Journal of Neurochemistry

JNC

JOURNAL OF NEUROCHEMISTRY | 2019 | 148 | 168–187

doi: 10.1111/jnc.14574

REVIEW

The S100B story: from biomarker to active factor in neural injury

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Abstract

S100B is a Ca^{2+}-binding protein mainly concentrated in astrocytes. Its levels in biological fluids (cerebrospinal fluid, peripheral and cord blood, urine, saliva, amniotic fluid) are recognized as a reliable biomarker of active neural distress. Although the wide spectrum of diseases in which the protein is involved (acute brain injury, neurodegenerative diseases, congenital/perinatal disorders, psychiatric disorders) reduces its specificity, its levels remain an important aid in monitoring the trend of the disorder. Mounting evidence now points to S100B as a Damage-Associated Molecular Pattern molecule which, when released at high concentration, through its Receptor for Advanced Glycation Endproducts, triggers tissue reaction to damage in a series of different neural disorders. This review addresses this novel scenario, presenting data indicating that S100B levels and/or distribution in the nervous tissue of patients and/or experimental models of different neural disorders, for which the protein is used as a biomarker, are directly related to the progress of the disease: acute brain injury (ischemic/hemorrhagic stroke, traumatic injury), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis), congenital/perinatal disorders (Down syndrome, spinocerebellar ataxia-1), psychiatric disorders (schizophrenia, mood disorders), inflammatory bowel disease. In many cases, over-expression/administration of the protein induces worsening of the disease, whereas its deletion/inactivation produces amelioration. This review points out that the pivotal role of the protein resulting from these data, opens the perspective that S100B may be regarded as a therapeutic target for these different diseases, which appear to share some common features reasonably attributable to neuroinflammation, regardless their origin.

Keywords: biomarker, DAMP, neuroinflammation, S100B.

J. Neurochem. (2019) **148**, 168–187.

The term S100B refers to a protein identified in the mid-1960s, characterized by its solubility in a 100% saturated solution with ammonium sulfate (Moore 1965), this peculiarity being at the basis of its denomination, which originally was simply S100 protein. Using chromatographic and electrophoretic methods, the protein was detectable in brain extracts but not in non-neural tissues, so that it was originally thought to be specific to the nervous system.

At present, the S100 protein family comprises more than 20 calcium-binding proteins exhibiting structural similarities that operate as calcium-activated switches in different tissues and modulate the activity of a large number of targets. They represent the largest subgroup within the EF-hand protein superfamily, characterized by a calcium-binding loop forming a conserved pentagonal arrangement around the calcium ion (EF-hand motif). In addition, some members of the S100

Received April 16, 2018; revised manuscript received July 19, 2018; accepted August 15, 2018.

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Abbreviations used: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; bFGF, basic fibroblast growth factor; FGFR1, basic fibroblast growth factor receptor 1; CCL6, chemokine (C-C motif) ligand 6; COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; CXCL10, C-X-C motif chemokine; DAMP, danger/damage-associated molecular pattern; DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; EGC, enteric glial cells; ENS, enteric nervous system; GFAP, glial fibrillary acidic protein; IBD, inflammatory bowel disease; IL, interleukin; iNOS, inducible nitric oxide synthase; LPC, lysophosphatidylcholine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; ONO-2506, arundic acid; PD, Parkinson's disease; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species; SCA1, spinocerebellar ataxia-1; SERT, serotonin transporter; Tg APP(sw)mice, transgenic mice over-producing mutant amyloid precursor protein; Tg huS100B mice, transgenic mice over-expressing human S100B; TLR, Toll-like receptor; TNF-alpha, tumor necrosis factor alpha.

protein family bind zinc and/or copper, suggesting the possibility that these metals might participate in the regulation of their biological activity.

S100B, in particular, is an acidic homodimer (2 beta subunits) of 9-14 kDa per monomer, constituting the bulk of the protein fraction originally isolated from brain extracts. Its cell distribution has been extensively investigated. In the nervous system, S100B has been shown to be concentrated in astrocytes and other glial cell types, such as oligodendrocytes, Schwann cells, ependymal cells, retinal Muller cells, enteric glial cells, and it has also been reported to be located in definite neuron subpopulations (Ludwin *et al.* 1976; Brockes *et al.* 1979; Ferri *et al.* 1982; Didier *et al.* 1986; Rickmann and Wolff 1995; Yang *et al.* 1995). It has also been demonstrated that the protein is not restricted to nervous tissue (Cocchia *et al.* 1981). Since then, its distribution has been shown in definite cell types of non-neural tissues (Cocchia *et al.* 1981, 1983; Stefansson *et al.* 1982; Michetti *et al.* 1983, 1985, 1986; Lauriola *et al.* 1985; Tubaro *et al.* 2010). While the cell distribution of S100B does not appear to offer clues to its functional role(s), its location in adipocytes is especially intriguing, and suggests potentially new scenarios, since adipose tissue constitutes a site of concentration for the protein comparable to that of nervous tissue, and the levels of S100B mRNA expressed in cerebral cortex and adipose tissue have been shown to be very similar (Michetti *et al.* 1983; Sjöstedt *et al.* 2015). Interestingly, the conformation and amino acid composition of this protein, as in other members of the S100 family, is highly conserved in vertebrate species, suggesting that it may have crucially conserved biological role(s) and, possibly, a functional specificity (Kessler *et al.* 1968; Fanò *et al.* 1995). Additionally, an S100-like protein has even been immunologically detected in planarians (Michetti and Cocchia 1982).

Intracellularly, S100B, as a calcium-sensor protein, appears to regulate a variety of activities, transferring signals from second messengers and interacting with different molecules in different cell types. In particular, S100B intervenes in cell proliferation, survival and differentiation (Baudier *et al.* 1992; Millward *et al.* 1998; Arcuri *et al.* 2005; Raponi *et al.* 2007; Saito *et al.* 2007; Riuzzi *et al.* 2011; Shimamoto *et al.* 2014; Li *et al.* 2016), participates in the regulation of cellular calcium homeostasis and enzyme activities (Zimmer and Van Eldik 1986; Heierhorst *et al.* 1996; Pozdnyakov *et al.* 1997; Xiong *et al.* 2000; Gentil *et al.* 2001; Brozzi *et al.* 2009; Tsoporis *et al.* 2009; Wen *et al.* 2012; Agam and Almong 2015; Gogl *et al.* 2016) and even interacts with the cytoskeleton (Baudier and Cole 1988; Donato 1988; Skripnikova and Gusev 1989; Mbele *et al.* 2002), but data currently available do not appear to converge toward a clearly defined function. In contrast, there is mounting evidence indicating an increasingly clearer role for extracellular S100B.

The S100B protein was first detected in the extracellular compartment in the late 1970s, when elevated levels of the protein were detected in the CSF of multiple sclerosis (MS) patients in the acute phase, whereas lower levels were found in the stationary phase of the disease (Michetti *et al.* 1979). Measurements of S100B levels in biological fluids were then proposed as a biomarker of cell injury in the nervous system (Michetti *et al.* 1980). Since then, research on S100B as a biomarker of brain injury has been extended to other biological fluids besides CSF. Peripheral blood (Kato *et al.* 1983), cord blood (Gazzolo *et al.* 2000), amniotic fluid (Gazzolo *et al.* 2001a), urine (Gazzolo *et al.* 2001b, 2005a), and saliva (Gazzolo *et al.* 2005b) have all been shown to contain detectable levels of S100B, which have been found to be increased in a variety of pathological conditions of the nervous system. These include acute brain injury (cardiovascular disorders and traumatic injury), neurodegenerative diseases (Alzheimer's disease – AD, Parkinson's disease – PD, amyotrophic lateral sclerosis – ALS, MS), congenital/perinatal disorders (Trisomy 21, pre-term and full term asphyxiated newborns, intrauterine growth retarded fetuses), psychiatric disorders (schizophrenia, mood disorders). From the bulk of data regarding S100B in biological fluids, this protein at present emerges as an established biomarker of active neural distress, although the wide spectrum of pathological conditions in which it is involved significantly reduces its specificity. In fact, the evaluation of its levels in biological fluids resulted to be an important aid in clinical diagnosis when symptoms are present, in monitoring the trend of the disorder and eventual clinical outcomes, in guiding therapeutic decision making by enabling identification of patients likely to respond to a specific therapy and, as a consequence, in monitoring the response to therapeutic interventions. The evaluation of S100B levels in biological fluids as a biomarker of neural distress has been extensively investigated, is still the goal of active research, and has been the object of recent valuable reviews focusing different disorders (Astrand *et al.* 2013; Chong 2016; Lai and Du 2016; da Rosa *et al.* 2016; Satriano *et al.* 2017; Thelin *et al.* 2017a,b).

Intriguingly, following early findings of S100B in melanocytes and melanoma tissue (Cocchia *et al.* 1981) the protein has been extensively used as a biomarker for this disease both in blood (Guo *et al.* 1995; Henze *et al.* 1997) and in pathologic tissue (Springall *et al.* 1983; Cochran *et al.* 1993). At present S100B is regarderd to be a well-established biomarker also for malignant melanoma, and useful in assessing tumor load, stage and prognosis for patients with this disease (Zarogoulidis *et al.* 2015; Gambichler *et al.* 2018). A role in melanoma tumorigenesis has also been attributed to S100B, since it has been shown to interact and down-regulate the transcription factor p53, which is regarded to exert a tumor suppressor effect (Lin *et al.* 2001, 2010). While the neuroectodermal origin of melanoma may suggest

a linkage between the relevance of S100B in this disease and the numerous neural disorders in which it is involved, at present a unifying scenario has not been delineated. However, the putative role played by the S100B-p53 interaction in melanoma processes has stimulated the development of research programs aimed at individuating molecules able to interfere with this interaction (Cavalier *et al.* 2016), which might finally result of wider utility.

In synthesis, mounting evidence now points to S100B as a factor actively participating in processes accompanying neural injury, even extending the range of neural pathological conditions where the protein is currently used as a biomarker: this perspective is addressed in this review.

S100B as an active factor in neural injury

Originally, the rationale of studies on S100B in biological fluids as a biomarker of neural injury interpreted the detection of the protein as a consequence of its leakage from damaged cells. However, S100B is also actively released by different cell types, especially in conditions of stress (Shashoua *et al.* 1984; Suzuki *et al.* 1984; Van Eldik and Zimmer 1987; Gerlach *et al.* 2006). Extracellular S100B has also been shown to interact with surrounding cell types through the Receptor for Advanced Glycation Endproducts (RAGE) (Hofmann *et al.* 1999; Huttunen *et al.* 2000). RAGE is a ubiquitous, transmembrane immunoglobulin-like receptor that binds to a diverse range of extracellular ligands and intracellular effectors, initiating a complex intracellular signaling cascade, which may also be associated with a series of pathological conditions, including neuroinflammatory reaction to neural injury, and concomitantly resulting in an up-regulation of RAGE itself (for review, Bongarzone *et al.* 2017). Data have also been reported indicating that extracellular S100B is captured by vesicles and re-uptaken by astrocytes in a RAGE-dependent manner (Lasic *et al.* 2016). Interestingly, the activity of S100B has been associated with multimerization, so that tetrameric S100B has been shown to exhibit a higher binding affinity than dimeric S100B to RAGE (Ostendorp *et al.* 2005). RAGE appears not to be the sole receptor for S100B. In a non-neural experimental system (cultured myoblasts), S100B has also been shown to interact with the basic fibroblast growth factor (bFGF)/FGF receptor 1 (FGFR1) system. In particular, at relatively high doses, S100B stimulates the mitogenic bFGF/FGFR1 signaling in low-density myoblasts, provided bFGF is present. In this context, S100B acts as a signal released from injured muscles that participates in skeletal muscle regeneration by activating the promyogenic RAGE or the mitogenic bFGF/FGFR1 depending on its own concentration, the absence or presence of bFGF, and myoblast density. (Riuzzi *et al.* 2011, 2012). These findings enlarge the perspective of possible druggable interferences on the S100B/receptor(s) system. The biological activity of extracellular S100B has been closely associated with its concentration. Earlier studies, subsequently confirmed, indicated a neurotrophic effect for S100B at low (nanomolar) concentrations, which are believed to be physiologic. Effects such as promotion of neurite extension, modulation of long-term potentiation, protection of neuron survival, counteraction to neurotoxicant insults, increased scavenger activity of reactive oxygen species (ROS) have been reported (Kligman and Marshak 1985; Winningham-Major *et al.* 1989; Bhattacharyya *et al.* 1992; Barger *et al.* 1995; Haglid *et al.* 1997; Iwasaki *et al.* 1997; Ahlemeyer *et al.* 2000; Nishiyama *et al.* 2002; Reali *et al.* 2005; Businaro *et al.* 2006; Clementi *et al.* 2016). Nanomolar S100B concentrations produce low amounts of signaling oxygen radicals that lead to the activation of the anti-apoptotic factor Bcl-2 (Donato *et al.* 2009). In contrast, toxic/pro-inflammatory effects have been shown to be induced by S100B at high (micromolar) concentrations (Koppal *et al.* 2001; Lam *et al.* 2001; Valencia *et al.* 2004; Schmitt *et al.* 2007; Piazza *et al.* 2013; Fujiya *et al.* 2014; Niven *et al.* 2015). Persistent activation of RAGE by micromolar concentrations of S100B produces increased amounts of oxygen radicals, and this could lead to mitochondrial dysfunction and induction of apoptosis. Moreover, its signaling pathways converge to the transcription of pro-apoptotic genes (Donato *et al.* 2009). This aspect (the 'Hyde side' of the protein) has been attracting increasing interest. In particular, micromolar S100B has been reported to up-regulate inducible nitric oxide synthase (iNOS), to induce NO release and the NO-dependent death of neurons and glia, to facilitate glutamate-induced neuronal death, to stimulate the activation status in astrocytes, to up-regulate cyclooxygenase-2 (COX-2) expression in microglia, to increase the production of ROS in neurons, to induce the perturbation of lipid homeostasis and cell cycle arrest and to impair oligodendrogenesis (Hu *et al.* 1996, 1997; Huttunen *et al.* 2000; Petrova *et al.* 2000; Esposito *et al.* 2007; Shanmugam *et al.* 2008; Bernardini *et al.* 2010; Bianchi *et al.* 2010; Villarreal *et al.* 2011; Reali *et al.* 2012; Santos *et al.* 2018). In the nervous system, astrocytes are currently regarded to be the main source of extracellular S100B (Fig. 1). In this respect, the finding that the protein activates a RAGE-dependent autocrine loop in astrocytes, turning them into a pro-inflammatory/neurodegenerative phenotype, promises to help clarify the role(s) played by the 'Hyde side' of S100B (Villarreal *et al.* 2014). Thus, S100B, in common with other proteins of the S100 family, may be joined to danger/damage-associated molecular pattern (DAMP) molecules, or alarmins, which are released in the endogenous microenvironment to trigger tissue reaction to damage (for reviews, Chen and Nunez 2010; Braun *et al.* 2017). Interestingly, some characteristics of S100B, such as its non-canonical secretion modality that bypasses the classical Golgi route, its interaction with RAGE and its ability to stimulate microglial migration, are shared with DAMPs (Foell *et al.* 2007; Sorci *et al.* 2010). Since DAMPs

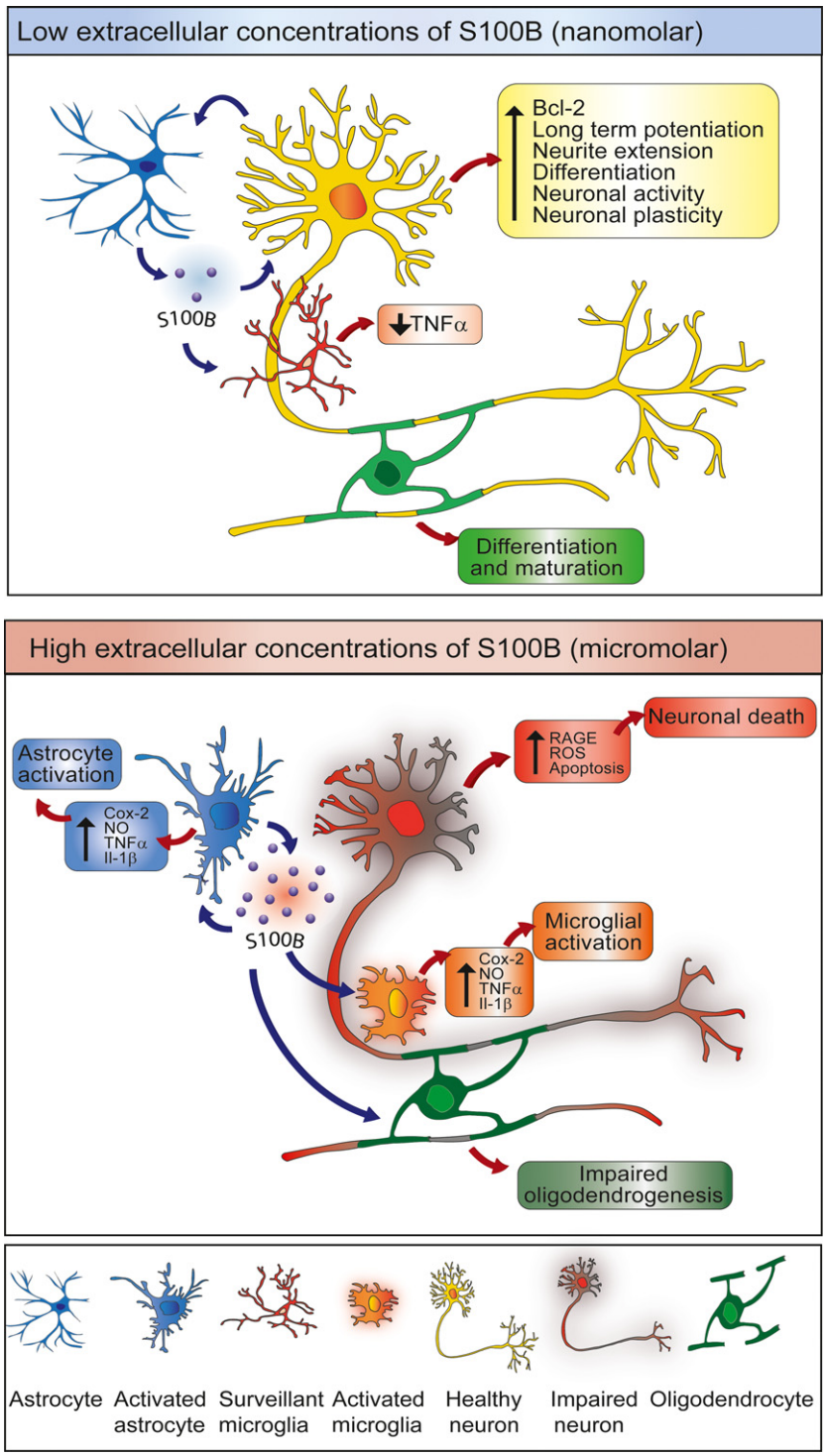

Fig. 1 Biological activity of extracellular S100B in the different cell types of the CNS at low and high concentrations.

can be released in the extracellular space in the early stages of diseases and their levels often correlate with the disease progression, they may be used as biomarkers for the appropriate diagnosis and prognosis of different pathologies. A paradigmatic example in this respect is High-Mobility Group Box 1 (HMGB1) (Walker *et al.* 2017), which behaves as a 'mechanistic' biomarker, since it is directly involved in the pathogenesis of diseases for which it acts as a biomarker. This appears to be also the case of S100B. Thus, in the light of these findings and considerations, the hypothesis that S100B, released at high concentrations, may actively participate in pathological processes of neural injury, where it is a

recognized biomarker, has been formulated (Michetti *et al.* 2012). There is now sufficient evidence to reasonably confirm a role for S100B in the pathogenic processes of a series of diseases variously involving the nervous system. Regardless of the origin of the disease, these processes appear to share some common features, which might be reasonably attributed to inflammatory processes, for which a pivotal role played by S100B is increasingly emerging.

Acute brain injury

Both CSF and blood S100B levels are currently regarded as reliable biomarkers for acute brain injury caused by cardiovascular disorders or traumatic injury, and a predictive value for the outcome of these patients is also currently attributed to S100B levels in biological fluids (de Azúa López *et al.* 2015; Chong 2016; Kellermann *et al.* 2016). The clinical utility of blood S100B levels in the assessment of traumatic brain injury has been recently reviewed (Thelin *et al.* 2017a). In this case, an extra-neural origin (namely adipose) for S100B in the blood appears to have a special relevance for the interpretation of results, since elevated S100B levels have also been shown in patients suffering from trauma in the absence of head injuries (Anderson *et al.* 2001). However, bearing in mind that S100B released from extracerebral origin appears to have a faster clearance than S100B released from the CNS (da Rocha *et al.* 2006), accurate timing in sampling reasonably reinforces the predictive value of S100B measurements.

Interesting indications of a role of the protein in pathogenic processes induced in acute brain injury are offered by experimental models. In an experimental model of traumatic brain injury (controlled cortical impact), S100B levels and expression of S100B mRNA increased in the injured tissue (Kleindienst *et al.* 2005b; Sandhir *et al.* 2008). In the same model, inhibition of the protein has been shown to reduce behavioral and pathologic changes. In particular, systemic treatment with a neutralizing anti-S100B antibody (Kabadi *et al.* 2015) induced significant improvement in memory retention and sensorimotor performance when compared with vehicle and IgG control-treated mice. Moreover, it reduced lesion size, improved cortical neuronal survival and attenuated microglial activation at 7 and 28 days after injury. Similar, though not overlapping, results were obtained after genetic ablation of S100B, using S100B knockout mice (Kabadi *et al.* 2015). On the other hand, intraventricular infusion of S100B has also been reported to induce dentate neurogenesis accompanied by improved cognitive function in a model of experimental traumatic brain injury (lateral fluid percussion) (Kleindienst *et al.* 2005a). These discrepancies could be ascribed to different concentrations of S100B (toxic or trophic) in affected tissues.

In rodent ischemia models the protein was over-expressed in the injured tissue as well as in the periinfarct area (Tateishi *et al.* 2002; Asano *et al.* 2005; Zhang *et al.* 2018). In addition, transgenic mice over-expressing human S100B (Tg huS100B mice), exhibited significantly larger infarct volumes and worse neurological deficits after permanent middle cerebral artery occlusion as compared to controls (Mori *et al.* 2008). On the contrary, the pharmacological blockade of S100B synthesis in astrocytes using arundic acid (Tateishi *et al.* 2002) resulted in the prevention of delayed infarct expansion, accompanied by an amelioration of neurologic deficits (Asano *et al.* 2005). More recently, RNA interference-mediated silencing of S100B has been shown to improve nerve function recovery and to inhibit hippocampal cell apoptosis in rats with ischemic stroke (Zhang *et al.* 2018) (Tables 1 and 2).

Neurodegenerative diseases

In the classic neurodegenerative disorders (AD, PD, ALS) S100B concentration in CSF usually reflects the severity of the pathological condition, whereas, in many cases, S100B levels in blood remains unchanged during the course of the disease. In MS, which is characterized by apparent inflammatory processes, S100B levels have been shown to reflect clearly the severity of the disease in both CSF and blood (for review, Michetti *et al.* 2012). Studies aimed at investigating different phases of the diseases and the dynamics of the protein in different fluid compartments will be needed to clarify these discrepancies. However, univocal indications for a role played by S100B in these diseases are offered by the study of the protein in patient and experimental model tissues.

There is a convergence of evidence indicating a role for S100B in the pathogenic processes associated with AD. Data have been emerging since the late 1980s indicating that the protein is up-regulated in tissues of human and experimental models of AD (Griffin *et al.* 1989; Marshak *et al.* 1992; Sheng *et al.* 1994, 1996; Van Eldik and Griffin 1994; Mrak *et al.* 1996; Craft *et al.* 2004). Interestingly, the protein exhibited higher expression levels in the most severely affected regions, and S100B-labeled astrocytes were clustered around and within Tau-2-labeled plaques, whereas no Tau-2-labeled plaques were found without S100B-labeled astrocytes (Sheng *et al.* 1994). In addition, the expression of S100B has been shown to increase in cultured astrocytes treated with the Abeta peptide, so that a pathogenic loop involving astrocytic S100B in AD processes may be hypothesized (Chow *et al.* 2010). Transgenic TghuS100B mice over-expressing the protein also exhibit an enhanced susceptibility to neuroinflammation, whereas no changes were found in the plaque load after Abeta infusion, when compared with non-transgenic mice (Craft *et al.* 2005). S100B over-expression has also been reported to exacerbate cerebral amyloidosis in the Tg2576 mouse model of AD, when these mice were crossed with transgenic mice over-expressing human S100B (TghuS100B mice) (Mori *et al.* 2010). Likewise, S100B over-expressing transgenic mice

Table 1 Alterations of nervous tissue S100B levels and distribution in different neural disorders

	S100B expression level		References
Pathology	Human	Experimental models	
Traumatic brain injury		Lateral fluid-percussion injury in rats: ↑whole brain	Kleindienst *et al.* (2005a)
		Controlled cortical impact injury in rats: ↑hippocampus	Sandhir *et al.* (2008)
Ischemic stroke		Permanent middle cerebral artery occlusion in rats: ↑periinfarct area and whole affected hemisphere	Tateishi *et al.* (2002)
		Middle cerebral artery occlusion in rats: ↑periinfarct area	Asano *et al.* (2005)
		Middle cerebral artery occlusion in rats: ↑hippocampus	Zhang *et al.* (2018)
Alzheimer's disease	↑temporal lobe		Griffin *et al.* (1989)
	↑temporal lobe		Marshak *et al.* (1992)
	↑hippocampus		Van Eldik and Griffin, (1994)
	↑hippocampus and adjacent temporal cortex: S100B+ astrocytes clustered around and within Tau-2-labelled plaques		Sheng *et al.* (1994)
	↑temporal lobe S100B+ astrocytes clustered around and within Tau-2-labelled plaques		Mrak *et al.* (1996)
		Intracerebroventricular Aβ infusion in rats: ↑hippocampus	Craft *et al.* (2004)
		↑rat cultured astrocytes treated with Aβ peptide	Chow *et al.* (2010)
Parkinson's disease		MPTP mice: ↑striatum and substantia nigra	Kato *et al.* (2004)
	↑substantia nigra pars compacta		Sathe *et al.* (2012)
		MPTP mice: ↑ventral midbrain area containing the substantia nigra pars compacta	Sathe *et al.* (2012)
		MPTP mice: ↑striatum	Viana et al (2016)
		6-hydroxydopamine injection in rats: ↑striatum	Morales *et al.* (2016)
	↑prefrontal cortex		Rydbirk *et al.* (2017)
Amyotrophic lateral sclerosis	↑brain cortex		Kamo *et al.* (1987)
	↑spinal cord		Migheli *et al.* (1999)
		SOD1-G93A rats: ↑spinal cord	Diaz-Amarilla *et al.* (2011)
		SOD1-G93A rats: ↑spinal cord	Serrano *et al.* (2017)
Multiple sclerosis	↑cortex both in acute and subacute plaques		Petzold *et al.* (2002)
	↑demyelinating regions in active and chronic active lesions		Barateiro *et al.* (2015)
		EAE in rats: ↑forebrain	Grygorowicz *et al.* (2016)

(continued)

Table 1. (continued)

Pathology	S100B expression level		References
	Human	Experimental models	
Down's syndrome	↑brain cortex		Jørgensen *et al.* (1990)
	↑brain cortex		Goodison *et al.* (1993)
	↑brain cortex		Chen *et al.* (2014)
Spinocerebellar Ataxia-1		SCA1 transgenic mice: ↑Purkinje cells accompanied with an abnormal morphology in dendritic spines	Vig *et al.* (2006)
	↑Purkinje cells		Vig *et al.* (2009)
		SCA1 transgenic mice: ↑Purkinje cells	Vig *et al.* (2009)
		SCA1 transgenic mice: ↑cerebellum	Vig *et al.* (2011)
Inflammatory bowel disease	↑duodenum		Esposito *et al.* (2007)
	↑rectum		Cirillo *et al.* (2009)
		DSS-induced acute colitis in mice: ↑colon	Esposito *et al.* (2012)
Schizophrenia	↑frontal cortex		Steiner *et al.* (2008)
	↓white matter of the anterior cingulate gyrus		Katsel *et al.* (2011)
	↓corpus callosum		Steiner *et al.* (2014)
		Maternal immune activation (gestational LPS treatment) in rats: ↑frontal cortex and hippocampus	deSouza *et al.* (2015)
Mood disorders	↓frontal cortex		Dean *et al.* (2006)
	↓density of S100B-immunopositive oligodendrocytes in the left hippocampal alveus		Gos *et al.* (2013)
	↓density of S100B-immunopositive astrocytes in hippocampal CA1 subfield		Gos *et al.* (2013)
		Chronic stress in rats: ↑intrasomal astrocytic expression	Tynan *et al.* (2013)
	↑gene expression in the hippocampus		Schroeter *et al.* (2014)
		Genetic rat model of depression (Flinders sensitive line): ↓amygdala, hippocampus, hypothalamus, prefrontal cortex, striatum	Strenn *et al.* (2015)

DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SCA1, spinocerebellar ataxia-1.

showed neuroinflammatory changes analogous with AD and Down syndrome (DS) (Shapiro *et al.* 2010). In addition, the administration of micromolar concentrations of the protein has been shown to induce tau hyperphosphorylation in cultured human neural stem cells (Esposito *et al.* 2008). Consistently, inhibition of S100B using different strategies attenuated AD-like pathology. In particular, inhibition of astrocytic S100B synthesis (arundic acid) reduced beta-amyloid deposits, as well as beta-amyloid plaque-associated reactive gliosis (astrocytosis and microgliosis) in transgenic mice overproducing mutant amyloid precursor protein (Tg APP(sw)mice) (Mori *et al.* 2006). Coherently, the administration of pentamidine, an antiprotozoal drug that also exhibits the intriguing feature of blocking the interaction between S100B and the transcription factor p53 (Hartman *et al.* 2013), resulted in attenuation of reactive gliosis and neuronal loss in a mouse model of AD induced by Abeta (1-42) peptide (Cirillo *et al.* 2015). In addition, genetic S100B ablation in the presenilin-1 amyloid precursor protein (PSAPP) double transgenic ($APP_{K670NM671L}$/$PS\text{-}1_{M146L}$)

Table 2 Correlates of S100B modulation in experimental models of different neural disorders

Pathology	S100B ↑	S100B ↓	Biological/clinical correlate	References
Traumatic brain injury				
Lateral fluid percussion (rats)	Intraventricular S100B administration		Enhancement of endogenous neurogenesis Improvement	Kleindienst *et al.* 2005b
Controlled cortical impact (mice)		S100B knockout	Reduction in lesion size Improvement	Kabadi *et al.* 2015
Controlled cortical impact (mice)		Neutralizing anti-S100B antibody treatment	Reduction in lesion size, enhancement of cortical neuron survival, attenuation of microglia activation Improvement	Kabadi *et al.* 2015
Ischemic stroke				
Permanent middle cerebral artery occlusion (rats)		Arundic acid treatment	Prevention of delayed infarct expansion Improvement	Tateishi *et al.* 2002
Middle cerebral artery occlusion (rats)		Arundic acid treatment	Prevention of delayed infarct expansion Improvement	Asano *et al.* 2005
Permanent middle cerebral artery occlusion (Tg huS100B mice)	Genetic over-expression		Increase in infarct volume and periinfarct gliosis Worsening	Mori *et al.* 2008
Middle cerebral artery occlusion (rats)		S100B siRNA	Inhibition of hippocampal cell apoptosis Improvement	Zhang *et al.* 2018
Alzheimer's disease				
Tg huS100B mice	Genetic over-expression		Enhanced susceptibility to neuroinflammation Worsening	Craft *et al.* 2005
Tg APP(sw)mice		Arundic acid treatment	Reduction of β-amyloid deposits and plaque-associated reactive gliosis Improvement	Mori *et al.* 2006
PSAPP double transgenic mice		S100B knockout	Reduction of cortical plaque numbers, reactive astrocytes and microglia and phospho-tau positive dystrophic neurons Improvement	Roltsch *et al.* 2010
Bigenic Tg2576-huS 100B mice	Genetic over-expression		Exacerbation of cerebral amyloidosis Worsening	Mori *et al.* 2010
Intrahippocampal injection of Aβ peptide (mice)		Pentamidine treatment	Attenuation of reactive gliosis and neuronal loss Improvement	Cirillo *et al.* 2015
Parkinson's disease				
MPTP-mice		Arundic acid treatment	Protection of dopaminergic neurons Improvement	Kato *et al.* 2004
Tg huS100B mice	Genetic over-expression		Reduction in dopamine-D2 receptor Worsening	Liu *et al.* 2011
MPTP-mice		S100B knockout	Reduction in dopaminergic neurons loss, microgliosis, RAGE and TNF expression Improvement	Sathe *et al.* 2012
Amyotrophic lateral sclerosis				
SOD1-G93A-derived astrocytic cultures		S100B siRNA	Down-regulation of pro-inflammatory molecules	Serrano *et al.* 2017
Multiple sclerosis				
LPC-treated cerebral organotypic cultures (mice)		Neutralizing anti-S100B antibody treatment	Reduced demyelination, down-regulation of pro-inflammatory molecules Improvement	Barateiro *et al.* 2016
EAE (rats)		Neutralizing anti-S100B antibody treatment	Onset delay, decreased disease intensity Improvement	Ganina *et al.* 2017

(continued)

Table 2. (continued)

Pathology	S100B ↑	S100B ↓	Biological/clinical correlate	References
Down's syndrome				
Astrocytes induced from pluripotent stem cells derived from DS patients		S100B siRNA	Reversion of astrocyte pathological phenotype Improvement	Chen *et al.* 2014
Spinocerebellar ataxia-1				
Cerebellar slice cultures from SCA1 Tg mice		TRTK12 treatment	Increase in dendritic length and branching	Vig *et al.* 2011
SCA1 Tg mice		Administration of TRTK12	Improvement	Vig *et al.* 2011
Inflammatory bowel disease				
DSS-induced acute colitis (mice)		Pentamidine. administration	Reduction in macroscopic signs and decrease in inflammatory molecules expression and release Improvement	Esposito *et al.* 2012
DSS-induced acute colitis (mice)		Palmitoylethanolammide treatment	Reduction of macroscopic signs and decrease in inflammatory molecules expression and release Improvement	Esposito *et al.* 2014

DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; LPC, lysophosphatidylcholine; RAGE, receptor for advanced glycation endproducts; SCA1, spinocerebellar ataxia-1; TNF, tumor necrosis factor alpha.

line, which mimics many facets of human AD, (including plaque deposition, dystrophic neurites, glial activation and memory deficits), has been shown to decrease cortical plaque numbers, reactive astrocytes and microglia, and phospho-tau positive dystrophic neurons (Roltsch *et al.* 2010). Finally, it may be relevant that the rs2300403 single nucleotide polymorphism in the S100B gene has been shown to be associated with low cognitive performance, dementia, and AD (Lambert *et al.* 2007).

In the pathogenic mechanisms of PD, a crucial role has been indicated for activated pro-inflammatory astrocytes, also involving the overproduction and release of S100B, in response to striatal dopaminergic denervation or 6-hydroxydopamine administration (Batassini *et al.* 2015; Morales *et al.* 2016). S100B was over-expressed in crucial brain regions such as substantia nigra and striatum both in PD patients (Sathe *et al.* 2012; Rydbirk *et al.* 2017) and in MPTP-treated mice (Sathe *et al.* 2012; Viana *et al.* 2016). In addition, transgenic mice over-expressing S100B have been reported to develop features of PD, such as the impairment of motor coordination and the expression of some molecular parameters, including the dopamine-D2 receptor (Liu *et al.* 2011). Accordingly, in S100B knockout mice, MPTP treatment resulted in a reduced loss of dopaminergic neurons, reduced microgliosis and reduced expression of both RAGE and tumor necrosis factor (TNF) alpha, as compared with MPTP-treated wild type mice (Sathe *et al.* 2012). Likewise, the inhibition of astrocytic S100B synthesis using arundic acid resulted in the protection of dopaminergic neurons against MPTP toxicity in mice (Kato *et al.* 2004). Finally, it might also be noteworthy that increased titers of autoantibodies to S100B have been reported in the blood of PD patients (Gruden *et al.* 2011).

In ALS patients, S100B has been shown to be increased in both cortical and spinal cord astrocytes (Kamo *et al.* 1987; Migheli *et al.* 1999). The protein was also over-expressed in astrocytes in the spinal cord of ALS rodent models (Díaz-Amarilla *et al.* 2011; Serrano *et al.* 2017). It is worth consideration that in SOD-G93A rats the over-expression of S100B has been observed in a specific subpopulation of astrocytes, defined as 'aberrant', which exhibit molecular peculiarities such as increased connexin-43 and a decrease in glutamate transporters GLT-1, and are regarded as responsible for toxicity (Díaz-Amarilla *et al.* 2011). Interestingly, the S100B receptor RAGE appeared to be increasingly expressed in astrocytes during the course of the disease, suggesting the occurrence of an autocrine pathway of S100B in this cell type during ALS (Serrano *et al.* 2017). Consistently, the transient over-expression of SOD1-G93A in C6 rat astrocytoma cells induced S100B over-expression and release, whereas S100B silencing in astrocytes derived from SOD1-G93A mice inhibited the expression of genes found to be increased in ALS astrocytes [glial fibrillary acidic protein, TNF-alpha, C-X-C motif chemokine, chemokine (C-C motif) ligand 6]. This finding suggests that S100B may influence the expression of a pro-inflammatory phenotype in mutant SOD1 astrocytes (Serrano *et al.* 2017).

Astrocytic dysfunction is a recognized feature of MS in both humans and experimental models of the disease (for review, Brosnan and Raine 2013). In an experimental model

of MS (experimental autoimmune encephalomyelitis-EAE), astrocytic activation and S100B overproduction occur in the early pre-symptomatic stage and during the course of the disease, and S100B levels appear to be even higher than those of glial fibrillary acidic protein (Grygorowicz *et al.* 2016). In addition, an increased expression of S100B has been detected in active demyelinating and chronic active MS lesions (Petzold *et al.* 2002), and a role for the protein in the induction of the disease in the EAE model has also been proposed (Kojima *et al.* 1994). Using an *ex vivo* demyelinating model (cerebral organotypic slice cultures treated with lysophosphatidylcholine), a marked astrocytic elevation of S100B was observed on demyelination, whereas the inhibition of S100B action using an anti-S100B neutralizing antibody reduced demyelination and down-regulated the expression of the inflammatory HMGB1, interleukin (IL)-18 and NOD-like receptor protein 3 (Barateiro *et al.* 2016). In line with these results, the administration of antibodies against S100B in EAE-induced rats has been shown to improve the clinical course of the disease, possibly reducing high (toxic) extracellular concentrations of S100B (Ganina *et al.* 2017). Interestingly, the blockade of the S100B receptor RAGE has also been shown to suppress demyelination and improve the clinical course in EAE animals (Yan *et al.* 2003). Although the above studies appear to point out essentially on astrocytic S100B, the possibility that oligodendrocytic S100B participates, at least in part, in these processes should also be taken into account. It may be relevant in this respect that in organotypic cerebellar cultures high S100B levels have recently been shown to impair oligodendrogenesis, resulting in reduced myelination (Santos *et al.* 2018) (Tables 1 and 2).

Congenital/perinatal disorders

In perinatal/pediatric medicine, the levels of S100B have been investigated in various biological fluids, including CSF, blood, amniotic fluid, urine, saliva, the latter resulting especially promising as non-invasive diagnostic tools (for review, Michetti *et al.* 2012). Particular importance has been attributed to the predictive value of S100B levels for the outcome of newborns, when clinical and radiological signs are still silent (for review, Satriano *et al.* 2017). In DS and spinocerebellar ataxia-1 (SCA1), data are also available indicating a mechanistic role for the protein.

Although the immunocytochemical distribution of S100B in neural cell types of Down patients does not differ from that of healthy subjects (Michetti *et al.* 1990), the concentration of both the protein and its mRNA, as well as the number of S100B-immunoreactive astrocytes, are markedly higher in the brain of Down patients, in some cases even exceeding the expected ratio of 1.5 (Jørgensen *et al.* 1990; Goodison *et al.* 1993; Chen *et al.* 2014). This may be attributable in part to a gene dosage effect, since the protein is coded by the chromosomal region 21q22 (Allore *et al.* 1988), and in part to an astrocytic reaction. Using computerized morphometric analysis quantifying astrocyte activation and astrocytic expression of S100B, a significantly positive correlation was observed between S100B expression and beta-amyloid deposition in the cerebral cortex of Down patients. Moreover, the number of activated S100B-immunolabeled astrocytes – but not of non-reactive S100B-negative astrocytes – and the numerical density of beta-amyloid plaques were positively correlated. This observation was regarded as supporting the idea that S100B over-expression promotes beta-amyloid plaque formation and progression in DS, as observed in AD, possibly through comparable neuroinflammatory processes (Royston *et al.* 1999; Wilcock and Griffin 2013; Hamlett *et al.* 2018). Interestingly, the over-expression of S100B has been shown to be responsible for the pathological phenotype (ROS generation, nitrite/nitrate production, proliferation) of astrocytes derived from Down patient-derived induced pluripotent cells, on the basis of data obtained after S100B inhibition by small interfering RNA, which reverses this phenotype (Chen *et al.* 2014).

A role for S100B may also be proposed in another congenital disorder, namely SCA1, although data concerning its levels in biological fluids of patients are not available at the moment. Interestingly, Purkinje cells of SCA1 patients, as well as of the transgenic mouse model of the disease, are characterized by cytoplasmic vacuoles enriched in S100B, accompanied by an abnormal morphology of dendritic spines (Vig *et al.* 2006, 2009). In addition, the expression of S100B mRNA has been shown to be increased in the cerebellum of SCA1 mice (Vig *et al.* 2011). In contrast, SCA1 cerebellar slice cultures treated with the S100B inhibitor TRTK12, that binds to the p53-binding site on S100B (Charpentier *et al.* 2010), exhibited a significant increase in dendritic length and branching (Ivanenkov *et al.* 1995), and SCA1 mice treated intranasally with TRTK12 displayed a significant improvement in their performance deficit on the Rotarod test (Vig *et al.* 2011) (Tables 1 and 2).

Inflammatory bowel disease

S100B protein is a constituent of enteric glial cells (EGC) (Ferri *et al.* 1982), and its expression has also been hypothesized to regulate the development of this cell type (Hao *et al.* 2017). In pathological conditions, inflammation can convert EGCs to a 'reactive EGC phenotype', resembling the behavior of astrocytes in the central nervous system (Sharkey 2015; Ochoa-Cortes *et al.* 2016). Ulcerative colitis and Crohn's disease are the two major clinically defined forms of inflammatory bowel disease (for review, Nishida *et al.* 2018). Although dysfunction of the mucosal immune system undoubtedly plays a role in the pathogenesis of inflammatory bowel disease (Kim and Cheon 2017), a role for the enteric nervous system (Goyal and Hirano 1996), located within the wall of the gastrointestinal tract, has been recognized in intestinal inflammation, also involving interactions with the intestinal microbiota (Margolis and Gershon

2016). Notably, enteric glial-derived S100B has been shown to be over-expressed, to correlate with the gut's inflammatory status and to stimulate NO production in human ulcerative colitis (Esposito *et al.* 2007; Cirillo *et al.* 2009). In contrast, the S100B inhibitor pentamidine ameliorates the severity of experimentally dextran sodium sulfate-induced acute colitis in mice, as shown by macroscopic evaluation and histological/biochemical assays in colonic tissues and in plasma (Esposito *et al.* 2012). Interestingly, data have been reported suggesting a common pathway involving S100B up-regulation and Toll-like receptor (TLR) stimulation in the colon inflammatory process (Esposito *et al.* 2014; Turco *et al.* 2014). Thus, enteroglial S100B protein, when over-expressed and released, is regarded as a pivotal participant in the cascade of events able to induce chronic inflammatory changes in gut mucosa (Capoccia *et al.* 2015; Ochoa-Cortes *et al.* 2016). However, serum S100B levels, when tested as a biomarker for enteroglial activation in patients with ulcerative colitis, have been reported to be significantly lower than in healthy controls. It should also be noted, in this respect, that the Authors point out the limitations of their study, including the restricted number of untreated patients (Celikbilek *et al.* 2014) (Tables 1 and 2). The use of S100B as a biomarker in these disorders deserves additional studies.

Psychiatric disorders

Both in schizophrenic patients and patients affected by mood disorders (major or minor depressive disorder, bipolar disorder) and in subjects experiencing emotional conditions of stress, alterations of S100B levels have been shown in biological fluids, but conflicting results in relationship with treatment have been observed (Aleksovska *et al.* 2014; da Rosa *et al.* 2016). In any case, data at present available from tissues of patients and experimental models propose in fact a role for S100B in psychiatric disorders.

The earliest studies regarding an involvement of S100B in psychiatric disorders reported an immune reaction to the protein in psychiatric patients (mainly schizophrenic and depressed subjects) (Jankovic′ *et al.* 1980, 1982). A role for S100B in psychiatric diseases is not surprising, in the light of the growing evidence indicating that in both humans and experimental models glial pathology is regarded as one of the most relevant substrates of mental diseases (Ongur *et al.* 1998 Cotter *et al.* 2001; Cotter *et al.* 2002; Webster *et al.* 2005; Czéh *et al.* 2006; Rajkowska and Miguel-Hidalgo 2007; Tynan *et al.* 2013; Koyama 2015). However, although at present high levels of S100B in biological fluids represent a recognized finding in patients affected by psychiatric disorders, so that they have even been proposed as a biomarker for these conditions (Ambrée *et al.* 2015; Gulen *et al.* 2016), complete and unambiguous information regarding the behavior of this protein in brain tissue is still lacking.

The protein has been shown to be up-regulated in the frontal cortex both of patients with paranoid schizophrenia (Steiner *et al.* 2008) and in the maternal immune activation model of schizophrenia (de Souza *et al.* 2015), but down-regulated in the deep white matter of the anterior cingulate gyrus (Katsel *et al.* 2011) and in the corpus callosum (Steiner *et al.* 2014) of schizophrenic patients, while conflicting data have been reported at the hippocampal level (de Souza *et al.* 2015). The antipsychotics haloperidol and risperidone have been shown to be able to inhibit the secretion of S100B in C6 glioma cells following IL-6 stimulation: this result has been interpreted as supporting the involvement of inflammatory processes in schizophrenia (de Souza *et al.* 2013). As an indirect indication that S100B may be involved in processes associated with structural brain changes in schizophrenia, a relationship between blood S100B levels and alterations in white matter (namely the posterior cingulate bundle and superior longitudinal fasciculus), as obtained from T1-weighted MR-images, has been reported in unmedicated schizophrenia patients (Milleit *et al.* 2016).

From the bulk of data on patients and animal models of depression and, more in general, mood disorders, the indications currently emerging are of a down-regulation of the protein in the frontal cortex (Dean *et al.* 2006; Strenn *et al.* 2015), while also in this case data obtained from the hippocampus are conflicting (Gos *et al.* 2013; Schroeter *et al.* 2014). It may be relevant in this respect that the antidepressant fluoxetine has been shown to increase hippocampal and CSF levels of both the protein and its receptor in rats exposed to chronic mild stress, reversing the decrease induced by stress treatment (Rong *et al.* 2010). Treatment with fluoxetine has also been reported to increase S100B levels in the hippocampus, frontal cortex and striatum, and S100B release from raphes (Manev *et al.* 2001; Akhisaroglu *et al.* 2003; Baudry *et al.* 2010; Bock *et al.* 2013).

It may be relevant in this respect that fluoxetine is known to act as a serotonin reuptake inhibitor (Caiaffo *et al.* 2016), and that the S100B and serotonin (5-HT) systems are believed to be interconnected (Azmitia *et al.* 1990; Whitaker-Azmitia *et al.* 1990; Shapiro *et al.* 2010). Notably, in this regard, it has been shown that the protein can be released by astrocytes in response to 5-HT binding to the 5-HT1A receptor, mainly expressed by astrocytes and involved in plasticity and neuroprotection, stimulating astrocytes to acquire a more mature morphology and to exert, at nanomolar concentration, neurotrophic and neuroprotective effects (Whitaker-Azmitia *et al.* 1990, 1993; Ahlemeyer *et al.* 2000; Chang *et al.* 2005). In particular, 5HT1A agonists have been shown to facilitate neuronal survival through increased S100B release (Ramos *et al.* 2004). Conversely, depletion of 5-HT has been related to astrocytic accumulation of S100B and morphological alterations of dendrites and neuronal cytoskeleton (Ramos *et al.* 2000). It should also be noted that the interaction between S100B and the serotonin 5-HT7 receptor regulates depressive-like

behavior (Stroth and Svenningsson 2015) and that S100B increases the expression of the serotonin transporter, a major regulator of serotonergic neurotransmission and anxiety-related behaviors (Yoon *et al.* 2013). Taken together these data suggest that the relationship between S100B and fluoxetine refer to the interactions between the S100B and serotonin systems. It should also be noted that venlafaxine, a serotonin and norepinephrine reuptake inhibitor (Williams *et al.* 2017), shows an opposite effect to fluoxetine, decreasing both S100B and related mRNA levels in the hippocampus of rats exposed to chronic unpredictable mild stress. This finding could indicate an anti-inflammatory effect of this drug (Wang *et al.* 2016). Interestingly, inflammation and serotonin neurotransmission have been regarded as interactive in the pathogenic mechanisms of psychiatric disorders (for review, Müller 2017).

The above data suggest a role for S100B in the pathogenic mechanisms of psychiatric disorders, but its precise nature is still nebulous and, in some respects, contradictory. The heterogeneity of the brain regions involved, as well as the difficulty of distinguishing between the intracellular and extracellular compartments of the protein, both reasonably involved in pathogenic processes, might explain the discrepancies in the data obtained. Regarding this latter aspect, a paradigmatic study showed that in the prefrontal cortex of rats exposed to chronic stress the number of S100B-immunolabeled cells was unchanged, while, using digital reconstructions of astrocytes, an increase in intrasomal S100B was observed in individual astrocytes, associated with an increase in extracellular S100B (Tynan *et al.* 2013). Finally, in the light of a putative extra-neural (adipose) origin of S100B in biological fluids reported in psychiatric disorders, a role for the adipose tissue, which is known to be a source of inflammatory molecules (for reviews, Ouchi *et al.* 2011; Dowal *et al.* 2017) and, in particular, a site of concentration for S100B (Michetti *et al.* 1983), cannot be ruled out in these disorders (Steiner *et al.* 2010a). This would not be surprising, as these diseases have already been correlated with inflammatory and/or metabolic disturbances (for reviews, Dantzer *et al.* 2008; Brown 2011; Nurjono *et al.* 2014). Indeed, several studies suggest that overweight, visceral obesity and peripheral/cerebral insulin resistance may be pivotal for at least part of the elevated S100B serum levels (Wartchow *et al.* 2016; Kheirouri *et al.* 2018). In the context of this framework of metabolic disturbances accompanying S100B elevation in schizophrenia, an involvement of adipose tissue, which also expresses high levels of S100B, might be considered (Steiner *et al.* 2010b,c) (Table 1).

Concluding remarks and perspectives

The above data indicate that S100B plays a relevant role in the pathogenic mechanisms involved in different nervous tissue disorders. In particular in acute brain injury, neurodegenerative diseases, SCA1 and inflammatory bowel disease, the findings observed cannot merely regarded as an epiphenomenon, but indicate a direct involvement of the protein in pathogenic processes, since manipulations of S100B concentrations have been shown to directly correlate with clinical symptoms and/or pathologic/biomolecular parameters (Table 2). This consideration foreshadows therapeutic perspectives for these disorders. However, current data regarding psychiatric disorders suggest a significant involvement of the protein, but do not allow to delineate how crucial its role could be.

The disorders considered in the present review are caused by different etiologic factors and display a variety of symptoms that could hardly be reconducted to a unifying pattern. However, regardless of the origin of these diseases, the involvement of processes which share aspects reasonably attributable to inflammation is detectable in their underlying pathogenic mechanisms (Giovannoni *et al.* 2007; Wilcock and Griffin 2013; King *et al.* 2014; Ochoa-Cortes *et al.* 2016; Hamlett *et al.* 2018; Stark *et al.* 2016; Kim *et al.* 2017; Chitnis and Weiner 2017; Labzin *et al.* 2018; Fehily and Fitzgerald 2017; Mizuma and Yenari 2017; Neal and Richardson 2017; Franklin *et al.* 2017; Prata *et al.* 2017; Santos and Ferreira 2017; Joshi and Singh 2017; Thelin *et al.* 2017a; Majd *et al.* 2017; Zhang *et al.* 2017; Zolezzi and Inestrosa 2017). This consideration has also been the object of a recent valuable review (Skaper *et al.* 2018). As noted above, S100B, which may be regarded as a DAMP, displays characteristics which are regarded to be typical of inflammatory molecules. In particular, the protein is expressed and secreted by human CD8(+)T and NK cells on stimulation (Steiner *et al.* 2011), induces the migration of microglia by up-regulating chemokine expression and release (Bianchi *et al.* 2011), and activates microglial cells, where it induces iNOS, COX-2, IL-1beta and TNF-alpha expression, as well as the release of matrix metalloproteinase 9 and nitric oxide (Adami *et al.* 2004; Bianchi *et al.* 2007, 2010; Xu *et al.* 2016). In addition, S100B induces a RAGE-dependent autocrine loop in astrocytes, resulting in a pro-inflammatory phenotype with expression of TLR-2, iNOS, IL-1beta (Villarreal *et al.* 2014), and in the stimulation of IL6 and TNF-alpha secretion (Ponath *et al.* 2007). Consistently, the inhibition of S100B in SOD1-G93A astrocytes has been shown to down-regulate the expression of pro-inflammatory genes such as TNF-alpha, C-X-C motif chemokine, chemokine (C-C motif) ligand 6 (Serrano *et al.* 2017). Thus, it is reasonable to suppose that S100B participates in the processes – possibly inflammatory – involved in mechanisms peculiar to these different pathological conditions, or in those they share, regardless of their different origins. This perspective opens up the possibility that S100B may represent a key pathogenic factor and points to its possible role as a therapeutic target that these disorders might even potentially share. It is interesting, in this respect, that

molecules able to inhibit the synthesis of S100B, such as arundic acid (Tateishi *et al.* 2002) or its activity, such as TRTK12 peptide (Ivanenkov *et al.* 1995) and pentamidine (Hartman *et al.* 2013) are already available. While the mechanism of action of arundic acid, which inhibits astrocytic S100B synthesis, has not been clearly elucidated, both pentamidine and TRTK12 peptide are known to block the interaction between S100B and the transcription factor p53 (Charpentier *et al.* 2010; Hartman *et al.* 2013). It may be relevant in this respect that the search for additional similarly useful molecules is being actively pursued via a structure-based approach (Cavalier *et al.* 2016). More recently, even extracts from traditional remedies have been used in an attempt to block the protein (Qin *et al.* 2018). The identification of molecules able to inactivate S100B, thereby offering a common therapeutic tool to combat apparently heterogeneous disorders of the nervous system, could be the next step in the story of this intriguing protein.

Acknowledgments and conflict of interest disclosure

This study was partially supported by the Nando and Elsa Peretti Foundation (Fabrizio Michetti– Contract number NaEPF 2016-033), funds from Università Cattolica del Sacro Cuore (UCSC) to FM (D3-2 line 2015) and to MCG (D1 line 2017). The authors declare that they have no conflicts of interests.

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