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Review

S100B's double life: Intracellular regulator and extracellular signal

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ABSTRACT

The Ca^{2+}-binding protein of the EF-hand type, S100B, exerts both intracellular and extracellular functions. Recent studies have provided more detailed information concerning the mechanism(s) of action of S100B as an intracellular regulator and an extracellular signal. Indeed, intracellular S100B acts as a stimulator of cell proliferation and migration and an inhibitor of apoptosis and differentiation, which might have important implications during brain, cartilage and skeletal muscle development and repair, activation of astrocytes in the course of brain damage and neurodegenerative processes, and of cardiomyocyte remodeling after infarction, as well as in melanomagenesis and gliomagenesis. As an extracellular factor, S100B engages RAGE (receptor for advanced glycation end products) in a variety of cell types with different outcomes (i.e. beneficial or detrimental, pro-proliferative or pro-differentiative) depending on the concentration attained by the protein, the cell type and the microenvironment. Yet, RAGE might not be the sole S100B receptor, and S100B's ability to engage RAGE might be regulated by its interaction with other extracellular factors. Future studies using S100B transgenic and S100B null mice might shed more light on the functional role(s) of the protein.

1. Introduction

S100B is a member of a family of Ca^{2+}-binding proteins of the EF-hand type comprising some 25 members (see Refs. [1–5] for reviews). S100B is expressed in varying abundance in a restricted number of cell types such as astrocytes, maturing oligodendrocytes, kidney epithelial cells, neural progenitor cells, pituicytes, ependymocytes, certain neuronal populations, chondrocytes, adipocytes, melanocytes, Langerhans cells, dendritic cells, certain lymphocyte subpopulations, skeletal myofibers, myoblasts [1,3,6–12], and muscle satellite cells[1]. Also, S100B expression is enhanced in several tumors arising from cell types normally expressing the protein as well as in the aging brain and in the brain of patients affected by Alzheimer's disease, chronic epilepsy or HIV infection and other brain pathological conditions [1,2,13–15]. The (level of) expression of S100B might strongly depend on environmental factors. For example, S100B is undetectable in normal cardiomyocytes, however it is induced in the myocardium post-infarction concomitantly with the downregulation of the fetal proteins, skeletal α-actin and β-myosin heavy chain [16] (Table 1). These observations suggest that the S100B gene expression is under complex transcriptional regulation. The S100B gene expression may be constitutively repressed in all cell types by negative regulatory elements, implying that the expression of S100B in a given cell type requires induction of an appropriate factor that counters the action of those elements [17]. Such a mechanism would allow a controlled expression of S100B in definite cell types, in the same cell type depending on the cell's functional states, or depending on the context. This might also explain why S100B can be detected in several cell lines derived from cell types that normally do not express the protein (for example, see the case of microglia which do not express S100B in tissue under normal and pathological conditions [18]; yet microglial cell lines [19] and primary microglia [20] do express S100B). Besides norepinephrine and phenylephrine in post-infarction cardiomyocytes as noted above, the proinflammatory cytokine, interleukin (IL)-1β [21], β-amyloid [22], antidepressants [23], brain-derived neurotrophic factor [24] and the neurotoxin 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP) [25] upregulate S100B expression in astrocytes (Table 1). In the latter case, the stimulatory effect of MPTP on S100B expression was shown to be modulated by endocannabinoids via CB_1 receptor activity [25]. Also, S100B is induced in enteric glia cells by food gliadin in the duodenal mucosa of patients affected by celiac disease [26] and in early-stage chondrocyte differentiation by sex-determining region Y-type high mobility group box 5, 6 and 9 (the so-called SOX trio) [27] (Table 1). On the other hand, epidermal growth factor and the proinflammatory cytokine, interferon (IFN)-γ, have been shown to downregulate S100B expression in astrocytes and microglial cells [19,28,29] (Table 1).

S100B localizes to the cytoplasm where it is found in a soluble form as well as associated with intracellular membranes, the centrosomes, microtubules and type III intermediate filaments [3]. Like other

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Table 1
Factors and/or conditions regulating S100B expression

Factors and/or conditions that increase S100B expression levels	Factors and/or conditions that decrease S100B expression levels
Norepinephrine and phenylephrine (post-infarction cardiomyocytes) [16]	IFN-γ (microglial cell lines and astrocytes) [19,28]
IL-1β (astrocytes) [21]	Epidermal growth factor (astrocytes) [29]
β-amyloid [22]	Dyslexia (astrocytes?) [33]
Antidepressants (astrocytes) [23]	Differentiation of and/or acquisition of quiescence (myoblasts)[1]
Brain-derived neurotrophic factor (astrocytes) [24]	
MPTP (astrocytes) [18,25]	
SOX trio (terminally differentiating chondrocytes) [27]	
Trisomy 21 [32]	
Alzheimer's disease (astrocytes) [13]	
Aging brain (astrocytes) [170]	
Chronic epilepsy (astrocytes) [15]	
HIV infection (astrocytes) [13–15]	
Cell confluency (astrocytes) [35]	
Gliadin (enteric glia) [26]	
Schizophrenia [191–193]	

Cell types(s) and Refs. in parentheses.

members of the family, S100B consists of a module of two Ca^{2+}-binding sites of the EF-hand (i.e., two helix–loop–helix motifs) interconnected by a hinge region, and of a C-terminal extension [1,2]. Also, like other members of the family (with exception of S100G [CALB3, calbindin D9k]), S100B exists within cells as a homodimer in which the two subunits are held together by non-covalent bonds and are arranged in an anti-parallel fashion [30]. However, S100B also can also exist as an S100B/S100A1 heterocomplex [1].

The human gene encoding S100B maps to chromosome 21q22.3 [31] with consequent overexpression of the protein in Down syndrome [32]. Recently, *S100B* has been identified as a novel dyslexia candidate gene along with three other genes (i.e., *PCNT*, *DIP2A*, and *PRMT2*) mapping to chromosome region 21q22.3 [33].

Within cells S100B acts as a Ca^{2+} sensor protein. Upon Ca^{2+} binding, helix III of individual S100B monomers becomes more perpendicular to helix IV, and this causes the hinge region to move apart [30]. In consequence of these conformational changes a number of hydrophobic residues in the hinge region, helices III and IV and the C-terminal extension become exposed to the solvent. These residues and, likely, residues in helix I of the opposite monomer define a hydrophobic cleft through which dimeric S100B binds to intracellular target proteins. However, other (as yet undefined) regions of the S100B dimer have been implicated in the recognition of certain target proteins within cells, and S100B-target protein interactions may not be Ca^{2+}-dependent in some cases [1,2,5]. In any case, S100B exerts its biological function by interacting with other proteins thereby affecting their activities. Thus, S100B was shown to take part in the regulation of cell proliferation, differentiation and shape, Ca^{2+} homeostasis, protein phosphorylation, transcription, the dynamics of microtubules and type III intermediate filaments, enzyme activity and metabolism; its relatively high abundance in the cell types where it is expressed and its cytoplasmic localization make it possible that S100B can interact with a rather large number of target proteins [1–3,5].

S100B also exerts extracellular effects. Indeed, S100B is actively released by astrocytes [34,35], adipocytes [36] and, possibly, other cell types. Also, S100B release by astrocytes can be augmented upon stimulation with 5-HT_{1A} [37], lysophosphatidic acid [38], glutamate [39] and the proinflammatory cytokine, tumor necrosis factor (TNF)-α [40], and during metabolic stress [41] (Table 2). Other stimulators of S100B release from astrocytes include such diverse agents as relatively high levels of cytosolic Ca^{2+} [42], natural anti-oxidants [43,44], branched-chain α-keto acids [45], the neurotoxin MPTP [25], and the neuroleptic risperidone [46] (Table 2). Recent evidence suggests that S100B is released by astrocytes via activation of metabotropic glutamate receptor 3 in a neural- and synaptic-activity-dependent manner [47]. In addition, S100B might leak from damaged cells thereby accumulating in the extracellular space and/or entering the bloodstream. For example, serum levels of S100B increase in patients with melanoma [48–50], during the acute phase of brain damage [51–54], following an intense physical exercise [55,56], and in the course of dilated cardiomyopathy [57], heart ischemia [58] and non-brain traumas [59]. Recently, S100B release has been suggested to occur in isolated Schwann cells through a process that requires activation of the cell surface receptor, RAGE (receptor for advanced glycation end products, a member of the immunoglobulin superfamily [60,61]), RAGE-dependent activation of the non-receptor Src tyrosine kinase, Src-mediated phosphorylation of caveolin-1, phosphorylated caveolin-1-dependent targeting of RAGE to Rab11-positive vesicles and targeting of internalized RAGE to vesicles containing endogenous S100B [62]. These results suggest that active S100B release might be dependent on the presence and activation of RAGE on the cell surface, and that S100B might stimulate its own release via RAGE engagement (see below). These results raise questions about S100B secretion by cells that do not express RAGE or express extremely low levels of the receptor, such as all cell types after completion of development and in the absence of pathological conditions, with the exception of certain lung cells [60,61,63]. On the other hand, S100B secretion might be reduced in e.g. primary astrocytes and Schwann cells treated with high glucose [64], following inhibition of Src kinase [62], or upon treatment with high doses of glutamate [65] as well as in confluent cells [35,42] (Table 2).

However, whatever the source of extracellular S100B and the mechanism of its release, extracellular S100B might attain local concentrations sufficient to affect cellular activities by acting in a paracrine, autocrine and endocrine manner. This latter issue calls for the identification of the cell surface molecule(s) transducing extracellular S100B effects. While there is substantial evidence that RAGE transduces extracellular effects of S100B on a variety of cell types [66,67], RAGE might not be the sole S100B receptor (see below). Concerning the S100B/RAGE interaction, there is evidence that S100B binds to the RAGE V-domain [68], that the non-reducing and high Ca^{2+} conditions found extracellularly might favor the formation of S100B

Table 2
Factors and/or conditions regulating S100B secretion/release

Factors and/or conditions that increase S100B secretion/release	Factors and/or conditions that decrease S100B secretion/release
Growth phase (astrocytes) [35]	High glucose (astrocytes) [63]
Catecholamines (adipocytes) [36]	Inhibition of Src kinase (astrocytes) [61]
5-HT_{1A} (astrocytes) [37]	High glutamate (astrocytes) [64]
Lysophosphatidic acid [38]	Cell confluency (astrocytes) [35,42]
Glutamate (astrocytes) [39]	
TNF-α (astrocytes) [40]	
Metabolic stress (astrocytes) [41]	
High cytosolic Ca^{2+} (astrocytes) [42]	
Natural antioxidants (astrocytes) [43,44]	
Branched-chain α-keto acids (astrocytes) [45]	
MPTP (astrocytes) [25]	
Risperidone (astrocytes) [46]	
Melanoma [47,48]	
Acute phase of brain damage (astrocytes) [50–52]	
Intense physical exercise (adipocytes?, skeletal myofibers?) [54,55]	
Dilated cardiomyopathy (astrocytes?, cardiomyocytes?) [56]	
Heart ischemia [57]	
Non-brain traumas (adipocytes?, skeletal myofibers[4]) [58]	

Cell types(s) and Refs. in parentheses.

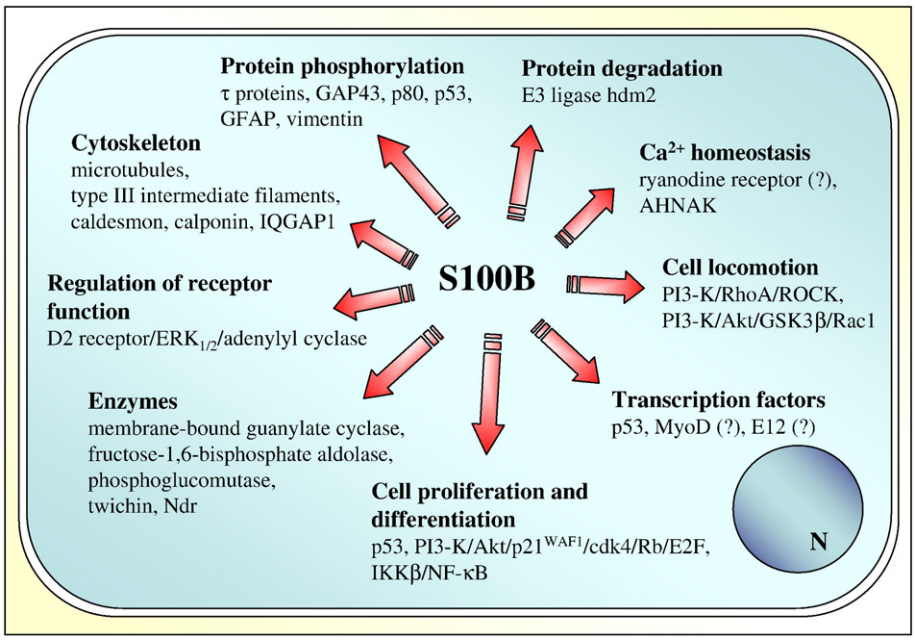

Fig. 1. Schematic representation of proposed intracellular regulatory effects of S100B.

multimers [68,69], and that S100B multimers cause RAGE dimerization [68] or stabilization of preformed RAGE oligomers [70], an event considered important for RAGE activation.

Several reviews have appeared describing intracellular and extracellular regulatory effects of S100 proteins [1–5,71–85], to which the reader can refer. However, the growing interest in S100B and the increasing body of experimental data on intracellular and extracellular S100B regulatory activities call for an updating of the information concerning this particular S100 family member.

2. Intracellular regulatory activities of S100B

2.1. S100B/cytoskeleton interactions

As mentioned above, S100B is found co-localized with the centrosomes, cytoplasmic microtubules, the center part of midbody in dividing cells, and type III intermediate filaments. S100B has been shown to modulate microtubule assembly and to cause microtubule disassembly in a Ca^{2+}- and pH-dependent manner and to increase Ca^{2+}-sensitivity of microtubules in situ [42,86,87]. Tubulin and the microtubule-associated τ protein have been reported to be S100B targets [88–90]. Also, expression of S100B protein in *E. coli* causes a filamenting bacterial phenotype characteristic of functional inhibition of FtsZ protein, the prokaryotic ancestor of tubulin and a major protein involved in bacterial division, and leads to missed rounds of cell division [91]. Moreover, disassembly of microtubules results in enhanced S100B release [42]. Further analyses are required to establish the functional relevance of S100B/tubulin and/or microtubule interactions. The same applies to S100B/intermediate filament interactions (Fig. 1).

S100B interacts with caldesmon in a Ca^{2+}-dependent manner inhibiting its phosphorylation and causing reversal of caldesmon-dependent inhibition of actomyosin ATPase activity [92]. Caldesmon is an actin-binding protein that is capable of stabilizing actin filaments against actin-severing proteins, inhibiting actomyosin ATPase activity, and inhibiting Arp2/3-mediated actin polymerization in vitro. Caldesmon is a substrate of cdc2 kinase and ERK1/2 MAPK, and phosphorylation by either of these kinases reverses the inhibitory effects of caldesmon [93,94]. In principle S100B/caldesmon interactions should result in stabilization of actomyosin (Fig. 1). However, S100B is not found associated with F-actin or stress fibers, and no functional correlates of S100B/caldesmon interactions in vivo have been reported.

S100B was shown to interact in a Ca^{2+}-dependent manner with the small GTPase Rac1 and Cdc42 effector, IQGAP1, at the polarized leading edge and areas of membrane ruffling in astrocytoma cell lines [95]. Hence, S100B has been proposed to regulate IQGAP1 activity in relation to cell migration. Rac1/Cdc42-regulated IQGAP1 cross-links F-actin and participates in the organization of microtubules at the cell cortical region, which leads to cell polarization and migration [96–98]. In this context, S100B might act as an activator of IQGAP1 thereby favoring cell migration (Fig. 1). Recent observations from our laboratory show that S100B knockout in astrocyte cell lines by small interference (si) RNA techniques results in disassembly of stress fibers, F-actin collapse onto plasma membranes, reduced migratory capacity and acquisition of a stellate phenotype.[2] These changes are dependent on reduced activity of PI3-K, a kinase acting upstream of the Akt (PKB)/GSK3β/Rac1 axis, which regulates the formation of long cytoplasmic extensions, and the small GTPase RhoA/ROCK axis, which governs stress fiber formation and cell locomotion [97,98]. Thus, S100B might regulate the supramolecular organization of F-actin by acting upstream of the PI3-K/Akt/RhoA/ROCK axis thereby favoring stress fiber formation and stimulating astrocyte migration (Fig. 1), which might be important during brain development and in the course of astrocytic neoplasias as well as in the course of brain insult when astrocytes become activated and migrate to the site of insult [99].

2.2. S100B in cell proliferation and survival

S100B has been long implicated in the regulation of cell proliferation following the observation that its levels are elevated in certain tumor cells and in astrogliosis [1,2] (Fig. 1). S100B was reported to bind to and activate in a Ca^{2+}-dependent manner Ndr (nuclear Dbf2-related) [100], a serine/threonine protein kinase belonging to subfamily of kinases implicated in the regulation of cell division and morphology [101]. Ca^{2+}/S100B was observed to increase autophosphorylation on Ser-281 and Thr-444, resulting in

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stimulation of Ndr activity in vitro [102]. However, regulation of Ndr by S100B is not associated with direct autoinhibition of the active site, but rather involves a conformational change in the catalytic domain triggered by Ca^{2+}/S100B binding to the junction region [103]. Yet, although S100B-dependent activation of Ndr in cell lines has been documented [100], no evidence has been presented that S100B-dependent activation of Ndr results in stimulation of cell proliferation and/or changes in cell morphology.

S100B interacts in a Ca^{2+}-dependent manner with the tumor suppressor, p53, inhibiting its phosphorylation [104,105]. Phosphorylation is a critical step of p53 activation [106–108] (Fig. 1). Also, S100B downregulates p53 expression, and in turn, p53 downregulates S100B expression in melanoma cells [109]. Upregulation of S100B in melanoma is an established notion [1,2], and use of S100B immunohistochemistry and dosage of serum levels of S100B in patients with melanoma is routinely performed for diagnostic and prognostic purposes [48–50]. For the S100B/p53 interaction, it was found that phosphorylation of specific serine and/or threonine residues reduces the affinity of the S100B-p53 interaction by as much as an order of magnitude, and is important for protecting p53 from S100B-dependent down-regulation [110]. However, there are conflicting data about functional implications of S100B/p53 interactions [109,111,112], and it is not known whether these interactions are relevant for tumor progression in other malignant neoplasias and in non-neoplastic cells. Work from our laboratory has shown that forced expression of S100B in neuronal PC12 cells has no effects on p53 levels or nuclear translocation, but it results in enhanced proliferation and reduced differentiation and apoptosis via activation of a PI3-K/Akt/$p21^{WAF1}$/cdk4/Rb/E2F pathway in the absence of serum mitogens [113] (Fig. 1).

Recently, we found that increasing S100B levels in myoblast cell lines results in no effects on the proliferation rate of asynchronously proliferating myoblasts; however, S100B-overexpressing myoblasts are more resistant to basal and H_2O_2-induced apoptosis in an IKKβ/NF-κB-mediated manner[1] (Fig. 1). Thus, increasing S100B levels in myoblasts results in augmented cell numbers in consequence of their increased survival rate. In addition, non-fused myocytes (i.e., mitotically quiescent myoblasts that are found in mixed myoblast-myotube cultures) transiently downregulate S100B expression,[1] suggesting that downregulation of S100B might be required either for acquisition of a quiescent status or for permitting myoblast terminal differentiation. However, S100B-overexpressing myoblasts are less prone to acquire mitotic quiescence and proliferate faster than control cells upon re-exposure to serum mitogens after quiescence (C. Tubaro, C. Arcuri, I. Giambanco and R. Donato, unpublished data). Proliferation of muscle satellite cells, the most relevant stem cell population in adult skeletal muscle tissue, and their resistance to death-inducing stimuli are critical for efficient muscle regeneration as well as for successful cell therapy of muscular dystrophy and wasting [114–117]. Thus, S100B, which is expressed in muscle satellite cells,[1] might contribute to muscle regeneration by reducing apoptosis and stimulating the expansion of activated satellite cells. By contrast, excess expression of S100B in satellite cells might be detrimental because its mitogenic effect might interfere with the reconstitution of the satellite cell reserve pool that normally occurs during the muscle regenerative process and requires that a fraction of cells stop proliferating and enter a quiescent state [114–117]. Future studies of the dynamics of satellite cells in muscles of S100B null and transgenic mice might help to verify the functional role(s) of S100B in these particular cell types.

Also, work from our laboratory suggests that reducing S100B expression in astrocyte cell lines results in a slight, though significant reduction of proliferation via reduced activity of the PI3-K/Akt module and consistent reduction of cyclin D1, a protein important for cell cycle progression[2] (Fig. 1). However, these effects were restricted to the first two days of inhibition of S100B expression by siRNA techniques, and no major effects of S100B levels at later time points could be observed despite S100B levels were still significantly lower than in control cells.

Collectively, these data suggest that S100B might intervene in the regulation of cell proliferation, survival and apoptosis by mechanisms that vary depending on the cell type, the context and, probably, the cell's normal or neoplastic condition. Further work is required to definitely establish the role of S100B in cell proliferation and survival in normal and neoplastic cells and to unravel the molecular mechanisms by which the protein affects these cellular states. Answering these questions also serves to establish whether elevation of S100B levels in neoplastic cells is a consequence of tumorigenesis or it is causally related to tumor progression.

2.3. S100B in cell differentiation

S100B appears to function as an inhibitor of cell differentiation. As mentioned above, expression of S100B in PC12 neuronal cells results in impaired NGF-induced differentiation via activation of a PI3-K/Akt/$p21^{WAF1}$/cdk4/Rb/E2F pathway [113] (Fig. 1). However, induction of S100B expression in NGF-differentiated PC12 neuronal cells does not reverse the differentiated phenotype [113], suggesting that the anti-differentiative activity of S100B might be restricted to early developmental stages and/or that other factors have to come into play for S100B to concur to cell de-differentiation. Also, S100B, induced in early-stage chondrocyte differentiation by the SOX trio, negatively regulates chondrocyte terminal differentiation via an as yet undetermined mechanism [27]. Interestingly, S100B expression in brain astrocytic cells is developmentally regulated with different characteristics depending on whether subventricular or cortical astrocytic cells are considered, however [29]. These studies have established during the time interval between post-natal days 2 and 8 ramified, differentiating (i.e., glial fibrillary acidic protein [GFAP] filament-positive) astrocytes are substantially S100B-negative. This suggests that during that time interval S100B might be downregulated, while the protein becomes re-expressed during the final phase(s) of astrocytic differentiation. Moreover, S100B is expressed in radial glial precursors [118], in the ventricular zone of embryonic mouse cerebellum [119] and in progenitors of cerebellar granule cells [120], the protein being expressed in these latter cells as long as they are migrating. We have observed that reduction of S100B levels in astrocyte cell lines results in reduced migration and acquisition of a differentiated phenotype (i.e. stellation) due to reduced activity of the PI3-K/RhoA/ROCK module, and increased activity of the GSK3β/Rac1 module[2] (Fig. 1). Also, differentiation of primary astrocytes is accompanied by a transient reduction of S100B expression, that is restored at later developmental stages, i.e. in ramified astrocytes.[2] These results are consistent with the possibility that repression of S100B expression at certain phases of development of astrocytes and certain neuronal populations might be functionally linked to their differentiation. Thus, S100B might contribute to confer migratory capacity on undifferentiated astrocytes and neuroblasts, and S100B expression needs to be repressed for differentiation to take place. In this context, S100B might act to avoid precocious differentiation besides favoring cell migration.

S100B might modulate the differentiation of myoblasts, the precursors of skeletal myofibers. Indeed, overexpression of S100B in myoblasts results in the blockade of the myogenic differentiation program via IKKβ/NF-κB-mediated inhibition of expression of the muscle-specific transcription factor, MyoD, and the MyoD-downstream effectors myogenin and $p21^{WAF1}$, and conversely, reduction of S100B expression in myoblasts by siRNA techniques results in reduced NF-κB activity and enhanced myogenic differentiation[1] (Fig. 1). It is known that NF-κB is a negative regulator of myogenic differentiation acting via inhibition of expression and/or reduction of stability of the muscle-specific transcription factor, MyoD [121–123]. Interestingly,

expression levels of S100B decrease in differentiating, non-fused wild-type myoblasts[1] [11], which again suggests that S100B levels need to decrease in certain cell types for their differentiation to occur, while levels of S100B remain relatively high in fused myoblasts (myotubes).

While EFG has been proposed to reduce S100B expression in developing astrocytes [29], the extracellular stimuli and intracellular factors causing downregulation of S100B expression during cell differentiation remain to be established. Also, as both mature astrocytes and skeletal myofibers express S100B [3], mechanisms should exist that cause re-expression of the protein at later stages of development. Overall, these observations suggest that functions of S100B might be different in developing and mature cells and that S100B might regulate different signaling pathways in different cell types.

2.4. S100B and Ca^{2+} homeostasis

S100B null mice are viable and fertile and do not show any overt phenotype [124] (but see below and the section Extracellular regulatory activities of S100B, Effects of S100B on neurons). However, astrocytes in cerebellar cultures derived from 6-days-old S100B null mice exhibit enhanced Ca^{2+} transients in response to treatment with KCl or caffeine, while granule neurons in the same cultures exhibit normal Ca^{2+} transients in response to treatment with KCl, caffeine, or N-methyl-D-aspartate [124] (Fig. 1). These results demonstrate a specific decrease in Ca^{2+}-handling capacity in astrocytes derived from S100B null mice and suggest that S100B plays a role in the maintenance of Ca^{2+} homeostasis in astrocytes. However, the mechanism by which S100B accomplishes this function remains to be elucidated.

The giant phosphoprotein AHNAK/desmoyokin, a desmosomal plaque protein in epithelial tissues, is implicated in Ca^{2+} flux regulation. In epithelial cells, AHNAK is present mainly in the cytoplasm when cells are kept in low Ca^{2+} medium but translocates to the plasma membrane after an increase in extracellular Ca^{2+} concentration or protein kinase C (PKC) activation [125]. Also, AHNAK has been found in cardiomyocytes associated with L-type Ca^{2+} channels. In these cells, AHNAK may play a role in cardiac Ca^{2+} signaling by modulating L-type Ca^{2+} channels in response to β-adrenergic stimulation [126]. S100B has been shown to interact with AHNAK in a Ca^{2+}-dependent manner, and the S100B/AHNAK interaction was proposed to participate in the S100B-mediated regulation of cellular Ca^{2+} homeostasis [127] (Fig. 1). However, definite evidence that this actually occurs in vivo is lacking.

As noted above, S100B is not expressed in cardiomyocytes in normal conditions, but it becomes expressed under the action of catecholamines in the cardiomyocytes surviving infarction and acts to limit the hypertrophic response via inhibition of expression of α-actin and β-myosin [16,128–130]. The activation of the S100B promoter was shown to be mediated through the PKC signaling pathway; α1-adrenergic stimulation induces the S100B gene after myocardial infarction through the PKC signaling pathway and this induction is modulated by transcription enhancer factor-1 (TEF-1) and related to TEF-1 (RTEF-1) [129]. However, how S100B inhibits the expression of α-actin and β-myosin remains to be elucidated. As the hypertrophic response consequent to heart infarction is reminiscent of myoblast/myotube hypertrophy in several aspects [131,132], the observation that intracellular S100B has the potential to prevent precocious myoblast differentiation via modulation of MyoD expression[1] might represent a possible link between catecholamine-dependent induction of S100B expression and reduced hypertrophic response in post-infarction cardiomyocytes. Whether there is any relationship between S100B-regulated AHNAK effects on Ca^{2+} fluxes [126] and S100B-dependent inhibition of post-infarction hypertrophic response in cardiomyocytes also is currently unknown. Experimentally, S100B null mice show enhanced hypertrophy of post-infarction cardiomyocytes, decreased apoptosis and mortality and a better preservation of cardiac function in the 35-day period of observation after myocardial infarction, compared with wild-type and S100B transgenic mice [129]. Whether these effects are mechanistic related to altered regulation of cytoplasmic Ca^{2+} in consequence of the absence of expression of S100B remains to be established.

As astrocytic Ca^{2+} elevations play an important role in neurophysiology and especially in modulation of neuronal activity [133] it would be interesting to investigate whether and to what extent the defective Ca^{2+}-handling capacity observed in astrocytes from S100B null mice translates into alterations of neuronal activity.

2.5. S100B and enzyme activity regulation

No advancement of information concerning Ca^{2+}/S100B-dependent regulation of fructose-1,6-bisphosphate aldolase, phosphoglucomutase, twitchin kinase and membrane-bound guanylate cyclase has been produced with respect to previous reviews [1–3] to which the reader is invited to refer. See above for S100B/Ndr interactions and potential regulatory effects of S100B on PI3-K/Akt, IKKβ and ERK1/2 (Fig. 1).

S100B has been shown to interact with the E3 ligase hdm2 implicated in p53 ubiquitination [110] (Fig. 1). Although the functional consequences of this interaction remain to be established, it has been proposed that S100B might act in concert with hdm2 to modulate p53 levels and function.

Recent results suggest that S100B interacts with the third cytoplasmic loop of the dopamine D_2 receptor thereby causing activation of ERK1/2 and inhibition of adenylyl cyclase activity via an undetermined mechanism [134] (Fig. 1). However, S100B is expressed sporadically and to a low level in striatal neurons [7,9], and it is not known whether the S100B/D_2 receptor interaction is regulated by cytosolic Ca^{2+}. Most importantly, D_2 receptor is expressed in astrocytes [135] and its activation has been shown to result in release in neurotrophic factors [136,137]. Future studies should analyze the functional relevance of S100B/D_2 receptor interactions in astrocytes.

3. Extracellular regulatory activities of S100B

3.1. Effects of S100B on neurons

Early studies have shown that S100B exerts neurotrophic effects on neurons stimulating neurite outgrowth and regeneration in vitro and in vivo [138–140], enhancing survival of neurons during development [141–145] and after injury [146], and preventing motor neuron degeneration in newborn rats after sciatic nerve section [147]. S100B protects neurons towards toxic stimuli by causing upregulation of the anti-apoptotic factor, Bcl-2 [148–150], via engagement of RAGE and activation of a Ras/MEK/ERK1/2/NF-κB pathway [149–152] (Fig. 2). Moreover, the intraventricular infusion of S100B induces neurogenesis within the hippocampus, which has been associated with an enhancement of cognitive functions following experimental traumatic brain injury [153,154], and the protein is released by in vitro trauma and reduces delayed neuronal injury [20,155,156]. The protective effect of S100B towards neurons may also be indirect, the protein stimulating uptake of the neurotoxic glutamate by astrocytes [157], reducing neurotoxin-dependent activation of microglia and astrocyte [158], and reducing neuronal and glial cytotoxicity under hypothermic conditions [159]. The neurite extension activity of S100B appears to be mediated by RAGE-dependent activation of Cdc42-Rac1 [149] (Fig. 2). RAGE engagement in neurons and myoblasts has been shown to result in Cdc42-Rac1-dependent stimulation of neurite formation [160,161] and differentiation and fusion into multinucleated myotubes [162], respectively. Also, reduction of RAGE activity in acutely damaged

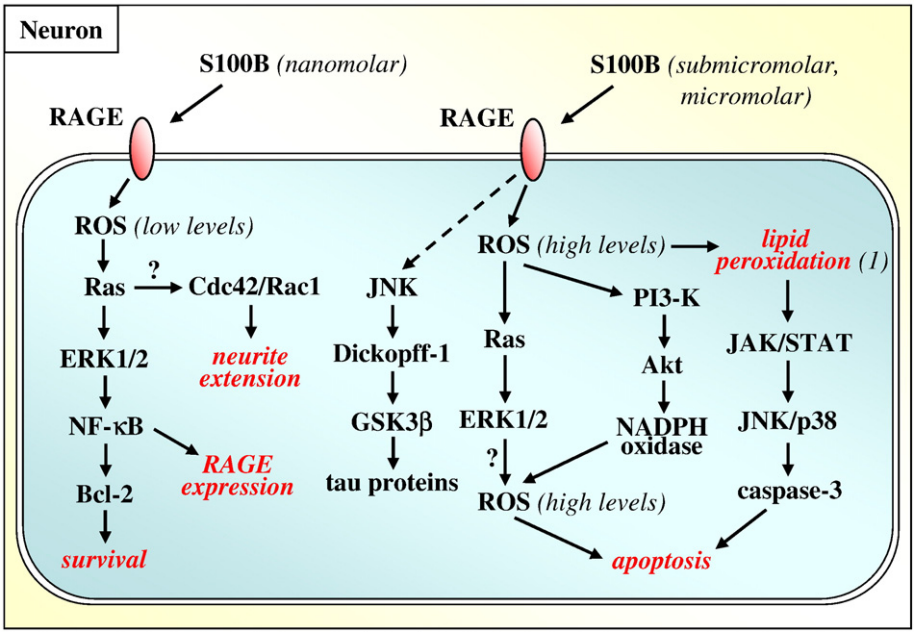

Fig. 2. Proposed model of effects of extracellular S100B on neurons. At low doses, S100B activates a RAGE-dependent production of moderate amounts of ROS and, probably, activation of Src tyrosine kinase with ensuing activation of a Ras-MEK-ERK1/2-NF-κB pathway leading to upregulation of expression the anti-apoptotic factor Bcl-2, and a Rac1-Cdc42 pathway leading to neurite extension. (B) At high doses, S100B activates a RAGE-dependent overproduction of ROS and excessive stimulation of the Ras-MEK-ERK1/2 pathway with accompanying cytochrome-*C* release from mitochondria and activation of caspase-3, leading to neuronal apoptosis. The target(s) of ERK1/2 under these latter conditions have not been elucidated. Schemes do not take into account multimerization of extracellular S100B and S100B-induced RAGE oligomerization and or RAGE oligomer stabilization. (1) S100B-RAGE-ROS-dependent lipid peroxidation has been described in neural progenitors from Down syndrome brain only (Ref. [171]). One cannot exclude that this mechanism can operate in any RAGE-expressing cell type exposed to high S100B concentration, however one should also take into account that responses of human Down syndrome neural progenitor cells to S100B might be strongly dependent on the altered transcriptional regulation of a subset of genes throughout the entire genome in consequence of the increased levels of expression of genes on chromosome 21.

peripheral nerves results in suppression of anatomical regeneration and functional recovery [163], supporting a role of RAGE in neurite outgrowth. Interestingly, peripheral nerve crush results in an increased expression of S100B in reactive Schwann cells in the proximal and distal nerve stumps while nerve transection results in a dramatic reduction of Schwann cell numbers and S100B content in the distal, but not proximal nerve stump [164]. This suggests that the S100B released by Schwann cells in acutely damaged peripheral nerves might contribute to nerve regeneration likely via RAGE engagement (also see Ref. [140]). By contrast, chronic activation of RAGE is suggested to contribute significantly to the impaired peripheral nerve regeneration observed in diabetics [165]. Although reduced release of S100B by Schwann cells occurs under high glucose conditions [64], the role of the protein in chronic diabetic neuropathy remains to be defined.

Chronic administration of antidepressants has been reported to result in proliferation of neuronal precursors in the adult brain [23]. Accordingly, antidepressants have been suggested to overcome stress-induced atrophy and loss of hippocampal neurons and to contribute to the therapeutic actions of antidepressant treatment. Antidepressants have been also proposed to upregulate S100B expression in astrocytes and RAGE expression in proliferating neuroblasts [23], suggesting the possibility that these drugs might contribute to neuroblast proliferation via stimulation of S100B release from astrocytes and S100B-induced RAGE signaling in neurons. However, direct evidence that antidepressants stimulate S100B release from astrocytes is lacking. For example, no information is available concerning effects of antidepressants on neuroblast proliferation in S100B null and transgenic mice.

Collectively, these data suggest that S100B might exert protective, neurotrophic effects during brain development, at early stages of brain insult and in the course of regeneration of injured peripheral nerves. Most importantly, neurotrophic effects are observed at nanomolar doses of S100B, i.e. at the S100B concentrations thought to be present in the brain extracellular space under normal conditions. By contrast, at doses ≥500 nM the protein exerts toxic effects on neurons again in a RAGE-mediated manner, via overproduction of reactive oxygen species (ROS) and excess ROS-dependent activation of MEK/ERK1/2 [149] (Fig. 2), and enhances β-amyloid neurotoxicity [150]. Moreover, at S100B doses >5 nM upregulates RAGE expression in neuronal cell lines in a dose-dependent manner likely due to RAGE-mediated ROS generation [150], in accordance with the notion that RAGE ligands can upregulate RAGE expression and that ROS generation has an important role in this effect [60,61]. These findings also suggest that even at concentrations commonly thought to be protective towards neurons, S100B might turn neurotoxic in the presence of excess ROS generation. However, it has been reported that S100B at as high as 5 μM promotes neuronal survival via RAGE-dependent activation of a PI3-K/Akt/NF-κB pathway [166], while others have shown that S100B at doses ≥250 nM activates a RAGE/ROS/PI3-K/Akt/NADPH oxidase/ROS pathway leading to lipid peroxidation and caspase-3 activation that cause dorsal root ganglia neuron apoptosis [167] (Fig. 2) and still others have found that S100B might cause neuronal cell death at doses ≥50 nM [25].

However, S100B transgenic mice show increased susceptibility to perinatal hypoxia–ischemia [168], to intracerebral infusion of β-amyloid [169] and to permanent middle cerebral artery occlusion [170], suggesting the detrimental effect of constantly high levels of the protein towards neurons. Significantly, human Down syndrome neural progenitor cell lines appear to have more the characteristics of glial cell precursors than of neuronal precursors, and upon switching them to EFG/FGF-deprived media they upregulate S100B expression in contrast to age-matched cells from normal brain which do not [171]. Administration of S100B to human Down syndrome neural progenitor cells results in a dose- and time-dependent ROS production and lipid peroxidation which lead to neuronal apoptosis via RAGE-dependent activation of JAK/STAT, JNK, p38 MAPK and caspase-3 [171] (Fig. 2). These effects begin to be seen at 50 nM S100B

and are maximal at micromolar doses of the protein. Moreover, S100B upregulates the expression of aquaporin-4, the major water channel localized to astrocytic foot processes and expressed at fluid-tissue barriers throughout the brain and crucially involved in water clearance and neuroprotection [172], in a RAGE- and ROS-dependent manner in human Down syndrome neural progenitor cells, but not in control cells [171]. The observation that an S100B-netralizing antibody reduces basal ROS generation, lipid peroxidation and aquaporin-4 expression suggests that upregulation of S100B in human Down syndrome neural progenitor cells results in enhanced release of the protein which then acts in an autocrine manner [171]. Interestingly, effects of administered S100B on ROS generation and lipid peroxidation are enhanced in neuronal cell lines in which aquaporin-4 has been downregulated [171], suggesting that S100B-induced upregulation of aquaporin-4 expression is protective in nature. It should be pointed out, however, that responses of human Down syndrome neural progenitor cells to S100B might be strongly dependent on the altered transcriptional regulation of a subset of genes throughout the entire genome in consequence of the increased levels of expression of genes on chromosome 21. Also, although experimental evidence is lacking to our best knowledge, RAGE is expected to be upregulated in Down syndrome neurons, which might contribute to the exquisite sensitivity of human Down syndrome neural progenitor cells to relatively low S100B concentrations. Collectively, these results suggest that not only might S100B contribute to the neuropathological changes typical of Down syndrome (and, likely, Alzheimer's disease); S100B might also contribute to alter neurogenesis in Down syndrome, reducing the number of neural progenitor cells.

Moreover, MPTP, a neurotoxin shown to produce neurological and pathological changes comparable to those observed in Parkinson's disease [173] has been reported to increase S100B expression in astrocytes in vivo [18] and in vitro [25]. This latter study has also shown that MPTP stimulates glial cell proliferation in coincidence with increased levels of S100B (however, no causal relationship between these two events has been described) and that the culture medium of MPTP-treated cells reduces PC12 neuronal cell viability, an effect that can be counteracted by an S100B-neutralizing antibody [25]. Reduced PC12 neuronal cell viability under these conditions has been thus attributed to enhanced release of S100B by astrocytes and S100B-induced cell death.

Following the observation that levels of S100B are elevated in several brain pathological conditions including Alzheimer's disease and Down syndrome [13–15,32] and in the aging brain [174] (Table 1), the idea has emerged that S100B might play a role in the pathophysiology/pathogenesis of neurodegeneration and brain inflammatory diseases, an idea corroborated by the astrocytosis and axonal growth found in the hippocampus of S100B transgenic mice [175], the neuronal cytoskeletal and behavioral signs of altered aging processes detected in the brain of S100B transgenic mice [176], the accelerated age-related deficits including loss of dendritic and synaptic markers in S100B transgenic mice [177], the increased expression of apoptotic markers in the brain of S100B transgenic mice [178], the losses in learning and memory detected in S100B transgenic mice [179], and the above mentioned increased susceptibility of S100B transgenic mice to perinatal hypoxia–ischemia, intracerebral infusion of β-amyloid and brain ischemic insult [168–170], and the neurotoxic effects of S100B on human Down syndrome neural progenitor cells [171]. Also, recent proteomic analyses of spinal cord injury classify S100B as a proinflammatory cytokine [180]. However, as outlined above, effects of S100B on neurons vary depending on the concentration and the context (i.e. the microenvironment), the protein exerting protective effects on neurons at concentrations up to a few nanomolar in vitro and turning detrimental at relatively high concentrations and/or above a critical threshold of ROS generation in neurons and/or nearby astrocytes and microglia [19,181,182]. Thus, it is possible that baseline levels of extracellular S100B in the normal brain and increases of S100B levels in the aging brain as well as at the very initial stages of brain insults may exert beneficial effects on neurons, the protein promoting neuronal survival and neurite growth, as noted above. However, the increases in baseline S100B levels seen with aging and even more so in Down syndrome and Alzheimer's disease may also increase susceptibility to pathologic processes characterized by S100B overexpression [183] along with induction/upregulation of RAGE expression. Significantly, the neurite growth-promoting effects of S100B have been implicated in the evolution of β-amyloid deposits from benign, non-neuritic forms to the pathogenic neuritic forms that are diagnostic of Alzheimer's disease [32,184], and there is also early and life-long overexpression of S100B in Down syndrome. In addition, recent data suggest that the oxidized/non-oxidized S100B ratio in the brain extracellular space might contribute to the protein's trophic effect via RAGE engagement in neurons or proinflammatory activity via RAGE engagement in microglia [185]. Also, recent evidence suggests that high levels of S100B cause GSK3β-dependent hyperphosphorylation of τ protein via RAGE-dependent activation of JNK and upregulation of Dickopff-1, a stimulator of GSK3β activity, in human neural stem cells [186] (Fig. 2). It is known that hyperphosphorylated τ protein is a major component of neurofibrillary tangles, a hallmark of Alzheimer's disease [187,188]. Together with the observation that S100B increases levels of β-amyloid precursor protein in neuronal cultures [189] and that elevation of levels of S100B in the brain of a mouse model of Alzheimer's disease precedes the appearance of neuritic β-amyloid plaques [190], these findings might represent a mechanistic link between overexpression of S100B in Alzheimer's disease and Down syndrome brain and the elevated expression of S100B in reactive astrocytes in proximity of neurofibrillary tangles [32].

Moreover, although experimental evidence suggests that S100B might act as a serotonergic growth factor [191–194], genetic analyses indicate that S100B null mice show normal development of serotonergic neurons [195]. While compensatory mechanisms might come into play in these mice, these authors however reported that S100B null mice exhibit enhanced spatial and fear memories as well as enhanced long-term potentiation (LTP) in the hippocampal CA1 region, and perfusion of hippocampal slices with S100B reverses the levels of LTP to those of the wild-type slices [196]. This suggests that extracellular S100B might play a role as a regulator of synaptic plasticity, although the molecular mechanism underlying this activity remains to be elucidated. S100B has long been implicated in learning and memory processes (for review see Refs. [1,177,197]), and it has been reported to affect neuronal electrical discharge activity by modulation of potassium currents at subnanomolar concentrations [198] (also see S100B and Ca^{2+} homeostasis above).

However, recent evidence shows that S100B release is increased in a mouse model of epilepsy, that the amplitude of hippocampal kainic acid-induced gamma oscillations is significantly reduced in S100B null mice compared with wild-type mice, and that released S100B enhances hippocampal kainic acid-induced gamma oscillations, an event that is abrogated by the local infusion of either an S100B neutralizing or a RAGE neutralizing antibody [47]. As the enhanced S100B release that occurs following kainic acid treatment was shown to be dependent on the activation of astrocytic metabotropic glutamate receptor 3 via a neural and synaptic activity [47], these results have been proposed to indicate that astrocytes release S100B during epileptic seizures under the action of neuronal glutamate, in accordance with the increased levels of brain S100B detected in epileptic patients [15]. It seems that a 4-fold (i.e. from 2.5 nM to 10 nM) increase in extracellular S100B concentration as measured in kainic acid-treated hippocampal slices, compared with control slices, and S100B-activated RAGE signaling make neurons more sensitive to the epileptogenic activity of kainic acid [47] via a mechanism that remains to be elucidated. How this can be reconciled with the neurotrophic, i.e. anti-apoptotic and neurite growth-promoting

effects of S100B/RAGE signaling and with the S100B-dependent neuronal membrane iperpolarization discussed above remains to be elucidated. It is possible that S100B iperpolarizes inhibitory interneurons in the hippocampus thereby causing dysinhibition of pyramidal neurons and enhancing their sensitivity to kainic acid. Overall, the cellular localization of RAGE in the model system used in Ref. [47] remains to be established.

On the other hand, a positive correlation has been found between serum and cerebrospinal levels of S100B and schizophrenia [199–201] (Table 1). The functional relevance of elevated levels of S100B in the pathophysiology of schizophrenia is still elusive, and information is lacking about the temporal and spatial expression of RAGE in the brain of schizophrenics. However, high S100B levels in schizophrenia seem not to represent a generic index of glial and/or neuronal damage; rather they reflect increased release of the protein [202]; epidemiological studies have indicated that the risk of developing neuropsychiatric disorders in offspring is enhanced by prenatal maternal infection [203]; and genetically mediated brain microvascular inflammatory disease has been proposed to contribute substantially to schizophrenia [204]. Thus, in principle high S100B levels might play a role in the pathophysiology of schizophrenia via RAGE engagement given the documented role of RAGE engagement in inflammatory processes [60,61,205] (also see below). Moreover, as noted above S100B reduces LTP, and LTP is depressed in schizophrenics [206].

It should be pointed out, however, that we ignore the exact levels of extracellular S100B in the brain under normal and pathological conditions (but see Ref. [47]), thus results obtained using cell models might not offer a realistic representation of events in which S100B is involved. In addition (and as in the case of any other extracellular factor affecting the activity of target cells), S100B effects on target cells might be modified by the myriad of distinct stimuli that likely modify the action of S100B in vivo. That said, the sometime opposing effects exerted by S100B on responsive cells at subnanomolar–nanomolar and submicromolar–micromolar concentrations in vitro together with the results of analyses of brain S100B levels in Down syndrome and Alzheimer's disease point to a dual regulatory role of the extracellular protein, that can be well expressed by the use of terms such as low and high (i.e., 2 to 3 orders of magnitude larger) doses.

3.2. Effects of S100B on astrocytes

S100B affects astrocytes in an autocrine manner. Early studies have shown that S100B stimulates astrocyte cell line proliferation at low doses [207], and inducible nitric oxide (iNOS) synthase activity and mRNA levels in rat cortical astrocytes at higher concentrations [208] via activation of NF-κB [209] (Fig. 3). The NO generated by high S100B causes astrocyte apoptosis [210] as well as apoptosis of co-cultured neurons [182]. Also, (high) S100B upregulates IL-1β expression in astrocytes and enhances β-amyloid-induced glial activation [211], and stimulates the release of IL-6 and TNF-α from astrocytes at doses ≥25 nM [212] (Fig. 3). Thus, S100B can activate astrocytes, i.e. it may take part in the process that switches astrocytes from trophic cells to cells that participate in the brain inflammatory response. It cannot be excluded, however, that S100B-induced apoptosis of astrocytes might contribute to reduce the number of activated astrocytes during the course of brain inflammatory processes. From this standpoint, S100B might play a role in the process of resolution of inflammation. Effects of S100B on astrocytes appear to be dependent on engagement of RAGE [212]. On the other hand, low (i.e., subnanomolar to nanomolar) doses of S100B have been shown to counter the activating effects of the neurotoxin, trimethyltin, on astrocytes [158].

S100B has been also shown to activate enteric glia cells in the duodenal mucosa of patients with celiac disease but not normal mucosa, upregulating iNOS expression and stimulating NO production and lipid peroxidation in a p38 MAPK-NF-κB-dependent manner and in a dose-dependent fashion with maximum effect in the micromolar range [26]. These results raise the possibility that gliadin-induced upregulation of S100B expression in and release from enteroglial cells might play an important role in the pathogenesis/pathophysiology of celiac disease.

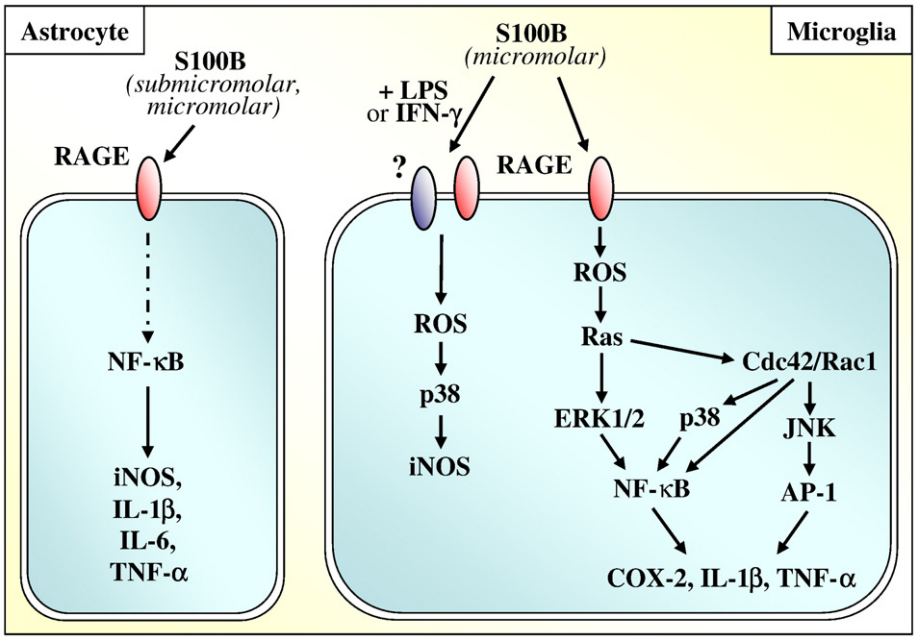

Fig. 3. Proposed model of effects of S100B on astrocytes and microglia. (Left) RAGE engagement by S100B results in NF-κB-dependent upregulation of IL-1β, IL-6, TNF-α and iNOS expression. (Right) At high doses S100B synergizes with IFN-γ to upregulate iNOS expression and NO production in microglia. The molecular mechanism by which S100B synergizes with IFN-γ is not known (?). At high doses S100B also causes a RAGE-dependent (over)production of ROS likely via activation of the NADPH oxidase complex. In turn, ROS activate a Ras-Rac1-Cdc42-MKK4/7-JNK-AP-1 pathway and a Ras-Rac1-NF-κB pathway with ensuing upregulation of expression of COX-2, IL-1β and TNF-α expression. A Ras-MEK-ERK1/2-NF-κB pathway and a Ras-Rac1-Cdc42-MKK6-p38 MAPK-NF-κB pathway might contribute to upregulation of IL-1β and TNF-α expression. Schemes do not take into account multimerization of extracellular S100B and S100B-induced RAGE oligomerization and or RAGE oligomer stabilization.

3.3. Effects of S100B on microglia

At subnanomolar to nanomolar doses S100B blocks activating effects of the neurotoxin, trimethyltin, on microglia [158], the brain resident macrophages. The receptor transducing these S100B effects is not known. However, these analyses were conducted on primary microglia [158] and it is known that RAGE is expressed in nervous cells during brain development [213,214]. Thus, at physiological levels S100B might counter neurotoxin effects on microglia via RAGE engagement. RAGE is also expressed in mature brain cells under normal conditions, albeit at a low level, and its expression increases in several neurodegenerative processes [215–218]. Thus, S100B might counter effects of neurotoxins in the mature brain at the initial phases of brain insults.

By contrast, at high doses S100B activates microglia, which are known to participate in the brain inflammatory response. Indeed, S100B synergizes with bacterial endotoxin and IFN-γ, to upregulate iNOS expression in and NO release from microglia [19,181] (Fig. 3), suggesting that on accumulation in the brain extracellular space the protein might participate in the brain inflammatory response in case of insults. S100B's ability to stimulate NO release by microglia is not dependent on RAGE transducing activity, though dependent on the density of RAGE molecules at the microglial surface, and requires the production of ROS and activation the MKK6-p38 mitogen-activated protein kinase (p38 MAPK) [219]. Because in the absence of co-factors the amount of S100B-induced NO release by microglia is marginal [19], one might speculate that in the course of brain inflammatory processes the RAGE extracellular domain might anchor and recruit S100B to the microglial surface thereby permitting the protein to potentiate bacterial endotoxin and IFN-γ ability to stimulate NO release.

By contrast, S100B upregulates the expression of the pro-inflammatory enzyme, cyclo-oxygenase (COX)-2, in microglia in the absence of co-factors, and this effect requires RAGE's transducing activity [220] (Fig. 3). The importance of COX-2 expression and activity is highlighted by its ability to convert arachidonic acid into prostaglandins, that are inflammation mediators; tight regulation of COX-2 expression in several cell types including microglia is a key feature controlling eicosanoid production in inflammatory syndromes [221]. RAGE engagement by S100B in microglia results in the activation of a Cdc42/Rac1-JNK and a Ras-Rac1-NF-κB pathway each of which is necessary and sufficient for S100B/RAGE to upregulate the enzyme [220]. Specifically, S100B/RAGE-dependent upregulation of COX-2 expression in microglia requires the concurrent activation of the Rac1-NF-κB module and the Rac1-JNK-AP-1 module [222]. These effects are seen at relatively high S100B concentrations, suggesting that S100B has to accumulate in the brain extracellular space for it to be able to induce COX-2 expression in microglia. However, at doses that do not result in COX-2 upregulation S100B upregulates the enzyme in microglia in the presence of concentrations of either IL-1β or TNF-α that do not affect COX-2 expression per se [222], implying that S100B might switch from protective to detrimental at the very beginning of the brain inflammatory response.

S100B also stimulates the production of IL-1β, via activation of ERK1/2, p38 MAPK and JNK in primary microglia [223] (Fig. 3). These effects are likewise dependent on RAGE engagement [222]. Moreover, S100B stimulates TNF-α production in microglia in a RAGE-dependent manner [222]. S100B/RAGE-dependent upregulation of IL-1β and TNF-α also occurs via the concurrent activation of the Rac1-NF-κB module and the Rac1-JNK-AP-1 module and the possible, though not critical contribution of the ERK1/2-NF-κB module and p38 MAPK-NF-κB module [222] (Fig. 3). In this context, it is noteworthy that TNF-α stimulates S100B release from astrocytes [40], suggesting the possibility that in case of brain insult TNF-α might concur to elevate the extracellular concentration of S100B thereby favoring the activating effects of S100B on microglia. Collectively, these data suggest that S100B might have a role in the pathogenesis of brain disorders associated with Alzheimer's disease, Down syndrome and other neurodegenerative processes, i.e. conditions in which microglia activation has been documented, as well as in neuroinflammation consequent to autoimmune diseases, infections and traumas.

3.4. Effects of S100B on monocytes/macrophages, T-lymphocytes, endothelial cells, vascular smooth muscle cell, retinal pigment epithelial cells, neutrophils and lens epithelial cells

S100B engages RAGE in the human monocytes cell line, THP-1, and human peripheral blood monocytes thereby upregulating COX-2 expression and increasing production of prostaglandins [224]. These effects require RAGE-dependent generation of ROS and activation of PKC, ERK1/2, p38 MAPK and NF-κB (Fig. 4). Moreover, S100B increases adherence of monocytes to vascular smooth muscle cells (VSMCs) again in a RAGE-PKC-p38 MAPK-ERK1/2-NF-κB-dependent manner [224]. S100B also increases IFN-γ-inducible protein (IP)-10 mRNA and protein levels in THP-1 monocytes as well as peripheral blood monocytes via augmentation of IP-10 mRNA half-life and stability, and TNF-α release from peripheral blood monocytes, in a RAGE-dependent manner [225,226]. Moreover, S100B primes O_2^- generation in monocytes via RAGE engagement [227] and stimulates NO production in macrophages via p38 MAPK activation [228]. In addition, at relatively high concentrations S100B engages RAGE in neutrophil-like HL-60 cells and induces the translocation of p47*phox*, a key component of the NADPH oxidase, to the cell membrane compartment at least in part via ERK1/2, leading to superoxide generation, and this effect is enhanced in high glucose conditions [229] (Fig. 4). Also, S100B enhances neutrophil sensitivity to N-formyl-methionyl-leucyl-phenylalanine, a chemoattractant molecule

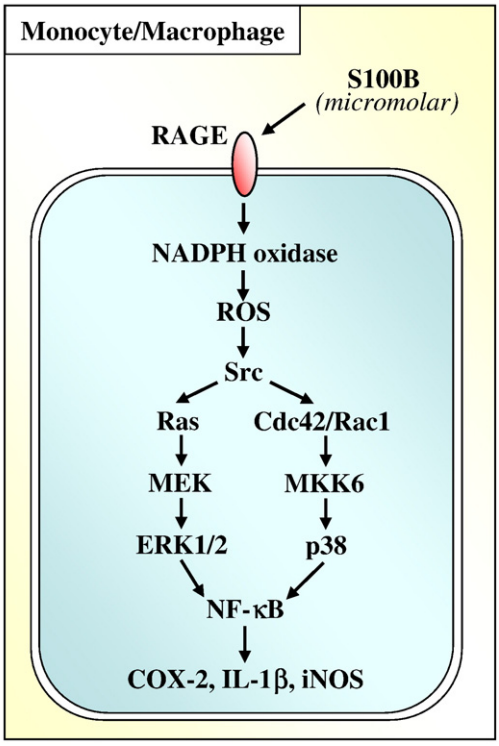

Fig. 4. Proposed model of effects of S100B on monocytes/macrophages. At high doses S100B cause a RAGE-dependent (over)production of ROS via activation of the NADPH oxidase complex. In turn, ROS activate Src tyrosine kinase which recruits a Ras-MEK-ERK1/2-NF-κB pathway and a Rac1-Cdc42-MKK6-p38 MAPK-NF-κB pathway with ensuing upregulation of IL-1β, TNF-α, COX-2 and iNOS expression. Schemes do not take into account multimerization of extracellular S100B and S100B-induced RAGE oligomerization and/or RAGE oligomer stabilization.

towards neutrophils [229]. Thus, S100B might participate in the first line of defense against bacterial invasion by engaging RAGE in neutrophils besides macrophages and microglia.

Collectively, these results suggest that by binding to and activating RAGE S100B can induce inflammatory gene expression and facilitate oxidative burst in monocytes/macrophages/microglia and neutrophils. As discussed elsewhere [67], it should be noted that serum S100B might hardly attain the high concentrations shown to be required for inducing inflammatory gene expression in circulating monocytes. Yet, locally accumulated S100B might activate tissue macrophages. For example, the large amount of S100B released from necrotic melanoma cells [230] might engage RAGE in macrophages thereby stimulating a local inflammatory response and release of TNF-α, a cytokine that is upregulated in tumor states and is responsible for several systemic effects in the course of neoplasias [231–233]. These findings underline the importance of S100B/RAGE interactions in macrophages, which might be important in relation to those chronic inflammatory states that accompany (and/or represent a relevant component of) several pathological conditions, including chronic inflammatory diseases, diabetes and tumors as well as in relation to acute inflammatory states.

S100B has been shown to chemoattract RAGE-expressing encephalitogenic $CD4^+$ Th1 T-cells in a model of experimental autoimmune encephalomyelitis (which mimics multiple sclerosis) thereby promoting T-cell infiltration of the central nervous system [234]. Thus, S100B might play an important role in the pathogenesis/pathophysiology of multiple sclerosis both by chemoattracting $RAGE^+$-$CD4^+$ T-cells and by activating astrocytes and microglia via RAGE engagement. Consistently, others have found that the expression of S100B is significantly reduced in Borna disease virus (BDV)-infected brains despite severe astrocytosis with increased GFAP immunoreactivity and that BDV infection may impair astrocyte functions via a down-regulation of S100B expression, leading to the maintenance of a persistent infection [235].

S100B engages RAGE in endothelial cells thereby activating NF-κB transcriptional activity [66], increasing expression of vascular cell adhesion molecule-1 [227] and inducing monocyte chemoattractant protein-1 (MCP-1) and RAGE transcripts [236] and eliminating sodium nitroprusside-potentiated vasodilatation in response to ACh in endothelial dysfunction in type II diabetic ($Lepr^{db}$) mice [237]. Also, S100B enhances the interaction of RAGE with the leukocyte β2-integrin Mac-1 thus potentially increasing leukocyte adhesion to endothelial cells [238].

RAGE engagement in VSMCs results in increased ROS generation via stimulation of NADPH oxidase, and janus kinase (JAK) 2 tyrosine phosphorylation via activation of phospholipase D2, these effects being enhanced in the presence of high glucose concentrations or angiotensin II [239]. These effects translate into VSMC proliferation. Moreover, RAGE engagement by S100B in VSMCs results in recruitment of the non-receptor Src tyrosine kinase and PKC and phosphorylation of caveolin-1, a component of caveolae, and that the effects of S100B/RAGE on VSMCs [239] plus stimulation of VSMC migration and release of IL-6, require p38 MAPK, ERK1/2, NF-κB and STAT3 activities, and ROS production [240]. Notably, the integrity of caveolae (i.e., stable membrane domains that are kept in place by the actin cytoskeleton and act as multifunctional organelles [241,242]) is required for assembly of RAGE with Src tyrosine kinase and for S100B-stimulated RAGE signaling via Src tyrosine kinase in VSMCs [240]. For a schematic representation of S100B effects on VSMCs see Fig. 3 in Ref. [66].

Immobilized (i.e., oligomeric) S100B increases vascular endothelial growth factor (VEGF) secretion by retinal pigment epithelial cells in vitro in a RAGE/NF-κB-dependent manner [69], thus potentially inciting or propagating neovascular macular disease.

S100B also upregulates RAGE and transforming growth factor-β in human lens epithelial cells as well as nuclear accumulation of phosphorylated Smad2/3 [243], which might have implications in the context of eye complications in diabetics.

In conclusion, the S100B/RAGE interaction might be important for macrophage/microglia and neutrophil activation, S100B having properties of the so-called defensins or alarmins. Also, the S100B/RAGE interaction might play a role in embryonic and reactive angiogenesis and in the pathophysiology of microcirculation defects, and in the course of several pathological conditions including diabetes, brain insults, infections, inflammatory diseases, and cardiac infarction (in the latter case because of the α_1-adrenergic-induced expression of S100B in surviving cardiomyocytes and leakage of S100B from damaged cardiomyocytes [129]). Moreover, while the number of cell types capable of expressing and releasing S100B under normal and pathological conditions is relatively small, in organs/tissues endowed with S100B-positive cells the release of the protein consequent to constitutive or stimulated secretion, leakage from damaged cells or cell necrosis might result in S100B-mediated activation of RAGE in endothelial cells and VSMCs and in VEGF-releasing cells.

3.5. Effects of S100B on myoblasts/muscle satellite cells

S100B exerts regulatory effects on myoblast proliferation and differentiation by activating of the mitogenic Ras/MEK/ERK1/2 module and inhibiting the promyogenic MKK6/p38 MAPK module in a receptor-mediated manner with half-maximum effect at ~50 pM and maximum effect at ~100 pM [244,245]. It is known that for myoblasts to differentiate into fusion-competent myocytes, they have to stop proliferating [114]. S100B also promotes myoblast survival by activating the Ras/MEK/ERK1/2/NF-κB module [245]. In light of the anti-myogenic activity of NF-κB [121–123], S100B-dependent activation of this transcription factor might contribute to the overall anti-differentiative activity of S100B on myoblasts. However, S100B's anti-myogenic effects appear to be exerted on high-density myoblasts only. Current work suggests, in fact, that S100B inhibits high-density myoblast differentiation by activating bFGF receptor-1 (FGFR1).[3] By contrast, in case of low-density myoblasts and as long as myoblasts are present at a low density, S100B stimulates proliferation *and* activates the myogenic program via RAGE-dependent stimulation of the mitogenic MEK/ERK1/2 and the promyogenic p38 MAPK, respectively, with no apparent role for FGFR1.[3] However, S100B does not bind FGFR1 and no S100B-dependent activation of FGFR1 occurs in the absence of bFGF.[3] Indeed, S100B interacts with bFGF although at relatively high S100B/bFGF molar ratios and likely potentiates bFGF-dependent FGFR1 activation.[3] Thus, a quaternary RAGE-S100B-bFGF-FGFR1 complex, in which an S100B/bFGF complex cross-links RAGE to FGFR1, forms in high-density myoblasts, and under these conditions RAGE is prevented from activating p38 MAPK, while in low-density myoblasts S100B can bind to and activate RAGE but not FGFR1 likely because of the high abundance of the bFGF released and lack of complex formation between S100B and bFGF under these conditions.[3] Myoblast density and the local concentration of bFGF thus appear to dictate the overall effect of S100B on myoblast differentiation. Also, the local injection of S100B into mouse muscles results in an enhancement of the satellite cell number and satellite cell proliferation, an effect not occurring in RAGE null mice.[4] Thus, it appears that the principal effect of S100B on myoblasts is that of stimulating their proliferation. Moreover, extracellular S100B activates quiescent myoblasts in vitro and stimulates their migration.[4] As mentioned in Introduction, serum levels of S100B increase following an intense physical exercise [55,56] during which the protein might be released from adipocytes under the action of

[3] F. Riuzzi, G. Sorci and R. Donato, manuscript in preparation.
[4] F. Riuzzi, G. Sorci and R. Donato, manuscript in preparation.

catecholamines [36] and/or from damaged skeletal myofibers.[4] It is known that an intense physical exercise causes skeletal myofiber damage that is followed by myofiber regeneration in a relatively short time under normal conditions via activation of muscle satellite cells, their emigration and proliferation, and their eventual differentiation into fusion-competent myocytes [114]. It is tempting to speculate that the S100B released locally by damaged myofibers might contribute to the process of muscle regeneration by virtue of its ability to activate and expand satellite cells. However, as with neuronal and astrocytic cell lines [149,150,210,246], at high doses S100B causes myoblast apoptosis in vitro via excess generation of ROS [247].

3.6. Structural requirements for S100B/RAGE interaction

Although RAGE engagement may not be the sole means whereby S100B brings about its effects on target cells, RAGE definitely is an important S100B's receptor. Recent work has shown that S100B tetramers and, likely, higher-order oligomers bind to the RAGE immunoglobulin V extracellular domain and cause RAGE oligomerization [67] and/or stabilization of preformed RAGE oligomers [69]. Notably, RAGE oligomerization is required for S100A12, S100A6, AGE-modified proteins and, likely, other S100 proteins to activate RAGE [66]. Also importantly, differences have been reported concerning the structural motifs of RAGE extracellular domain engaged by the various RAGE ligands, possibly explaining the differential effects exerted by the different RAGE ligands in different cell types.

3.7. Concluding remarks

Increasing evidence indicates that S100B exerts functional roles by acting as an intracellular regulator and an extracellular signal. Within cells, S100B acts as a stimulator of proliferation and migration and an inhibitor of apoptosis and differentiation. These S100B effects might be important during brain, cartilage and skeletal muscle development, activation of astrocytes in the course of brain insults and neurodegenerative processes and satellite cells in the course of muscle regeneration, and of cardiomyocyte remodeling after infarction, as well as in gliomagenesis and melanomagenesis.

S100B is secreted by several cell types and released by damaged cells. Once released, S100B exerts regulatory effects on a relatively larger number of cell types in an autocrine, paracrine and, possibly, endocrine manner. Thus, S100B also is an extracellular signal. RAGE has been identified as an S100B receptor, transducing S100B effects on a variety of cell types with different outcomes (i.e. beneficial or detrimental, pro-proliferative or pro-differentiative) depending on the concentration attained by the protein and the cell type. The physicochemical state, i.e. dimeric, tetrameric, octameric or oligomeric, of S100B appears to have an important role in the intensity (and duration of) activation of RAGE and, hence, in the final effects of RAGE-mediated S100B actions. Environmental parameters such as the Ca^{2+} and/or ROS concentration and the S100B clearance rate also might influence S100B/RAGE final effects. However, RAGE might not be the sole S100B receptor, and not always S100B/RAGE interactions might be physiologically/pathophysiologically relevant. In fact, S100B is being used as a RAGE agonist in several experimental settings that might not correspond to conditions where S100B is really present or it is present at the concentrations tested.

In face of the plethora of data on intracellular and extracellular regulatory effects of S100B, few data are available by genetic approaches. Availability of S100B null and transgenic mice, RAGE null mice and, hopefully, double S100B/RAGE null mice might help to distinguish between functionally relevant effects of S100B and irrelevant results.

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References

[1] R. Donato, S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles, Int. J. Biochem. Cell. Biol. 33 (2001) 637–668.
[2] C.W. Heizmann, G. Fritz, B.W. Schaefer, S100 proteins: structure, functions and pathology, Front. Biosci. 7 (2002) d1356–d1368.
[3] R. Donato, Intracellular and extracellular roles of S100 proteins, Microsc. Res. Tech. 60 (2003) 540–551.
[4] I. Marenholz, C.W. Heizmann, G. Fritz, S100 proteins in mouse and man: from evolution to function and pathology (including an update of the nomenclature), Biochem. Biophys. Res. Commun. 322 (2004) 1111–1122.
[5] L. Santamaria-Kisiel, A.C. Rintala-Dempsey, G.S. Shaw, Calcium-dependent and -independent interactions of the S100 protein family, Biochem. J. 396 (2006) 201–214.
[6] M.G. Rambotti, I. Giambanco, A. Spreca, R. Donato, S100B and S100A1 proteins in bovine retina: their calcium-dependent stimulation of a membrane-bound guanylate cyclase activity as investigated by ultracytochemistry, Neuroscience 92 (1999) 1089–1101.
[7] M. Rickmann, J.R. Wolff, S100 protein expression in subpopulations of neurons of rat brain, Neuroscience 67 (1995) 977–991.
[8] S. Hachem, A. Aguirre, V. Vives, A. Marks, V. Gallo, C. Legraverend, Spatial and temporal expression of S100B in cells of oligodendrocyte lineage, Glia 51 (2005) 81–97.
[9] V. Vives, G. Alonso, A.C. Solal, D. Joubert, C. Legraverend, Visualization of S100B-positive neurons and glia in the central nervous system of EGFP transgenic mice, J. Comp. Neurol. 457 (2003) 404–419.
[10] J.C. Deloulme, E. Raponi, B.J. Gentil, N. Bertacchi, A. Marks, G. Labourdette, J. Baudier, Nuclear expression of S100B in oligodendrocyte progenitor cells correlates with differentiation toward the oligodendroglial lineage and modulates oligodendrocytes maturation, Mol. Cell. Neurosci. (2004) 453–465.
[11] G. Sorci, R. Bianchi, I. Giambanco, M.G. Rambotti, R. Donato, Replicating myoblasts and fused myotubes express the calcium-regulated proteins S100A1 and S100B, Cell Calcium 25 (1999) 93–106.
[12] C. Arcuri, I. Giambanco, R. Bianchi, R. Donato, Annexin V, annexin VI, S100A1 and S100B in developing and adult avian skeletal muscles, Neuroscience 109 (2002) 371–388.
[13] S.W.T. Griffin, J.G. Sheng, M.C. Royston, S.M. Gentleman, J.E. McKenzie, D.I. Graham, G.W. Roberts, R.E. Mrak, Glial-neuronal interactions in Alzheimer's disease: the potential role of a "cytokine cycle" in disease progression, Brain Pathol. 8 (1998) 65–72.
[14] R.E. Mrak, W.S. Griffin, The role of activated astrocytes and of the neurotrophic cytokine S100B in the pathogenesis of Alzheimer's disease, Neurobiol. Aging 22 (2001) 915–922.
[15] L.J. Van Eldik, M.S. Wainwright, The Janus face of glial-derived S100B: beneficial and detrimental functions in the brain, Restor. Neurol. Neurosci. 21 (2003) 97–108.
[16] J.N. Tsoporis, A. Marks, H.J. Kahn, J.W. Butany, P.P. Liu, D. O'Hanlon, T.G. Parker, S100β inhibits α1-adrenergic induction of the hypertrophic phenotype in cardiac myocytes, J. Biol. Chem. 272 (1997) 31915–31921.
[17] F. Castets, W.S.T. Griffin, A. Marks, L.J. Van Eldik, Transcriptional regulation of the human S100β gene, Mol. Brain Res. 46 (1997) 208–216.
[18] Y. Muramatsu, R. Kurosaki, H. Watanabe, M. Michimata, M. Matsubara, Y. Imai, T. Araki, Expression of S-100 protein is related to neuronal damage in MPTP-treated mice, Glia 42 (2003) 307–313.
[19] C. Adami, G. Sorci, E. Blasi, A.L. Agneletti, F. Bistoni, R. Donato, S100B expression in and effects on microglia, Glia 33 (2001) 131–142.
[20] E.F. Ellis, K.A. Willoughby, S.A. Sparks, T. Chen, S100B protein is released from rat neonatal neurons, astrocytes, and microglia by in vitro trauma and anti-S100 increases trauma-induced delayed neuronal injury and negates the protective effect of exogenous S100B on neurons, J. Neurochem. 101 (2007) 1463–1470.
[21] J.G. Sheng, K. Ito, R.D. Skinner, R.E. Mrak, C.R. Rovnaghi, L.J. Van Eldik, W.S. Griffin, In vivo and in vitro evidence supporting a role for the inflammatory cytokine interleukin-1 as a driving force in Alzheimer pathogenesis, Neurobiol. Aging 17 (1996) 761–766.
[22] L.A. Peña, C.W. Brecher, D.R. Marshak, β-Amyloid regulates gene expression of glial trophic substance S100β in C6 glioma and primary astrocyte cultures, Mol. Brain Res. 34 (1995) 118–126.
[23] H. Manev, T. Uz, R. Manev, Glia as a putative target for antidepressant treatments, J. Affect. Disord. 75 (2003) 59–64.

[24] S. Djalali, M. Höltje, G. Grosse, T. Rothe, T. Stroh, J. Grosse, D.R. Deng, R. Hellweg, R. Grantyn, H. Hörtnagl, G. Ahnert-Hilger, Effects of brain-derived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development, J. Neurochem. 92 (2005) 616–627.
[25] T. Iuvone, G. Esposito, D. De Filippis, T. Bisogno, S. Petrosino, C. Scuderi, V. Di Marzo, L. Steardo, Cannabinoid CB1 receptor stimulation affords neuroprotection in MPTP-induced neurotoxicity by attenuating S100B up-regulation in vitro, J. Mol. Med. 85 (2007) 1379–1392.
[26] G. Esposito, C. Cirillo, G. Sarnelli, D. De Filippis, F.P. D'Armiento, A. Rocco, G. Nardone, R. Petruzzelli, M. Grosso, P. Izzo, T. Iuvone, R. Cuomo, Enteric glial-derived S100B protein stimulates nitric oxide production in celiac disease, Gastroenterology 133 (2007) 918–925.
[27] T. Saito, T. Ikeda, K. Nakamura, U.I. Chung, H. Kawaguchi, S100A1 and S100B, transcriptional targets of SOX trio, inhibit terminal differentiation of chondrocytes, EMBO Rep. 8 (2007) 504–509.
[28] S.K. Halonen, T. Woods, K. McInnerney, L.M. Weiss, Microarray analysis of IFN-γresponse genes in astrocytes, J. Neuroimmunol. 175 (2006) 19–30.
[29] E. Raponi, F. Agenes, C. Delphin, N. Assard, J. Baudier, C. Legraverend, J.C. Deloulme, S100B expression defines a state in which GFAP-expressing cells lose their neural stem cell potential and acquire a more mature developmental stage, Glia 55 (2007) 165–177.
[30] R.R. Rustandi, D.M. Baldisseri, D.J. Weber, Structure of the negative regulatory domain of p53 bound to S100Bβ, Nat. Struct. Biol. 7 (2000) 570–574.
[31] R. Allore, D. O'Hanlon, R. Price, K. Neilson, H.F. Willard, D.R. Cox, A. Marks, R.J. Dunn, Gene encoding the β subunit of S100 protein is on chromosome 21: implications for Down's syndrome, Science 239 (1988) 1311–1313.
[32] R.E. Mrak, W.S. Griffin, Trisomy 21 and the brain, J. Neuropathol. Exp. Neurol. 63 (2004) 679–685.
[33] G. Poelmans, J.J. Engelen, J. Van Lent-Albrechts, H.J. Smeets, E. Schoenmakers, B. Franke, J.K. Buitelaar, M. Wuisman-Frerker, W. Erens, J. Steyaert, C. Schrander-Stumpel, Identification of novel dyslexia candidate genes through the analysis of a chromosomal deletion, Am. J. Med. Genet. B. Neuropsychiatr. Genet. (2008) doi:10.1002/ajmg.b.30787.
[34] V.E. Shashoua, G.W. Hesse, B.W. Moore, Proteins of the brain extracellular fluid: evidence for release of S-100 protein, J. Neurochem. 42 (1984) 1536–1541.
[35] L.J. Van Eldik, D.B. Zimmer, Secretion of S100 from rat C6 glioma cells, Brain Res. 436 (1987) 367–370.
[36] F. Suzuki, K. Kato, T. Nakajima, Hormonal regulation of adipose S-100 protein release, J. Neurochem. 43 (1994) 1336–13341.
[37] P.M. Whitaker-Azmitia, R. Murphy, E.C. Azmitia, S100 protein is released from astroglial cells by stimulation of 5-HT_{1A} receptors, Brain Res. 528 (1990) 155–158.
[38] S.S. Pinto, C. Gottfried, A. Mendez, D. Gonçalves, J. Karl, C.A. Gonçalves, S. Wofchuk, R. Rodnight, Immunocontent and secretion of S100B in astrocyte cultures from different brain regions in relation to morphology, FEBS Lett. 486 (2000) 203–207.
[39] R. Ciccarelli, P. Di Iorio, V. Bruno, G. Battaglia, I. D'Alimonte, M. D'Onofrio, F. Nicoletti, F. Caciagli, Activation of A_1 adenosine or mGlu3 metabotropic glutamate receptors enhances the release of Nerve Growth Factor and S100β protein from cultured astrocytes, Glia 27 (1999) 275–281.
[40] M.M. Edwards, S.R. Robinson, TNF-α affects the expression of GFAP and S100B: implications for Alzheimer's disease, J. Neural. Transm. 113 (2006) 1709–1715.
[41] R. Gerlach, G. Demel, H.G. König, U. Gross, J.H. Prehn, A. Raabe, V. Seifert, D. Kögel, Active secretion of S100B from astrocytes during metabolic stress, Neuroscience 141 (2006) 1697–1701.
[42] G.E. Davey, P. Murmann, C.W. Heizmann, Intracellular Ca^{2+} and Zn^{2+} levels regulate the alternative cell density-dependent secretion of S100B in human glioblastoma cells, J. Biol. Chem. 276 (2001) 30819–30826.
[43] L.M. de Almeida, C.C. Piñeiro, M.C. Leite, G. Brolese, F. Tramontina, A.M. Feoli, C. Gottfried, C.A. Gonçalves, Resveratrol increases glutamate uptake, glutathione content, and S100B secretion in cortical astrocyte cultures, Cell. Mol. Neurobiol. 27 (2007) 661–668.
[44] R.T. Abib, A. Quincozes-Santos, P. Nardin, S.T. Wofchuk, M.L. Perry, C.A. Gonçalves, C. Gottfried, Epicatechin gallate increases glutamate uptake and S100B secretion in C6 cell lineage, Mol. Cell. Biochem. 310 (2008) 153–158.
[45] C. Funchal, F. Tramontina, A. Quincozes dos Santos, D. Fraga de Souza, C.A. Gonçalves, R. Pessoa-Pureur, M. Wajner, Effect of the branched-chain alpha-keto acids accumulating in maple syrup urine disease on S100B release from glial cells, J. Neurol. Sci. 260 (2007) 87–94.
[46] A. Quincozes-Santos, R.T. Abib, M.C. Leite, D. Bobermin, V. Bambini-Junior, C.A. Gonçalves, R. Riesgo, C. Gottfried, Effect of the atypical neuroleptic risperidone on morphology and S100B secretion in C6 astroglial lineage cells, Mol. Cell. Biochem. 314 (2008) 59–63.
[47] S. Sakatani, A. Seto-Ohshima, Y. Shinohara, Y. Yamamoto, H. Yamamoto, S. Itohara, H. Hirase, Neural-activity-dependent release of S100B from astrocytes enhances kainate-induced gamma oscillations in vivo, J. Neurosci. 28 (2008) 10928–10936.
[48] A.J. Cochran, H.F. Lu, P.X. Li, R. Saxton, D.R. Wen, S-100 protein remains a practical marker for melanocytic and other tumours, Melanoma Res. 3 (1993) 325–330.
[49] L. Brochez, J.M. Naeyaert, Serological markers for melanoma, Br. J. Dermatol. 143 (2000) 256–268.
[50] R. Harpio, R. Einarsson, S100 proteins as cancer biomarkers with focus on S100B in malignant melanoma, Clin. Biochem. 37 (2004) 512–518.
[51] M. Rothermundt, M. Peters, J.H. Prehn, V. Arolt, S100B in brain damage and neurodegeneration, Microsc. Res. Tech. 60 (2003) 614–632.
[52] S. Korfias, G. Stranjalis, A. Papadimitriou, C. Psachoulia, G. Daskalakis, A. Antsaklis, D.E. Sakas, Serum S-100B protein as a biochemical marker of brain injury: a review of current concepts, Curr. Med. Chem. 13 (2006) 3719–3731.
[53] S.M. Bloomfield, J. McKinney, L. Smith, J. Brisman, Reliability of S100B in predicting severity of central nervous system injury, Neurocrit Care 6 (2007) 121–138.
[54] A. Kleindienst, F. Hesse, M.R. Bullock, M. Buchfelder, The neurotrophic protein S100B: value as a marker of brain damage and possible therapeutic implications, Prog. Brain Res. 161 (2007) 317–325.
[55] M.O. Dietrich, A.B. Tort, D.V. Schaf, M. Farina, C.A. Gonçalves, D.O. Souza, L.V. Portela, Increase in serum S100B protein level after a swimming race, Can. J. Appl. Physiol. 28 (2003) 710–716.
[56] M. Hasselblatt, F.C. Mooren, N. von Ahsen, K. Keyvani, A. Fromme, K. Schwarze-Eicker, V. Senner, W. Paulus, Serum S100β increases in marathon runners reflect extracranial release rather than glial damage, Neurology 62 (2004) 1634–1636.
[57] G.S. Mazzini, D.V. Schaf, E.R. Vinadé, E. Horowitz, R.S. Bruch, L.M. Brunm, C.A. Gonçalves, F. Bacal, D.O. Souza, L.V. Portela, S. Bordignon, Increased S100B serum levels in dilated cardiomyopathy patients, J. Card. Fail. 13 (2007) 850–854.
[58] G.S. Mazzini, D.V. Schaf, A.R. Oliveira, C.A. Gonçalves, A. Belló-Klein, S. Bordignon, R.S. Bruch, G.F. Campos, D.V. Vassallo, D.O. Souza, L.V. Portela, The ischemic rat heart releases S100B, Life Sci. 77 (2005) 882–889.
[59] R.E. Anderson, L.O. Hansson, O. Nilsson, R. Dijlai-Merzoug, G. Settergren, High serum S100B levels for trauma patients without head injuries, Neurosurgery 48 (2001) 1255–1258.
[60] A.M. Schmidt, S.D. Yan, S.F. Yan, D.M. Stern, The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses, J. Clin. Invest. 108 (2001) 949–955.
[61] A. Bierhaus, P.M. Humpert, M. Morcos, T. Wendt, T. Chavakis, B. Arnold, D.M. Stern, P.P. Nawroth, Understanding RAGE, the receptor for advanced glycation end products, J. Mol. Med. 83 (2005) 876–886.
[62] L. Perrone, G. Peluso, M.A. Melone, RAGE recycles at the plasma membrane in S100B secretory vesicles and promotes Schwann cells morphological changes, J. Cell. Physiol. 217 (2008) 60–71.
[63] P. Morbini, C. Villa, I. Campo, M. Zorzetto, S. Inghilleri, M. Luisetti, The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease? Mod. Pathol. 19 (2006) 1437–1445.
[64] P. Nardin, F. Tramontina, M.C. Leite, A.C. Tramontina, A. Quincozes-Santos, L.M. de Almeida, A.M. Battastini, C. Gottfried, C.A. Gonçalves, S100B content and secretion decrease in astrocytes cultured in high-glucose medium, Neurochem. Int. 50 (2007) 774–782.
[65] Gonçalves, D., Karl, J., Leite, M., Rotta, L., Salbego, C., Rocha, E., Wofchuk, S., Gonçalves, C.A. High glutamate decreases S100B secretion stimulated by serum deprivation in astrocytes. Neuroreport 27;13 (2002) 1533–1535.
[66] M.A. Hofmann, S. Drury, C. Fu, W. Qu, A. Taguchi, Y. Lu, C. Avila, N. Kambham, A. Bierhaus, P. Nawroth, M.F. Neurath, T. Slattery, D. Beach, J. McClary, M. Nagashima, J. Morser, D. Stern, A.M. Schmidt, RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides, Cell 97 (1999) 889–901.
[67] R. Donato, RAGE: a single receptor for several ligands and different cellular responses. The case of certain S100 proteins, Curr. Mol. Med. 7 (2007) 711–724.
[68] T. Ostendorp, E. Leclerc, A. Galichet, M. Koch, N. Demling, B. Weigle, C.W. Heizmann, P.M. Kroneck, G. Fritz, Structural and functional insights into RAGE activation by multimeric S100B, EMBO J. 26 (2007) 3868–3878.
[69] W. Ma, S.E. Lee, J. Guo, W. Qu, B.I. Hudson, A.M. Schmidt, G.R. Barile, RAGE ligand upregulation of VEGF secretion in ARPE-19 cells, Invest. Ophthalmol. Vis. Sci. 48 (2007) 1355–1361.
[70] J. Xie, S. Reverdatto, A. Frolov, R. Hoffmann, D.S. Burz, A. Shekhtman, Structural basis for pattern recognition by the receptor for advanced glycation end products (RAGE), J. Biol. Chem. 283 (2008) 27255–27269.
[71] M. Schneider, J.L. Hansen, S.P. Sheikh, S100A4: a common mediator of epithelial–mesenchymal transition, fibrosis and regeneration in diseases? J. Mol. Med. 86 (2008) 507–522.
[72] C.W. Heizmann, G.E. Ackermann, A. Galichet, Pathologies involving the S100 proteins and RAGE, Subcell. Biochem. 45 (2007) 93–138.
[73] U. Rescher, V. Gerke, S100A10/p11: family, friends and functions, Pflugers Arch. 455 (2008) 575–582.
[74] D. Foell, H. Wittkowski, J. Roth, Mechanisms of disease: a 'DAMP' view of inflammatory arthritis, Nat. Clin. Pract. Rheumatol. 3 (2007) 382–390.
[75] J. Markowitz, A.D. MacKerell Jr, D.J. Weber, A search for inhibitors of S100B, a member of the S100 family of calcium-binding proteins, Mini. Rev. Med. Chem. 7 (2007) 609–616.
[76] S. Tarabykina, T.R. Griffiths, E. Tulchinsky, J.K. Mellon, I.B. Bronstein, M. Kriajevska, Metastasis-associated protein S100A4: spotlight on its role in cell migration, Curr. Cancer Drug Targets 7 (2007) 217–228.
[77] P. Most, A. Remppis, S.T. Pleger, H.A. Katus, W.J. Koch, S100A1: a novel inotropic regulator of cardiac performance. Transition from molecular physiology to pathophysiological relevance, Am. J. Physiol. Regul. Integr. Comp. Physiol. 293 (2007) R568–R577.
[78] P. Svenningsson, P. Greengard, p11 (S100A10)—an inducible adaptor protein that modulates neuronal functions, Curr. Opin. Pharmacol. 7 (2007) 27–32.
[79] D.B. Zimmer, P. Wright Sadosky, D.J. Weber, Molecular mechanisms of S100-target protein interactions, Microsc. Res. Tech. 60 (2003) 552–559.
[80] E.D. Emberley, L.C. Murphy, P.H. Watson, S100 proteins and their influence on pro-survival pathways in cancer, Biochem. Cell. Biol. 82 (2004) 508–515.
[81] R.L. Eckert, A.M. Broome, M. Ruse, N. Robinson, D. Ryan, K. Lee, S100 proteins in the epidermis, J. Invest. Dermatol. 123 (2004) 23–33.

[82] S.C. Garrett, K.M. Varney, D.J. Weber, A.R. Bresnick, S100A4, a mediator of metastasis, J. Biol. Chem. 281 (2006) 677–680.
[83] O.V. Moroz, G.G. Dodson, K.S. Wilson, E. Lukanidin, I.B. Bronstein, Multiple structural states of S100A12: a key to its functional diversity, Microsc. Res. Tech. 60 (2003) 581–592.
[84] M. Kwon, T.J. MacLeod, Y. Zhang, D.M. Waisman, S100A10, annexin A2, and annexin a2 heterotetramer as candidate plasminogen receptors, Front. Biosci. 10 (2005) 300–325.
[85] I. Prudovsky, A. Mandinova, R. Soldi, C. Bagala, I. Graziani, M. Landriscina, F. Tarantini, M. Duarte, S. Bellum, H. Doherty, T. Maciag, The non-classical export routes: FGF1 and IL-1alpha point the way, J. Cell Sci. 116 (2003) 4871–4881.
[86] R. Donato, Calcium independent, pH regulated effects of S-100 proteins on assembly–disassembly of brain microtubule protein in vitro, J. Biol. Chem. 263 (1988) 106–110.
[87] G. Sorci, A.L. Agneletti, R. Donato, Effects of S100A1 and S100B on microtubule stability. An in vitro study using triton-cytoskeletons from astrocyte and myoblast cell lines, Neuroscience 99 (2000) 773–783.
[88] R. Donato, Quantitative analysis of the interaction between S-100 proteins and brain tubulin, Cell Calcium 8 (1987) 283–297.
[89] J. Baudier, R.D. Cole, Interactions between the microtubule-associated tau proteins and S100b regulate tau phosphorylation by the Ca2+/calmodulin-dependent protein kinase II, J. Biol. Chem. 263 (1988) 5876–5883.
[90] W.H. Yu, P.E. Fraser, S100β interaction with tau is promoted by zinc and inhibited by hyperphosphorylation in Alzheimer's disease, J. Neurosci. 21 (2001) 2240–2246.
[91] P.L. Ferguson, G.S. Shaw, Human S100B protein interacts with the Escherichia coli division protein FtsZ in a calcium-sensitive manner, J. Biol. Chem. 279 (2004) 18806–18813.
[92] E.V. Skripnikova, N.B. Gusev, Interaction of smooth muscle caldesmon with S-100 protein, FEBS Lett. 257 (1989) 380–382.
[93] C.M. Hai, Z. Gu, Caldesmon phosphorylation in actin cytoskeletal remodeling, Eur. J. Cell Biol. 85 (2006) 305–309.
[94] P. Gunning, G. O'Neill, E. Hardeman, Tropomyosin-based regulation of the actin cytoskeleton in time and space, Physiol. Rev. 88 (2008) 1–35.
[95] G.O. Mbele, J.C. Deloulme, B.J. Gentil, C. Delphin, M. Ferro, J. Garin, M. Takahashi, J. Baudier, The zinc- and calcium-binding S100B interacts and co-localizes with IQGAP1 during dynamic rearrangement of cell membranes, J. Biol. Chem. 277 (2002) 49998–50007.
[96] M.W. Briggs, D.B. Sacks, IQGAP proteins are integral components of cytoskeletal regulation, EMBO Rep. 4 (2003) 571–574.
[97] T. Watanabe, S. Wang, J. Noritake, K. Sato, M. Fukata, M. Takefuji, M. Nakagawa, N. Izumi, T. Akiyama, K. Kaibuchi, Interaction with IQGAP1 links APC to Rac1, Cdc42, and actin filaments during cell polarization and migration, Dev. Cell 7 (2004) 871–883.
[98] A.B. Jaffe, A. Hall, Rho GTPases: biochemistry and biology, Annu. Rev. Cell. Dev. Biol. 21 (2005) 247–269.
[99] B.V. Zlokovic, The blood–brain barrier in health and chronic neurodegenerative disorders, Neuron 57 (2008) 178–201.
[100] T.A. Millward, C.W. Heizmann, B.W. Schäfer, B.A. Hemmings, Calcium regulation of Ndr protein kinase mediated by S100 calcium-binding proteins, EMBO J. 17 (1998) 5913–5922.
[101] A. Hergovich, H. Cornils, B.A. Hemmings, Mammalian NDR protein kinases: from regulation to a role in centrosome duplication, Biochim. Biophys. Acta 1784 (2008) 3–15.
[102] R. Tamaskovic, S.J. Bichsel, H. Rogniaux, M.R. Stegert, B.A. Hemmings, Mechanism of Ca^{2+}-mediated regulation of NDR protein kinase through autophosphorylation and phosphorylation by an upstream kinase, J. Biol. Chem. 278 (2003) 6710–6718.
[103] S. Bhattacharya, E. Large, C.W. Heizmann, B. Hemmings, W.J. Chazin, Structure of the Ca^{2+}/S100B/NDR kinase peptide complex: insights into S100 target specificity and activation of the kinase, Biochemistry 42 (2003) 14416–14426.
[104] J. Baudier, C. Delphin, D. Grunwald, S. Khochbin, J.J. Lawrence, Characterization of the tumor suppressor protein p53 as a protein kinase C substrate and a S100b-binding protein, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 11627–11631.
[105] R.R. Rustandi, A.C. Drohat, D.M. Baldisseri, P.T. Wilder, D.J. Weber, The Ca^{2+}-dependent interaction of S100B(ββ) with a peptide derived from p53, Biochemistry 37 (1998) 1951–1960.
[106] K. Kuribayashi, W.S. El-Deiry, Regulation of programmed cell death by the p53 pathway, Adv. Exp. Med. Biol. 615 (2008) 201–221.
[107] T. Riley, E. Sontag, P. Chen, A. Levine, Transcriptional control of human p53-regulated genes, Nat. Rev. Mol. Cell. Biol. 9 (2008) 402–412.
[108] A.C. Joerger, A.R. Fersht, Structural Biology of the Tumor Suppressor p53, Annu. Rev. Biochem. 77 (2008) 557–582.
[109] J. Lin, Q. Yang, Z. Yan, J. Markowitz, P.T. Wilder, F. Carrier, D.J. Weber, Inhibiting S100B restores p53 levels in primary malignant melanoma cancer cells, J. Biol. Chem. 279 (2004) 34071–34077.
[110] P.T. Wilder, J. Lin, C.L. Bair, T.H. Charpentier, D. Yang, M. Liriano, K.M. Varney, A. Lee, A.B. Oppenheim, S. Adhya, F. Carrier, D.J. Weber, Recognition of the tumor suppressor protein p53 and other protein targets by the calcium-binding protein S100B, Biochim. Biophys. Acta 1763 (2006) 1284–1297.
[111] C. Scotto, C. Delphin, J.C. Deloulme, J. Baudier, Concerted regulation of wild-type p53 nuclear accumulation and activation by S100B and calcium-dependent protein kinase C, Mol. Cell. Biol. 19 (1999) 7168–7180.
[112] M.R. Fernandez-Fernandez, D.B. Veprintsev, A.R. Fersht, Proteins of the S100 family regulate the oligomerization of p53 tumor suppressor, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 4735–4740.
[113] C. Arcuri, R. Bianchi, F. Brozzi, R. Donato, S100B increases proliferation in PC12 neuronal cells and reduces their responsiveness to NGF via Akt activation, J. Biol. Chem. 280 (2005) 4402–4414.
[114] S.B. Chargé, M.A. Rudnicki, Cellular and molecular regulation of muscle regeneration, Physiol. Rev. 8 (2004) 209–238.
[115] P.S. Zammit, T.A. Partridge, Z. Yablonka-Reuveni, The skeletal muscle satellite cell: the stem cell that came in from the cold, J. Histochem. Cytochem. 54 (2006) 1177–1191.
[116] A.S. Brack, T.A. Rando, Intrinsic changes and extrinsic influences of myogenic stem cell function during aging, Stem Cell Rev. 3 (2007) 226–237.
[117] F. Le Grand, M.A. Rudnicki, Skeletal muscle satellite cells and adult myogenesis, Curr. Opin. Cell Biol. 19 (2007) 628–633.
[118] C.F. Landry, G.O. Ivy, R.J. Dunn, A. Marks, I.R. Brown, Expression of the gene encoding the beta-subunit of S-100 protein in the developing rat brain analyzed by in situ hybridization, Brain Res. Mol. Brain Res. 6 (1989) 251–262.
[119] A. Reymond, V. Marigo, M.B. Yaylaoglu, A. Leoni, C. Ucla, N. Scamuffa, C. Caccioppoli, E.T. Dermitzakis, R. Lyle, S. Banfi, G. Eichele, S.E. Antonarakis, A. Ballabio, Human chromosome 21 gene expression atlas in the mouse, Nature 420 (2002) 582–586.
[120] S. Hachem, A.S. Laurenson, J.P. Hugnot, C. Legraverend, Expression of S100B during embryonic development of the mouse cerebellum, BMC Dev. Biol. 15 (2007) 7–17.
[121] D.C. Guttridge, M.W. Mayo, L.V. Madrid, C.Y. Wang, A.S. Baldwin Jr., NF-κB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia, Science 289 (2000) 2363–2366.
[122] F. Mourkioti, P. Kratsios, T. Luedde, Y.H. Song, P. Delafontaine, R. Adami, V. Parente, R. Bottinelli, M. Pasparakis, N. Rosenthal, Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration, J. Clin. Invest. 116 (2006) 2945–2954.
[123] N. Bakkar, J. Wang, K.J. Ladner, H. Wang, J.M. Dahlman, M. Carathers, S. Acharyya, M.A. Rudnicki, A.D. Hollenbach, D.C. Guttridge, IKK/NF-κB regulates skeletal myogenesis via a signaling switch to inhibit differentiation and promote mitochondrial biogenesis, J. Cell Biol. 180 (2008) 787–802.
[124] Z. Xiong, D. O'Hanlon, L.E. Becker, J. Roder, J.F. MacDonald, A. Marks, Enhanced calcium transients in glial cells in neonatal cerebellar cultures derived from S100B null mice, Exp. Cell Res. 257 (2000) 281–289.
[125] T. Hashimoto, S. Gamou, N. Shimizu, Y. Kitajima, T. Nishikawa, Regulation of translocation of the desmoyokin/AHNAK protein to the plasma membrane in keratinocytes by protein kinase C, Exp. Cell Res. 217 (1995) 258–266.
[126] H. Haase, T. Podzuweit, G. Lutsch, A. Hohaus, S. Kostka, C. Lindschau, M. Kott, R. Kraft, I. Morano, Signaling from beta-adrenoceptor to L-type calcium channel: identification of a novel cardiac protein kinase A target possessing similarities to AHNAK, FASEB J. 13 (1999) 2161–2172.
[127] B.J. Gentil, C. Delphin, G.O. Mbele, J.C. Deloulme, M. Ferro, J. Garin, J. Baudier, The giant protein AHNAK is a specific target for the calcium- and zinc-binding S100B protein: potential implications for Ca^{2+} homeostasis regulation by S100B, J. Biol. Chem. 276 (2001) 23253–23261.
[128] J.N. Tsoporis, A. Marks, H.J. Kahn, J.W. Butany, P.P. Liu, D. O'Hanlon, T.G. Parker, Inhibition of norepinephrine-induced cardiac hypertrophy in S100β transgenic mice, J. Clin. Invest. 102 (1998) 1609–1616.
[129] J.N. Tsoporis, A. Marks, A. Haddad, F. Dawood, P.P. Liu, T.G. Parker, S100B expression modulates left ventricular remodeling after myocardial infarction in mice, Circulation 111 (2005) 598–606.
[130] J.N. Tsoporis, A. Marks, L.J. Van Eldik, D. O'Hanlon, T.G. Parker, Regulation of the S100B gene by alpha 1-adrenergic stimulation in cardiac myocytes, Am. J. Physiol. Heart Circ. Physiol. 284 (2003) H193–H203.
[131] I. Shiojima, K. Walsh, Regulation of cardiac growth and coronary angiogenesis by the Akt/PKB signaling pathway, Genes Dev. 20 (2006) 3347–3365.
[132] P. Ahuja, P. Sdek, W.R. MacLellan, Cardiac myocyte cell cycle control in development, disease, and regeneration, Physiol. Rev. 87 (2007) 521–544.
[133] C. Agulhon, J. Petravicz, A.B. McMullen, E.J. Sweger, S.K. Minton, S.R. Taves, K.B. Casper, T.A. Fiacco, K.D. McCarthy, What is the role of astrocyte calcium in neurophysiology? Neuron 59 (2008) 932–946.
[134] Y. Liu, D.C. Buck, K.A. Neve, Novel interaction of the dopamine D2 receptor and the Ca^{2+}-binding protein S100B: role in D2 receptor function, Mol. Pharmacol. 74 (2008) 371–378.
[135] Z.U. Khan, P. Koulen, M. Rubinstein, D.K. Grandy, P.S. Goldman-Rakic, An astroglia-linked dopamine D2-receptor action in prefrontal cortex, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 1964–1969.
[136] K. Ohta, S. Kuno, I. Mizuta, A. Fujinami, H. Matsui, M. Ohta, Effects of dopamine agonists bromocriptine, pergolide, cabergoline, and SKF-38393 on GDNF, NGF, and BDNF synthesis in cultured mouse astrocytes, Life Sci. 73 (2003) 617–626.
[137] A. Li, H. Guo, X. Luo, J. Sheng, S. Yang, Y. Yin, J. Zhou, J. Zhou, Apomorphine-induced activation of dopamine receptors modulates FGF-2 expression in astrocytic cultures and promotes survival of dopaminergic neurons, FASEB J. 20 (2006) 1263–1265.
[138] D. Kligman, D.R. Marshak, Purification and characterization of a neurite extension factor from bovine brain, Proc. Natl. Scad. Sci. U. S. A. 82 (1985) 7136–7139.
[139] F. Winningham-Major, J.L. Staecker, S.W. Barger, S. Coats, L.J. Van Eldik, Neurite extension and neuronal survival activities of recombinant S100β proteins that differ in the content and position of cysteine residues, J. Cell Biol. 109 (1989) 3036–3071.
[140] K.G. Haglid, Q. Yang, A. Hamberger, S. Bergman, A. Widerberg, N. Danielsen, S100β stimulates neurite outgrowth in the rat sciatic nerve grafted with acellular muscle transplants, Brain Res. 753 (1997) 196–201.

[141] L.J. Van Eldik, B. Christie-Pope, L.M. Bolin, E.M. Shooter, W.O. Whetsell Jr., Neurotrophic activity of S100β in cultured dorsal root ganglia from embryonic chick and fetal rat, Brain Res. 542 (1991) 280–285.
[142] A. Bhattacharyya, R.W. Oppenheim, D. Prevette, B.W. Moore, R. Brackenbury, N. Ratner, S100 is present in developing chicken neurons and Schwann cells and promotes motor neuron survival in vitro, J. Neurobiol. 23 (1992) 451–466.
[143] E.C. Azmitia, Enhanced synaptophysin immunoreactivity in rat hippocampal culture by 5-HT_{1A} agonist, S100b, and corticosteroid receptor agonists, Synapse 23 (1996) 1–9.
[144] S. Ueda, E.T.K. Leonardi, J. Bell, E.C. Azmitia, Serotoninergic sprouting into transplanted C-6 gliomas is blocked by S100β antisense gene, Mol. Brain Res. 29 (1995) 365–368.
[145] A.R. Alexanian, J.R. Bamburg, Neuronal survival activity of S100ββ is enhanced by calcineurin inhibitors and requires activation of NF-κB, FASEB J. 13 (1999) 1611–1620.
[146] S.W. Barger, L.J. Van Eldik, M.P. Mattson, S100β protects hippocampal neurons from damage induced by glucose deprivation, Brain Res. 677 (1995) 167–170.
[147] Y. Iwasaki, T. Shiojima, M. Kinoshita, S100β prevents the death of motor neurons in newborn rats after sciatic nerve section, J. Neurol. Sci. 151 (1997) 7–12.
[148] B. Ahlemeyer, H. Beier, I. Semkova, C. Schaper, J. Krieglstein, S100β protects cultured neurons against glutamate- and staurosporine-induced damage and is involved in the antiapoptotic action of the $5HT_{1A}$-receptor agonist, Bay × 3702, Brain Res. 858 (2000) 121–128.
[149] H.J. Huttunen, J. Kuja-Panula, G. Sorci, A.L. Agneletti, R. Donato, H. Rauvala, Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through RAGE activation, J. Biol. Chem. 275 (2000) 40096–40105.
[150] R. Businaro, S. Leone, G. Sorci, R. Donato, G.M. Lauro, L. Fumagalli, S100B protects LAN-5 neuroblastoma cells against Aβ amyloid-induced neurotoxicity via RAGE engagement at low doses but increases Aβ amyloid neurotoxicity at high doses, J. Neurosci. Res. 83 (2006) 897–906.
[151] D. Kögel, M. Peters, H.G. König, S.M. Hashemi, N.T. Bui, V. Arolt, M. Rothermundt, J.H. Prehn, S100B potently activates p65/c-Rel transcriptional complexes in hippocampal neurons: clinical implications for the role of S100B in excitotoxic brain injury, Neuroscience 127 (2004) 913–920.
[152] P. Pichiule, J.C. Chavez, A.M. Schmidt, S.J. Vannucci, Hypoxia-inducible factor-1 mediates neuronal expression of the receptor for advanced glycation end products following hypoxia/ischemia, J. Biol. Chem. 282 (2007) 36330–36340.
[153] A. Kleindienst, M.J. McGinn, H.B. Harvey, R.J. Colello, R.J. Hamm, M.R. Bullock, Enhanced hippocampal neurogenesis by intraventricular S100B infusion is associated with improved cognitive recovery after traumatic brain injury, J. Neurotrauma 22 (2005) 645–655.
[154] A. Kleindienst, M. Ross Bullock, A critical analysis of the role of the neurotrophic protein S100B in acute brain injury, J. Neurotrauma 23 (2006) 1185–1200.
[155] K.A. Willoughby, A. Kleindienst, C. Müller, T. Chen, J.K. Muir, E.F. Ellis, S100B protein is released by in vitro trauma and reduces delayed neuronal injury, J. Neurochem. (2004) 1284–1291.
[156] A. Brusco, The 5-HT_{1A} receptor agonist, 8-OH-DPAT, protects neurons and reduces astroglial reaction after ischemic damage caused by cortical devascularization, Brain Res. 1030 (2004) 201–220.
[157] F. Tramontina, A.C. Tramontina, D.F. Souza, M.C. Leite, C. Gottfried, D.O. Souza, S.T. Wofchuk, C.A. Gonçalves, Glutamate uptake is stimulated by extracellular S100B in hippocampal astrocytes, Cell. Mol. Neurobiol. 26 (2006) 81–86.
[158] C. Reali, F. Scintu, R. Pillai, R. Donato, F. Michetti, V. Sogos, S100B counteracts effects of the neurotoxicant trimethyltin on astrocytes and microglia, J. Neurosi. Res. 81 (2005) 677–686.
[159] K.R. Schmitt, C. Kern, P.E. Lange, F. Berger, H. Abdul-Khaliq, S. Hendrix, S100B modulates IL-6 release and cytotoxicity from hypothermic brain cells and inhibits hypothermia-induced axonal outgrowth, Neurosci. Res. 59 (2007) 68–73.
[160] H.J. Huttunen, C. Fages, H. Rauvala, Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways, J. Biol. Chem. 274 (1999) 19919–19924.
[161] L. Wang, S. Li, F.B. Jungalwala, Receptor for advanced glycation end products (RAGE) mediates neuronal differentiation and neurite outgrowth, J. Neurosci. Res. 86 (2008) 254–266.
[162] G. Sorci, F. Riuzzi, C. Arcuri, I. Giambanco, R. Donato, Amphoterin stimulates myogenesis and counteracts the anti-myogenic factors, bFGF and S100B, via RAGE binding, Mol. Cell. Biol. 24 (2004) 4880–4894.
[163] L.L. Rong, W. Trojaborg, W. Qu, K. Kostov, S.D. Yan, C. Gooch, M. Szabolcs, A.P. Hays, A.M. Schmidt, Antagonism of RAGE suppresses peripheral nerve regeneration, FASEB J. 18 (2004) 1812–1817.
[164] A. Spreca, M.G. Rambotti, M. Rende, C. Saccardi, M.C. Aisa, I. Giambanco, R. Donato, Immunocytochemical localization of S-100b protein in degenerating and regenerating rat sciatic nerves, J. Histochem. Cytochem. 37 (1989) 441–446.
[165] C. Toth, J. Martinez, D.W. Zochodne, RAGE, diabetes, and the nervous system, Curr. Mol. Med. 7 (2007) 766–776.
[166] E. Leclerc, G. Fritz, M. Weibel, C.W. Heizmann, A. Galichet, S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE (receptor for advanced glycation end products) immunoglobulin domains, J. Biol. Chem. 282 (2007) 31317–31331.
[167] A.M. Vincent, L. Perrone, K.A. Sullivan, C. Backus, A.M. Sastry, C. Lastoskie, E.L. Feldman, Receptor for advanced glycation end products activation injures primary sensory neurons via oxidative stress, Endocrinology 148 (2007) 548–558.
[168] M.S. Wainwright, J.M. Craft, W.S. Griffin, A. Marks, J. Pineda, K.R. Padgett, L.J. Van Eldik, Increased susceptibility of S100B transgenic mice to perinatal hypoxia–ischemia, Ann. Neurol. 56 (2004) 61–67.
[169] J.M. Craft, D.M. Watterson, A. Marks, L.J. Van Eldik, Enhanced susceptibility of S-100B transgenic mice to neuroinflammation and neuronal dysfunction induced by intracerebroventricular infusion of human β-amyloid, Glia 51 (2005) 209–216.
[170] T. Mori, J. Tan, G.W. Arendash, N. Koyama, Y. Nojima, T. Town, Overexpression of human S100B exacerbates brain damage and periinfarct gliosis after permanent focal ischemia, Stroke 39 (2008) 2114–2121.
[171] G. Esposito, J. Imitola, J. Lu, D. De Filippis, C. Scuderi, V.S. Ganesh, R. Folkerth, J. Hecht, S. Shin, T. Iuvone, J. Chesnut, L. Steardo, V. Sheen, Genomic and functional profiling of human Down syndrome neural progenitors implicates S100B and aquaporin 4 in cell injury, Hum. Mol. Genet. 17 (2008) 440–457.
[172] A.S. Verkman, D.K. Binder, O. Bloch, K. Auguste, M.C. Papadopoulos, Three distinct roles of aquaporin-4 in brain function revealed by knockout mice, Biochim. Biophys. Acta 1758 (2006) 1085–1093.
[173] J.R. Richardson, W.M. Caudle, M. Wang, E.D. Dean, K.D. Pennell, G.W. Miller, Developmental exposure to the pesticide dieldrin alters the dopamine system and increases neurotoxicity in an animal model of Parkinson's disease, FASEB J. 20 (2006) 1695–1697.
[174] J.G. Sheng, R.E. Mrak, C.R. Rovnaghi, E. Kozlowska, L.J. Van Eldik, W.S.T. Griffin, Human brain S100β and S100β mRNA expression increases with age: pathogenic implications for Alzheimer's disease, Neurobiol. Aging 17 (1996) 359–363.
[175] R.H. Reeves, J. Yao, M.R. Crowley, S. Buck, X. Zhang, P. Yarowsky, J.D. Gearhart, D.C. Hilt, Astrocytosis and axonal proliferation in the hippocampus of S100b transgenic mice, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 5359–5363.
[176] P.M. Whitaker-Azmitia, M. Wingate, A. Borella, R. Gerlai, J. Roder, E.C. Azmitia, Transgenic mice overexpressing the neurotrophic factor S-100 beta show neuronal cytoskeletal and behavioral signs of altered aging processes: implications for Alzheimer's disease and Down's syndrome, Brain Res. 776 (1997) 51–60.
[177] L.A. Shapiro, P.M. Whitaker-Azmitia, Expression levels of cytoskeletal proteins indicate pathological aging of S100B transgenic mice: an immunohistochemical study of MAP-2, drebrin and GAP-43, Brain Res. 1019 (2004) 39–46.
[178] L.A. Shapiro, A. Marks, P.M. Whitaker-Azmitia, Increased clusterin expression in old but not young adult S100B transgenic mice: evidence of neuropathological aging in a model of Down Syndrome, Brain Res. 1010 (2004) 17–21.
[179] R. Gerlai, J. Roder, Spatial and nonspatial learning in mice: effects of S100β overexpression and age, Neurobiol. Learn. Mem. 66 (1996) 143–154.
[180] M.C. Tsai, L.F. Shen, H.S. Kuo, H. Cheng, K.F. Chak, Involvement of aFGF in spinal cord injury repair processes revealed by a proteomic approach, Mol. Cell. Proteomics 7 (2008) 1668–1687.
[181] V. Petrova, J. Hu, L.J. Van Eldik, Modulation of glial activation by astrocyte-derived protein S100B: differential responses of astrocyte and microglial cultures, Brain Res. 853 (2000) 74–80.
[182] J. Hu, A. Ferreira, L.J. Van Eldik, S100β induces neuronal cell death through nitric oxide release from astrocytes, J. Neurochem. 69 (1997) 2294–2301.
[183] R.E. Mrak, W.S. Griffin, Glia and their cytokines in progression of neurodegeneration, Neurobiol. Aging 26 (2005) 349–354.
[184] A. Nordberg, Amyloid imaging in Alzheimer's disease, Neuropsychologia 46 (2008) 1636–1641.
[185] L.A. Bialowas-McGoey, A. Lesicka, P.M. Whitaker-Azmitia, Vitamin E increases S100B-mediated microglial activation in an S100B-overexpressing mouse model of pathological aging, Glia 56 (2008) 1780–1790.
[186] G. Esposito, C. Scuderi, J. Lu, C. Savani, D. De Filippis, T. Iuvone, L. Steardo Jr, V. Sheen, L. Steardo, S100B induces tau protein hyperphosphorylation via Dickopff-1 up-regulation and disrupts the Wnt pathway in human neural stem cells, J. Cell. Mol. Med. 12 (2008) 914–927.
[187] V.M. Lee, B.J. Balin, L. Otvos Jr., J.Q. Trojanowski, A68: a major subunit of paired helical filaments and derivatized forms of normal Tau, Science 251 (1991) 675–678.
[188] M. Goedert, M.G. Spillantini, A century of Alzheimer's disease, Science 314 (2006) 777–781.
[189] Y. Li, J. Wang, J.G. Sheng, L. Liu, S.W. Barger, R.A. Jones, L.J. Van Eldik, R.E. Mrak, W.S. Griffin, S100 beta increases levels of beta-amyloid precursor protein and its encoding mRNA in rat neuronal cultures, J. Neurochem. 71 (1998) 1421–1428.
[190] J.G. Sheng, K.R.E. Mra, K.R. Bales, B. Cordell, S.M. Paul, R.A. Jones, S. Woodward, X.Q. Zhou, J.M. McGinness, W.S. Griffin, Overexpression of the neuritotrophic cytokine S100beta precedes the appearance of neuritic beta-amyloid plaques in APPV717F mice, J. Neurochem. 74 (2000) 295–301.
[191] E.C. Azmitia, K. Dolan, P.M. Whitaker-Azmitia, S-100B but not NGF, EGF, insulin or calmodulin is a CNS serotonergic growth factor, Brain Res. 516 (1990) 354–356.
[192] J.P. Liu, J.M. Lauder, S-100β and insulin-like growth factor-II differentially regulate growth of developing serotonin and dopamine neurons in vitro, J. Neurosci. Res. 33 (1992) 248–256.
[193] S. Ueda, X.F. Gu, P.M. Whitaker-Azmitia, I. Naruse, E.C. Azmitia, Neuro-glial neurotrophic interaction in the S-100β retarded mutant mouse (Polydactyly Nagoya) I. Immunocytochemical and neurochemical studies, Brain Res. 633 (1994) 275–283.
[194] S. Ueda, E.T. Kokotos Leonardi, J. Bell 3rd, E.C. Azmitia, Serotonergic sprouting into transplanted C-6 gliomas is blocked by S-100β antisense gene, Brain Res. Mol. Brain Res. 29 (1995) 365–368.
[195] H. Nishiyama, M. Takemura, T. Takeda, S. Itohara, Normal development of serotonergic neurons in mice lacking S100B, Neurosci. Lett. 32 (2002) 49–52.
[196] H. Nishiyama, T. Knopfel, S. Endo, S. Itohara, Glial protein S100B modulates long-term neuronal synaptic plasticity, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 4037–4042.
[197] R. Donato, Functional roles of S100 proteins, calcium-binding proteins of the EF-hand type, Biochim. Biophys. Acta 1450 (1999) 191–231.

[198] H. Kubista, R. Donato, A. Hermann, S100 calcium binding protein affects neuronal electrical discharge activity by modulation of potassium currents, Neuroscience 90 (1999) 493–508.
[199] M. Rothermundt, G. Ponath, V. Arolt, S100B in schizophrenic psychosis, Int. Rev. Neurobiol. 59 (2004) 445–470.
[200] J. Liu, Y. Shi, J. Tang, T. Guo, X. Li, Y. Yang, Q. Chen, X. Zhao, G. He, G. Feng, N. Gu, S. Zhu, H. Liu, L. He, SNPs and haplotypes in the S100B gene reveal association with schizophrenia, Biochem. Biophys. Res. Commun. 328 (2005) 335–341.
[201] N.J. van Beveren, J.J. van der Spelt, L. de Haan, D. Fekkes, Schizophrenia-associated neural growth factors in peripheral blood. A review, Eur. Neuropsychopharmacol. 16 (2006) 469–480.
[202] J. Steiner, H. Bielau, H.G. Bernstein, B. Bogerts, M.T. Wunderlich, Increased cerebrospinal fluid and serum levels of S100B in first-onset schizophrenia are not related to a degenerative release of glial fibrillar acidic protein, myelin basic protein and neurone-specific enolase from glia or neurones, J. Neurol. Neurosurg. Psychiatry 77 (2006) 1284–1287.
[203] U. Meyer, M. Nyffeler, A. Engler, A. Urwyler, M. Schedlowski, I. Knuesel, B.K. Yee, J. Feldon, The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology, J. Neurosci. 26 (2006) 4752–4762.
[204] D.R. Hanson, I. Gottesman, Theories of schizophrenia: a genetic-inflammatory-vascular synthesis, BMC Med. Genet. 6 (2005) 7.
[205] R. Clynes, B. Moser, S.F. Yan, R. Ramasamy, K. Herold, A.M. Schmidt, Receptor for AGE (RAGE): weaving tangled webs within the inflammatory response, Curr. Mol. Med. 7 (2007) 743–751.
[206] H.I.L. Payne, The role of transmembrane AMPA receptor regulatory proteins (TARPs) in neurotransmission and receptor trafficking (Review), Mol. Membr. Biol. 25 (2008) 353–362.
[207] R.H. Selinfreund, S.W. Barger, W.J. Pledger, L.J. Van Eldik, Neurotrophic protein S100β stimulates glial cell proliferation, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 3554–3558.
[208] J. Hu, F. Castets, J.L. Guevara, L.J. Van Eldik, S100β stimulates inducible nitric oxide synthase activity and mRNA levels in rat cortical astrocytes, J. Biol. Chem. 271 (1996) 2543–2547.
[209] A.G. Lam, T. Koppal, K.T. Akama, L. Guo, J.M. Craft, B. Samy, J.P. Schavocky, D.M. Watterson, L.J. Van Eldik, Mechanism of glial activation by S100B: involvement of the transcription factor NFkappaB, Neurobiol. Aging 22 (2001) 765–772.
[210] J. Hu, L.J. Van Eldik, S100β induces apoptotic cell death in cultured astrocytes via a nitric oxide-dependent pathway, Biochim. Biophys. Acta 1313 (1996) 239–245.
[211] J. Hu, L.J. Van Eldik, Glial-derived proteins activate cultured astrocytes and enhance β-amyloid-induced glial activation, Brain Res. 842 (1999) 46–54.
[212] G. Ponath, C. Schettler, F. Kaestner, B. Voigt, D. Wentker, V. Arolt, M. Rothermundt, Autocrine S100B effects on astrocytes are mediated via RAGE, J. Neuroimmunol. (2007) 214–222.
[213] O. Hori, J. Brett, T. Slattery, R. Cao, J. Zhang, J.X. Chen, M. Nagashima, E.R. Lundh, S. Vijay, D. Nitecki, J. Morser, D. Stern, A.M. Schmidt, The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system, J. Biol. Chem. 270 (1995) 25752–25761.
[214] R. Alarcon, C. Fuenzalida, M. Santibanez, R. von Bernhardi, Expression of scavenger receptors in glial cells. Comparing the adhesion of astrocytes and microglia from neonatal rats to surface-bound beta-amyloid, J. Biol. Chem. 280 (2005) 30406–30415.
[215] L.F. Lue, D.G. Walker, L. Brachova, T.G. Beach, J. Rogers, A.M. Schmidt, D.M. Stern, S.D. Yan, Involvement of microglial receptor for advanced glycation endproducts (RAGE) in Alzheimer's disease: identification of a cellular activation mechanism, Exp. Neurol. 171 (2001) 29–45.
[216] N. Sasaki, M. Takeuchi, H. Chowei, S. Kikuchi, Y. Hayashi, N. Nakano, H. Ikeda, S. Yamagishi, T. Kitamoto, T. Saito, Z. Makita, Advanced glycation end products (AGE) and their receptor (RAGE) in the brain of patients with Creutzfeldt–Jakob disease with prion plaques, Neurosci. Lett. 326 (2003) 117–122.
[217] L. Ma, L.F. Nicholson, Expression of the receptor for advanced glycation end products in Huntington's disease caudate nucleus, Brain Res. 1018 (2004) 10–17.
[218] L.F. Lue, S.D. Yan, D.M. Stern, D.G. Walker, Preventing activation of receptor for advanced glycation endproducts in Alzheimer's disease, Curr. Drug Targets CNS Neurol. Disord. 4 (2005) 249–266.
[219] C. Adami, R. Bianchi, G. Pula, R. Donato, S100B-stimulated NO production by BV-2 microglia is independent of RAGE transducing activity but dependent on RAGE extracellular domain, Biochim. Biophys. Acta 1742 (2004) 169–177.
[220] R. Bianchi, C. Adami, I. Giambanco, R. Donato, S100B binding to RAGE in microglia stimulates COX-2 expression, J. Leukoc. Biol. 81 (2007) 108–118.
[221] L. Minghetti, Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases, J. Neuropathol. Exp. Neurol. 63 (2004) 901–910.
[222] R. Bianchi, I. Giambanco, R. Donato, S100B/RAGE-dependent activation of microglia via NF-κB and AP-1. Co-regulation of COX-2 expression by S100B and IL-1β and TNF-α, Neurobiol. Aging (2008) doi:10.1016/j.neurobiolaging.2008.05.017.
[223] S.H. Kim, C.J. Smith, L.J. Van Eldik, Importance of MAPK pathways for microglial pro-inflammatory cytokine IL-1β production, Neurobiol. Aging. 25 (2004) 431–439.
[224] N. Shanmugam, Y.S. Kim, L. Lanting, R. Natarajan, Regulation of cyclooxygenase-2 expression in monocytes by ligation of the receptor for advanced glycation end products, J. Biol. Chem. 278 (2003) 33444–34834.
[225] N. Shanmugam, R.M. Ransohoff, R. Natarajan, Interferon-γ-inducible protein (IP)-10 mRNA stabilized by RNA-binding proteins in monocytes treated with S100b, J. Biol. Chem. 281 (2006) 31212–31221.
[226] J.V. Valencia, M. Mone, C. Koehne, J. Rediske, T.E. Hughes, Binding of receptor for advanced glycation end products (RAGE) ligands is not sufficient to induce inflammatory signals: lack of activity of endotoxin-free albumin-derived advanced glycation end products, Diabetologia 47 (2004) 844–852.
[227] Y. Ding, A. Kantarci, H. Hasturk, P.C. Trackman, A. Malabanan, E. Van Dyke, Activation of RAGE induces elevated O2− generation by mononuclear phagocytes in diabetes, J. Leukoc. Biol. 81 (2007) 520–527.
[228] G. Esposito, D. De Filippis, C. Cirillo, G. Sarnelli, R. Cuomo, T. Iuvone, Astroglial-derived S100β protein stimulates the expression of nitric oxide synthase in rodent macrophages through p38 MAP kinase activation, Life Sci. 78 (2006) 2707–2715.
[229] K. Omori, T. Ohira, Y. Uchida, S. Ayilavarapu, E.L. Batista Jr., M. Yagi, T. Iwata, H. Liu, H. Hasturk, A. Kantarci, T.E. Van Dyke, Priming of neutrophil oxidative burst in diabetes requires preassembly of the NADPH oxidase, J. Leukoc. Biol. 84 (2008) 292–301.
[230] G. Ghanem, B. Loir, R. Morandini, F. Sales, D. Lienard, A. Eggermont, F. Lejeune, EORTC Melanoma Group, On the release and half-life of S100B protein in the peripheral blood of melanoma patients, Int. J. Cancer. 94 (2001) 586–590.
[231] C. Bubici, S. Papa, K. Dean, G. Franzoso, Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance, Oncogene 25 (2006) 6731–6748.
[232] A. Saini, N. Al-Shanti, C.E. Stewart, Waste management-cytokines, growth factors and cachexia, Cytokine Growth Factor Rev. 17 (2006) 475–486.
[233] A. Yoshimura, Signal transduction of inflammatory cytokines and tumor development, Cancer Sci. 97 (2006) 439–447.
[234] S.S. Yan, Z.Y. Wu, H.P. Zhang, G. Furtado, X. Chen, S.F. Yan, A.M. Schmidt, C. Brown, A. Stern, J. LaFaille, L. Chess, D.M. Stern, H. Jiang, Suppression of experimental autoimmune encephalomyelitis by selective blockade of encephalitogenic T-cell infiltration of the central nervous system, Nat. Med. 9 (2003) 287–293.
[235] N. Ohtaki, W. Kamitani, Y. Watanabe, Y. Hayashi, H. Yanai, K. Ikuta, K. Tomonaga, Downregulation of an astrocyte-derived inflammatory protein, S100B, reduces vascular inflammatory responses in brains persistently infected with Borna disease virus, J. Virol. 81 (2007) 940–948.
[236] L. Feng, C. Matsumoto, A. Schwartz, A.M. Schmidt, D.M. Stern, J. Pile-Spellman, Chronic vascular inflammation in patients with type 2 diabetes: endothelial biopsy and RT-PCR analysis, Diabetes Care 28 (2005) 379–384.
[237] X. Gao, H. Zhang, A.M. Schmidt, C. Zhang, AGE/RAGE produces endothelial dysfunction in coronary arterioles in type II diabetic mice, Am. J. Physiol. Heart. Circ. Physiol. 295 (2008) H491–H498.
[238] T. Chavakis, A. Bierhaus, N. Al-Fakhri, D. Schneider, S. Witte, T. Linn, M. Nagashima, J. Morser, B. Arnold, K.T. Preissner, P.P. Nawroth, The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment, J. Exp. Med. 198 (2003) 1507–1515.
[239] S.S. Shaw, A.M. Schmidt, A.K. Banes, X. Wang, D.M. Stern, M.B. Marrero, S100B-RAGE-mediated augmentation of angiotensin II-induced activation of JAK2 in vascular smooth muscle cells is dependent on PLD2, Diabetes 52 (2003) 2381–2388.
[240] M.A. Reddy, S.L. Li, S. Sahar, Y.S. Kim, Z.G. Xu, L. Lanting, R. Natarajan, Key role of Src kinase in S100B-induced activation of the receptor for advanced glycation end products in vascular smooth muscle cells. J. Biol. Chem. 281 (2006) 13685–13693.
[241] B. van Deurs, K. Roepstorff, A.M. Hommelgaard, K. Sandvig, Caveolae: anchored, multifunctional platforms in the lipid ocean, Trends Cell Biol. 13 (2003) 92–100.
[242] R.G. Parton, K. Simons, The multiple faces of caveolae, Nat. Rev. Mol. Cell. Biol. 8 (2007) 185–194.
[243] Y.S. Kim, N.H. Kim, S.W. Lee, Y.M. Lee, D.S. Jang, J.S. Kim, Effect of protocatechualdehyde on receptor for advanced glycation end products and TGF-beta1 expression in human lens epithelial cells cultured under diabetic conditions and on lens opacity in streptozotocin-diabetic rats, Eur. J. Pharmacol. 569 (2007) 171–179.
[244] G. Sorci, A.L. Agneletti, F. Riuzzi, C. Marchetti, R. Donato, S100B inhibits myogenic differentiation and myotube formation in a RAGE-independent manner, Mol. Cell. Biol. 23 (2003) 4870–4881.
[245] F. Riuzzi, G. Sorci, R. Donato, S100B stimulates myoblast proliferation and inhibits myoblast differentiation by independently stimulating ERK1/2 and inhibiting p38 MAPK, J. Cell. Physiol. 207 (2006) 461–470.
[246] G. Fanò, M.A. Mariggiò, P. Angelella, I. Nicoletti, A. Antonica, S. Fulle, P. Calissano, The S-100 protein causes an increase of intracellular calcium and death of PC12 cells, Neuroscience 53 (1993) 919–925.
[247] G. Sorci, F. Riuzzi, A.L. Agneletti, C. Marchetti, R. Donato, S100B causes apoptosis in a myoblast cell line in a RAGE-independent manner, J. Cell. Physiol. 199 (2004) 274–283.