MMP-12 is predominantly expressed in alveolar macrophages, in airway epithelial and smooth muscle cells (Belaaouaj et al., 1995; Shapiro et al., 1992) under the control of other matrix components, such as hyaluronan fragments, cytokines and growth factors (*e.g.*, TGF-β, IFN-γ and EGF), and serine protease, such as thrombin and plasmin (Horton et al., 1999; Raza et al., 2000). A peculiar feature of MMP-12 is that it autocatalytically loses its hemopexin-like domain shortly after activation, apparently without loss of the elastin-degrading function (Curci et al., 1998).

The functional role of MMP-12 appears related to the remodeling of the extracellular matrix in tissues from fetal development to the entire adult life (Kerkela et al., 2001) and it is highly associated with inflammatory diseases involving macrophage infiltration, such as skin diseases (Saarialho-Kere et al., 1999), atherosclerosis (Matsumoto et al., 1998), aneurysms (Curci et al., 1998) and cancers (Kerkela et al., 2000). Moreover, MMP-12 is predominantly involved in acute and chronic pulmonary inflammatory diseases associated with an intense airway remodeling, particularly in the pathogenesis of COPD and emphysema.

Beside elastin, MMP-12 can cleave many of the other components of the extracellular matrix, such as fibronectin, fibrillin-1, laminin, entactin, type IV collagen fragments, vitronectin, heparin and chondroitin sulfates (Chen, 2004; Taddese et al., 2010) as well as non-matrix proteins, such as myelin basic protein, tissue factor pathway inhibitor (TFPI) (Belaaouaj et al., 2000), pro-TNF-α, (Chandler et al., 1996) plasminogen (Dong et al., 1997) and the blood plasma serpin α1-proteinase inhibitor (Banda et al., 1988) (see Table 3). MMP-12 is also involved in the *in vivo* activation of other MMPs, such as pro-MMP-2 and pro-MMP-3, which in turn can activate pro-MMP-1 and pro-MMP-9 (Bhaskaran et al., 2008). Moreover, unlike other MMPs, MMP-12 exhibits the unique property of being able to cleave N-terminal of Arg residues (Gronski et al., 1997).

8.1.2. Neoplastic diseases

8.1.2.1. Epidemiological aspects. MMP-12 has been proven to be of relevance for cancers development and prognosis in various organ systems. Increased expression and polymorphisms of MMP-12 have been shown to affect the development of several cancers. In addition, MMP-12 turns out to be the most efficient MMP for producing an endogenous inhibition of endothelial cell proliferation from specific degradation of plasminogen, thus identifying MMP-12 as one of the regulators of angiogenesis and tumor evolution (Shapiro, 1998).

Recently, an association between functional polymorphisms on MMP-12 gene promoter region and epithelial ovarian carcinoma has been described (Jia et al., 2010). MMP-12 genotype is also associated with an elevated esophageal adenocarcinoma (EA) risk and may have prognostic significance in EA patients (Bradbury et al., 2009). Moreover, increased expression of MMP-12 correlates with invasion and differentiation of endometrial adenocarcinoma, epidermal tumors and lung cancer, suggesting an involvement of MMP-12 in tumorigenesis (Hofmann et al., 2005; Kerkela et al., 2000; Yang et al., 2007b).

8.1.2.2. Tumorigenesis. Latest findings report that MMP-12 overexpression in myeloid lineage cells significantly contributes to modulate myelopoiesis, immune suppression and lung tumorigenesis (Qu et al., 2011). Furthermore, human patients affected by Chronic obstructive pulmonary disease (COPD), especially with a smoking history, are a high-risk population for developing lung cancer (Mannino et al., 2003). The molecular mechanism that links COPD and lung cancer is poorly understood, but evidence for an association of polymorphisms of MMP-12 with an higher risk of lung cancer has been provided (Su et al., 2006; Sun et al., 2006). In addition, a comparative genomic hybridization analysis identified in non-small cell lung cancer (NSCLC) an amplified MMP cluster region (11q22) with overexpression of MMP-1, MMP-12 and MMP-13 (Dehan et al., 2007).

The clinical relevance of MMP-12 has been observed in NSCLC, wherefore MMP-12 expression significantly correlates with local recurrence and metastatic disease (Hofmann et al., 2005). Although these studies showed association of MMP-12 overexpression with lung cancer, the role of MMP-12 up-regulation remains to be defined. Qu and colleagues tried to delineate the involvement of MMP-12 in the transition process between emphysema (and its associated inflammation) and tumor (Qu et al., 2009). Since MMP-12 overexpression in epithelial cells has been reported in inflammation-triggered lung remodeling, a murine CCSP-rtTA/(tetO)7-MMP-12 bitransgenic model was used. As a result of MMP-12 overexpression, sequential appearance of emphysema, epithelial dysplasia, and bronchioalveolar adenocarcinoma was developed, supporting that MMP-12 acts as a key player that controls emphysema to tumor transition in the lung. This seems partially achieved through the activation of the pro-inflammatory IL-6/Stat3 pathway and inflammatory cell infiltration (Qu et al., 2009).

8.1.3. Non-neoplastic diseases

8.1.3.1. Diseases of the cardiovascular system. Data have been accumulating that indicate that MMP-12 gene polymorphisms contribute to inter-individual differences in susceptibility to and outcome of cardiovascular diseases (CVD). Functional polymorphisms in the MMP-12 gene have also been related to coronary artery disease, arterial stiffness, and/or abdominal aortic aneurysm (Jormsjo et al., 2000; Ye, 2006). Furthermore, MMP-12 is up-regulated in atherosclerotic lesions and aneurysms and it may contribute to the activation of other MMPs, which in turn degrade other extracellular matrix proteins (Liang et al., 2006); therefore, this enzyme may represent a potential drug target for CVD treatment and prevention.

In a recent study Tanner and coworkers have evaluated the pharmacogenetic effects of MMP-12 variants on coronary heart disease, stroke, heart failure, combined coronary heart disease and cardiovascular disease. Their data highlight an interaction between antihypertensive drugs and MMP-12 levels for coronary heart disease and composite cardiovascular

disease, suggesting that the expression of MMP-12 gene may provide useful clinical information with respect to treatment decisions (Tanner et al., 2011).

8.1.3.1.1. Atherosclerosis. Based on histopathological findings, such as the activation of foamy macrophages, the local production of cytokines and chemokines and the involvement of MMPs (Janssens and Lijnen, 2006), atherosclerosis and related diseases are often compared with chronic inflammatory diseases (Hansson and Libby, 2006). The use of animal models strengthens the view that MMP-12 is a player in the hardening and narrowing of the arteries; indeed, MMP-12 knockout mice studies reveal reductions in atherosclerotic lesions size and macrophage number (Johnson et al., 2005) and overexpression of MMP-12 in transgenic rabbits, which induces a stimulation of plaque growth (Liang et al., 2006).

Moreover, Johnson and colleagues have shown that in apolipoprotein E-deficient mouse, inhibition of MMP-12 (using a selective compound) delays atherosclerotic plaque development, thus supporting the hypothesis that MMP-12 is critical for both plaque initiation and progression (Johnson et al., 2008). Recently, Yamada and coworkers have investigated macrophage migration and elastolysis in relation to fatty streaks in human MMP-12 transgenic (hMMP-12 Tg) rabbits, finding that MMP-12 production by macrophages plays a role in the transition from fatty acids to fibrous plaques during the progression of atherosclerosis (Yamada et al., 2008). On the basis of these results a specific MMP-12 inhibitor might eventually turn out to be useful for the treatment of progressive atherosclerosis.

8.1.3.1.2. Aortic aneurysms. MMP-12 has been shown to be upregulated in abdominal aortic aneurysm (AAA), an inflammatory disorder characterized by local connective tissue degradation, macrophage recruitment and infiltration leading to aortic dilation and rupture (Curci et al., 1998). MMP-12 deficiency (see Table 6) attenuates aneurysm growth, possibly by decreasing macrophage recruitment (Longo et al., 2002, 2005). Savio and colleagues support a mechanism whereby MMP-12 inactivation reduces macrophage recruitment into aneurysmal lesion sites by a decrease of proinflammatory cytokines expression and of the consequent vascular wall destruction (Savio et al., 2008). Moreover, recent findings indicate that MMP-12 activity significantly contributes to angiotensin II–induced aneurysm progression in the context of TGF-β neutralization and it is critically required for full elastin degradation and vessel rupture (Wang et al., 2010b).

Further, evidence has been provided that deficiency of MMP-12 protects apolipoprotein E-deficient mice against atherosclerotic media degradation and the accompanying ectasia and aortic dilatation (Luttun et al., 2004). However, even in the absence of MMP-12 aneurysms can still form, suggesting that its function is restricted to an enhancement of the elastic fiber degeneration by other MMPs (Longo et al., 2002; Pyo et al., 2000).

8.1.3.2. Diseases of the nervous system. With respect to the CNS, the literature on MMP-12 is sparse. Several studies highlight a linkage between MMP-12 activity and various CNS pathologies.

8.1.3.2.1. Encephalomyelitis. MMP-12 is up-regulated during experimental autoimmune encephalomyelitis and might play an active role during mononuclear cell infiltration in response to CNS infection (Pagenstecher et al., 1998). Several MMPs are increased in experimental autoimmune encephalomyelitis (EAE), an animal model of brain inflammation, with different roles in the pathogenesis. In particular, it was found that MMP-12 plays a protective role by favoring a T-helper 2 (TH2) bias, thereby reducing the TH1 autoimmune response (Weaver et al., 2005).

8.1.3.2.2. Meningitis. Evidence of an association between MMP-12-dependent elastin degradation and the inflammatory reaction of the angiostrongyliasis meningitis has been provides (Wei et al., 2011).

8.1.3.2.3. Multiple sclerosis. Myelin formation is critical for the proper function and survival of axons (Lappe-Siefke et al., 2003). During this event, oligodendrocytes (OLs) mature and they extend processes to contact and enwrap axons (Trapp et al., 1997). The loss of myelin thus results in multiple sclerosis (MS), where demyelination and concurrent axonal loss lead to a relevant disability. It has been reported that MMP-12 is present in active MS lesions in which its expression could be localized into phagocytic macrophages (Vos et al., 2003). In addition, investigation of serum, cerebrospinal fluid and brain tissue of patients with multiple sclerosis has revealed an increase in MMP-12 activity (Kurzepa et al., 2005). MMP-12 is also produced in large amounts by OLs *in vitro* to regulate their maturation and morphological differentiation (Larsen and Yong, 2004). Many growth factors are involved in the normal development of myelin, among these the insulin-like growth factor 1 (IGF-1) is very important for oligodendrocyte maturation (D'Ercole et al., 2002). IGF binding protein 6 (IGFBP-6), which sequesters IGF-1 and is synthesized in the CNS by astrocytes and OLs (Mewar and McMorris, 1997), is a substrate for MMP-12 processing (see Table 3), suggesting a function for MMP-12 in developmental myelination through the regulation of IGF-1 bioavailability (Larsen et al., 2006).

8.1.3.2.4. Spinal cord injury (SCI). Spinal cord injury (SCI) is a leading cause of permanent disability in young adults, resulting in partial or complete loss of motor and sensory function below the lesion site. Wells and colleagues have evaluated the role of MMP-12 in SCI showing that the expression of MMP-12 is markedly enhanced after mouse spinal cord compression and that MMP-12 null mice have better recovery from SCI than WT controls (Wells et al., 2003).

8.1.3.2.5. Intracerebral hemorrhage. An involvement of MMP-12 in intracerebral hemorrhage (ICH) has also been postulated, since MMP-12 expression has a negative impact on sensorimotor function following intracerebral hemorrhage in mice (Wells et al., 2005).

8.1.3.3. Disease of joints and muscular system.

8.1.3.3.1. Joints disease. Medial collateral ligament (MCL) injuries heal by a wound repair scar response controlled by a complex cellular and cytokine environment. Many enzymes participate in wound repair, particularly the matrix metalloproteinases. Investigations on MMP-12-deficient and wild-type (WT) mice indicate that MMP-12 is critical in the multifactorial cascade of knee MCL injury healing in both the early inflammatory phase and in tissue repair and remodeling (Wright et al., 2006). Moreover, an involvement of MMP-12 in the etiology of the anterior cruciate ligament (ACL) ruptures has been postulated (September et al., 2007), being also supported by the evidence of an association between the chromosomal region 11q22, in which MMP-12 gene localizes, and the risk of ACL rupture (Posthumus et al., in press).

8.1.3.3.2. Rheumatoid arthritis. Rheumatoid arthritis (RA) is a chronic disease characterized by articular tissue destruction and irreversible joint damage (Firestein, 2003). Ample evidence has shown that in the synovial membrane of RA patients, the number of macrophages is correlated to the extent of joint destruction (Tak et al., 1997). Further, it has been demonstrated that synovial tissue and fluid obtained from patients with rheumatoid arthritis contained higher activity of MMP-12 (Liu et al., 2004).

In addition, the effects of overexpressed MMP-12 on the development of experimentally induced inflammatory arthritis has been investigated using human MMP-12 transgenic rabbits which specifically express the human MMP-12 transgene in the macrophage lineage. These results demonstrate that an increased proteolytic activity of MMP-12 magnifies the degradation of the articular connective tissue and cartilage, thus playing a critical role in the development of an inflammatory joint disease (Wang et al., 2004c). Association of MMP-12 genotype with functional disability in rheumatoid arthritis patients was further demonstrated (Ye et al., 2007).

8.1.3.4. Diseases of the respiratory system. The role of MMP-12 is well documented in the pathogenesis of acute and chronic pulmonary inflammatory diseases associated with an intense airway remodeling. Its production stems from macrophage activation but also from resident cells synthesis (*i.e.*, epithelial cells, smooth muscle cells and endothelial cells along alveolar wall of lungs) (Lavigne et al., 2004; Lian et al., 2005).

8.1.3.4.1. Emphysema/chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) refers to chronic lung diseases, such as chronic bronchitis (CB), refractory asthma and emphysema, that are generically characterized by progressive airflow limitation and increased shortness of breath (Barnes et al., 2003). COPD represents a worldwide health problem largely attributable to exposure to tobacco smoke (Murray and Lopez, 1997). The pathogenesis of COPD is mainly characterized by an increase in inflammatory cells, such as macrophages, neutrophils and dendritic cells (DCs), in small airways and lung parenchyma (Barnes et al., 2003; Domagala-Kulawik et al., 2003). These cells are all capable of releasing proteinases in excess of their inhibitors, leading to an injury of the extra-cellular matrix (ECM) in the respiratory tract (Van der Vaart et al., 2004).

An essential aspect of COPD and emphysema involving MMP-12 is the degradation of elastin. Elastin is vital for the elastic recoil of the small airways and their ability to resist to a negative pressure collapse. In emphysema, elastin content of the lung parenchyma is decreased and elastic fibers are disorganized and probably nonfunctional (Shapiro, 2000). Moreover, elastin degradation products, such as desmosine, are increased in the urine of subjects with COPD (Stone et al., 1995) and correlate with the rate of lung function decline (Gottlieb et al., 1996).

In vitro studies on alveolar macrophages collected from COPD patients have shown their ability to degrade more elastin than macrophages collected from healthy volunteers (Russell et al., 2002). Furthermore, the resulting elastin fragments are chemotactic for monocytes, resulting in perpetuation of the inflammation (Houghton et al., 2006). Evidence from genetic studies, animal models and human disease linked variations in MMP-12 expression with both lung function in smokers and the risk of developing COPD (Babusyte et al., 2007; Demedts et al., 2006; Hautamaki et al., 1997; Hunninghake et al., 2009). Recently, case-control genetic studies on MMP-12 have given evidence for an association between MMP-12 polymorphisms and severe COPD (Haq et al., 2010, in press).

In several mouse models of COPD, deletion of MMP-12 expression induces resistance to emphysema despite prolonged cigarette-smoke exposure, impairing recruitment of monocytes/macrophages into lung possibly due to the loss of MMP-12 mediated generation of elastin fragments (chemotactic for monocytes) (Churg et al., 2002; Hautamaki et al., 1997; Leclerc et al., 2006) (see Table 6). Inflammatory lesions in mouse lung exposed to cigarette smoke is also associated with a significant increase of alveolar macrophages expressing MMP-12 (Valença et al., 2004).

Elevated MMP-12 protein levels have been also detected in the airways of patients affected by COPD. Specifically, MMP-12 production by macrophages is significantly increased in sputum (Demedts et al., 2006; LaPan et al., 2010) in bronchoalveolar lavage (BAL) and bronchial biopsies of COPD subjects (Babusyte et al., 2007; Molet et al., 2005).

The macrophage recruitment in lungs and emphysema induced by long-term exposure to cigarette smoke is linked to the elastolytic properties of MMP-12 (Hautamaki et al., 1997). Indeed, it was suggested that elastin degradation took place during development of pulmonary change in mice exposed to cigarette smoke and activation of MMP-12 may be a susceptibility factor for emphysema (Valença et al., 2004). Furthermore, Churg and coworkers have shown that in neutrophils from the bronchoalveolar lavage (BAL) of an acute model of smoke exposure desmosine and hydroxyproline, markers for elastin and collagen breakdown, respectively, cannot be detected in MMP-12 knockout mice; this evidence indeed suggests that acute smoke-induced connective tissue breakdown requires both neutrophils and MMP-12 and that the neutrophil influx is dependent on the presence of MMP-12 (Churg et al., 2002). The mechanism by which MMP-12 triggers cell activation and recruitment associated with inflammatory process in mouse airways involves the induction of TNF-α release from

macrophages, followed by endothelial cell activation, neutrophil recruitment and secretion of matrix degrading proteases (Churg et al., 2003, 2004). The direct effect of MMP-12 has been also evaluated using a recombinant form of human MMP-12 (rhMMP-12). It was reported that rhMMP-12 catalytic domain, directly injected in the airways of mice, is able to induce an intense inflammatory response characterized by a rapid accumulation of neutrophils correlated to a transient increase in cytokines and chemokines levels (TNF-α, MIP-1α, MCP-1, IL-6, and KC) and to gelatinase activation. A later response was also observed mainly due to macrophage recruitment (Nenan et al., 2005). The effect of rhMMP-12 was also examined on human alveolar type II-like epithelial cells (A549) and on human bronchial epithelial cells (BEAS-2B), showing that rhMMP-12 enhances the release of several chemokines by A549 cells, in particular, monocyte chemoattractant protein-1 (MCP-1)/CCL2, growth-related oncogene-α (GRO-α)/CXCL1, and IL-8/CXCL8 (Le Quement et al., 2008). In their study Chen and colleagues have partially elucidated the immunological mechanisms leading to pathologic changes associated to COPD (Chen et al., 2011b). They have shown that cigarette smoke is a powerful T helper 17 [Th17] cells adjuvant and that interleukin 17A receptor [IL-17RA] signaling is required for chemokine expression necessary for MMP-12 induction and tissue emphysema (Chen et al., 2011b).

A protective role for MMP-12 inhibitors has been postulated (Hu et al., 2007; Lagente et al., 2009), since MMP-12 inhibitors can substantially ameliorate morphological emphysema, small airway remodeling and the functional consequences of these lesions in a non-murine species. These findings strengthen the idea that MMP-12 is an important mediator of the anatomical changes behind COPD in humans, identifying MMP-12 as a potential therapeutic target (Churg et al., 2007).

8.1.3.4.2. Bronchial asthma. Asthma is associated with airway inflammation induced by environmental factors, such as allergens, pollutants and respiratory infections. During the course of the disease, an airway remodeling develops that includes epithelial damage, smooth muscle and mucus gland hyperplasia, bronchial hyper-responsiveness, angiogenesis, collagen deposition and airway wall fibrosis (Pascual and Peters, 2005). Few data have been published on the potential role of MMP-12 in asthma or in allergic airway inflammation; however, MMP-12 mRNA levels have been shown to increase in the lungs of mice subjected to allergens exposure, as compared to sham exposed counterparts (Cataldo et al., 2002). MMP-12 deficient mice display less inflammation than wild type mice and show a less important peribronchial fibrosis when challenged repetitively for 3 months with allergens (Warner et al., 2004), clearly indicating that in these models MMP-12 plays an important proinflammatory role in the development of the allergic response. In another experimental model of allergic bronchial asthma it has been shown an elevated MMP-12 up-regulation after the induction of asthmatic reaction in rats (Chiba et al., 2007).

MMP-12 is mainly expressed in airway epithelia and alveolar macrophages under the control of TNF-α, EGF and IFN-γ (Lavigne et al., 2004). An up-regulation of MMP-12 was also observed in bronchial smooth muscle cells by IL-1β and TNF-α, contributing to the altered extracellular matrix composition and to the degradative environment in the airway during chronic asthma (Araujo et al., 2008).

8.1.3.4.3. Lung fibrosis. Lung fibrosis is characterized by an increase in the number of fibroblasts in the interalveolar septa together with an increase in collagen and elastin deposition. This thickening of the septa results in the loss of elasticity and decreased gas exchange and the most severe forms of lung fibrosis (such as idiopathic pulmonary fibrosis) are fatal. The administration of bleomycin in rodent airways induces similar inflammatory and fibrotic responses as those observed in patients with pulmonary fibrosis. During the acute phase of this bleomycin-induced injury, a significant activation of MMP-12 has been observed in mice and rats (Koslowski et al., 1998; Swiderski et al., 1998). It has also been shown that pro-MMP-12 is converted into its active form earlier after bleomycin treatment during the peak time of macrophage levels and is associated only to areas of hemorrhagy (Swaisgood et al., 2000). In an immune complex-induced acute lung injury model using mice containing a targeted disruption of the MMP-12 gene, neutrophil influx into the alveolar space and lung permeability in knockout mice has been reduced by 50% of that observed in wild-type littermates. These results have been correlated with the histological evidence of a reduced injury in MMP-12-knockout mice (Warner et al., 2001b).

Using inducible transgenic mouse models for IL-13 and/or TGF-β it has been shown that MMP-12 deficiency regulates cytokine-induced inflammation and fibrosis; however, the mechanism remains unclear (Kang et al., 2007; Lanone et al., 2002). MMP-12-knockout mice were reported to be protected against Fas-L and bleomycin or transforming growth factor-β (TGF-β)-induced fibrosis (Kang et al., 2007; Matute-Bello et al., 2007), even though another study failed to detect any change in inflammation or collagen deposition in MMP-12-deficient mice in bleomycin-induced pulmonary fibrosis (Manoury et al., 2006).

Finally, it has been observed that IL-13-induced alveolar enlargement, lung enlargement, compliance alterations, and respiratory failure and death were markedly decreased in the absence of MMP-12. A deficiency in MMP-12 decreases the recovery of leukocytes, eosinophils, and macrophages, but not of lymphocytes or neutrophils (Lanone et al., 2002).

8.1.3.4.4. Idiopathic pneumonia syndrome (IPS). Idiopathic pneumonia syndrome (IPS) is a significant clinical problem encountered among patients treated with bone marrow transplantation (BMT). Although the specific etiology of IPS remains unclear, its mechanism includes cytokine-modulated immunological mechanisms during the acute and chronic phases after BMT leading to progressive, inflammatory and fibrotic lung disease. In recent findings it was shown that MMP-12 is important for limiting the development of IPS by allowing proper remodeling of extracellular matrix and effective repair of BMT-related injury (England et al., 2011).

8.1.3.5. Diseases of the digestive system. Infection with the parasitic helminth *Schistosoma mansoni* brings about a significant liver fibrosis and extracellular matrix (ECM) remodeling. Global gene analysis reveal that MMP-12 is highly induced in the

liver and lung in response to *S. mansoni* eggs (Sandler et al., 2003); therefore, a role of MMP-12 in the chronic helminth-induced inflammation and fibrosis has been postulated. In their study Satish and co-workers, using MMP-12-deficient mice, observe that MMP-12 promotes inflammation and Th2 cytokine-driven fibrosis in schistosomiasis by limiting the expression of ECM-degrading MMPs, such as MMP-2 and MMP-13 (Madala et al., 2010).

8.2. MMP-19

8.2.1. Structure and activation

MMP-19, also known as RASI-1, is a soluble 54 kDa protease with structural features that hinder its classification in each MMPs subfamily (see Fig. 1 and Table 2): the separated chromosomal localization (14q21) further reinforces this statement (Pendas et al., 1997).

Since the three-dimensional structure of the molecule is not available, some major structural insights have been deduced from its primary sequence and include: (i) an acidic residues-rich hinge region, (ii) a 26 residues-tail at the C-terminus hemopexin-like domain, where two putative N-glycosylation sites are further located (iii) an additional cysteine residue in the catalytic site with no apparent functional role (Mueller et al., 2000a; Pendas et al., 1997; Stracke et al., 2000).

The catalytic zinc ion is coordinated by the conserved consensus sequence, but the domain structure significantly differ from that of other soluble MMPs and does not harbor any predictable glycosylation sites (Stracke et al., 2000). The hemopexin domain adopts the classical β-propeller conformation and includes several Thr residues essential for cell surface localization of the enzyme (Mysliwy et al., 2006).

8.2.2. Biological features

Promoter elements of MMP-19 gene suggest either a constitutive or inducible expression of the enzyme (Mueller et al., 2000a). As a matter of the fact, vascular smooth muscle cells, epithelial and basal keratinocytes *in vitro* constitutively secrete the enzyme, whereas endotheliocytes and macrophages do express it upon stimulation (Murphy et al., 1999). Similarly, the MMP-19 distribution *in vivo* is physiologically relevant in adult lung, intestine, pancreas, ovary and placenta, while circulating leukocytes and monocytes/macrophages do not secrete appreciable amount of this enzyme. Stimuli that trigger its expression have not been defined yet with the exception of TNF-α (Hieta et al., 2003).

Substrates of MMP-19 initially included collagen IV, tenascin C, fibrin, fibrinogen, laminin, nidogen envisaging, consistently with the constitutive basal expression, the association of MMP-19 biological activity to pro-homeostatic role in ECM turn-over and remodeling (Pendas et al., 1997) (see Table 3). The subsequent identification of novel substrates, as aggrecan, IGFBP-3 and plasminogen has revealed a broader contribute of MMP-9 to the aetiology of physiological and pathological processes (Brauer et al., 2011). Inhibition by natural inhibitors mainly occurs through interaction of the hemopexin domain with TIMP-2 and TIMP-4.

8.2.3. Neoplastic diseases

8.2.3.1. Epidemiological and molecular aspects. Association of MMP-19 with tumor aetiology is controversial as from divergent findings in animal models and in epidemiological studies. Only few aspects of its activity have been recently clarified (Brauer et al., 2011; Müller et al., 2010), and several aspects still remain obscure.

Elevated concentrations of MMP-19 are found in the microenvironment of some human tumors. In particular, tumors from the central nervous system, such as glioma, display a diffuse MMP-19 expression which further correlates with an advanced state and invasiveness of the tumor (Brauer et al., 2011; Chan et al., 2011; Velinov et al., 2007). Nonetheless, MMP-19 quantification has become a WHO-accepted value for human glioma stadiation (Lettau et al., 2010; Müller et al., 2010; Stojic et al., 2008).

MMP-19 expression further increases during melanoma progression being maximal in the advanced "vertical growth" phase and MMP-19$^{-/-}$ mice show normal development but decreased susceptibility to skin tumors. Notably, the enzyme up-regulation inversely correlates to the E-cadherin loss, suggesting the existence of a cell adhesiveness-related modulation of MMP-19 transcription which could account for the requisite of inducibility (Müller et al., 2010).

8.2.3.2. Invasiveness. The affinity for matrix and, mainly, basement membrane components inevitably links MMP-19 activity to cell invasiveness. In this respect, consistent evidences highlight a role in the modulation of cell motility even under physiological conditions: degradation of laminin is associated to promotion of epithelial cells as well as keratinocytes migration and proliferation (Sadowski et al., 2003, 2005). Myeloid cells and T-lymphocytes efficiently compartmentalize the enzyme at their leading edge through interaction with unknown cell surface molecules, to improving extravasation and migration toward the flogistic site (Beck et al., 2008; Mauch et al., 2002). Additional evidence of a positive influence of MMP-19 in tumor growth come from studies *in vitro* on breast cancer cells where siRNA-mediated inhibition of the enzyme down-regulates tumor invasiveness (Hegedüs et al., 2008).

However, the controversy about MMP-19 association to neoplastic diseases stems from several evidences that question the pro-malignant effect; thus, in the advanced grade human tumors MMP-19 is found down-regulated (Müller et al., 2010). Furthermore, in experimental models MMP-19 content in epithelial cells is detectable until the malignant transformation occurs (Impola et al., 2003). Similarly, mice lacking MMP-19 show increased angiogenesis and tumor malignancy (Jost et al., 2006).

8.2.3.3. Angiogenesis. There is compelling evidence that angiogenesis is a critical step of tumor progression which could be targeted by MMP-19. The contribution of the enzyme to the promotion of physiological angiogenesis is documented; thus, MMP-19-mediated degradation of nidogen provides a scaffold for endothelial cells migration, furnishing stimuli for the de-differentiation (Titz et al., 2004). Conversely, an anti-angiogenic role in tumors is actually more convincing, as from MMP-19 deficient mice which show early onset of tumoral angiogenesis (Jost et al., 2006). Intriguingly, a molecular rationale for this observation comes from plasminogen: fragments released upon MMP-19 degradation exhibit angiostatin-like properties and reduce endothelial cells proliferation and sprouting (Brauer et al., 2011).

8.2.4. Non neoplastic diseases

8.2.4.1. Diseases of the nervous system.

8.2.4.1.1. Multiple sclerosis. MMP-19 expression is highly up-regulated in multiple sclerosis lesions and decreases upon therapeutical administration of interferon-β (Van Horssen et al., 2006).

Glial cells provide the reservoir of MMP-19 and, interestingly, surrounding-lesions astrocytes, which do not constitutively secrete the enzyme, induce the expression in response to not yet identified pro-inflammatory stimuli.

In MS lesions, aberrant degradation of Tenascin C occurs, leading to impaired neurite remyelinization. As previously reported, tenascin C is cleaved very efficiently by MMP-19.

MMP-19 further cleaves aggrecan, another molecule which undergoes proteolytical degradation in the onset and progression of MS. Therefore, MMP-19 pathogenic activity is presumably linked to destruction of axons architecture (Bernal et al., 2009).

8.2.4.2. Diseases of joints and muscular system. RASI-I, the alternative scientific name of the enzyme, is the acronym of Rheumatoid Arthritis Synovium Inflamed −1 because the enzyme has been initially found in the inflamed synovium of patients affected by this auto-immune disease (Sedlacek et al., 1998). Subsequent investigations about its role and biology have revealed the insights above discussed, but the association of MMP-19 and rheumatoid arthritis, even though devoid of molecular findings, has always represented an intriguing matter of discussion. In this sense, IgG Anti-MMP-19 antibodies have been identified in synovial fluid, allowing to hypothesize a direct involvement of the enzyme in the onset of auto-immune cascade (Sedlacek et al., 1998). Moreover, MMP-19 degrades the cartilage Oligomeric Matrix Protein (COMP) and aggrecan, compromising cartilage integrity (Stracke et al., 2000).

8.3. MMP-21

8.3.1. Structure

No details about the MMP-21 structure are available up to now. On the other hand, bio-informatic analysis of the amino-acidic sequence suggests a conserved domain composition, including the propeptide, the catalytic and the hemopexin-like domains (Marchenko et al., 2003).

8.3.2. Biological Features

The only available informations come from analysis of promoter elements which envisage a highly tissue-specific distribution of the enzyme. Transcription factors binding sites suggest that its expression should be modulated during differentiative processes and in embryogenesis (Ahokas et al., 2002, 2003; Skoog et al., 2009).

8.3.3. Neoplastic diseases

In several human tumors, including colorectal cancer, breast cancer, prostate cancer, pancreatic cancer, Merkel cell carcinoma, hepatocellular carcinoma, up-regulated levels of MMP-21 have been found, generally in association with poor prognosis (Bister et al., 2007; Hegedüs et al., 2008; Huang et al., 2011; Suomela et al., 2009; Wu et al., 2011b).

However, no molecular mechanisms of its pathological activity have been described.

8.4. MMP-28

8.4.1. Structure and function

Matrix metalloproteinase-28 (MMP-28), also known as epilysin, is a newly discovered MMP expressed in a number of normal tissues, such as testis, lung, intestine, heart brain and skin (Bernal et al., 2005; Illman et al., 2001; Lohi et al., 2001) as well as in a variety of tumors and tumor cell lines (Marchenko and Strongin, 2001).

MMP-28 is a 59 kDa protein, closely related to MMP-19 at the level of the amino acid sequence (Mueller et al., 2000b), with a great similarity (97%) in the catalytic domain between human and mouse proteins and overall 85% identity (Illman et al., 2008).

MMP-28 contains an activation sequence recognized by the furin endoprotease following the pro-domain (Mueller et al., 2000a,b), but it does not include domains characteristic of other furin-dependent MMP families (such as the disintegrin and thrombospondin-like regions) or the transmembrane group, as found in membrane-type MMPs (Lohi et al., 2001) (see Fig. 1). Moreover, the MMP-28 promoter has a unique conserved GF-box that is required for basal expression in keratinocytes (Illman et al., 2001).

An overexpression of MMP-28 was observed in multiple disease states (Overall and Kleifeld, 2006b), but it was particularly evident in osteoarthritic cartilage, degenerated intervertebral disc (IVD) tissue and during conditions of demyelation (Davidson et al., 2006; Kevorkian et al., 2004; Werner et al., 2008).

Despite increasing interest in the role of MMP-28, little is known about its substrates (see Table 3). Recombinant MMP-28 has been reported to degrade casein *in vitro* and it is thought to cleave several neural proteins such as neurite outgrowth inhibitor A (Nogo-A), neural cell adhesion molecule (NCAM-1) and neuregulin 1 (NRG1) (Lohi et al., 2001; Werner et al., 2007, 2008).

8.4.2. Neoplastic diseases

Increased expression of MMP-28 was observed in a variety of tumors and tumor cell lines and its role seems to vary based on tumor type and stage of the disease (Lin et al., 2006; Marchenko and Strongin, 2001; Wallard et al., 2006). Only in the case of colon carcinoma MMP-28, unlike other MMPs, is downregulated, as compared to normal tissues (Bister et al., 2004).

Lin and colleagues have observed a closed correlation between MMP-28 levels and oral squamous cell carcinoma (OSCC), supporting a role for MMP-28 in the anchorage-independent growth of both OSCC and esophageal carcinomas (Lin et al., 2006).

Importantly, an overexpression of MMP-28 in lung adenocarcinoma cells induces an epithelial to mesenchymal transition (EMT) via activation of the latent transforming growth factor β (TGF-β) (Illman et al., 2006; Illman et al., 2008). MMP-28-induced EMT is associated with loss of E-cadherin, a major mediator of cell–cell adhesion, as well as increased expression of MMP-9 (gelatinase B) and MMP-14 (MT1-MMP) (Illman et al., 2006; Illman et al., 2008).

Recent immuno-histochemical studies indicate a marked overexpression of MMP-28 in gastric carcinoma relative to normal epithelial cells (Jian et al., 2011). MMP-28 appears to be significantly associated with the depth of tumor invasion, lymph node metastasis and a poorer overall survival, representing a potential novel therapeutic target for the prevention and treatment of metastases in gastric cancer (Jian et al., 2011).

8.4.3. Non-neoplastic diseases

8.4.3.1. Disease of the nervous system. MMP-28 activity was shown to be involved in the development of several aspects of the neural microenvironment (Werner et al., 2007). MMP-28 plays an evolutionarily conserved role in neural development and it likely modulates the axonal–glial extracellular microenvironment (Werner et al., 2007). In addition, protein expression is inversely correlated with the expression of myelin-associated glycoprotein (MAG) during nerve regeneration (Werner et al., 2007).

Given the temporally regulated pattern of expression of MMP-28 prior to myelination in both developmental and regenerative states, it is likely that MMP-28 plays a functional role in the maturation of nerves. Moreover, under conditions of demyelination *in vivo*, MMP-28 is upregulated, inducing signaling *in vitro* consistent with myelination inhibition and suggesting that inhibition of MMP-28 may be beneficial for promoting the myelin repair (Werner et al., 2008).

8.4.3.2. Disease of joints and muscular system. The regulation and elevation in expression of the catabolic MMPs is of high importance in the human intervertebral disc (IVD), since it results in matrix destruction associated with disc degeneration. A role of MMP-28 in ECM modulation in the healthy and degenerating disc has been suggested (Gruber et al., 2009), reporting that both MMP-28 and the MMP-28 precursor are detectable in the disc cell cytoplasm and in the ECM of more degenerated specimens, with greater cellular localization in the outer annulus and in herniated disc specimens (Gruber et al., 2009). Recently, the expression levels of MMP-28 have been investigated in traumatic and degenerative human intervertebral disc (IVD) tissue with different degrees of degeneration (Klawitter et al., 2011). The findings demonstrate that while MMP-28 expression increases in individual cases with trauma or disc degeneration, there is no significant correlation between the grade of disease and MMP-28 expression. In addition, unlike many other MMPs, MMP-28 is not regulated by various inflammatory mediators (IL-1β, TNF-α, LPS) or by the histone deacetylase inhibitor trichostatin A (Klawitter et al., 2011). Future studies are needed to identify the role of MMP-28 in the intervertebral disc more conclusively.

8.4.3.3. Wound healing. MMP-28 is expressed in the basal and suprabasal epidermis in intact skin, whilst in the injured skin its expression is observed in basal keratinocytes both at the wound edge and some distance from it (Lohi et al., 2001; Saarialho-Kere et al., 2002). Wound healing studies showed that MMP-28 was spatially and temporally regulated, with a strong up-regulation of MMP-28 occurring in mitotic cells of wounded skin; this suggests that MMP-28 may be required to restructure the basement membrane or to degrade adhesive proteins between keratinocytes in order to supply new cells for the migrating front (Lohi et al., 2001; Saarialho-Kere et al., 2002). In primary cultures of human keratinocytes, MMP-28 expression is strongly stimulated by tumor necrosis factor α (TNF-α) (Saarialho-Kere et al., 2002). Moreover, mechanical compression significantly up-regulates MMP-28 secretion in hypertrophic scars (Reno et al., 2005).

In a recent work, the localization of both catalytically active and mutated inactive, overexpressed MMP-28 has been characterized in established epithelial cell lines (Heiskanen et al., 2009). These authors found that the protein localizes abundantly to the basolateral side of the cells and associates with a drastic reduction of basolateral ECM, as observed by the disappearance of collagen type IV, laminin and fibronectin.

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