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Review

Binding of S100 proteins to RAGE: An update

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ABSTRACT

The Receptor for Advanced Glycation Endproducts (RAGE) is a multi-ligand receptor of the immunoglobulin family. RAGE interacts with structurally different ligands probably through the oligomerization of the receptor on the cell surface. However, the exact mechanism is unknown. Among RAGE ligands are members of the S100 protein family. S100 proteins are small calcium binding proteins with high structural homology. Several members of the family have been shown to interact with RAGE *in vitro* or in cell-based assays. Interestingly, many RAGE ligands appear to interact with distinct domains of the extracellular portion of RAGE and to trigger various cellular effects. In this review, we summarize the modes of S100 protein–RAGE interaction with regard to their cellular functions.

1. Introduction

The Receptor for Advanced Glycation Endproducts (RAGE) has been first described in 1992 and since then attracted increasing attention due to its involvement in various diseases including diabetic complications, tumour outgrowth, chronic inflammation, and neuro-degenerative disorders like Alzheimer disease or multiple sclerosis. We are focusing in this review on the role of RAGE as receptor for the S100 proteins and will discuss how members of this family interact and activate the receptor.

2. S100 proteins

The S100 protein family consists of 21 members. S100s are small proteins (9–13 kDa) that bind calcium via EF hand motifs and are exclusively expressed in vertebrates where their expressions are tissue and cell-type specific [1–4]. Most S100 protein genes are clustered on a region of human chromosome 1q21 that is prone to chromosomal rearrangements, suggesting a link between S100 proteins and metastasis and tumor formation [1,5–7].

The S100 proteins have been shown to interact with and to regulate various proteins involved in a large number of cellular functions such as calcium homeostasis, cell growth and differentiation, dynamic of cytoskeleton or energy metabolism (reviewed in [2,6,8]). Calcium binding to the EF-hand occurs in response to increases in intracellular calcium concentration and triggers structural changes in the S100 protein that allow the interaction with target proteins and the modulation of their activity [1,2,9,10]. Binding of S100 proteins to their targets is typically calcium-dependent, but calcium-independent interactions have also been described [11]. Besides calcium, some S100 proteins have also been shown to bind zinc or copper [1,12,13].

All S100 proteins function as dimers except for S100G (Calbindin D_{9k}) which is monomeric [14]. Within the dimer, both subunits are related by a two-fold rotational axis, resulting in an antiparallel orientation of S100 binding domains on one face of the dimer [1]. Because of their sequence and structural homology S100 proteins are capable of hetero-dimer formation with distinct physiological functions: S100A1/B, S100A8/A9, S100A1/A4, S100A1/P [15–18]. Certain members of S100 proteins can also form active tetramers, hexamers or larger oligomers (S100B [19], S100A4 [20], S100A8/A9 [21], S100A12 [22–24]).

Secretion has been demonstrated for several members of the S100 protein family. S100B can be actively secreted from astrocytes [25,26], neurons, microglia [27], glioblastoma [28], or Schwann cells [29]. Moreover, the S100B serum level in melanoma patients is an established biomarker for prognosis [30]. S100A8/A9 is actively secreted by monocytes/macrophages [31]. S100A12 is released by neutrophils at sites of inflammation in various diseases [32]. S100A4 has been shown to be secreted in embryoid bodies by parietal endoderm and to promote cardiomyogenesis [33]. S100A1 is released in the extracellular medium during ischemic myocardial injury [34]. S100A2 was found secreted in the medium of cultured LLC-PK1 [35]. We previously showed that S100A6 could be secreted from human glioblastoma after calcium stimulation of the cells, in physiologically relevant S100 concentrations [36]. In certain pathological conditions, S100A7 is released from keratinocytes [37] and possesses antibacterial cytokine activity [38–40].

Growing evidence suggests that all secreted S100 proteins act in either an autocrine or paracrine manner through a common receptor: the Receptor for Advanced Glycation Endproduct [41,42].

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3. RAGE

RAGE is a member of the immunoglobulin protein family of cell surface molecules [43,44] and shares structural homology with other immunoglobulin like receptors [45,46]. Although RAGE is not essential to life [47], it plays important roles in certain human pathologies including diabetes, Alzheimer's disease and cancer [48]. The mature 382 amino-acid long RAGE is composed of an extracellular part (314 aa), a single transmembrane spanning helix (27 aa) and a short cytosolic domain (41 aa) (Fig. 1) [44]. The extracellular part of RAGE contains one variable like V-domain (residues 24–127) and two constant like C type domains frequently referred to as C1 (residues 132–230) and C2 domains (residues 239–320). Recent studies suggests that RAGE forms oligomers at the cell surface [49]. RAGE possesses two N-glycosylation sites, one adjacent to the V-domain and the second one within the V-domain [44,50].

RAGE is highly expressed during development, especially in the brain, but its expression level decreases in adult tissues. RAGE is found in low level in neurons, smooth muscle cells, mesangial cells, mononuclear phagocytes, hepatocytes and cardiac myocytes, but is found in high level in lung tissue [51]. RAGE expression is also augmented by increased levels of ligands in pathologic states [48]. RAGE signaling is complex and depends of the cell type, the type and the concentration of the ligand (for recent review on RAGE/S100 signaling see [6,42]). The internalization/recycling of RAGE is poorly understood but a recent study showed that in the presence of S100B, RAGE was internalized and recycled to the cell membrane after fusion with S100B containing secretory vesicles [29].

3.1. RAGE isoforms

Understanding of the transcriptional regulation of RAGE is important to understand RAGE signaling. Based on mRNA twenty RAGE isoforms have been identified so far in various tissues and cells including rat liver and kidney [52], human lung [53–55], human aortic smooth muscle cells [55], human vascular endothelial cells and pericytes [56] and human brain [57–59]. Recently, the different RAGE gene splice variants have been classified and renamed (RAGE, RAGE_v1 to RAGE_v19) according to the Human Gene Nomenclature Committee [55]. At the DNA level, the RAGE gene consists of 11 introns/exons that can be alternatively spliced to produce the different variants [44,60]. The prevalent RAGE isoforms appear to be the full-length RAGE (RAGE), a secreted isoform of RAGE_v1 (previously named sRAGE, secretory C-truncated RAGE, esRAGE, hRAGEsec or sRAGE1/2/3) and a N-terminally truncated isoform RAGE_v2 (previously named Nt-RAGE, N-RAGE or N-truncated RAGE) [55]. The relative expression levels of these isoforms appear to be tissue specific suggesting strict tissue regulation [53]. RAGE is the main isoform in human lung, human aortic smooth muscle cells and pericytes [55,56]. RAGE_v1 is the prevalent isoform in endothelial cells and human brain [56,59]. This isoform lacks both the cytosolic and transmembrane domain and is characterized by an unique C-terminal sequence due to reading frameshift. RAGE_v1 is released in the extracellular space where it can interact with circulating RAGE ligands resulting in decreased RAGE activation [53–56]. The variant RAGE_v2 is currently subject to controversy and may not be expressed in cells but would rather be degraded at the mRNA level [55]. Recent studies have shown that the circulating extracellular part of RAGE (sRAGE) can also be generated by proteolytic degradation [61,62]. sRAGE is found elevated in broncho-alveolar lavage and plasma in case of pulmonary tissue injury [63]. Interestingly, recent studies failed to identify spliced soluble isoforms of RAGE in murine lung although sRAGE could be isolated suggesting different mechanisms of RAGE regulation between mouse and human species [64].

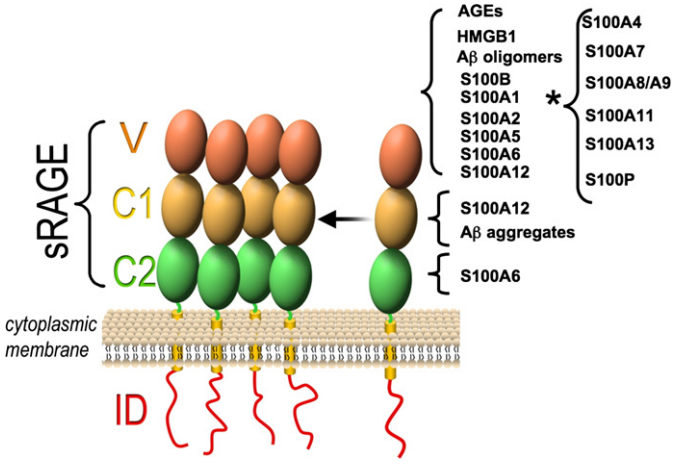

Fig. 1. Schematic representation of RAGE. The extracellular part comprises three immunoglobulin like domain, the V, C1 and C2 domain. A single transmembrane helix connects the extracellular domain with the short intracellular domain (ID). RAGE ligands interact with the extracellular domains as indicated. * indicates that the RAGE domain where S100 binds is not known.

3.2. RAGE ligands

RAGE was initially identified as receptor for the AGE products [43,44]. Besides AGEs, RAGE interacts with other structurally unrelated ligands which include amphoterin (High Mobility Group Box 1, HMGB1) [65], amyloid β peptide [66], immunoglobulin light chain amyloid fibrils [67], transthyretin [68], members of the S100 protein family [48,69], and β2-integrin Mac-1[70] (Fig. 1). AGEs form a heterogeneous class of compounds that result from the reaction between reducing carbohydrates or carbohydrate breakdown products and primary amine groups of proteins (reviewed in [71]). Early experiments showed that *in vitro* prepared AGE-BSA, resulting from the incubation of BSA with high concentration of glucose, interacted with RAGE with high affinity ($K_D = 50$ nM) [43]. Further studies showed that AGEs purified from diabetic patients could trigger the upregulation of endothelial cells in a RAGE dependent manner [72]. AGE-BSA-induced RAGE signaling was further demonstrated in many experimental settings [73–76]. The most prevalent AGE products *in vivo*, Carboxy-Methyl-Lysine or CML-AGEs [77–79] were also shown to trigger RAGE dependent activation in cell assays and in mouse models [74,76,80,81]. Recently, additional AGE products such as pronyl glycine were also shown to bind to RAGE and to trigger RAGE dependent signaling [82]. However, recent studies suggest that not all AGEs are capable of binding to the receptor and/or triggering RAGE dependent signaling effects [67,83,84]. Discrepancies between the published data may arise from differences in composition and concentration of the AGE products used and differences in cell types. In *in vitro* assays, AGEs, including AGE-BSA and CML-AGE were found to interact specifically with the V-domain of RAGE [49,80,85]. However there are also discrepancies again between the observed binding affinities, from sub-micromolar ($K_D = 76$ nM, [80]; $K_D = 61$ nM, [85]; $K_D = 0.23$–1.4 μM [86]), to high micromolar ($K_D = 10$ μM, [49]) resulting probably from differences in AGE composition. Glycosylation of RAGE has been shown to influence binding of certain AGEs to RAGE. Although CML-BSA bound to glycosylated RAGE, no binding was detected with non-glycosylated RAGE [67]. On the contrary, a stronger binding was observed between certain AGEs products and deglycosylated RAGE than with glycosylated RAGE [87].

The second class of RAGE ligand is formed by amphoterin. Amphoterin is a 30 kDa DNA- and heparin-binding protein with both intracellular and extracellular functions. In the cell, amphoterin stabilizes the formation of the nucleosome and facilitates transcription [88–90]. Amphoterin can be passively released from necrotic cells [91] or can be actively secreted by several cells including monocytes, macrophages and endothelial cells [92,93] and plays a role as pro-inflammatory cytokine [92,94] and is proangiogenic [95,96]. When

added extracellularly, amphoterin has been shown to promote neurite outgrowth and neuronal cell differentiation by mechanisms involving RAGE (reviewed by Huttunen et al. [97]). Amphoterin-induced RAGE signaling has also been shown to play an important role in cancer as shown in rat C6 gliomas [98]. Amphoterin was reported to interact with the V-domain of RAGE based on binding competition experiments with AGE-BSA [65]. Glycosylation has been shown to influence binding of RAGE to amphoterin by slightly increasing binding affinity ($K_{D\text{-}Glyco.} = 10.7$ nM versus $K_{D\text{-}deglyco.} = 18.2$ nM) [50].

Amyloid forming peptides or proteins constitutes a third class of RAGE ligand. Amyloid β peptide (Aβ) is a proteolytic fragment of amyloid protein precursor (APP) and mediates oxidative stress and NF-κB activation through RAGE [99–102]. The interaction of Aβ peptide to RAGE was initially suggested to interact with the N-terminal portion of RAGE based on modeling experiments [103]. By using a combination of RAGE domain specific antibodies and purified RAGE domains, we recently demonstrated that binding of Aβ to RAGE depended of the state of oligomerization of the amyloid forming peptide [102]. Whereas oligomers of Aβ were shown to interact with the V-domain of RAGE, Aβ aggregates interacted with the C1 domain (Fig. 1) [102].

In the following paragraph, we will describe in more detail a fourth class of RAGE ligands constituted by the S100 proteins. Many of the S100 proteins interact with RAGE *in vitro* and trigger RAGE dependent signaling in cell-based assays. Some S100 proteins have also been shown to trigger RAGE signaling in animal models.

4. S100 proteins that interact with RAGE

4.1. S100B

S100B and S100A1 are the best characterized proteins of the S100 family [104]. S100B is mainly present in the brain and is particularly highly expressed and secreted by astrocytes [105,106], oligodendrocytes [107] and Schwann cells [29]. S100B binds two calcium ions per subunit with moderate affinity (2–20 μM) [108]. Besides calcium, S100B binds zinc with high affinity ($K_D = 0.1$–1 μM) and zinc binding to S100B increases both calcium binding and target protein binding affinities [108]. S100B also binds copper with sub-micromolar affinity and has been suggested to play a role against copper induced oxidative stress in cells [109].

The three-dimensional structure of S100B has been solved by NMR and crystallography in the calcium-free state [110,111], calcium bound state [19,112–114] and in the presence of target protein derived peptides (p53 [115], Ndr-kinase [116], capZ [117]). The N-terminal S100 specific EF-hand of S100B exhibits only minor conformational changes upon calcium binding whereas the C-terminal canonical EF-hand changes its conformation significantly upon calcium binding. The change of conformation in the C-terminal domain correlates with a 90° C change in angle between helix III and IV upon calcium binding. This change of conformation allows the exposure of residues critical for the binding to target proteins (reviewed by Heizmann et al. [1]). S100B interacts with a large variety of target proteins in either a calcium dependent or independent manner resulting in various intra- and extra-cellular functions (Table 1, and reviewed in [2,11]).

High levels of S100B have been detected with various clinical conditions such as brain trauma, ischemia and neurodegenerative, inflammatory and psychiatric diseases [118]. Glioblastoma in culture have also been shown to secrete S100B [28]. Besides the brain, S100B is a well-established prognostic marker for melanoma and high serum concentration of S100B correlate with poor prognosis [30,119]. Animal studies with S100B knout-out or S100B overexpressing transgenic mice revealed that S100B is not an essential protein for life. However, S100B plays important roles in spatial and fear memory, learning capabilities, epileptogenesis and myocardial functions [120–126].

S100B together with S100A12 were the first members of the S100 protein family that were shown to interact with RAGE and to trigger

Table 1
Target proteins of selected S100 proteins

Protein	Target proteins
S100B	Neuromodulin GAP-43 [322]
	Tau [323]
	GFAP [324,325]
	Vimentin, microtubules, intermediates filaments type III [326]
	Annexin VI [327–329]
	p53 [330,331]
	Sgt-1 [332]
	CacyBP/BP [214]
	AHNAK [333]
	Phosphoglucomutase [334]
	Fructose 1,6-biphosphatase, aldolase [335]
	Calponin [336]
	Caldesmon [337]
	Neurocalcin [338]
	CapZ [339]
	RAGE [19,69,144]
S100A1	Fructose 1,6-biphosphate, aldolase [335]
	Glycogen phosphorylase [340]
	Adenylate cyclase [341]
	Phosphoglucomutase [334]
	Tubulin [342]
	GCAP [339]
	MyoD [343]
	Intermediate filaments type III [344]
	Annexin VI [327]
	Synapsin I [345,346]
	Ryanodine receptor [347]
	Twitchin kinase [348]
	SERCA-2a [349,350]
	Hsp70, Hsp90, FKBP52, CyP40 [351]
	Titin [352]
	P53 [169]
	RAGE [127]
S100A2	p53 [168,169]
	Hsp70/Hsp90 organizing protein Hop [171]
	Kinesin light chain [171]
	RAGE [This study]
S100A4	Non-muscle tropomyosin [185];
	p53 [331,353]
	Non-muscle myosin [184,354]
	Map [355]
	RAGE [20] [This study]
S100A5	RAGE [This study]
S100A6	Glyceraldehyde 3-phosphate dehydrogenase [216]
	CacyBP/SIP [214,332]
	Tropomyosin [215]
	Annexin I, II, VI, XI, [216–219]
	p30 [356]
	P53 [169]
	Hsp70/Hsp90 organizing protein Hop [171]
	Kinesin Light Chain [171]
	RAGE [36]
S100A7	Epidermal-fatty acid binding protein [227]
	RanBMP [229]
	Jab-1 [230]
	RAGE [231]
S100A8/A9	CD36 receptor [258]
	NADPH oxidase [260]
	Toll-like receptor 4 [261]
	RAGE [262,263]
S100A11	Annexin A1 [271]
	Annexin A2 [357]
	RAD54B [317]
	P53 [169]
	RAGE [281,283]
S100A12	NADP+ dependent isocitrate dehydrogenase, [301]
	Fructose 1,6 bisphosphate aldolase A, [301]
	Glyceraldehyde-3 phosphate dehydrogenase, [301]
	Annexin V, [301]
	S100A9, [301]
	RAGE [24,69]
S100A13	Fibroblast growth factor 1 [307,308]
	C2A [304]

(continued on next page)

Table 1 (*continued*)

Protein	Target proteins
	RAGE [309] (Direct binding not yet demonstrated)
	Non-muscle myosin A heavy chain [15]
S100P	S100PBPR [319]
	S100A1 [15]
	Ezrin [317,318]
	RAGE [320]

Only S100 proteins that have been shown to interact with RAGE are presented in this table.

cellular signaling [69]. Since then the interaction of S100B with RAGE has been demonstrated in many cell-types. In N18 neurons transfected with RAGE, Huttunen et al. showed that S100B had dual RAGE dependent cellular effects depending of the concentration of the ligand [127]. Whereas nanomolar concentration of S100B triggered neurite outgrowth, micromolar concentration of the ligand resulted in apoptosis [127]. At the intracellular level, low concentrations of extracellular S100B triggered the up-regulation of the anti-apoptotic factor Bcl-2 whereas high concentration resulted in the activation of caspase 3 through the activation of the oxidant stress dependent MEK/ERK pathways, leading to apoptosis [127]. In rat hippocampal neurons low concentration of S100B were shown to protect the cells against the toxic effect of N-methyl-D-aspartate, through the activation of NF-κB and possibly through the engagement of RAGE [128]. In LAN-5 neuroblastomas, low concentration of S100B was shown to protect against the cellular toxicity of Aβ peptide, in a RAGE dependent manner, by inhibiting the decrease in expression of the anti-apoptotic factor Bcl-2 [129].

We recently showed that in human SH-SY5Y cells, high concentration of S100B (5 μM) promoted cell survival through the PI3K/Akt/NF-κB pathway in a RAGE dependent manner and through the generation of reactive oxygen species [36]. In Neuro2a cells transfected with RAGE, high concentration (5 μM) of S100B triggered mitogenic signaling through RAGE and the p42/44 MAP kinase pathway [130]. In dorsal root ganglia neuron, submicromolar concentration (500 nM) of S100B triggered RAGE dependent activation of PI3/Akt kinase pathway and of NAD(P)H oxidase through the generation and amplification of reactive oxygen [131]. In astrocytes, which are the cells with the highest expression of S100B, S100B-induced RAGE activated the release of TNF-α and IL-6 [132].

In microglia, the immune system of the central nervous system, the role of S100B/RAGE appears to be more complex [133]. Although S100B regulates NF-κB transcriptional activity in BV-2 microglia in a RAGE dependent manner, the production of NO by these cells in response to S100B appeared to be independent of RAGE, since the release of NO was similar in cells that were either transfected with the full-length RAGE or with RAGE deleted of the cytoplasmic domain (DN-RAGE) [133]. However, the release of NO by S100B-activated microglia was significantly stronger in microglia transfected with RAGE than mock transfected, suggesting a possible role of RAGE in concentrating S100B at the cell surface [133]. In these cells, S100B-activated RAGE also triggered the up-regulation of cyclo-oxygenase-2 expression through the independent stimulation of a Rac1/JNK/SP-1 pathway and a Rac1/NF-κB pathway [134,135].

S100B/RAGE dependent activation of COX-2 expression through the activation of p38/ERK/NF-κB has also been shown in both primary and established (THP-1) cultures of monocytes [136]. S100B also triggered the production of superoxide O_2^- through the activation of NADPH oxidase in the same cells, in a RAGE dependent manner [137]. TNF-α can be released from human peripheral blood mononuclear cells following activation of RAGE by S100B [83] and S100B significantly increased IP-10 mRNA and protein levels in these cells in a RAGE dependent manner [138].

Endothelial cells stimulated with S100B have been shown to activate NF-κB [69] and to up-regulate the expression of the vascular cell adhesion molecule 1 (VCAM-1) in a RAGE dependent manner [83]. In human aortic endothelial cells, S100B was shown to induce the expression of monocyte chemoattractant protein 1 (MCP-1) and RAGE transcripts [139], also in a RAGE dependent manner. In vascular smooth muscle cells (VSMCs), S100B stimulated angiotensin II induced tyrosine phosphorylation of JAK2 and cell proliferation in a RAGE dependent manner [140]. In the same cell type, S100B was shown to stimulate caveolin-1 tyrosine phosphorylation by Src kinase and the activation of the MAPK/NF-κB-STAT3 pathway, in a RAGE dependent manner, resulting in up-regulation of IL-6 and the macrophage-chemoattractant protein 1 (MCP-1) [141]. A direct interaction between RAGE and the β2-integrin Mac-1 protein on endothelial cells correlated with leukocyte recruitment and was augmented by S100B [70].

Although RAGE appears to be an important mediator in S100B dependent cellular signaling, recent studies in myoblasts and microglia suggest that RAGE is not the sole receptor of this calcium binding protein [133,142,143].

Comprehension of the molecular mechanisms of the interaction of RAGE with its ligands is key to understand how RAGE signaling functions. Surface plasmon resonance (SPR) allows to follow the interaction between two partners in real time and was used to investigate in great details the interaction of several S100 proteins with RAGE [19,20,144]. The SPR technology requires the immobilization of one of the partners on a sensor surface, a procedure that can influence the interaction between the binding partners. To minimize this problem, the protein of interest can be captured on the surface in a defined orientation. For this purpose, we have used a chimeric GST-RAGE fusion construct, where the extracellular part of RAGE was fused to the gluthatione-S-transferase protein [19,36,84]. Other groups have used a chimeric sRAGE-Fc where the Fc portion was captured via a specific antibody covalently bound to the surface [20]. The fusion protein allows to anchor the chimeric protein in a specific orientation on the surface of the sensor chip, therefore mimicking the orientation of RAGE on a cell membrane. In our studies, the GST-RAGE fusion protein was captured onto the surface by anti-GST specific antibodies covalently immobilized onto the surface of the sensor chip (Fig. 2). An

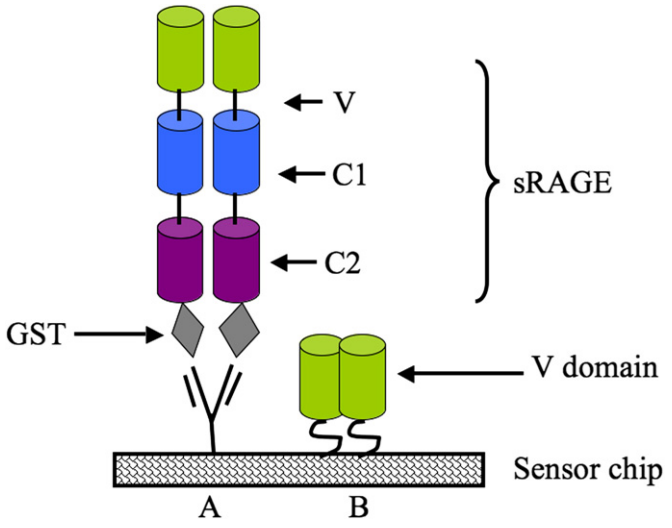

Fig. 2. Schematic representation of immobilized GST-RAGE (A) or V-domain (B) on a sensor chip used for the SPR measurements. The surface of the chip is covered with a mesh of dextran that provides large flexibility of the bound proteins. (A) In case of GST-RAGE, an IgG antibody specific to GST is covalently coupled to the surface. In a second step, GST-RAGE is injected over the surface allowing the capture of GST-RAGE by the anti-GST antibody, resulting in specific orientation of the chimeric RAGE protein. The two GST-RAGE molecules are thus very close in space and can form dimers. (B) When the V-domain is directly coupled to the surface, it can also form dimers due to the inherent properties of the dextran layer.

Table 2
Summary of S100/RAGE interaction as determined by SPR

S100	RAGE domain	Affinity	Reference
S100B	V	3.6 μM (62%) 2.2 nM (38%)	[144]
Dimers	VC1	11 nM (84%) 0.2 μM (16%)	[144]
	GST-RAGE	8.3 μM	[19]
	sRAGE	3.6 μM (62%) 2.2 nM (38%)	[36]
S100B Tetramers	GST-RAGE	1.1 μM (66%) 42 nM (34%)	[19]
S100A1	GST-RAGE	23 μM (85%) 6.8 nM (15%)	*Leclerc et al., unpublished data
	V-domain	0.6 μM	This study
S100A2	GST-RAGE	5.46 μM (70%) 56 nM (30%)	*Leclerc et al., unpublished data
	V-domain	89.5 nM	This study
S100A4	GST-RAGE	0.62 μM (79%) 1.7 μM (21%)	*Leclerc et al., unpublished data
Dimers	sRAGE-Fc	0.138 μM	[20]
	sRAGE-Fc	0.138 μM	[20]
S100A4 Oligo.			
S100A5	V-domain	6.59 μM	This study
S100A6	V	13.5 μM (97%) 0.5 μM (3%)	[36]
	VC1	5.8 μM (82%) 0.6 μM (18%)	[36]
	C2	1 μM (55%) 28 nM (45%)	[36]
	sRAGE	0.6 μM (51%) 0.5 μM (49%)	[36]
S100A12 Dimers	sRAGE-Fc	79 nM	[20]
S100A12 Tetramers	V-domain	167 nM	This study

In most cases, the binding curves were fitted with a two independent binding sites model. The numbers in bracket correspond to the percentile of the S100 population that binds to RAGE with the indicated affinity.
*Leclerc, E., Fritz, G., Weibel, M., Heizmann, C.H. and Vetter, S.W., Molecular characterization of the interaction of S100A1, S100A2, S100A6 and S100A4 with the Receptor for Advanced Glycation Endproducts., unpublished results.

advantage using this system is that the GST-RAGE molecules are close in space on the sensor chip due to the bivalence of the IgG used in the capture. Moreover, the surface of the sensor chips used in our studies (CM series) is covered with a branched dextran layer that forms a flexible mesh. This mesh gives to the bound protein, even when directly bound to the surface, some freedom of movement (Fig. 2). Indeed, previous studies using SPR have demonstrated the formation of dimers among immobilized receptors [145]. Our initial study was performed with S100B and showed micromolar affinity with RAGE [19]. Using the same approach, we showed that tetrameric S100B binds more tightly to RAGE suggesting that RAGE could form oligomers when interacting with its ligands. In a second study we investigated in more detail the interaction of dimeric S100B to RAGE to the isolated V-domain (residues 23–132) and showed specific interaction between S100B and RAGE with sub-micromolar affinity ($K_D \approx 0.5$ μM) (Fig. 1 and [144]). Using non-glycosylated and glycosylated sRAGE, our studies showed that glycosylation does not significantly influence binding of S100B to RAGE [19,36,144].

4.2. S100A1

S100A1 was co-discovered with S100B in the brain [104]. However, S100A1 is mainly expressed in the heart and is present in lower levels in other tissues [6,7,146]. Like S100B, S100A1 binds two calcium ions per subunit with moderate affinity ($K_D = 10$ μM) [108]. Calcium bound S100A1 interacts with a large variety of targets (Table 1) and regulates cardiac performance as shown by *in vitro* studies and S100A1 transgenic animal models [147–152]. Recent studies with S100A1 knock-out mice showed that it associated with an anxiety related behavior [153]. Little is known about the interaction of S100A1 with RAGE besides that S100A1 was shown to promote neurite outgrowth and to activate the transcription factor NF-κB in concert with amphoterin in a RAGE dependent manner [127]. We have newly characterized the interaction of S100A1 with RAGE *in vitro* using SPR with GST-RAGE (Table 2). As for S100B, binding to RAGE was in the micromolar range and strictly calcium dependent (Table 2). A more detailed analysis of this interaction suggests that S100A1 interacts with the V-domain of RAGE (Fig. 3).

4.3. S100A2

S100A2 was first detected as a tumor suppressor in human mammary epithelial cells [154]. The peculiarity of S100A2 is its primary nuclear location [155]. S100A2 tissue distribution is rather

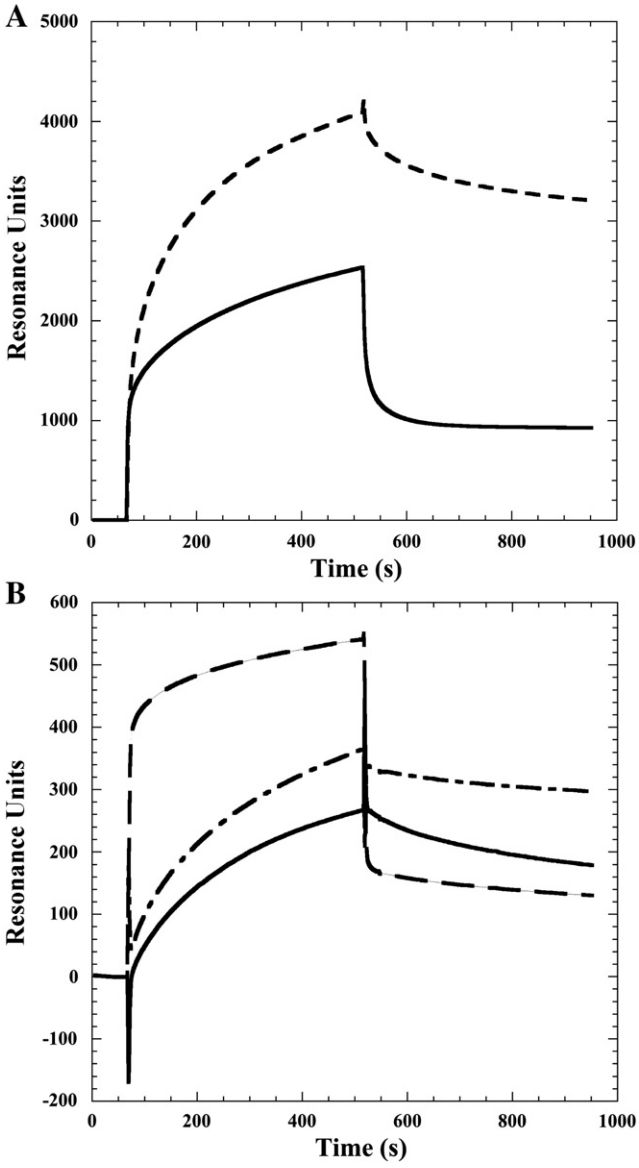

Fig. 3. RAGE V-domain was expressed in *E. coli* and purified as described in [144]. About 6500 RU were immobilized on a CM5 Biacore sensor chip according to previously described procedures [144]. Association and dissociation of each S100 protein was followed in real-time. After each cycle, the surface was regenerated as previously described [144]. Protein concentrations were as follow. S100B: 12.6 μM, S100A1: 10 μM, S100A2: 7.5 μM, S100A5: 30 μM, S100A12: 4 μM. The sensograms are depicted as follow. Panel A, S100B: full line; S100A2: dashed line. Panel B, S100A1: dashed line. S100A5: full line. S100A12: point and dash line. Fast association and dissociation are observed for S100B and S100A2, whereas S100A2, S100A5 and S100A12 associate and dissociate more slowly to and from RAGE V-domain suggesting different mechanisms of interaction between S100B, S100A1 and S100A2, A5 and S100A12.

large since it is present in many organs or tissues including lung, kidney, liver and breast epithelia [156,157]. Besides calcium, S100A2 binds zinc with high affinity ($K_D = 25$ nM) and zinc binding to S100A2 reduces significantly the affinity of S100A2 for calcium [13]. The three-dimensional structure of a mutant of S100A2 in the apo form has recently been solved by crystallography and showed similarities with the structures of calcium free S100A3, S100A4 or S100A6 [158]. S100A2 is found down-regulated in many cancers including melanoma [159], prostate [160], oral [161], lung [162] and breast cancer [163]. Interestingly, up-regulation of S100A2 was found in other cancers including esophageal squamous carcinoma [164], non-small cell lung carcinoma [165], gastric [166] and ovarian cancer [167]. At the molecular level S100A2 has been shown to interact with and increase the transcriptional activity of the tumor suppressor protein p53 (Table 1) [168,169] and a positive correlation between S100A2 and favorable patient outcome was found in tumor with p53 wild type phenotype [170] suggesting a complex role of S100A2 and p53 in tumor biology. S100A2 also interacts with the Hsp70/Hsp90-organizing protein (Hop) and the kinesin-light chain (KLC) and thus participates in protein folding [171]. Earlier studies failed to demonstrate the interaction between RAGE and S100A2 [20]. However, we have recently characterized the interaction of S100A2 with RAGE *in vitro* (Fig. 1, Table 2) and showed micromolar affinity between S100A2 and GST-RAGE, with strict calcium dependency (Table 2). Our further analysis of RAGE/S100A2 interaction showed that S100A2 interacts with the V-domain of the receptor (Fig. 3).

4.4. S100A4

S100A4 is also known as metastasin or Metastasis Associated Protein due to its link with metastasis formation. The gene of S100A4 was originally isolated and characterized from metastatic cells [172] and was later shown to control tumor metastasis [173–175]. In normal tissue S100A4 is predominantly found in the nervous system and is thought to play a role in neuronal plasticity under normal and pathological conditions [176–178]. Besides calcium, S100A4 binds zinc [3]. The three-dimensional structure of calcium free and calcium loaded S100A4 has been determined by NMR [179] and X-ray crystallography [180,181] revealing high similarity with S100A6. Animal studies with S100A4 transgenic and knock-out mice confirmed the role of S100A4 in tumor progression and development [182,183]. At the molecular level, S100A4 has been shown to interact with non muscle myosin and tropomyosin (Table 1) and to play a role in cytoskeleton rearrangements, therefore influencing cellular motility [184–188]. S100A4 has also been shown to induce the activity of several matrix metalloproteinase in osteosarcomas [189,190]. S100A4 interacts with RAGE *in vitro* as demonstrated by SPR studies using either chimeric sRAGE-Fc or biotinylated RAGE ($K_D = 138$ nM; [20]). Using the same technology but a GST-RAGE fusion protein as choice of binding partner, we showed affinities in the same order of magnitude and strict calcium dependency for this interaction (Table 2). Interestingly, both S100A4 dimers and oligomers were reported to bind to RAGE *in vitro* [20]). Although S100A4 binds to RAGE *in vitro*, the role of S100A4/RAGE interaction *in vivo* appears to be more complex. Indeed S100A4 has been shown to trigger RAGE independent neuritogenesis in primary rat hippocampal neurons [20] whereas S100A4 could stimulate RAGE dependent signaling cascades leading to activation of MMP13 in osteoarthritic cartilage [191]. Further studies will be necessary to investigate in more details the role of S100A4/RAGE axis *in vivo*.

4.5. S100A5

S100A5 was first isolated from bovine brain [192] but was also found in restricted areas of the kidney [193]. In the brain, S100A5 expression is limited to a few areas such as the olfactory bulb, the brainstem and the spinal trigeminal tract [192,194]. S100A5 binds calcium with higher affinity ($K_D = 6$ μM) than most of the other members of the S100 protein family [192]. It also binds zinc and copper with low micromolar affinity and copper binding strongly impairs the binding to calcium [192]. Due to its binding affinity for copper S100A5 could play a role as either a copper delivery protein or protect other proteins from copper induced oxidative stress [192]. The three-dimensional structure of the protein is so far unknown. S100A5 is overexpressed in astrocytic tumors [195] and has been suggested to be a marker of recurrence in certain meningiomas [196]. So far, no cellular target had been described (Table 1). In order to understand how S100 proteins interact with RAGE, we studied the interaction of S100A5 with RAGE by SPR and could show low micromolar affinity between S100A5 and the V-domain and strict calcium dependency for the binding (Fig. 3). Further studies will be necessary to characterize this interaction in more detail and to investigate if this interaction is physiologically relevant.

4.6. S100A6

S100A6 was first isolated from Ehrlich ascites [197]. It is found in high levels in various organs including muscle, lung, kidney, spleen and brain [198,199]. S100A6 has been shown to translocate from the cytoplasm to the nuclear envelope and the plasma membrane in a calcium dependent manner [200]. Calcium dependent translocation of S100A6 between different organelles was also found in endothelial cells and neuroblastomas [201,202]. Besides calcium, S100A6 binds zinc with micromolar affinity [203]. The three-dimensional structure of S100A6 has been determined by NMR and X-ray crystallography both in the calcium free- and calcium bound conformation revealing similar conformational changes in S100A6 and S100B following binding to calcium [[204–206]. S100A6 appears to play an important role in cancer and is found overexpressed in many cancers including colorectal cancer [207], hepato-cellular carcinoma [207], melanoma [159], lung cancer [208] or gastric cancer [209,210]. In pancreatic cancer, S100A6 concentration increases with malignancy [209] and a high nuclear concentration of S100A6 has been shown to correlate with poor prognosis [211]. S100A6 may also play a role in several neurodegenerative diseases as it was found overexpressed in a mouse model of amyotrophic lateral sclerosis [212] as well as in patients with Alzheimer's disease [213]. At the molecular level, S100A6 interacts with several proteins *in vitro* including CacyBP/SIP [214], tropomyosin [215], annexins II, XI [216–219], Hop, KLC [171], P53 [169] and RAGE [36] (Figs. 1, 4, Table 1). We showed recently that S100A6 could interact

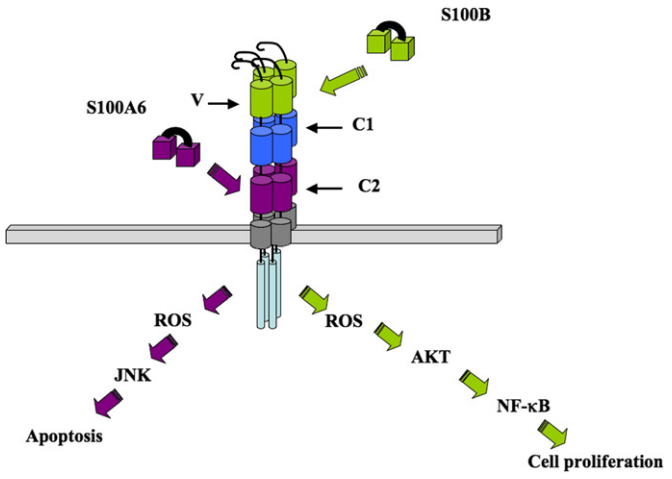

Fig. 4. Example of RAGE signaling triggered by S100B or S100A6 in human SH-SY5Y neuroblastomas. Micromolar concentration of S100B and S100A6 triggered distinct cellular pathways involving Akt and JNK respectively, leading to either cell survival, proliferation (S100B), or apoptosis (S100A6) [36].

with both the V and C2 domains of RAGE *in vitro* [36]. As with the other S100 proteins described above, S100B, S100A1, S100A2, S100A4 and S100A5, binding of S100A6 to GST-RAGE appeared to be strictly calcium dependent, as determined by SPR. Interestingly, the cellular effects triggered by S100A6 in human neuroblastoma SH-SY5Y cells appear to occur via binding to the C2 domain (Figs. 1, 4) [36]. Our studies have also shown that glycosylation of RAGE does not significantly influence binding of S100A6 to RAGE [19,36,144].

4.7. S100A7

S100A7 was first identified in inflamed psoriatic skin [220]. S100A7 binds calcium ($K_D = 150$ μM) and zinc with low affinity ($K_D = 100$ μM) [221]. The 3-D structure of S100A7 has been solved, in the presence of calcium and in the presence and absence of zinc and showed only one bound calcium ion per subunit [222,223]. Contrary to other S100 proteins, binding of calcium to S100A7 does not result in large conformational changes of the protein [222]. S100A7 has been shown to be released from keratinocytes surrounding epidermal wounds and to possess cytokine [37] and antibacterial activity [38–40]. S100A7 is also thought to play a role in various cancers such as lung squamous cell carcinoma, ductal or invasive breast carcinoma [224–226]. At the molecular level, S100A7 interacts with the epidermal fatty acid binding protein (E-FABP), RanBMP and Jab-1 and RAGE (Table 1) 227–230]. Recent studies demonstrate that S100A7 was chemotactic for granulocytes, monocytes and lymphocytes, in a RAGE dependent manner [231].

4.8. S100A8/A9

S100A8 and S100A9 are predominantly expressed by cells of myeloid origin [232–236] but are also expressed in epithelial cells and keratinocytes during inflammation [235,237]. S100A8/A9 can form heterodimers in the absence of calcium and heterotetramers $(S100A8/A9)_2$ in the presence of calcium [238,239]. The three-dimensional structure of the $(S100A8/S100A9)_2$ has been determined by crystallography revealing that the calcium bound C-terminal EF-hand loops are necessary for tetramerisation [240]. S100A8/A9 heterotetramers appear to play important biological functions such as formation of microtubules [21].

S100A8 and S100A9 homodimers have been solved by crystallography and show similarities with the calcium bound structures of other S100 proteins [241,242]. S100A8/A9 plays a role in myeloid differentiation [232], in inflammation [243] and exerts antimicrobial activity [244]. Moreover, elevated serum levels of these S100 proteins are found in patients suffering from inflammatory diseases such as rheumatoid arthritis, cystic fibrosis or Crohn's disease [2,18,245–247]. High levels of S100A8/A9 have also been found in the microglia of patients with Alzheimer's disease or suffering from ischemic lesions [248,249] (reviewed in [250]) and may also play a role in several cancers such as gastric cancer [251,252], colorectal carcinoma [253] or prostate cancer [254]. S100A8 is an essential gene for life since S100A8 knock-out mice died during embryonic development [255]. Surprisingly, S100A9 knock-out mice do not show any obvious phenotype demonstrating distinct functions between S100A8 and S100A9 [256,257]. At the molecular level, the heterocomplex S100A8/A9 interacts with the scavenger receptor CD36 [258], with heparin and heparan sulfate glycosaminoglycans [259] and with components of the NADPH oxidase complex [260]. Recently S100A8/A9 was shown to interact with the Toll-like receptor 4, via the interaction with S100A8, promoting endotoxin-induced shock [261]. S100A8/A9 also interacts with RAGE as shown by immunoprecipitation experiments [262,263]. However, the role of RAGE/S100A8/A9 interaction *in vivo* is currently not clearly understood. Although S100A8/A9 have been shown to promote cell growth via p38MAPK and p44/42 kinase activation in tumor cells [263] and to mediate endotoxin-induced cardiomyocyte dysfunction [262] in a RAGE dependent manner, RAGE dependent signaling was observed in human umbilical aortic cells (HUVEC) treated with S100A8/A9, only after pretreatment with AGEs products [246]. In rheumatoid arthritis, S100A8/A9 amplified proinflammatory cytokine production by macrophages via the activation of NF-κB and p38 MAPK, in a RAGE independent manner [264]. In several tumor cell lines, S100A8/A9 induces cell death in a RAGE independent manner [265]. In prostate cancer cell lines, S100A8/A9 was found to induce the co-localization of RAGE with the two S100 proteins. In these cells, the activation of MAP kinase and NF-κB signaling pathways triggered by S100A8/A9 was not reduced in the presence of anti-RAGE antibody, suggesting a RAGE independent signaling pathway as well [252]. To increase the complexity of RAGE/S100A8/A9 signaling a recent report demonstrated the presence of CML-modified S100A8/A9 in inflamed intestinal tissue that were able to activate NF-κB and to elicit a RAGE-dependent intestinal inflammatory response [266], suggesting a complex interplay between AGEs, S100 proteins and RAGE. In a different study, S100A8/A9 was shown to interact specifically with a subpopulation of RAGE carrying carboxylated glycans and to trigger RAGE dependent NF-κB activation and cellular proliferation [267].

4.9. S100A11

S100A11 was first isolated in chicken gizzard smooth muscle and later purified and characterized [268]. S100A11 is present in many tissues but in higher amount in lung and smooth muscle tissues [268,269]. The three-dimensional structure of S100A11 has been solved by NMR and crystallography, in the calcium free [270] and calcium bound form in the presence of annexin I binding domain [271]. S100A11 binds to annexins A1 and A2, the DNA-dependent ATPase Rad54B, p53 and RAGE (Table 1). The interaction of S100A11 with Rad54B suggests a role in DNA double strand repair mechanism and cell cycle progression [272]. S100A11 has been found elevated in several tumors and was suggested to play a role either as tumor promoter, such as in prostate, breast and pancreatic cancer [273–275] or tumor suppressor such as in bladder and renal carcinoma [276,277]. Moreover, in normal human keratinocytes, phosphorylation of S100A11 by protein kinase C in response to TGFβ-1 and high calcium concentrations resulted in growth inhibition [278,279]. S100A11 is not essential for life since S100A11 knock-out mice do not show any obvious phenotype [280]. S100A11 has been shown to modulate osteoarthritis (OA) via the interaction with RAGE (Table 1) [281]. In this study, RAGE and S100A11 expression were up-regulated in OA cartilages. More recently, S100A11 was shown to be secreted by chondrocytes and in the same cells S100A11/RAGE activation resulted in hypertrophy [281,282]). S100A11 has also been shown to be secreted and to exert RAGE dependent signaling in human keratinocytes [283]. At the molecular level, the interaction of S100A11 with RAGE has not yet been characterized.

4.10. S100A12

S100A12 was identified and isolated from resting neutrophils [284] later sequenced [285], cloned, expressed [286] and characterized [287]. Besides neutrophils, S100A12 is found in monocytes [284] and lymphocytes [288]. S100A12 translocates from the cytosol to the membrane in the presence of increased calcium concentration [284]. The crystal structure of calcium bound S100A12 showed either dimeric [289] or hexameric [22] arrangements suggesting oligomeric specific biological functions. The structure of S100A12 in the presence of copper also revealed the putative role of copper in the function of the protein [290]. S100A12 is strongly expressed in inflammatory diseases such as Crohn's disease, cystic fibrosis, atherosclerosis, rheumatoid arthritis, psoriasis or Kawasaki disease [247,291–297]. Overexpression of S100A12 was recently found in inflammation of mammary tissue [298] as well as in inflamed gastric mucosa of

Helicobacter pylori-infected children [299]. Interestingly, S100A12 was also shown to promote neurite outgrowth of primary rat hippocampal neurons through the activation of the MAPK pathway and phospholipase C pathway [300]. The physiological relevance of this interaction needs to be further clarified. At the molecular level, S100A12 interacts with several metabolic enzymes including cytosolic $NADP^+$-dependent isocitrate dehydrogenase (IDH), fructose-1,6-bisphosphate aldolase A (aldolase), glyceraldehyde-3-phosphate dehydrogenese (GAPDH), annexin V, S100A9, and RAGE (Table 1) [301]. S100A12 was suggested to bind to the V-domain of RAGE ($K_D = 90$ nM) based on competition experiments with AGE-BSA [69,80]. Later, binding studies between a sRAGE-Fc fusion protein and S100A12 showed low nanomolar affinity [20]. Recently Xie et al. suggested from fluorescence and NMR spectroscopy that S100A12 bound specifically with the C1 domain of the receptor (Fig. 1), both in the presence and absence of calcium, the interaction of apo-S100A12 with RAGE being about 1000 times weaker than that in the presence of calcium form [24]. In this study hexameric S100A12 was complexed with tetrameric RAGE [24]. We used SPR to measure the interaction of S100A12 with RAGE and our experiments revealed a submicromolar binding affinity between tetrameric S100A12 and the V-domain (Table 2 and Fig. 3). Further studies will be necessary to understand the discrepancies between these studies.

4.11. S100A13

S100A13 was discovered by screening expressed sequence tag data bases [302] and was later cloned, recombinantly expressed and characterized at the protein level [303]. S100A13 binds two calcium ions per subunit with strong cooperativity ($K_{D1} = 8$ μM and $K_{D2} = 400$ μM). Besides calcium, S100A13 binds copper with micromolar affinity, independently from calcium [304]. S100A13 has been found at the mRNA level in many tissues and organs including heart, kidney, brain, ovary and spleen [302,303]. It was recently suggested to be a marker of angiogenesis in human astrocytic gliomas [305] and to play a role in lung cancer [306]. *In vivo*, S100A13 was identified as part of a brain-derived heparin-binding multiprotein aggregate/complex containing fibroblast growth factor 1 (FGF-1), suggesting a possible interaction with FGF-1 (Table 1) [307]. This interaction was later confirmed by quartz crystal microbalance [308]. S100A13 also interact with copper binding C2A protein ($K_D = 85$ μM), suggesting a role as a copper chaperon [304]. Binding to RAGE has been suggested from the RAGE dependent translocation of S100A13 from the nucleus to the cytoplasm in endothelial cells, in response to extracellular addition of S100A13 [309]. More experiments will be necessary to support this hypothesis. The interaction of S100A13 with RAGE at the molecular level has not yet been studied.

4.12. S100P

S100P was first identified in placenta and later cloned, expressed and characterized [310]. S100P binds two calcium ions with different affinities: a low affinity binding site ($K_D = 800$ μM) and a high affinity binding site ($K_D = 1.6$ μM) [310]. Besides placenta, S100P is expressed in normal organs or cells including esophagus, stomach, duodenum, large intestine, prostate and leukocytes [311,312] and plays a role in cytokine-induced differentiation of human myeloid leukemia cells [313]. S100P is also present in many tumors including ovarian, pancreatic, gastric, colorectal, breast and prostate carcinomas [312,314–316. S100P form a S100P/S100A1 heterodimer with high affinity, both *in vitro* and in cultured cells [15]. It interacts with ezrin in a calcium dependent manner [317] and has been suggested to play a role in the transendotelial migration of tumor cells [318]. S100P was also shown to interact with S100PBPR, in a calcium dependent manner, and to play a role in early pancreatic cancer [319]. The direct interaction of S100P with RAGE was suggested from co-immunoprecipitation experiments in NIH3T3, BxPC3 (pancreatic cancer) and SW480 (colon cancer) cells [314,320,321]. In BxPC3 and SW480 cells, S100P was shown to trigger the activation of NF-κB through the MAPK pathway in a RAGE dependent manner [320,321].

5. Conclusion

A large number of S100 proteins have been shown to interact with RAGE *in vitro* (S100B, S100A1, S100A2, S100A4, S100A5, S100A6, S100A7, S100A8/A9, S100A11, S100A12, S100P). Moreover, in cell-based assays, all these members, except for S100A2 and S100A5, have been shown to trigger RAGE dependent signaling. However, the role of S100/RAGE interaction *in vivo* appears to be very complex and so far not all S100 proteins have been shown to trigger RAGE signaling in animal models. The molecular mechanisms of the interaction between S100 proteins and RAGE are slowly getting unraveled. There is experimental evidence that the S100 proteins might form sub-groups which bind to different sites on RAGE. Indeed, whereas S100B appears to bind strictly to the V-domain, S100A6 can interact with the V- and C2-domain, and S100A12 with the V- and C1-domain. Furthermore, several S100 proteins such as S100B, S100A4, S100A8/A9 and S100A12 also interact with RAGE in their oligomeric states. Interestingly, the binding characteristics of the S100 proteins in the oligomeric states are distinct from the corresponding dimers suggesting another level of signal modification and regulation. The physiological significance of these interactions has yet to be understood in greater detail. From the RAGE perspective, carboxylated glycans might be a factor as well modulating the interactions of certain S100 proteins with RAGE, as shown with S100A8/A9. From the S100 perspective, the findings are challenged by the recent identification of CML-modified S100 proteins (S100A8/A9) as RAGE ligand. The many different findings on RAGE/S100 interactions suggest that further variations will be found. In the light of the different reported RAGE/S100 interactions it is essential to establish standardized direct *in vitro* binding assays such as those performed by surface plasmon resonance. The knowledge of these binding affinities in combination with the knowledge of the structures of the S100 proteins will provide valuable information on the nature and location of critical surface residues involved in RAGE/S100 interaction. This analysis will help to deduce a more general scheme of RAGE ligand recognition and binding. Future studies combining *in vitro* and cell-based assays will be necessary to improve our understanding of RAGE activation.

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