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The importance of Ca^{2+}/Zn^{2+} signaling S100 proteins and RAGE in translational medicine

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1. ABSTRACT

The Receptor for Advanced Glycation Endproducts (RAGE) is a multiligand receptor involved in a large number of human disorders. Identified first as the receptor for the Advanced Glycation Endproducts (AGEs), RAGE has emerged in recent years as a major receptor for many members of the S100 calcium and zinc binding protein family. The interaction with and the signaling triggered by several S100 proteins such as S100B and S100A12 have been studied in details and have shown concentration and cell type dependent signaling cascades. The S100 protein family consists of more than 20 members which present high amino-acid sequence and structural similarities. These small EF-hand calcium binding proteins interact with a large number of protein targets and are almost all been shown to be involved in cancer. In this review we discuss the recent knowledge about the role of S100 proteins and RAGE in human disorders.

2. INTRODUCTION

Calcium is a major secondary messenger involved in many cellular functions that include fertilization, muscle contraction, gene transcription, proliferation and cell death (1-4). In the presence of external stimuli such as hormones, neurotransmitters and growth factors, the intracellular calcium concentration rises following complex mechanisms that involve first the release of calcium from intracellular calcium stores followed by entry of calcium through the plasma membrane (reviewed in (5)). This mechanism of capacitative calcium release or store-operated calcium influx (SOC) requires the presence of calcium release activated calcium channels (CRAC) on the surface of the plasma membrane that open in response to sensor molecules (STIM1, STIM2) linked to the depletion of the intracellular calcium stores (5).

In the cell, the calcium-dependent processes are mediated by calcium binding proteins characterized by the

Table 1. Post-translational modifications in S100 proteins

Modifications	Proteins	References
Nitrosylation	S100B, S100A1, S100A8	32, 33, 39
Phosphorylation	S100A8/A9, S100A11	31
Carboxymethylation	S100A8/A9	35
Citrullination	S100A3	34
Transamidation	S100A11	37
Oxydation	S100A8/A9	296
Myristoylation	S100A14	377
Glutathionylation	S100A1	36
Sumoylation	S100A4	38

EF-hand structural motif. These proteins constitute the largest family of calcium binding proteins with more than 3000 related entries in the NCBI Reference Sequences Data Bank (6). EF-hands calcium binding proteins are involved in almost all aspects of the cell function in normal and pathologic conditions (4, 7). EF-hand domains were first described in carp parvalbumin (8) and have been recently identified in bacterial and viral proteins (9, 10).

EF-hand calcium binding proteins bind calcium via helix-loop-helix motifs often present in multiple copies. The members of the EF-hand superfamily can be divided into two main categories, according to their calcium affinity and their ability to change conformation following binding of calcium (11). The calcium sensors form the first group and include calmodulin, the S100 proteins and the neuronal calcium sensors (NCS). The second group of proteins is constituted by the calcium-buffering proteins including parvalbumin, S100G (previously named calbindin D9k, CaBP9k, calbindin-3 or CABP1) (12) calbindin-D28k which also functions as a calcium sensor and zinc binding protein (13-15) and calretinin (16). In this review, we will focus on the specific group of calcium signaling proteins, the S100 proteins and discuss the role of these proteins and their receptors RAGE and Toll-like receptor in normal and pathophysiological conditions.

3. GENERAL FEATURES OF S100 PROTEINS

S100 proteins constitute the largest sub-group of calcium binding proteins. S100 proteins are involved in a large number of cellular functions such as calcium homeostasis, cell growth and differentiation, invasion and metastasis, dynamic of cytoskeleton or energy metabolism (reviewed in (17-19)). The "S100" name originates from the solubility of the first identified S100 proteins in 100% ammonium sulfate solution. S100 proteins are present only in vertebrates. Other EF-hand proteins-for example troponin C-are found in invertebrates, and calmodulin is even found in protozoa. This suggests that S100 proteins form a phylogenetically young group among the EF-hand proteins. The expression of members of the S100 protein family is often tissue and cell type specific. Within the cells S100 proteins often translocate from one compartment to another (nucleus, cytoplasm) in response to changes in calcium concentration or concentration of extracellular S100 using different translocation pathways (20, 21). Of the twenty genes encoding S100 proteins identified so far, sixteen are clustered on a region of chromosome 1q21 that is prone to molecular rearrangements linking S100 proteins and cancer (12, 22). S100 proteins are small (MW = 9-12 kD) acidic proteins that are present mostly in the form of homo- or hetero-dimers. Recent studies suggest that the dimeric form is favored in the presence of physiologically relevant salt concentration (23). S100 proteins can also form tetramers or hexamers (reviewed in (24)). S100 proteins contain two EF-hand domains: a classical EF-hand at the C-terminus common to all S100 proteins and a N-terminal EF-hand that is variable and characteristic for each S100 protein. S100 proteins display a relatively large range of calcium binding affinity (K_D = 20-500 μM) and can also bind zinc (reviewed in (25)) and copper resulting in modulation of their activities (17, 26). Binding of zinc and copper occur at distinct sites than the calcium ones allowing S100 proteins to bind simultaneously different metals ions.

Calcium binding to the EF-hand triggers structural changes in the S100 protein that allow the interaction with target proteins and the modulation of their activity (4, 26-28). Binding of the target protein in the presence of calcium often results in increase in calcium affinity of the S100 protein as well (29). Binding of S100 proteins to their targets is typically calcium-dependent, but calcium-independent interactions have also been described (30).

S100 proteins can be modified post-translationally by phosphorylation (S100A8/A9, S100A11) (31), nitrosylation (S100A1, S100B, S100A8) (32, 33), citrullination (S100A3) (34), carboxymethylation (S100A8/A9) (35), glutathionylation (36), transamidation (S100A11) (37) or sumoylation (38) (Table 1). These modifications often modulate the interaction with calcium or target proteins (31, 32, 35-37, 39). Additionally, the promoters of several S100 proteins have been found hypo- or hyper-methylated, resulting in epigenetic changes in protein expression (40, 41).

Besides their intracellular functions, certain S100 proteins can also be secreted and can exert the role of cytokine through the activation of various cell surface receptors. One of these receptors is the receptor for advanced glycation endproducts (RAGE), an immunoglobulin like multi-ligand receptor (24, 27, 42-44). The role of RAGE/S100 interactions in human pathologies will be reviewed here.

4. THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (RAGE)

RAGE was initially isolated as receptor for the advanced glycation endproducts (AGEs) (45) and therefore to play an important role in complications of diabetes (46). RAGE was later found to be receptor for amyloid β peptides (47) and to play a role in Alzheimer's disease as well (48-51), The search for new ligands of RAGE resulted in the identification of S100A12 in animal models of acute and chronic inflammation (44, 46, 52-55). RAGE has also been shown to play a role in cancer (56) and cardiovascular

Table 2. Association of RAGE with human diseases

- Rheumatoid arthritis
- Osteoarthritis
- Cardiovascular diseases
- Inflammatory bowel disease
- Chronic renal disease
- Diabetic neuropathy
- Cancer (brain, breast, colon, colorectal, lung, prostate, oral squamous cell, ovarian, lymphoma, melanoma)
- Lung diseases
- Alzheimer's disease

References: (58-60, 74, 416-419)

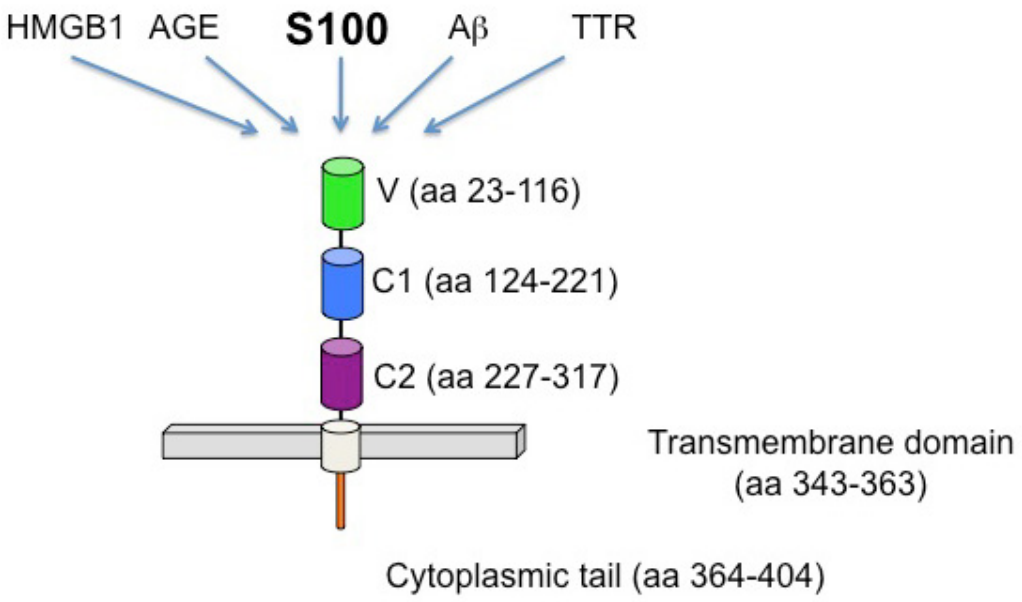

Figure 1. Schematic representation of RAGE. RAGE is constituted of three immunoglobulin like domains V, C1 and C2 of approximately 100 residues each, a single transmembrane domain and a short intracellular domain (40 residues). Various classes of ligands interact with and activate the receptor. Ligands include the Advanced Glycation Endproducts (AGEs), several members of the S100 protein family, High mobility group box 1 protein (HMGB1), amyloid β peptide (Aβ), and transthyretin (TTR).

disease (46, 57, 58) (Table 2). The physiological role of RAGE is not fully understood but recent studies suggest that RAGE may play a protective role in the lung (59, 60), a beneficial role in in peripheral nerve regeneration (61, 62), and in auditory stimuli in mice (63). RAGE is characterized by the large structural heterogeneity of its ligands. RAGE ligands include AGEs, the high mobility group box 1 protein (HMGB1 = amphoterin), amyloid forming peptides and proteins (amyloid β-peptide) and many members of the S100 protein family (17, 24, 43) (Figure 1). AGEs are very heterogeneous and originate from non-enzymatic modification of proteins or lipids by reducing carbohydrates (reviewed in (64)). The concentration of AGEs is increased in patients suffering for diabetes. AGEs are also found elevated at sites of active inflammation (65). RAGE can also be activated by amyloid forming proteins or peptides such as Aβ peptide that accumulates in the brain of Alzheimer's disease (AD) patients (47, 66) or transthyretin (TTR) that is responsible of familial amyloid polyneuropathy or cardiomyopathy (67). Aβ accumulation in the brain is believed to play a key role in the development of AD and RAGE has been shown to mediate the transport of Aβ through the neuronal cell membrane and blood brain barrier (47, 68-70). Moreover, recent studies aimed at comparing the levels of anti-RAGE and anti-A-β peptide antibodies in Alzheimer's patients (71, 72) found a positive correlation between the levels of the IgGs and the severity of dementia (72). Deregulation of calcium homeostasis is also believed to play an important role in AD (73, 74).

The DNA binding protein amphoterin is another ligand of RAGE that plays a role in neuronal development, inflammation and cancer (75) (reviewed in (76, 77)).

The main isoform of RAGE is the full-length RAGE, present at the surface of cells. Full length RAGE (FL-RAGE) is present at low levels in most adult tissues but at relatively high levels in lungs (78) (45, 79). FL-RAGE is composed of an extracellular part (314 aa), a single transmembrane spanning helix (27 aa) and a short cytosolic domain (41 aa) (Figure 1) (80). The extracellular

part contains an Ig-like V-domain (residues 24-127) and two constant Ig-like C1 (residues 132-230) and C2 domains (residues 239-320). RAGE possesses two N-glycosylation sites, one adjacent to the V-domain (residue 26) and the second one within the V domain (residue 81) (Figure 1) (80, 81). Recent studies suggest that RAGE glycosylation modulate the interaction of RAGE with AGEs, amphoterin and certain S100 proteins (S100A8/A9, S100A12) (81-85).

The structure of the V domain of RAGE has been solved by NMR and showed a structure very similar than the V domain of other immunoglobulins (86). Binding studies between the V domain and *in vitro* generated AGE products demonstrated three basic residues of the V domain (K43, K44, R104) essential for the interaction with AGEs (86). It would be interesting to know if these residues are also important for the interaction with S100B.

An important form of RAGE is the soluble form of the receptor. This form orginates either from splicing (RAGE_v1) or proteolytic degradation (87-91). Soluble RAGE lacks the transmembrane and cytoplasmic portion and is released in the extracellular space. Soluble RAGE when present at sufficiently large concentration, is believed to function as a decoy receptor that reduces the levels of circulating free RAGE ligands. The splicing variant RAGE_v1 includes parts of intron 9 resulting in the presence of amino-acids that are absent in full-length RAGE or in soluble RAGE generated by proteolytic degradation. This difference between proteolytic and spliced soluble RAGE can be determined by using specific antibodies against residues only present in RAGE_v1 (88, 92-94). RAGE_v1 appears to be the prevalent isoform in endothelial cells and in human brain (93, 95). Interestingly, the expression of RAGE_v1 is reduced in certain pathological conditions such as in patients suffering from AD, and was suggested to be a biomarker of certain diseases (96-99). However, more recent studies aiming at finding a correlation between levels of soluble RAGE and disease showed contradictory correlations (reviewed in (100)). For instance although a reduced level of sRAGE (RAGE_v1) correlated with carotid atherosclerosis in both diabetic patients and non-diabetic individuals in one study (101), no correlation between the level of sRAGE or RAGE_v1 correlated with the intima-media thickness, a predictor of cardiovascular disease, in another group of diabetic patients (102).

Moreover, recent series of clinical studies measuring the level of sRAGE in the serum of diabetic and breast cancer patients and healthy individuals showed very low concentration of sRAGE (10 pM-50 pM) suggesting that sRAGE might not play an efficient role in counteracting the effect of RAGE ligands *in vivo* (46, 103, 104).

Polymorphisms have been found in both promotor and coding region of gene of RAGE (105). A link between RAGE polymorphism and multiple sclerosis, chronic fatigue, Alzheimer's disease or other pathologies has been described recently (106-109).

5. STRUCTURE AND FUNCTIONS OF S100 PROTEINS AND RAGE: ASSOCIATION WITH HUMAN PATHOLOGIES

5. 1. S100B

S100B is mainly expressed in the brain and is secreted by astrocytes in response to various stimuli (18). S100B binds calcium, zinc and copper (110, 111). Besides its expression in the brain, S100B can be strongly secreted by melanoma cells. S100B is not an essential protein for life as demonstrated by viable S100B knout-out animals (112, 113). S100B plays important roles in spatial and fear memory, learning processes, epileptogenosis and myocardial functions (114-117).

S100B exerts both intra- and extracellular functions through the interaction with specific targets (reviewed in (118)). Among other functions, S100B regulates microtubule assembly and plays a role in cell proliferation, survival or differentiation (for instance myoblasts (119)) and in calcium homeostasis (118). A new target for S100B was recently identified in oligodendrocyte progenitor cells (mitochondrial ATAD3A protein) (120). The interaction of S100B with its targets involves target specific conformational changes within S100B as shown by structural studies (reviewed in (11, 121)). Whereas the interaction of S100B with most of its targets is calcium dependent, it can also be calcium independent (30, 118).

S100B is a well-studied prognosis biomarker in melanoma (Table 3) (122, 123). High S100B serum concentration correlates with poor survival rate (124). S100B level also correlates with the probability of stroke after cardiac surgery (125) and correlates with stroke severity and outcome in patients suffering from stroke (126). S100B is a potential biomarker as well in patients suffering from mood disorder, depression, schizophrenia, Alzheimer's disease and has also emerged as a potential marker for embryonic neural tube mis-formation (127-130). Interestingly, high levels of S100B are also found in the cerebrospinal fluid of rabbits suffering from pneumococcal meningitis suggesting a potentially important role of S100B in infectious diseases (131).

The interaction of S100B with some of its targets is an important research area for new drugs development. S100B interacts with the tumor suppressor p53 (132) and inhibitors of this interaction would be valuable anti-cancer drugs (133). Recently, nitrosylation of S100B was found to increase binding with p53 suggesting complex mechanism of regulation between the S100 protein and the tumor suppressor (32).

S100B triggers cellular signaling through RAGE in a large number of cells that include neurons, astrocytes, microglia and in monocytes/macrophages (Figure 2) (reviewed in (118). RAGE activation by S100B is cell specific and depends of the concentration of S100B. At low nanomolar concentration S100B promotes neurite outgrowth whereas at sub-micromolar and micromolar

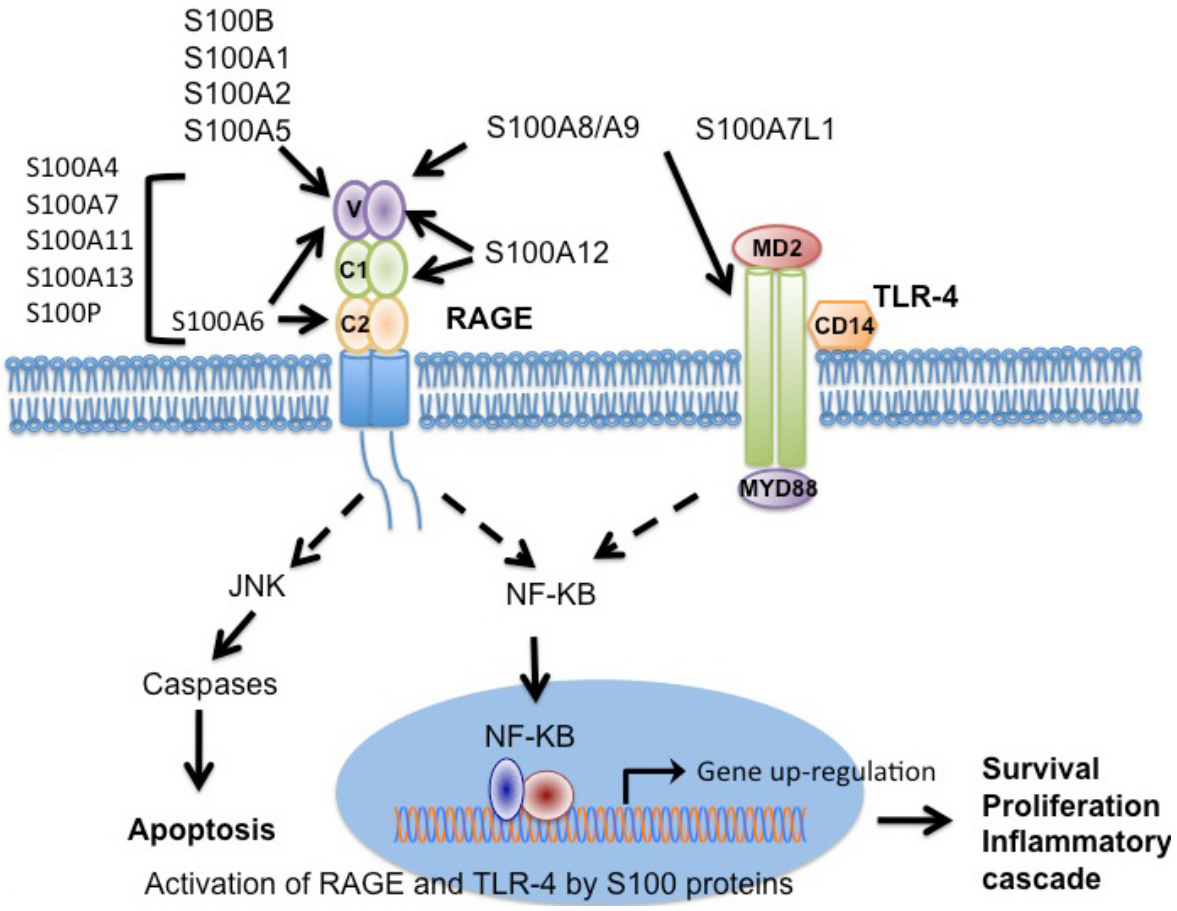

Figure 2. Activation of RAGE and TLR-4 by S100 proteins. S100 proteins interact with distinct domains of RAGE. S100B interacts mainly through the V domain whereas S100A12 and S100A6 have been described to interact with both the V and C1 domain (S100A12) and with the V and C2 domain (S100A6). The exact binding site of S100A8/A9 within RAGE has not yet been described. Activation of RAGE by some S100 proteins (S100B, S10A12, S100A8/A9) can lead to the activation of the MAPK pathways and the translocation of NF-κB from the cytosol to the nucleus, resulting in the up-regulation of genes involved in cell survival and proliferation. In other instances, as observed with S100A6, the apoptosis cascade is activated through the activation of JNK and caspases. S100A4, S100A7, S100A11, S100A13 and S100P also interact with and/or activate RAGE (left part of figure), however, their exact binding site within RAGE is not known. S100A8/A9 can also activate TLR-4 that also result in the activation of NF-κB and the up-regulation of genes involved in cellular inflammatory responses. In addition to S100A8/A9, S100A7L1 has been suggested to activate TLR-4 as well. Other receptors or membrane associated proteins have been described for the S100 proteins: these include scavenger receptors for S100A8/A9 and S100A12 (302, 362) the serotonin receptor for S100A10 (317), and annexin II for S100A4 and S100A10 (211, 312).

concentration it triggers apoptosis (134). Downstream RAGE signaling involves classical cascades involving MAP kinases, Rho GTPases, NF-κB or COX-2 activation reviewed in details in (118, 135, 136).

In order to understand RAGE signaling by S100B, and to understand how nanomolar and micromolar concentrations of S100B lead to the activation of distinct signaling cascades, it is essential to understand how S100B interacts with RAGE. In recent years, our laboratory and others have studied in detail the interaction of S100B with RAGE *in vitro* using an array of biophysical methods. For instance, we showed that S100B interacts preferentially with the V domain of RAGE and suggested that RAGE could form oligomers upon binding with S100B (137-139). The V domain of RAGE is also the binding site of AGEs and TTR (140-143). However it is currently unknown if these ligands interact with the same binding site of RAGE.

5. 2. S100A1

S100A1 was first co-purified with S100B in the brain but is mainly present in the heart (17, 144-146). Calcium bound S100A1 interacts with a large variety of targets including the immunophilin FKBP52 (147) (reviewed in (148)) and regulates cardiac performance and vascular tone (Table 3) (reviewed in (149-151)). Interestingly S100A1 and calmodulin compete for the same binding site on the ryanodine receptor suggesting a role of S100A1 in calcium homeostasis (152). The proof of principle of the therapeutic potential of S100A1 gene

Table 3. Association of S100 proteins with human diseases

Proteins	Association with Diseases	References
S100B	Alzheimer's disease	128
	Down syndrome	128
	Brain trauma and ischemia	126, 128
	Schizophrenia	127
	Infectious pathologies	131
	Depression, mood disorder	129
	Cancer	124
S100A1	Cardiac performance	148, 414
	Alzheimer's disease	145
	Cancer	154, 155
S100A2	Cancer, (up- or down-regulation)	166, 177
S100A3	Cancer	185, 186
S100A4	Cancer, metastasis	192
	Rheumatoid arthritis	420
	Fibrosis, cardiac disease	421
S100A5	Cancer	185, 225
S100A6	Cancer	238
	Amyotrophic lateral sclerosis (ALS)	241, 242
S100A7	Psoriasis	244
	Allergic reactions	254
	Anti-bactericide	245
	Cancer	255-257
S100A7L1	Psoriasis	263
S100A8/A9	Inflammation	422
	Cystic fibrosis	422
	Wound healing	422
	Juvenile rheumatoid arthritis	423
	Atherosclerosis	281
	Alzheimer's disease	285
	Sepsis	300
	Acute myocardial infarction	288
	Cancer	293, 294
S100A10	Cancer	313-315
	Depression	316-319
S100A11	Cancer	330-332
	Osteoarthritis	37, 338
S100A12	Inflammatory diseases	282, 346, 350-353, 357
	Cancer	424
	Aortic aneurysm	357
	Alzheimer's disease	284, 356
S100A13	Cancer	370, 375
S100A14	Cancer	377, 378
S100A16	Cancer	381, 382
S100P	Cancer carcinomas	392-395
S100Z	Cancer	405

therapy to restore heart function was shown recently in rats (153). In these animals, viral-based delivery of S100A1 to isolated failing cardiomyocytes restored normal contractile function and cellular calcium handling (153). S100A1 may also play a role in Alzheimer's disease. Indeed, recent studies showed a role of S100A1 in Aβ peptide induced cell death and in amyloid precursor protein expression (145). S100A1 was also suggested to be a marker in ovarian and endometrial cancers (154) and nephrogenic adenoma (155).

Like S100B, S100A1 is not an essential protein for life and S100A1 knock-out animals show only mild phenotypes (156, 157). The absence of strong phenotype in S100A1 ablated mice might be caused by compensation mechanisms in which another S100 protein (or calmodulin for instance (152)) takes over the function of the missing S100A1 protein. Indeed, the same target protein can be activated by distinct S100 proteins. An example is fructose 1,6 biphosphate aldolase which can be activated by both S100B and S100A1 (158). However, S100 proteins can also modulate the activity of the same target protein with different or opposite results. In this regard binding of S100A1 and S100B to phosphoglucomutase results in opposite effects (159). Similarly S100B and S100A1 bind differently to the common target p53 (32).

Protein nitrosylation is an emerging signaling mechanism in which key proteins are modified by NO in response to changes in redox in the cells (Table 1) (160). Both S100B and S100A1 can be nitrosylated *in vitro* and the modification rate is increased in the presence of calcium suggesting a cross-link between redox-based and metal-based signaling pathways (39). Nitrosylation of S100B results in a two-fold increase in binding affinity towards the monomeric tetramerization domain of p53 (residues 325-355) as well as towards the negative regulatory domain (residues 367-393) (32).

S100A1 has been shown to promote neurite outgrowth in the presence of amphoterin in a RAGE dependent manner (134) and we recently demonstrated direct binding with RAGE *in vitro* (24). The physiological role of this interaction needs further investigation.

5. 3. S100A2

S100A2 is unique among the S100 proteins because of its nuclear localization (161). S100A2 is expressed in a large variety of organs and tissues that include lung, kidney, liver and breast epithelia (161). S100A2 binds calcium and zinc. Binding to zinc (K_D = 25 nM) reduces significantly the affinity of S100A2 for calcium (162). Moreover, calcium and zinc appear to have opposite effects on the stability of S100A2, calcium being a protein stabilizer and zinc a protein destabilizer (163). The three-dimensional structure of S100A2 shows similarities with the structures of calcium free S100A3, S100A4 or S100A6 (164). S100A2 is distinct among the other S100 proteins by its role of tumor suppressor as shown in human mammary epithelial cells (Table 3) (165). Down-regulation of S100A2 has thus been found in melanoma, prostate, oral, lung and breast cancer (166-171). Interestingly, up-regulation of S100A2 has also been found in other cancers including esophageal squamous carcinoma, gastric and ovarian cancer (172-174). The role of S100A2 in non-small cell lung cancer (NSCLC) is more complex and both up-regulation and down-regulation of S100A2 have been observed depending of the sub-type of tumor (i.e adenocarcinoma, squamous cell carcinoma or large cell carcinoma) (175-177). In a recent study, high expression of S100A2 correlated with poor survival in surgically resected patients with NSCLC (178). S100A2 over-expression was shown to strongly induce metastasis in NOD/NUDE mice (178). In a different study, the presence of S100A2 correlated with a favorable outcome in patients carrying p53 negative tumors (179) suggesting a complex role of S100A2 and p53 in tumor biology. Mutations and polymorphisms within S100A2 have also been reported in

NSCLC (176). At the molecular level S100A2 interacts with cyclophilin CyP40 (147) and the tumor suppressor protein p53 resulting in increase of its transcriptional activity (p53) (32, 180, 181). Binding of S100A2 to p53 is increased when p53 is phosphorylated (32). S100A2 also interacts with the Hsp70/Hsp90-organizing protein (Hop) and the kinesin-light chain (KLC) and thus participates in protein folding (182).

As with S100A1, S100A2 does interact with RAGE *in vitro* but this interaction must be further evaluated *in vivo* (24).

5. 4. S100A3

S100A3 has an unique tissue distribution. It is mainly expressed in hair follicles (183, 184). Contrarily to the other S100 proteins, S100A3 binds weakly to calcium but presents a high affinity towards zinc, probably due to its ten cysteine residues (183). Another particular feature of S100A3 is the modification of many arginine residues into citrulline (citrunillation) by calcium dependent peptidylarginine deiminases (Table 1) (34). The citrullination of arginine residues triggers the tetramerization of S100A3 that may play a role in the function of S100A3. Interestingly, S100A3 might be a biomarker in astrocytic tumors (185) and a recent in silico study also suggests a potential role of S100A3 as biomarker in gastric tumors (Table 3) (186). The interaction of S100A3 with RAGE has not been described yet.

5. 5. S100A4

S100A4 was first isolated in mouse adenocarcinoma cells as a gene associated with metastasis ((187-191) and reviewed in (192)). S100A4 is both a calcium and zinc binding protein (193). S100A4 is structurally very similar to S100A6 as shown by NMR and X-ray crystallography and reveals high structural similarity (194-196). In normal conditions, S100A4 is expressed in a large number of normal cells that include fibroblasts, leukocytes, smooth muscle cells and endothelial cells (197). S100A4 is also found in the nervous system where it is thought to play a role in neuronal plasticity (198). The role of S100A4 in metastasis has been evidenced in several animal studies. In one study, injection of highly metastatic mouse mammary carcinoma cells into S100A4 -/- mice resulted in the absence of metastasis formation whereas the control S100A4 +/+ animals showed a large number of metastases (199). In another study, when mice over-expressing S100A4 were crossed with a strain of mice spontaneously developing non-metastatic tumours (GRS/A), the resulting transgenic mice developed a large number of metastatic tumours (199, 200). S100A4 has also been shown to promote angiogenesis in endothelial cells, to induce the activity of the matrix metalloproteinase MMP-2 in osteosarcomas and to play a role in rheumatoid arthritis and osteoclastogenesis (Table 3) (201-204). Recently S100A4 has also been shown to play a role in the recruitment of macrophages to the sites of inflammation as shown in S100A4 knock-out mice (205). At the molecular level, S100A4 has been shown to interact with both intracellular (non-muscle myosin, tropomyosin) and extracellular targets (annexin II, plasminogen, EGFR ligands) (206-212). Binding of S100A4 to myosin-IIA can be disrupted by phenothiazine compounds which simultaneously trigger S100A4 oligomerization suggesting a new mode of inhibition of S100/target protein interaction (213). Binding of S100A4 with the insulin like family member relaxin was shown recently to play a role in human thyroid carcinoma (214). Importantly, S100A4 interacts with the tumor suppressor p53 protein, inhibits p53 oligomerization and its interaction with its target DNA (32, 181, 215). The role of S100A4/p53 complex in metastasis has recently been evaluated (216). Metastasis induced by S100A4 has been shown recently to depend of the self-association of S100A4 (217). This result provides new avenues for the development of anti-metastatic drugs (217). S100A4 interacts with RAGE *in vitro* as demonstrated by SPR studies using either chimeric sRAGE-Fc or biotinylated RAGE (218). Interestingly, both S100A4 dimers and oligomers were reported to bind to RAGE *in vitro* (218)). 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 (218) whereas S100A4 could stimulate RAGE dependent signaling cascades leading to activation of MMP13 in osteoarthritic cartilage (219). S100A4 has also been shown recently to modulate the motility of human pulmonary artery smooth muscle cells in a RAGE dependent manner (220).

5. 6. S100A5

S100A5 is found in restricted areas of the brain and kidney (221-223). S100A5 binds calcium, zinc and copper and copper binding strongly impairs the binding to calcium (221). S100A5 has been suggested to play a role in copper delivery to another target protein or to protect other proteins from copper induced damages (221). The three-dimensional structure of calcium free and calcium bound S100A5 has recently been solved by NMR and shows only slight differences between S100A5 and the closely related S100A4 and S100A6 proteins (224).

Recent studies suggest a role of S100A5 in cancer (Table 3). Indeed S100A5 is overexpressed in astrocytic tumors (185) and has been suggested to be a marker of recurrence in certain meningiomas (225). A correlation between S100A5 and RAGE in cancer has not been found yet. We showed recently the binding of S100A5 to RAGE *in vitro* (24). However, the physiological relevance for this interaction still needs to be proven.

5. 7. S100A6

S100A6 is present in a large number of tissues and organs including muscle, lung, kidney, spleen, and brain (226, 227). S100A6 has been shown to translocate between the cytoplasm and the nucleus in a calcium dependent manner (20, 228, 229). S100A6 binds calcium and zinc with micromolar affinity (230). S100A6 is structurally very similar to S100B, both in the presence and absence of calcium, as shown by NMR and X-ray crystallography (231-233). The function of S100A6 is not well known and recent findings have been reviewed in (234). S100A6 is over-expressed in many cancers including

colorectal cancer, pancreatic, hepato-cellular carcinoma melanoma, lung cancer or gastric cancer (Table 3) (166, 235-239). In pancreatic cancer, high S100A6 concentration was shown to positively correlate with malignancy and poor prognosis (238, 240). S100A6 may also play a role in amyotrophic lateral sclerosis and Alzheimer's disease (241, 242). At the molecular level, S100A6 interacts with a dozen target proteins *in vitro* including the tumor suppressor p53 and RAGE (24, 139, 181, 243). By using biophysical methods and cell culture we showed that S100A6 could interact *in vitro* with both the V and C2 domain (Figure 2) (139). However, studies using human neuroblastoma cells showed that only the C2 domain of RAGE could transmit a signaling cascade following binding to S100A6 (139). Further characterization of the interaction of S100A6 with the distinct domains will be necessary to understand these differences.

5. 8. S100A7

S100A7 has a very restricted tissue distribution and is almost only present in inflamed psoriatic skin where it is released from keratinocytes (244, 245). S100A7 binds only one calcium per monomer with low affinity (K_D= 150 μM) (246). Following binding to calcium, the conformation of S100A7 does not change significantly, contrarily to other members of the family such as S100B or S100A6 (247, 248). S100A7 also binds zinc with low affinity (KD = 100 μM) (246-248). Interestingly S100A7 uses its zinc binding properties to sequester zinc from E. coli resulting in antibacterial activity (245, 249, 250 (255) (Table 3) , 251, 252) (Table 3). S100A7 is also thought to play a role in allergic reactions (253, 254). S100A7 is also associated with lung (255) and breast cancer (253, 255-257). S100A7 has been shown to interact with the Jun activating binding protein1 (Jab-1) (258, 259), with the. epidermal fatty acid binding protein (E-FABP) and RanBMP. S100A7 also present chemo-attractant activities that have been shown to be mediated by RAGE (260-262) (263). Interestingly, these activities appear to be dependent of the presence of zinc (263).

5. 9. S100A7-like1 (S100A7L1)

S100A7L1 or formerly S100A15 (12, 22) is highly homologous to S100A7 (93 % amino acid homology) and like S100A7 is expressed by specific cell types of the skin and present chemo-attractant activities to subsets of leukocyte populations (263) S100A7L1 is involved in epidermal differentiation and inflammation and might therefore be important for the pathogenesis of psoriasis (Table 3). Interestingly, although S100A7 functions through RAGE, S100A7L1 has been suggested to function through toll-like receptor 4 and a Gi protein coupled receptor (263, 264).

5. 10. S100A8/A9

S100A8 and S100A9 are secreted as heterodimers mainly from neutrophils and macrophages (265-269). Together with S100A12, they were previously named calgranulins and possess both anti-infective and anti-inflammatory functions that include oxidant scavenging, antimicrobial and chemokine-like activities (Table 3) (270). S100A8 and S100A9 can form both homodimers and heterodimers. The structure of these different complexes have been solved by crystallography and showed similarity with the structure of other S100 proteins (271, 272). In addition, in the presence of calcium only, S100A8/A9 can form tetramers, that have been shown to play a role in the formation of microtubules (273-276). Moreover amyloid forms of S100A8/A9 have been found in the aging prostate (277). The role of these amyloids is not well understood.

S100A8/A9 plays various functional roles. S100A8/A9 plays a role in inflammation (278) and elevated serum levels of S100A8/A9 are found in patients suffering from inflammatory diseases such as rheumatoid arthritis, cystic fibrosis or Crohn's disease (27, 279-282). Moreover, high levels of S100A8/A9 are present in the microglia of patients suffering from Alzheimer's disease (AD) or presenting ischemic lesions (283, 284). A role of S100A9 in AD is further supported by recent studies in AD mice models (Tg2576) where silencing of S100A9 improved the cognitive decline and the amyloid burden (285). Moreover, S100A8/A9 are over-expressed in atherosclerotic plaques and have been suggested to actively participate in the formation and rupture of these plaques (281, 286-288). S100A8/A9 also plays an important role in several cancers (reviewed in (289)) including gastric cancer (290, 291), colorectal carcinoma (292) or prostate cancer (293). S100A8 was recently found to be a marker of bladder cancer (294). In pre-metastatic lungs, S100A8/A9 released by macrophages has been shown to trigger Toll-like Receptor 4 (TLR-4) through serum amyloid A, resulting in acceleration of metastasis (295). However, S100A8 has also been suggested to have a protective effect through nitrosylation (33, 296). Phosphorylation of S100A9 has been shown to be essential in the translocation of S100A8/A9 from the cytosol to the plasma membrane leading to the activation of neutrophil NADPH oxidase that plays a role in the host defense against invading pathogens through the generation of reactive oxygen species (Table 1) (31).

S100A8 is an essential gene for life since S100A8 knock-out mice died during embryonic development (297). Surprisingly, S100A9 knock-out mice do not show any obvious phenoptype demonstrating distinct functions between S100A8 and S100A9 (298, 299).

A limited number of targets for S100A8/A9 are described so far. S100A8 has been shown to interact with TLR-4 complexed with MD2, promoting endotoxin-induced shock (Figure 2) (300). Activation of TLR-4 by S100A8/A9 appears to be key for the development of auto-immunity (301). S100A8/A9 also interacts with the scavenger receptor CD36 (302), with heparin and heparan sulfate glycosaminoglycans (303) and with components of the NADPH oxidase complex (304).

Although S100A8/A9 have been shown to interact with RAGE in some studies, the physiological role of this interaction is not well understood. In breast cancer cells, S100A8/A9 promotes cell growth via p38MAPK and p44/42 kinase activation in a RAGE dependent manner

(Figure 2) (305). Similarly, S100A8/A9 mediates endotoxin-induced cardiomyocyte dysfunction in a RAGE dependent manner as well (306). Carboxy-methyl modified S100A8/A9 has also been shown to sustain RAGE dependent signaling in intestinal inflammation (35). In human umbilical aortic cells (HUVEC), only AGE pre-treated cells could respond to S100A8/A9 and trigger RAGE dependent signaling (281). In macrophages S100A8/A9 amplified proinflammatory cytokine production via the activation of NF-κB and p38 MAPK, in a RAGE independent manner (307). A recent study also suggested that the carboxylated dextran carried by RAGE are important for RAGE dependent signaling, NF-κB activation and cellular proliferation (308). S100A8/A9 has also been shown to trigger RAGE independent signaling in other sudies (291, 308, 309). The direct binding between S100A9 homodimer and RAGE has been studied by surface plasmon resonance and was shown to be dependent of the presence of both calcium and zinc (310).

5. 11. S100A10

S100A10, formerly annexin II light chain or p11, is expressed in many tissues, including brain. S100A10 is unique among the S100 proteins due to the fact that the protein is always in the calcium bound conformation (reviewed in (311)). The main target of S100A10 is the membrane protein annexin II (312). S100A10 plays an important role in plasminogen dependent macrophage migration in inflammatory stress as well as in cell invasion in tumors (Table 3) (313-315). S100A10 also modulates depression through the interaction with serotonin receptors (316-319). Serotonin receptor is also a target for the EF-hand sensor calcium binding protein calmodulin (320). Another target of S100A10 is the neuron-specific sensory sodium channel where it regulates its expression (321). Binding of S100A10 to RAGE has not yet been demonstrated.

5. 12. S100A11

S100A11 is present in many tissues but is in higher abundance in smooth muscle tissues where it was first isolated and characterized (322, 323). S100A11 is not essential for life since S100A11 knock-out mice do not show any obvious phenotype (324). The three-dimensional structure of S100A11 in the calcium free form and in the calcium bound form in the presence of annexin I peptide have been solved by NMR and crystallography (325, 326). These structures showed a new mechanism of interaction between a S100 protein and its target peptide with one peptide bound per S100 monomer (326). Interestingly, S100A11 interacts with annexin II, the main target protein of S100A10 and could substitute for S100A10 in certain conditions (327). S100A11 binds to p53 as well (181). The interaction of S100A11 with Rad54B suggests a role in DNA double strand repair mechanism and cell cycle progression (328). S100A11 appears to play dual roles in tumor progression and development (table 3) (reviewed in (329)). It has been found to promote tumor formation in prostate, breast and pancreatic cancer (330-332). However it might play the role of tumor suppressor in bladder and renal carcinoma (333, 334). In normal cells such as human keratinocytes, it also triggers growth inhibition through its phosphorylation by protein kinase C (Table 1) (324, 335-337).

S100A11 has also been shown to play a role in osteoarthritis (OA) via the interaction with RAGE and the activation of the p38 MAPK pathway (338). RAGE dependent signaling was dependent of the transamidation of S100A11 by the transglutaminase TG2 although both non-modified and covalently modified S100A11 were able to bind to RAGE (Table 1) (37). S100A11 has also been shown to exert RAGE dependent signaling in human keratinocytes (339).

5. 13. S100A12

S100A12 was first isolated from resting neutrophils (340). It is also secreted from monocytes and lymphocytes (340). S100A12 translocates from the cytosol to the membrane in the presence of increased calcium concentration (340). The crystal structure of calcium bound S100A12 showed dimeric and hexameric arrangements (341, 342) that have been suggested to have biological functions. S100A12 also binds copper that could play a role in early immune responses (343). Recent studies by the same authors showed the important role of zinc and calcium in S100A12 oligomerization and function (344, 345).

S100A12 is strongly expressed in inflammatory diseases that include Crohn's disease, cystic fibrosis, atherosclerosis, rheumatoid arthritis, psoriasis or Kawasaki disease (Table 3) (282, 346-353). S100A12 has also been found in other inflammatory settings such as in inflamed mammary tissue (354), in inflamed gastric mucosa of *Helicobacter pylori*-infected children (355), and in microglia of patients suffering from sporadic AD (284, 356). Recently, over-expression of human S100A12 in smooth muscle mice resulted in the activation of pathogenic pathways through the modulation of oxidative stress, inflammation and vascular remodeling (357).

The list of targets of S100A12 has been described in a previous review (24). Besides binding to RAGE that will be reviewed in the next paragraph, the targets of S100A12 include the $NADP^+$-dependent isocitrate dehydrogenase (IDH), fructose-1,6-bisphosphate aldolase A, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and annexin V (358). Interestingly, S100A12 has been shown to interact with S100A9, however, the physiological relevance of this complex has yet to be determined (44, 358, 359).

Activation of RAGE by S100A12 was first demonstrated in endothelial cells, mononuclear phagocytes and lymphocytes (Figure 2) (44). In these cells, RAGE activation by S100A12 resulted in downstream activation of key molecules involved in inflammatory processes. In endothelial cells, over-expression of RAGE and S100A12 were observed following hyperglycemia dependent increases of reactive oxygen species (360). In monocytes, the RAGE/S100A12 activation pathway was recently shown to be triggered by the C-reactive protein and inhibited by statins (361). Recently S100A12 has been

found to bind not only to RAGE but also to other scavenger receptor (SR) (362).

The interaction of S100A12 with RAGE has been investigated in several studies with some contradictory results. We and others showed binding of S100A12 to the V domain of RAGE (24, 44, 141) whereas fluorescence and NMR spectroscopy data suggested that S100A12 bound primarily with the C1 domain of the receptor (Figure 2) (359). These contradictory results may originate from differences in the methods used to measure these interactions. Binding of S100A12 to RAGE was shown to be dependent upon the presence of calcium (24, 345, 363) and zinc (345) and was increased by the presence of carboxylated glycans of RAGE (84). S100A12/RAGE interaction has also been shown to be inhibited by the presence of heparin (363).

5. 14. S100A13

S100A13 has a large tissue and organ distribution that includes heart, kidney, brain, ovary and spleen (364, 365). S100A13 binds two calcium ions per subunit with strong positive cooperativity (K_{D1} = 8 μM and K_{D2} = 400 μM). S100A13 is a copper binding protein and has also been shown to bind to the copper binding C2A protein, suggesting that S100A13 might play the role of copper chaperon (366). The structure of S100A13 has been solved at several pH and shows strong similarities with S100A8/A9 and S100A1 (367-369).

S100A13 is thought to play a role in lung cancer invasiveness (370) and is involved in the non-classical release of fibroblast growth factor 1 (FGF-1) through the interaction with the fibroblast growth factor itself and synaptotagmin (Table 3) (371-374). S100A13 has recently been suggested to be an angiogenic marker in melanoma (375). The complex between S100A13/FGF-1/synaptotagmin play an important role in angiogenesis formation and recent studies have shown that the anti-allergic small molecule drug amlexanox could inhibit the formation of the complex between S100A13 and FGF-1 and could be a new promising drug against angiogenesis (376).

Although the direct binding of S100A13 to RAGE has yet to be demonstrated, this interaction has been suggested from earlier experiments where the extracellular addition of S100A13 to endothelial cells resulted in RAGE dependent translocation of S100A13 from the nucleus to the cytoplasm (21).

5. 15. S100A14

S100A14 was identified from a human lung cancer cell line (377). It presents 68% homology with S100A13 and possesses a myristoylation motif (Table 1). It is widely distributed in normal tissues (377). Comparison of the expression of S100A14 in tumors shows a dual pattern. The protein was found over-expressed in breast, ovary and uterus tumors and under-expressed in kidney, rectum and colon tumors (Table 3) (377). Under-expression of S100A14 was also observed in esophageal squamous cell carcinoma (378). No target has been described yet for S100A14.

5. 16. S100A16

S100A16 is ubiquitously expressed (379). It binds two calcium ions per monomer and binding of calcium triggers conformational changes as observed with other S100 proteins. S100A16 translocates from the nucleus to the cytoplasm in response to increases in calcium concentration (380). S100A16 may play a role in metastasis as it was found over-expressed in circulating cancer cells in advanced stages of cancers (381). S100A16 is also suggested to play a role in glioma proliferation (382). No target has been described yet for S100A16.

5. 17. S100G

S100G was previously named calbindin D9k, CaBP9k, calbindin-3 or CABP1 and was very recently included in the list of S100 proteins (12, 22). It is not a sensor protein but exerts the function of calcium buffering (reviewed in (383). S100G is unique among the S100 proteins in that it is present as a monomer only. The structure of apo- and calcium loaded S100G has been solved both by crystallography and NMR and showed little conformational changes upon calcium binding (384-386). S100G is expressed in a large number of tissues such as intestine, uterus, placenta, kidney and bone and plays a role in calcium transport during absorption (Table 3) (387). S100G expression was shown recently to be regulated by glucocorticoids (388). S100G is not essential to life despite its function as shown in studies with S100G knock-out mice (389). In these studies the lost function of S100G is suggested to be compensated by calbindin D28K similarly to what is observed in studies with calbindin D28k knock-out mice (i.e compensation by calbindin D9k; (15, 389)). Binding to RAGE has not been reported yet.

5. 18. S100P

S100P is expressed in a large number of tissue and organs including placenta where it was first isolated (390, 391). S100P binds two calcium ions with distinct affinities (K_{D1} = 800 μM; K_{D2} = 1.6 μM) (390).

S100P is believed to play a role in tumor biology and it is found over-expressed in ovarian, pancreatic, gastric, colorectal, breast and prostate carcinomas (Table 3) (392-395). S100P was also found to be up-regulated following the granulocytic differentiation of human myeloid leukemia HL-60 cells with isopentenyladenine (396). Interestingly, human gastric cancer cells treated with the non steroid anti-inflammatory drug celecoxib responded to the drug by up-regulating the expression of S100P, resulting in decreased anti-tumorigenic effects of the drug (397). Recently, S100P was found to be under the control of several key regulatory elements such as SMAD, STAT or SP and to be up-regulated following activation of glucocorticoid receptors suggesting complex mechanisms of regulation (398).

S100P binds to several target proteins. It forms a heterodimer with S100A1 whose function is yet to be determined (399). The S100P homodimer interacts with ezrin and this interaction is believed to be important in tumor invasion (400, 401). The S100P binding protein

(S100PBPR) is a recently discovered target and is suggested to play a role in early pancreatic cancer (402).

S100P interacts with the RAGE receptor and the interaction has been shown to activate the MAPK pathway resulting in the downstream activation of the transcription factor NF-κB (392, 403, 404)

5. 19. S100Z

S100Z was isolated from a human prostate cDNA library (405). It binds two calcium ions that trigger conformational changes in the protein (405). It is widely distributed in tissues and found down-regulated in several tumors (Table 3) (405). Binding to RAGE has not been reported yet.

6. COMPLEXITY OF RAGE/S100 INTERACTION

The binding of RAGE to so many S100 proteins is puzzling. As described above, S100B, S100A4, S100A6, S100A7, S100A8/A9, S100A12, S100A13 and S100P are all able to trigger RAGE dependent signaling in cells. *In vitro* interaction with purified protein has also been described for S100A1, S100A2 and S100A5 as well (24). *In vitro*, S100 proteins appear to bind to distinct sites of RAGE. Indeed, S100A6 has been shown to bind to the isolated V and C2 domains (139) and S100A12 also has been described to bind to the V (44, 139, 141) and C1 domains (359). Binding of S100 proteins also appears to be metal dependent. For many S100 proteins, *in vitro* binding to purified RAGE is strictly calcium dependent (24). Interestingly, although it has not been yet characterized, the zinc requirement of RAGE activation by S100A7 predicts a zinc dependent RAGE/S100A7 interaction as well (263). The three-dimensional structures of most S100 proteins have been solved either by crystallography or by NMR. The structure of the V and VC1 domains have recently been solved by NMR (86) and crystallography as well (406) . The structure of the complexes between RAGE and the S100 proteins will certainly be solved in a near future and these structures will help to understand the mechanism (s) of interaction between RAGE and the S100 proteins and to develop S100/RAGE inhibitors.

7. RAGE/S100 IN HUMAN DISEASES AND THERAPEUTIC APPROACHES

Both RAGE (407, 408) and S100 proteins have been associated with human diseases (Table 2 and 3). The realization that RAGE is an important signaling receptor for a large number of S100 proteins has brought emphasis on the importance of RAGE/100 interactions in human diseases.

Several approaches are currently employed to reduce RAGE mediated cellular damages (408). These approaches do not target specifically RAGE/S100 interactions but rather aim to inhibit the interaction of RAGE with all of its ligands (i.e AGEs, amphoterin, amyloid β peptide). The first approach consists in using soluble RAGE as decoy of the cell-surface receptor. In animal or cell culture studies, soluble RAGE is used at concentrations significantly higher than the physiological concentration of circulating sRAGE (98, 409). Treatment with soluble RAGE results in RAGE inhibition by quenching all RAGE ligands but it also results in decreasing the activation of other target/receptors by RAGE ligands (410). A more targeted approach consists in using antibodies against RAGE to block the access of RAGE ligands to the receptor. Polyclonal antibodies are mainly used for this purpose. Efforts are currently devoted to generate high affinity anti-RAGE monoclonal antibodies that could be used both as diagnostic (411) and therapeutics (412). A third approach to get further inside into the role of RAGE in human diseases uses RAGE knock-out animals (410). Ideally, it will be possible to develop highly selective small molecule RAGE inhibitors. One such compound is currently in phase 2 clinical trials (Pfizer: PF-04494700 (413)).

8. CONCLUSION

In recent years the S100 proteins have emerged as potential targets for treating human diseases. Gene therapy with S100A1 has been shown to restore cardiac performance in rats (414). S100B is used in routine diagnostics in many hospitals to predict survival of patients with melanoma (123) and to predict extent of brain damage in patients with stroke (18). The formely named calgranulins (S100A8/A9 and S100A12) are strong markers of inflammatory conditions such as arthritis (415).

The understanding of role of S100 proteins in human diseases has been accelerated in the past decade after the identification of RAGE initially as receptor for S100B and S100A12 (44). Due to the large number of S100 proteins that have been found to bind RAGE *in vitro*, RAGE has been considered to be a common receptor for all S100 proteins (24, 42). However, studies in cells have also shown that not all S100 proteins could transmit cellular signaling through RAGE. For instance, although it seems well demonstrated that the interaction of RAGE with S100B, S100A12 or S100P are physiologically relevant, further studies are needed to confirm the role of other S100s in RAGE dependent signaling cascades (S100A4 or S100A8/A9). Toll-like receptors and particularly TLR-4, have also emerged as important receptors for the S100 proteins. The interaction of S100A8 with TLR-4 and its role in autoimmune diseases has been demonstrated (300) and a possible interaction between S100A7L1 and TLR-4 has been recently suggested (264).

Comprehensive studies of the interaction of each S100 protein with its receptor will help to characterize key residues in these interactions and to understand the mechanisms of selectivity for S100s. Complex mechanisms of regulation of S100/RAGE or S100/TLR signaling also emerge with the recent discovery of a large array of post-translational modifications affecting the S100 proteins (phosphorylation, transamidation, citrullination, carboxymethylation, sumoylation or nitrosylation).

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Abbreviations: SOC: store operated calcium channel, CRAC: calcium release activated calcium channels, NCS: neuronal calcium sensors, NSCLC: non-small cell lung cancer, SR: scavenger receptor, S100PBPR: S100P binding protein, RAGE: Receptor for Advanced Glycation Endproducts, AGE: Advanced Glycation Endproducts, HMGB1: high mobility group protein 1, Aβ: amyloid beta, AD: Alzheimer disease, TTR: transthyretin, FL-RAGE: full-length RAGE, sRAGE: soluble RAGE, Hop: Hsp70/Hsp90 organizing protein, KLC: kinesin-light chain, MMP-2: matrix metalloproteinase, EGFR: epithelial growth factor receptor, E-FABP: epidermal fatty acid binding protein, HUVEC: human umbilical vein endothelial cells, MAPK: mitogen activated protein kinase, NF-κB: nuclear factor kappa B, IDU: isocitrate dehydrogenase, GAPDH: glyceraldehyde-3-phosphate dehydrogenase, TLR-4: Toll like receptor 4.

KEY WORDS Calcium, Zinc, Copper, EF-hand, S100 proteins, RAGE, Toll-Like Receptors, Neurological Diseases, Inflammation, Cardiovascular, Biomarker, Review

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