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Review

Autoantibodies in inflammatory arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease characterized by extensive synovitis resulting in erosions of articular cartilage and marginal bone with joint destruction. The lack of immunological tolerance in RA represents the first step toward the development of autoimmunity. Susceptible individuals, under the influence of environmental factors, such as tobacco smoke, and silica exposure, develop autoimmune phenomena that result in the presence of autoantibodies. HLA and non-HLA haplotypes play a major role in determining the development of specific autoantibodies differentiating anti-citrullinated antibodies (ACPA)-positive and negative RA patients. Rheumatoid factor (RF) and ACPA are the serological markers for RA, and during the preclinical immunological phase, autoantibody titers increase with a progressive spread of ACPA antigens repertoire. The presence of ACPA represents an independent risk factor for developing RA in patients with undifferentiated arthritis or arthralgia. Moreover, anti-CarP antibodies have been identified in patients with RA as well as in individuals before the onset of clinical symptoms of RA. Several autoantibodies mainly targeting post-translational modified proteins have been investigated as possible biomarkers to improve the early diagnosis, prognosis and response to therapy in RA patients. Psoriatic arthritis (PsA) is distinguished from RA by infrequent positivity for RF and ACPA, together with other distinctive clinical features. Actually, specific autoantibodies have not been described. Recently, anti-CarP antibodies have been reported in sera from PsA patients with active disease. Further investigations on autoantibodies showing high specificity and sensibility as well as relevant correlation with disease severity, progression, and response to therapy are awaited in inflammatory arthritides.

Contents

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1. Mechanisms of autoantibody formation in inflammatory arthritis

Inflammatory arthritis is a group of rheumatologic conditions affecting approximately 3% of the adult population [1]. Rheumatoid arthritis (RA) is the most prevalent inflammatory chronic systemic disease characterized by extensive synovitis and an autoimmune response leading to cartilage and bone erosions with consequent joint destruction [2]. The loss of the immunological tolerance to self-antigens represents the first step toward the development of autoimmune phenomena. Susceptible individuals, under the influence of genetic and environmental factors, develop an underlying autoimmunity that manifests as the presence of autoantibodies [3]. (See Fig. 1.)

1.1. Genes implicated in autoantibody formation

It is well known that several genes contribute to the loss of tolerance. For instance, gene factors may affect antigen processing and presentation, lymphocyte proliferation and differentiation, and may encode for receptors of T and B cells [4]. HLA haplotypes still play a major role in determining the development of specific autoantibodies. In particular, in RA, the amino acid sequence QKRAA, QRRAA, or RRRAA at positions 70–74 of the DRβ1 chain, called "shared epitope" (SE), is associated with the production of anti-citrullinated antibodies (ACPA) and with the disease susceptibility [5–7]. Multiple alleles in the DRB1 gene share the SE such as HLA-DRB1*0401, *0404, *0405, *0408, *0101, *0102, *1001, and *1402 [8]. Indeed, the conversion of arginine to citrulline at multiple pockets dramatically increases peptide affinity for DRB1*0401 and other SE alleles [9]. The increased peptide–MHC affinity leads to the activation of CD4 + T cells and can initiate an autoimmune response to citrullinated self-antigens in RA patients [10,11]. The peculiarity of the HLA-DRB1-SE is the association with a more severe disease characterized by early onset, rapid radiographic progression, and the presence of ACPA [12]. It has also been demonstrated that SE acts as a signal transduction ligand that binds to cell surface calreticulin and activates the NO-mediated oxidative signal in turn influencing the regulation of immunity [13,14]. The SE is also important in dendritic cells in which promotes the production of IL-6 and IL-23, activating and expanding Th17 cells [15]. The SE can also directly enhance the differentiation of Th17 cells expressing the receptor activator for NF-κB ligand [16]. Very recently, a protective role for the development of ACPA in RA has been identified for the HLA-DRB1*13 alleles; indeed, patients with the HLA-DRB1*13 have lower ACPA levels and decreased citrullinated epitope recognition [17]. Seronegative and seropositive RA can also be distinguished by non-HLA genes [18]. For instance, the second most important genetic association in Caucasian population is in the gene protein tyrosine phosphatase non-receptor type 22 (PTPN22) encoding a tyrosine phosphatase, Lyp, a powerful inhibitor of T cell activation. It has been hypothesized that the disease-associated allele would produce a protein affecting the threshold for B and T cell receptor signaling [19]. The single nucleotide polymorphism in PTPN22 increases the risk of RA by 40–80% (OR 1.4–1.8) [20–22]. In contrast, in the Asian population, the most important genetic association is with the peptidylarginine deiminases citrullinatin isoenzyme 4 (PADI4) gene [23,24]. PADI4 is one of several isoenzymes carrying the post-translational conversion of arginine residues to citrulline, and this may be related to the production of ACPA [25]. ACPA-positive and ACPA-negative patients have partial genetic overlap, but evidences supporting a different genetic risk profile are increasing, suggesting that not only from a genetic perspective but also from pathogenic and clinical perspective, ACPA-positive and ACPA-negative represent two forms of RA [26–28]. For ACPA-negative disease, HLA-DRB1*03 and the gene interferon regulatory factor 5 seem to predispose to ACPA-negative RA [29–35]. Recently, Viatte et al. have confirmed the results from the Rheumatoid Arthritis Consortium International evidencing known markers, including ANKRD55 (a gene of unknown function), and identifying new and specific markers of anti-CCP negative RA, such as prolactin and NFIA [36].

1.2. Environmental factors implicated in autoantibody formation

Data gathered from the literature point at an interaction with environmental factors, which seems necessary for the development of inflammatory arthritides. The risk factors suggested so far include diet, coffee intake, alcohol, and body mass index [37]. Cigarette smoking is the only risk factor clearly associated with disease susceptibility. Smoke has several detrimental arrows including complement activation

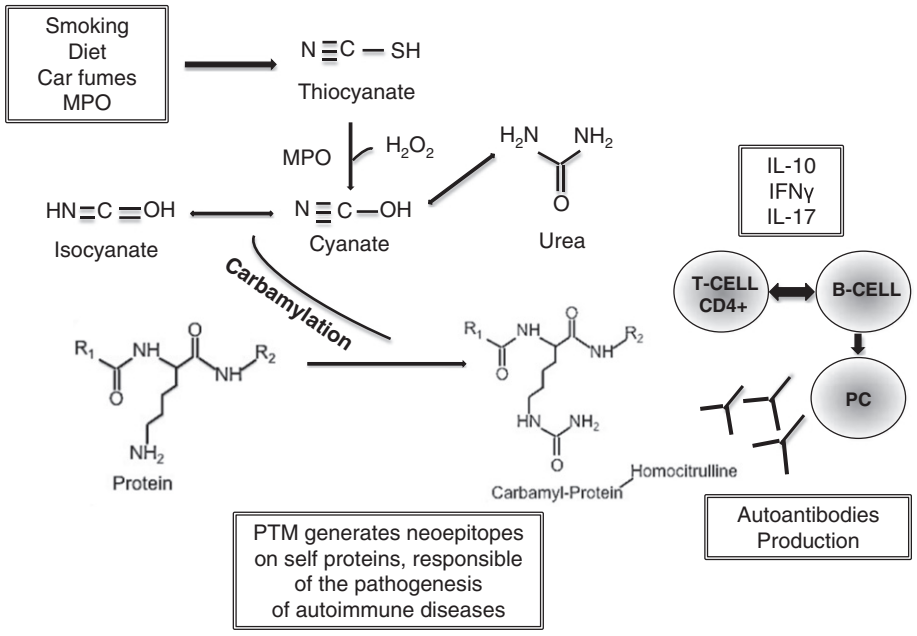

Fig. 1. *Carbamylation occurs on different amino acids via different mechanisms.* Homocitrulline is one methylene group longer and is generated from a lysine residue following a reaction of cyanate, which is present in the body in equilibrium with urea. Most carbamylation is believed to take place during inflammation when myeloperoxidase (MPO) is released from neutrophils. MPO converts thiocyanate to cyanate, now allowing more carbamylation to occur. PTM: post-translational modification; PC: plasmacells.

in vitro, induction of pro-inflammatory IL-1α, IL-1β, IL-6, and IL-8 and changes in gene expressions with a significant up-regulation of the heat-shock proteins in synovial fibroblasts [38–41]. Of interest, the association is true for ACPA-positive RA rather than ACPA-negative RA patients [42]. The number of the SE copies further modifies the risk. Smokers who do not carry the SE have a 1.5-fold elevated risk of developing ACPA and RA compared with non-smokers who do not carry the SE. This risk increases to 21-fold in smokers carrying two copies of the SE. Moreover, smoking increases the proportion of citrulline-positive cells in the lungs [43]. These findings suggested that smoking triggers citrullination in lungs through activation of PAD providing a substrate for the immune activation [43]. Carbamylation is a process similar to citrullination but the main difference concerns the modification of lysine instead of arginine [44]. Effects of carbamylation on proteins include changing of their polymerization ability, sensitivity to proteinases, and antibody antigen binding avidity [45,46]. Most of the carbamylation process is believed to take place during inflammation when myeloperoxidase (MPO) is released from neutrophils indicating that MPO released from neutrophils can further increase the level of carbamylation during inflammation [47,44]. Consequences of carbamylation have been reported to occur at the protein, cellular, and systemic level [48]. Anti-CarP antibodies have been identified in patients with RA and in individuals before the onset of clinical symptoms of RA [44,49]. The presence of anti-CarP antibodies in RA patients did not show significant associations with genetic risk factors (HLA-DRB1 alleles and PTPN22) and smoking suggesting that different biological mechanisms may be involved in the formation of anti-CarP and anti-CCP antibodies [50]. Another environmental risk factor identified in RA is the notorious *Porphyromonas* (*P.*) *Gingivalis*, the only bacterium known so far of containing the enzyme PAD involved in citrullination of both bacterial and human proteins such as arginine in fibrin in periodontal tissue [51,52]. RA is prevalent in individuals with chronic periodontitis [53]. Therefore, *P. gingivalis* can potentially contribute to the generation of *de novo* epitopes that may trigger the formation of autoantibodies. Contradictory data have been published regarding the correlation between the levels of antibodies against *P. gingivalis* and ACPA in RA patients [51,54,55]. ACPA might be produced outside the joint in the mucosal sites such as lung and gingiva. As a consequence, ACPA might cross-react through molecular mimicry with citrullinated epitopes in the joint initiating an inflammatory response in genetically susceptible individuals. Other substances may be associated with a higher risk of developing ACPA-positive RA, such as silica [56], especially in tobacco smokers. Silica exposure has been linked with the development of autoimmunity in several contests, probably associated with an alteration of Fas-mediated apoptosis in T lymphocytes [57].

2. Preclinical immunological phase in rheumatoid arthritis

The identification of patients in a preclinical phase may lead to an early diagnosis and a prompt treatment with better disease outcomes. Recent studies have demonstrated the presence of both rheumatoid factor (RF) and ACPA up to 10 years before the onset of RA in the so-called "pre-articular or lymphoid phase" of the disease [58–61]. The autoantibody titers increase as the onset of disease approach together with a progressive increase of ACPA antigens repertoire, known as epitope spreading [62]. Indeed, ACPA reactivity against characteristic specificities, in particular α-enolase, fibrinogen β36–52 and β74, and filaggrin seem to increase before disease onset in asymptomatic individuals [63]. This immunologic phenomenon has also been associated with a higher risk of progression to RA [64,65]. All together, these data suggested that the adaptive immune response against autoantigens is initiated years before the clinical signs of the disease. Likewise, in certain murine models of arthritis, it has been observed an increase in antibody levels before the onset of clinical symptoms or before the relapse of arthritis [66,67]. Recently, anti-CarP antibodies were detected in mice with collagen-induced arthritis (CIA) and appeared after immunization, which caused local inflammation, combined with the notion that inflammation can induce carbamylation and lead to a break of B cell tolerance to carbamylated proteins [66]. Furthermore, in a model of chronic antigen-mediated polyarthritis the production of ACPA, RF, and anti-type II collagen (CII) antibodies was observed in the absence of clinical signs of arthritis and increased before the relapse of arthritis [67].

3. Autoantibodies in undifferentiated arthritis

The term "undifferentiated arthritis" is used to describe those patients with early inflammatory arthritis during the first weeks to months following symptom onset, where it is not possible to establish a specific diagnosis. Many of these patients reach spontaneous remission without need to take a chance to adverse effect of treatment while others will eventually be diagnosed with RA after further evolution of the symptoms and findings [68]. In this contest, it is essential to recognize those patients with undifferentiated arthritis and positive predictive factors of RA development. ACPA-positive patients with undifferentiated arthritis have a chance of 90% to progress to full-blown RA within 3 years [69]. Indeed, ACPA represents an independent risk factor for developing RA in patients with undifferentiated arthritis or arthralgia [64,70,71]. Moreover, also the titer of ACPA in patients with arthralgia seems to predict future arthritis [72,73]. The ACPA isotype switching to IgG, IgA, IgM, or IgE occurs before disease onset in undifferentiated arthritis, without further changes after diagnosis [61]. In a recent large cohort study of subjects with general musculoskeletal symptoms ($n = 2028$), anti-CCP positivity was associated with a risk rate (RR) of 36.8 for a diagnosis of inflammatory arthritis and an RR of 50.4 for a diagnosis of RA. The sensitivity and specificity of anti-CCP for the diagnosis of inflammatory arthritis were 57.4% and 98.1%, respectively, while they increased to 64.9% and 97.9% for the diagnosis of RA [74]. Recently, also anti-CarP antibodies have been associated with the risk of developing RA (hazard ratio 1.56) in 340 patients with arthralgia during a median follow-up period of 3 years independently to anti-CCP antibody positivity [75]. Furthermore, the levels of anti-CarP antibodies were higher in individuals who subsequently developed RA compared with controls, and their concentration and frequency increased gradually after the disease onset. The sensitivity of anti-CarP antibodies was 13.9% in pre-symptomatic individuals and increased to 42.2% after the development of RA [76]. Indeed, current hypothesis suggests that these antibodies could be involved in the pathogenesis of RA since they appear several years before RF appearance and before the diagnosis of RA, similarly to what occurs for ACPA [49,72,77]. However, anti-CarP antibodies have been also detected in other forms of non-RA early arthritis such as in juvenile idiopathic arthritis (16.7%), reactive arthritis (16%), spondyloarthritis (15%) or psoriatic arthritis (9%) [78,79]. Further investigations are needed to shed more light on the presence of anti-CarP antibodies in other autoimmune/inflammatory arthritis different from RA.

4. Autoantibodies in rheumatoid arthritis

4.1. Classical autoantibodies

RF and ACPA are well-known serological markers for RA diagnosis according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [80]. RF is present in about 50–80% of patients affected by RA. It has a moderate specificity, around 66%, as it is detected in other autoimmune diseases, systemic infections, and in up to 10% of healthy subjects [81]. Nevertheless, many differences exist between RF in health and disease. The former is an IgM produced by B1 cells as "natural" antibody that shows low affinity and polyreactivity, the last undergoes isotype switching and somatic hypermutation as consequence of B cells

receiving help from T cells [82]. The lack of high specificity of RF has stimulated the research of other autoantibodies more specific for the diagnosis of RA. The identification of ACPA led to relevant and novel insights into RA diagnosis and etiopathology. Indeed, RA constitutes at least two clinical syndromes, ACPA-positive and ACPA-negative RA, that share many clinical features, but differ with respect to genetic background, predisposing environmental factors and clinical progression/remission [30,69,83,84]. ACPA recognize a variety of post-translational modified proteins generated from the enzymatic reaction catalyzed by PAD, such as filaggrin, fibrinogen, vimentin, type II and type I collagen, alpha enolase, heat-shock protein-90, and many others (Table 1). Citrullination is the critical step for the recognition of the different proteins, highly expressed in the synovial membrane during inflammation, by ACPA [85]. Interestingly, PAD enzymes were found in monocytes (PADI4) and macrophages (PADI2 and PADI4) in synovial fluid suggesting that citrullination may take place locally in the joint and B cells secreting ACPA have been detected in synovial fluid from RA patients [2,86–88]. Another observation that strongly supports the role of ACPA in RA pathogenesis comes from genetic studies such as the associations, abovementioned, with the gene encoding PADI4 or with HLA-DRB1 genes [25,69]. These autoantibodies show high specificity (98%), sensitivity comparable with RF (68%) [89]. There are different assays for measuring ACPA, the widely used are based on cyclic citrullinated peptides (CCP), both second-generation (CCP2) (patients peptide libraries) or third-generation CCP (CCP3) (combinatorial peptide libraries) [70,90,91]. There is no evidence so far that testing ACPA fine specificities may improve specificity and sensitivity of anti-CCP assays, although they could be important for understanding disease progression [65,92].

4.2. Additional autoantibodies

Other autoantibodies have been studied in RA and suggested as possible biomarkers, when considered alone or in combination, to improve diagnosis, prognosis, and response to therapy [93]. Most of them can be recognized by ACPA being part of this subgroup of autoantibodies (refer to Table 1). Anti-Ra33 antibodies (directed against an antigen of 33 kDa) recognize both unmodified and citrullinated heterogeneous nuclear protein (hnRNP) A2/B1, proteins present in spliceosome. They have been described in approximately 36% of patients affected by RA and they showed a high specificity (90–96%) and a low sensitivity (32%) [94,95]. Anti-Ra33 antibodies have been associated with early arthritis and also with a mild disease leaving a possible space as a prognostic marker [96]. In a recent study, Konig et al. identified three subgroups of RA patients; the first one who presented antibodies against citrullinated Ra33 with long-lasting disease and erosive pattern, those anti-native Ra33-positive, entirely in early phases and with minimal erosions, and lastly, patients positive for both native and citrullinated Ra33 that showed rapidly progressive disease [97]. Anti-mutated citrullinated vimentin (MCV) antibodies bind a mutated and citrullinated vimentin expressed in synovial tissues. The mutations occurring in vimentin (glycine to arginine) increase antigenicity and diagnostic value compared with anti-citrullinated vimentin antibodies, also known as anti-Sa antibodies [98]. In early RA, anti-MCV sensitivity and specificity (64% and 97%) are higher than those of RF [99]. A recent meta-analysis, which included a total of 12 studies and 2003 RA patients, demonstrated a higher sensitivity of anti-MCV (68.6%) than anti-CCP (61.7%) in the diagnosis of RA, although anti-MCV specificity (94.2%) remained lower than that of anti-CCP (97.1%) [100]. High levels of anti-MCV antibodies seem to predict a rapid erosive disease in early RA and have been associated with active disease and worst outcomes [101,102]. Anti-malondialdehyde (MDA) and anti-malondialdehyde acetaldehyde (MAA) antibodies are the result of post-translational modifications such as the lipid peroxidation [93]. Antibodies against MDA adducts, especially MDA-LDL, have been identified in RA patients and associated with cardiovascular disease as myocardial infarction [103]. A recent study demonstrated the presence of both MAA adducts and anti-MAA adducts in RA patients suggesting that these are more stable than MDA adducts and more likely to be present in vivo [104]. Furthermore, a positive correlation was observed between anti-MAA antibodies and the presence of ACPA revealed by multiplex antigen array [104]. However, anti-MAA antibodies are not very specific and not suitable for diagnostic purpose since they have been detected also in patients affected by alcohol-induced hepatitis or cirrhosis and type 2 diabetes [105,106]. Antibodies anti-PAD4 have been identified in 22–45% of RA patients and they show a specificity that is lower than 50% [107–109]. A specific group of anti-PAD4 antibodies cross-reacts with PAD3 and anti-PAD3 antibodies were detected in 12–18% of RA patients [110]. Patients with the cross-reactive PAD3/PAD4 antibodies seem to display an aggressive RA in terms of radiographic joint damage and progression of the disease [110]. BRAF, a serine–threonine kinase involved in the MAPK pathway, has been identified in RA by a proteomic approach aimed at the identification of autoantigens [109]. Anti-BRAF antibodies have been detected in 21–32% of RA patients [109,111]. However, anti-BRAF antibodies display a low specificity since they were detected also in systemic lupus erythematosus (SLE) and Sjogren's syndrome in almost similar percentages [93].

Anti-CII antibodies have been detected in about 30% of RA patients and they show a low specificity since they were detected also in other autoimmune diseases such as SLE, systemic sclerosis, and recurrent polychondritis. Anti-CII antibodies recognize different epitopes in human RA and murine models of arthritis, some of them shared between the different species including citrullinated-CII, C1, and U1 epitope [112]. High titers of anti-CII antibodies in RA synovial fluid and B cells producing anti-CII antibodies in RA synovia were reported [114,115]. Moreover, it has been demonstrated that serum and synovial titers of anti-CII IgG correlate with levels of acute phase proteins and pro-inflammatory cytokines, as TNF-α and IL-6 [116]. Immune-

Table 1
Anti-citrullinated protein antibodies in sera of patients with rheumatoid arthritis.

Antigen	Sensitivity (%)	Specificity (%)	Assay	Correlation	References
Keratine	36–59	88–99	ELISA	Early disease	[1]
Filaggrin	76	96	ELISA CCP-1	Unknown	[2,3]
CCP-patients peptide libraries	75.4	94.4–99	ELISA CCP-2	Severity and erosive disease	[4]
CCP-combinatorial peptide libraries	75–81.6	92–96.8	ELISA CCP-3	Early disease	[5,6]
Fibrinogen/fibrin	60.9–83	95–98.7	Immuno blotting	Unknown	[7,8]
Vimentin	47	98	Immuno blotting	Severity and erosive disease	[9–11]
MCV	64–82	97–98	ELISA	Severity and rapid erosive disease	[11–14]
Collagen type II	41	94	ELISA	Early acute inflammation and early radiographic damage	[15–17]
Collagen type I	32	99	ELISA	Unknown	[18]
alpha-enolase	37–62	98	ELISA	Unknown	[19]
BiP	95	Not known	Immuno blotting	Unknown	[23]
HSP-90	29	96	ELISA	Interstitial lung disease	[24]

CCP: cyclic citrullinated peptides; MCV: mutated citrullinated vimentin; BiP: stress protein immunoglobulin heavy-chain binding protein; ELISA: enzyme-linked immunosorbent assay; HSP-90: heat-shock protein-90.

complexes containing anti-CII were detected in human RA sera and could induce cytokine production such as TNF-α, IL-1β, CXCL8 via Fcγ receptor IIa expressed on macrophages [117]. Antibodies against the stress protein immunoglobulin heavy-chain binding protein (BiP), in the native and citrullinated forms, are found in 64–72% of RA patients and display a specificity of 71% and a sensitivity of 73% [118,119]. They have been implicated in the pathogenesis of RA since BiP was found to stimulate synovial T-cell and polymorphonuclear cell proliferation [120,121]. Anti-CarP antibodies have been extensively described in RA patients. These antibodies are a family different from ACPA that were identified for the first time in 35–45% of RA patients, mostly in ACPA-positive patients (49–74%), but also in ACPA-negative patients (16–30%) [122,123]. Inhibition studies confirmed that these antibodies overlapped only partially with the occurrence of ACPA [123]. In a recent study anti-CarP antibodies demonstrated in early arthritis a sensitivity of 44% and a specificity of 89%, both lower than those of anti-CCP and RF [78]. Therefore, anti-CarP antibodies could be useful for early diagnosis especially in ACPA-negative patients and for identifying patients that require an aggressive treatment [76,124]. How anti-CarP antibodies would contribute to arthritis is unknown but may involve immune complex formation between anti-CarP antibodies and carbamylated proteins in the joint.

4.3. Autoantibodies are associated with disease outcome

Autoantibodies have been largely investigated in order to establish serological markers able to early confirm clinical diagnosis of RA and to predict disease evolution [2].

High RF serum levels have been associated with an aggressive articular disease, extra-articular manifestations, and a worse outcome [125,126]. Likewise, ACPA have been associated with disease severity, radiological progression of the disease, disability, and increased mortality in RA [83,127–131]. The combination of ACPA and RF positivity correlates with a more severe and erosive disease and they associate with a worse disease outcome when compared with seronegative RA [132]. RF seems to enhance the pathological effects of ACPA through preferential binding to ACPA and potentiation of the subsequent immune response. Moreover, the course of ACPA-positive disease seems to be characterized by more persistent inflammation than its ACPA-negative counterpart [133]. Similar results were obtained in patients with undifferentiated arthritis where the presence of ACPA seems to predict more joint damage, progression to RA, and severe disease resulting in poor prognosis compared to ACPA-negative patients [64,83,134–136]. However, despite the fact that almost 40% of RA patients are ACPA negative, aggressive disease and severe radiologic progression can be present. For these reasons, new biomarkers are needed for early diagnosis and prognosis [58,91]. The presence of anti-CarP antibodies in ACPA-negative RA patients has been associated with increased disease activity and severe joint damage [123]. Comparable to ACPA, anti-CarP antibodies are independently associated with increased joint damage at the baseline of RA diagnosis [76]. Recently, anti-CarP antibodies have been associated in a large cohort of patients with inflammatory arthritides ($n = 1995$) with increased disability and higher disease activity [137]. Therefore, anti-CarP antibodies may be a useful biomarker to identify ACPA-negative patients who might evolve in RA and newly diagnosed RA patients who would require prompt and aggressive treatment [44]. Nonetheless, their significance in RA is still under investigation. For instance, Alessandri et al. found that anti-CarP can be detected in up to 9.2% of healthy first-degree relatives of patients with RA, a similar prevalence than anti-CCP and RF. Besides, it is not known whether these subjects will develop RA, it should be underlined that these autoantibodies did not correlate with anti-CCP neither with RF [138]. Anti-MCV antibodies have been demonstrated to perform better than ACPA as predictor of radiographic damage; conversely, its additional diagnostic and prognostic role in comparison to ACPA in both early and established RA is controversial [139]. Some authors found that anti-MCV might identify a subset of RA patients with aggressive early erosive disease [140]. Recently published ESPOIR cohort study compared the ability of ACPA, against anti-MCV antibodies and citrullinated fibrinogen to predict 1-year rapid radiographic progression in early RA, and suggested that anti-MCV antibodies can be more discriminant to predict radiographic progression risk [101]. Anti-CII antibodies seem to characterize an early inflammatory/destructive phenotype, in contrast to the late appearance of an inflammatory/destructive phenotype in ACPA-positive RA patients [141]. Anti-CII antibodies have been associated with increased radiographic damage at the time of diagnosis in a prospective cohort of early RA patients [141].

Autoantibody presence also seems to correlate with extra-articular clinical manifestations, such as the heart involvement. It is well reported that RA is an independent risk factor for cardiovascular events, which cause up to 40% of deaths in these patients [142,143]. Lopez-Longo et al. investigated the association between ACPA and ischemic heart disease in RA patients, and they found that ACPA presence is independently associated with the development of ischemic heart disease that is irrespective of the titers of autoantibodies [144]. The presence of autoantibodies characterize RA phenotype not only in terms of outcome but also in terms of clinical intervention [133]. Stratifying patients with undifferentiated arthritis or RA on ACPA presence led to the identification of more homogenous patient groups in terms of both disease course and response to treatment. Evidence from the literature suggested that low/intermediate pretreatment levels of ACPA were associated with a more favorable response to methotrexate treatment in recent-onset ACPA-positive arthritis, whereas high levels were associated with an insufficient response [145]. Likewise, in another study, methotrexate postponed RA diagnosis and retarded radiographic joint damage in ACPA-positive patients compared with undifferentiated ACPA-negative patients [146]. The BeSt study described that RA ACPA-positive patients treated only with DMARDS undergo greater joint destruction, while no difference in radiographic progression in RA ACPA-positive and RA ACPA-negative patients with combination therapy occurred [147]. More recently, 2-year results from the AMPLE trial investigated the impact of baseline ACPA concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab. In both treatment groups, ACPA-negative patients responded worse than antibody-positive patients. Patients with the highest baseline ACPA concentrations had a better clinical response to abatacept than patients with lower concentrations had. Such observation was not found in the adalimumab treated group [148]. Moreover, Gardette et al. investigated whether serum anti-CCP antibody could predict a good response to rituximab (RTX) in RA patients [149]. In this study, 114 RA patients were evaluated for a primary end point (decrease in DAS28 > 1.2 at 6 months) and secondary efficacy criteria including a good response and remission according to EULAR criteria. In accordance with this study, high anti-CCP antibody levels were associated with good response together with trend for remission [149].

5. Autoantibodies in psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy seronegative for RF, and associated with psoriasis [150]. PsA is classified among the SpA group because it shares with SpA several clinical manifestations as peripheral and axial joints involvement (arthritis, spondylitis, and sacro-ileitis), skin and nail diseases, dactylitis and enthesitis [151]. The overall prevalence of PsA has been reported to range from 0.01% (95% CI 0.00–0.17) in the Middle East to 0.19% (95% CI 0/16–0.32) in Europe [152]. Peripheral joint involvement is a potentially debilitating feature of PsA: it is commonly symmetrical and polyarticular that often affects distal interphalangeal joints distinguishing PsA from RA [153]. Characteristic extra-articular manifestations of PsA include psoriasis, nail psoriasis, uveitis, and inflammatory bowel disease (IBD), that may be frequently unrecognized or undertreated [154]. The extra-articular concomitant diseases, also

called comorbidities, such as obesity, dyslipidemia, type II diabetes, liver disease, and cardiovascular disease, are reported to be increased in patients with PsA, and their role in the progression and clinical response to treatment remains under investigations [154–157]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) developed and recently updated the treatment recommendations for the key manifestations of PsA, including related comorbidities [158]. The development of the Classification Criteria for Psoriatic Arthritis (CASPAR) facilitates clinicians in the classification of PsA [159]. Among the several classification criteria that have been published, CASPAR criteria result to be simple and easy to use and show high sensitivity by introducing the family history of psoriasis [160]. Medical history, physical examination, blood tests, and imaging (radiography, ultrasound, and magnetic resonance) of the joints are used for diagnostic purposes [161]. The diagnosis of PsA is thus mainly clinical and diagnostic biomarkers are not yet available. Enthesitis seems to be the *primum movens* of the disease, as well as the prominent clinical feature at presentation in up to 38% of PsA patients [162]. Monocyte-derived cytokines, as myeloid-related protein (S100A8/A9), seem to play a role in the propagation and perpetuation of the inflammatory process in patients with psoriasis and PsA, because of an activated monocyte/macrophage system involved in the "enthesal-complex" [163]. Evidence from the literature suggests that autoimmune processes may drive features of PsA [164]. Autoimmunity, in PsA pathogenesis, has been suggested by the presence of lymphoid aggregates in synovial tissues [165]. Histologically, PsA is characterized by lining layer hyperplasia, B and T lymphocytes' infiltrates, innate immune cells' activation, and joint vascular remodeling and angiogenesis [165]. We previously reported an abnormal distribution of peripheral blood B cell in both RA and PsA patients suggesting a role of B cells in PsA pathogenesis [166]. An autoimmune model describing potential autoantigens in the skin and joints of PsA patients has not been identified so far [151]. PsA is distinguished from RA by infrequent positivity for RF and ACPA, together with other distinctive clinical features [167,168]. Few studies looked for ACPA in PsA patients and found far lower prevalence compared to patients with RA (Table 2). However, authors described that presence of ACPA was significantly correlated with polyarticular involvement (often symmetric), presence of erosions, and presence of the shared epitope [169]. Prevalence and prognostic value of ACPA in PsA remain debated [170–175]. Detection of antinuclear antibodies (ANA) was recently reported as more frequent in sera from PsA patients than in those from controls suggesting that ANA could be a diagnosis orientation tool in autoimmune arthropathies [176]. TNF-α antagonists commonly used for treatment of moderate-to-severe psoriasis and PsA have been associated with induction of autoantibodies in PsA patients [177–179]. Recently, it has been described that routine autoantibodies monitoring in RA and PsA patients do not represent useful tool to predict the development of anti-adalimumab antibodies [180]. Indeed anti-adalimumab antibodies have been proposed as an early marker associated to a poor clinical response to the treatment [180]. Specific anti-PsA peptide antibodies were described in PsA patients and only in a small proportion of patients with psoriasis without PsA, suggesting that they could be specific for PsA [181]. Anti-PsA peptide antibodies target peptide epitopes expressed in skin proteins (fibrillin, desmocollin, and keratin) and in N-RAP, highly expressed within the entheses [181]. Moreover, these autoantibodies bind the Toll-like receptors (TLR)2 that play critical roles in the activation of innate immunity contributing to autoimmunity [181]. More recently, authors reported a gene array analysis of paired synovial membranes and peripheral blood cells in patients with PsA. They identified the modulation of cluster of genes encoding for molecules involved in cell migration and tissue invasion, in neoangiogenesis, in the process of bone formation, and in a T cell immune response with prevalent up-regulation of several Th17-related genes [182]. Anti-CarP antibodies were reported in sera from PsA patients with active disease in the absence of RF and/or ACPA specificities [151]. In accordance with such evidence, the measurement of anti-CarP antibodies shows a good

Table 2
Prevalence of several autoantibodies in the sera of patients with Psoriatic Arthritis.

Authors	PsA patients (*N*)	Controls (*N*)	Autoantibodies tested	Autoantibodies positivity in PsA
Silvy et al., 2015	232	HC (91)	ANA*	ANA 54%**
			RF	RF 15%
			Anti-CCP	Anti-CCP 1.7%
Chimenti et al., 2015	30	HC (40)	Anti-CarP	Anti-CarP 30.8%
			ANA*	ANA 3.4% §
			RF	RF 6.7%
			Anti-CCP	No patients with anti-CCP
Dalmády et al., 2013	46	PsO (42)	Anti-MCV	Anti-MCV levels
		HC (40)		Significantly higher in PsA than those in PsO
Pasquetti et al., 2009	218	None	Anti-CCP	Anti-CCP 0.9%
			RF	No patients with RF
Inanc et al., 2007	56	RA (79)	Anti-CCP	Anti-CCP 12.5%
		HC (39)	RF	RF 5.4%
Ouédraogo et al., 2007	102	None	Anti-CCP	Anti-CCP 1.9%
			RF	RF 2.9%
Alenius et al., 2006	160	PsO (146)	Anti-CCP	Anti-CCP 7%
		RA (101)	RF	RF 11%
		HC (102)		
Vander Cruyssen et al., 2005	192	None	Anti-CCP	Anti-CCP 7.9%
			RF	RF 8.3%
Korendowych et al., 2005	126	RA (40)	Anti-CCP	Anti-CCP 5.6%
		HC (40)	RF	RF 8.7%
Bogliolo et al., 2005	102	None	Anti-CCP	Anti-CCP 15.7%
			RF	RF 18.6%
Riente et al., 2004	75	AS (43)	Bovine tTg (IgA)	No differences between the groups
		RA (79)	Human tTg (IgA, IgG)	
		HC (78)	ASCA (IgA, IgG)	
Hoffmann et al., 2003	45	RA (56)	ASCA (IgA, IgG)	No differences between the groups
		HC (45)		

PsA: psoriatic arthritis; RA: rheumatoid arthritis; HC: healthy controls; PsO: psoriasis; AS: ankylosing spondylitis; ANA: antinuclear antibodies; RF: rheumatoid factor; anti-CCP: antibodies to cyclic citrullinated peptides; MCV: mutated citrullinated vimentin; tTg: anti-tissue transglutaminase antibodies; ASCA: anti-*Saccharomyces cerevisiae* antibodies.

* Detected by indirect immunofluorescence (IFI) on HEp-2 cells.

** At serum dilution 1:160.

accuracy as diagnostic test to discriminate PsA patients from healthy controls [151]. In PsA patients with the highest anti-CarP levels, correlations between anti-CarP autoantibodies and the disease activity were also described [151]. Carbamylation may thus be relevant in inducing autoimmunity in PsA, and given its systemic effects, it may represent a trigger for metabolic pathways such as anaerobic cysteine metabolism and oxidative stress in PsA [183]. Authors investigated the prevalence of anti-MCV in PsA patients and reported that anti-MCV levels were significantly higher in PsA patients than those in patients with psoriasis [184]. Moreover, the presence of tender knee joints and nail psoriasis resulted significantly associated with anti-MCV positivity in the PsA group [184]. As above specified, PsA is classified among the SpA group and, given that seronegative SpA, especially ankylosing spondylitis (AS), is shown to be associated with IBD, several studies were performed to investigate whether anti-*Saccharomyces cerevisiae* antibodies (ASCA), a marker for Crohn's disease (CD), were present in SpA and in the subgroups PsA, AS, undifferentiated SpA (uSpA) [185–187]. Recent evidence described an elevated serum antibody profile with respect to anti-flagellin antibodies (anti-CBir1) in AS patients without bowel symptoms suggesting that anti-CBir1 may be an indicator of subclinical bowel inflammation or predictor of future IBD in AS patients [188]. An earlier study reported ASCA IgA levels to be significantly higher in SpA, and more specifically in AS, than in healthy controls and patients with RA representing one of the first serum marker associated with SpA and also a potential marker of radiological damage and a more severe AS [186]. Other authors analyzed ASCA and IgA antibodies to bovine tissue tranglutaminase (tTg) and failed to show an increased prevalence of these antibodies in patients with AS and PsA [189]. Moreover, authors described a significantly elevated prevalence of IgA antibodies to human tTg in AS patients with low 25-vitamin D3 levels suggesting that a positive human tTg status entails the risk of a bad vitamin D supply [190]. More recently, anti-Helicobacter pylori antibodies were detected in patients with axial SpA more frequently than in patients with CD while ASCA resulted to be more abundant in CD than in SpA [187]. Nowadays no specific markers detectable in the sera of PsA patients have been described that can improve the diagnosis and the clinical and therapeutic management of these patients. Moreover, biomarkers able to distinguish between PsA and other inflammatory arthropathies and/or psoriasis and that could be used as prognostic markers are still lacking.

6. Conclusion

Increasing evidence suggests that autoantibodies are associated with inflammatory arthritides including RA and “seronegative” SpA. The well-characterized autoantibodies in RA are RF and ACPA, while other novel antibodies targeting mutated proteins, such as anti-CarP, are extensively under investigation. Autoantibodies appear to improve the early diagnosis in both symptomatic and preclinical patients and may represent a tool to evaluate/predict the response to the therapy. While correlations between autoantibodies and disease course are supported by studies in humans and animal models, their pathogenicity in inflammatory arthritides needs further studies.

Take-home messages

- In susceptible individuals, under the influence of environmental factors, autoantibodies may be produced in the joints or outside in the mucosal sites such as lung and gingiva.
- The most relevant autoantibodies in rheumatoid arthritis (RA) appear to be anti-citrullinated peptide antibodies (ACPA) that recognize a variety of post-translational modified proteins, such as filaggrin, fibrinogen, vimentin, type II collagen, alpha enolase, and others.
- Several autoantibodies have been investigated and proposed as potential biomarkers to improve diagnosis and outcome in RA patients.
- Carbamylation seems to take place during inflammation when neutrophils release myeloperoxidase. The presence of anti-CarP antibodies in ACPA-negative RA patients was associated with increased disease activity and with more severe joint damage.
- Anti-CarP antibodies have been described in sera of psoriatic arthritis (PsA) patients representing the first evidence of autoantibodies in PsA. Correlations between anti-CarP levels and disease activity were also reported in PsA.

Competing interests

The authors declare they have no competing interests.

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This paper is dedicated to the memory of our dear Professor Sergio Chimenti.

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