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RAGE and Its Ligands in Melanoma

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1. Introduction

Melanoma is a complex disease with both genetic and epigenetic components [1-3]. Once melanoma has formed distant metastases, melanoma patients have generally poor prognoses; less than 10% of these patients will survive 10 years [4]. For many years, treatment with the cytotoxic drug dacarbazine was the standard treatment for patients with metastatic melanoma, but the response rates were low and varied from 5-20% [4]. Intense research efforts on understanding the molecular mechanisms of melanoma progression led to the discovery and the approval by the FDA of two new drugs in 2011, vemurafenib and ipilimumab, which raised great hopes among melanoma patients [5-12]. Although treatment with vemurafenib has resulted in high overall responses rates [11], resistance against the drug appeared in treated melanoma patients within a year of treatment, leading to tumor regrowth [13-16]. On the other hand, treatment with ipilimumab does not result in resistance but can produce life threatening autoimmune adverse effects [17]. In addition, ipilimumab works best in patients whose tumors present abundant tumor infiltrated immune cells [18]. It is therefore essential to identify new therapeutic targets in melanoma.

One potential therapeutic target is the receptor for advanced glycation end products (RAGE). A possible role of RAGE in melanoma is emerging and has been the topic of a growing number of studies in the past decade [19-25]. These studies will be reviewed here and we will also discuss the RAGE ligands that play important roles in melanoma progression.

2. The Receptor for Advanced Glycation End Products (RAGE)

2.1. RAGE function

RAGE is an immunoglobulin-like cell-surface receptor that is involved in a large number of pathologies, including Alzheimer's disease, cancer, infectious diseases and complications of

diabetes [31-38]. The ligands of RAGE are numerous (Table 1) and belong to distinct families of molecules. However, they also share structural features such as the propensity to form oligomers [39]. It is believed that RAGE recognizes similar structural elements or patterns within its numerous ligands and therefore RAGE is described as a pattern recognition receptor [40, 41].

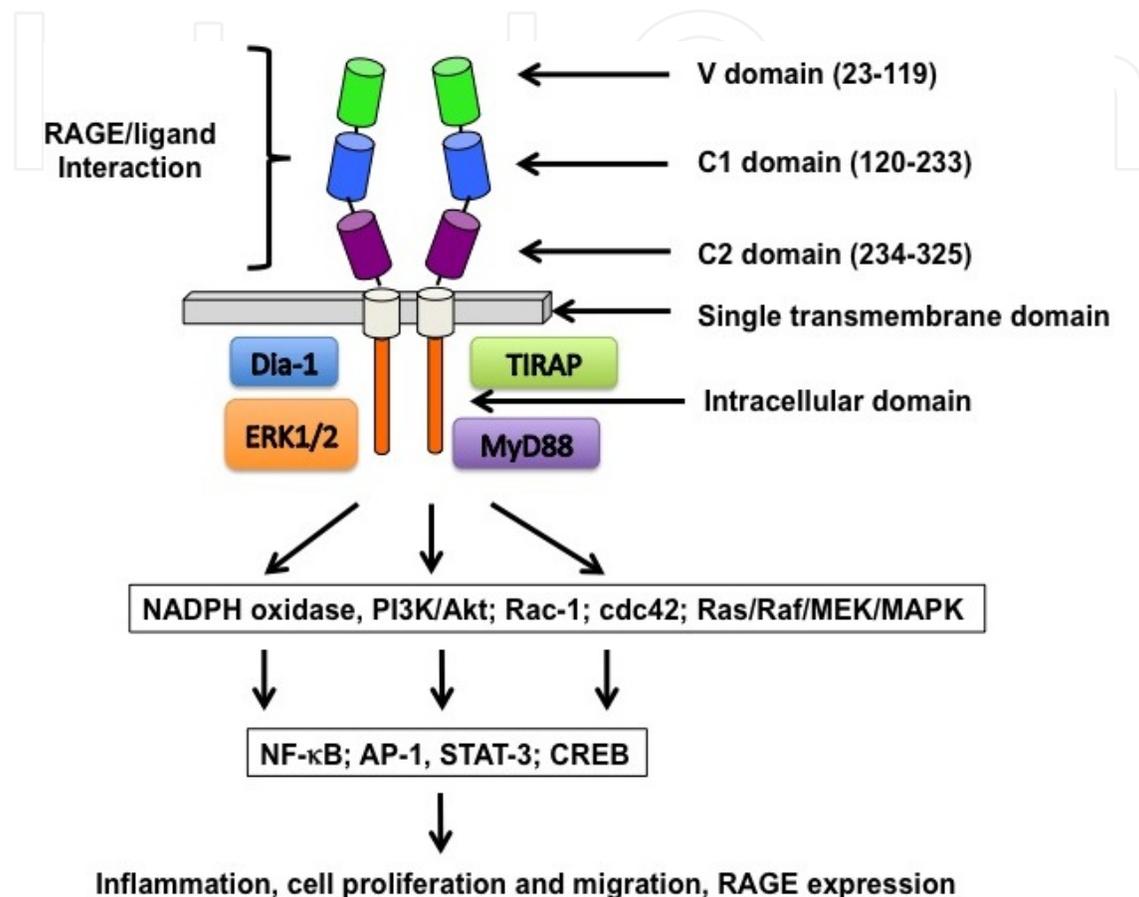


Figure 1. Schematic representation of RAGE. The extracellular part of RAGE is composed of three distinct immunoglobulin-like domains (V, C1 and C2). The V and C1 domains form a structural and functional unit [26]. Most ligands interact with the V-C1 domain. Four adaptor molecules have been suggested to bind to the intracellular domain of RAGE: ERK1/2 [27], diaphanous-1 (Dia-1) [28], TIRAP and MyD88 [29]. Following activation of RAGE by its ligands, multiple signaling pathways (MAPK, PI3K/Akt) or molecules (NADPH oxidase, Rac-1, cdc42) are activated and lead to the transcription of genes related to inflammation, cell proliferation and migration, and to the expression of RAGE itself, resulting in a positive feedback loop [30].

The physiological role of RAGE is not yet fully understood. Studies have shown that RAGE plays a role in the innate but not adaptive immunity and has been shown to play an important function in peripheral nerve repair [42-44]. A characteristic of RAGE is that it is expressed at low basal level in most tissues except in lungs where it has been suggested to exert a protective effect [45-48]. RAGE has also been shown to modulate the auditory system in mice [49].

Several spliced isoforms of RAGE have been described. Besides full-length RAGE, presented in Figure 1, RAGE exists as a soluble form (sRAGE) lacking the intracellular and transmembrane domains. The soluble form can result either from a splicing event or from the action of

a metalloprotease such as ADAM 10 [50-58]. Other major identified spliced isoforms lack the N-terminal domain or present a deletion in the intracellular domain, resulting in abnormal ligand interaction and cell signaling activities, respectively [51, 56, 59]. sRAGE has been used in many animal experiments to validate the role of RAGE in various diseases such as Alzheimer's disease, atherosclerosis or encephalomyelitis [60-62]. Two different models explaining the mechanism of action of sRAGE have been proposed. The "classic" mechanism suggests that sRAGE acts as a decoy receptor and interacts with circulating RAGE ligands, which results in the absence of RAGE/ligand complex formation and RAGE activation. Recently, the group of Fritz has proposed a second mechanism of action for sRAGE: Fritz et al. suggest that sRAGE could form a complex with the extracellular part of another full-length receptor and that this receptor complex would not be functional because it possesses only one intracellular domain [63]. According to this hypothesis, RAGE can only transmit a signal if two intracellular domains form a dimer [63].

The role of sRAGE as biomarker has also been investigated in many diseases but has resulted in contradictory data for certain pathologies. In Alzheimer's disease patients, the circulating plasma levels of sRAGE have been shown to be significantly reduced compared to healthy individuals [64]. A more detailed immunohistological examination of AD brain showed that the reduction in sRAGE was more pronounced in the hippocampus of AD brains than normal brains [65]. Systemic low levels of sRAGE have also been found in patients with emphysema, a form of chronic obstructive pulmonary disease (COPD) and sRAGE is suggested to be a biomarker for this lung disease [66, 67]. However, in diabetes, the situation is more complex and in different studies the levels of sRAGE have been either positively or negatively correlated with the disease (reviewed and discussed in [68])

In cancer, an association between sRAGE and the progression of cancer has also been shown. Significantly lower levels of sRAGE have been found in lung, breast, liver or pancreatic cancer patients than in normal individuals [69-72]. Our study of 40 melanoma human samples also showed significantly lower transcript levels of the spliced form of RAGE in 90% of melanoma stage III and stage IV tissue samples compared to normal samples [73].

2.2. RAGE structure and signaling

RAGE is a single transmembrane receptor with a large extracellular part comprising of three domains that share structural features with immunoglobulin domains: a variable type (V) domain (residues 23-119), and two constant type domains (C1: residues 120-233, and C2: residues 234-325) (Figure 1) [74]. The V and C1 domains form a structural and functional unit and are the site of binding of most ligands [26].

Recent studies have suggested that RAGE structure is as complex as RAGE signaling is, and multiple conformational forms of RAGE in complex with its ligands have been proposed [75]. Recent evidence suggests that RAGE exists as a dimer on the surface of cells, in the absence of ligand [76, 77]. It has been suggested that the interaction of RAGE with its ligands occurs mainly through electrostatic interactions between the positive charges present on the V and C1 domains of RAGE and the negative charges present on RAGE ligands [39, 63]. Because both RAGE and its ligands can form oligomers, several oligomeric models of RAGE in complex

with its ligands have been proposed to reflect the possible RAGE/ligand interactions [39, 63, 75-79]. RAGE oligomerization could occur through contacts between the V domain [80], C1 domain [80], [77] or C2 domain, [75, 79], in a ligand dependent manner [79].

RAGE signaling is complex and RAGE/ligand interaction results in the activation of multiple signaling pathways that are ligand and tissue specific (Figure 1) [34, 81-84]. In general, RAGE engagement by its ligand leads to the activation of key elements of the PI3K/Akt pathways or the mitogen-activated protein (MAP) kinase signaling pathways which include ERK1/2, p38 and JNK. Small GTPases such as p21-Ras, Rac-1 or cdc42 can also be activated as a result of RAGE activation [28, 81, 85-87]. In many cases, RAGE activation by its ligands leads to the initiation of, and sustained inflammation through the activation of the transcription factor NF- κ B, but also AP-1, STAT-3 and CREB (Figure 1) [36-38, 68, 88].

2.3. RAGE in melanoma

A role of RAGE in melanoma progression was first suggested by Huttunen et al [19]. In their study, the authors generated tumors in mice using the mouse melanoma B16F10 cell-line expressing either full-length RAGE or a form of RAGE lacking the cytoplasmic domain [19]. Comparison of the number of metastases formed in the two groups of mice revealed that mice that were implanted with cells expressing the mutant form of RAGE generated significantly less tumors than mice implanted with cells expressing full-length RAGE. In a different study, Abe et al. showed that the growth of xenograft tumor in mice could be reduced using anti-RAGE antibodies [21]. We showed that RAGE overexpression in the WM115 human melanoma cell line resulted in a significant decrease in cell proliferation, but also in a significant increase in cell migration and invasion suggesting that RAGE can modulate different aspects of cancer [24]. We demonstrated that the decrease in cell proliferation was accompanied with a decrease in the activity of ERK1/2 [24] and p38 (Meghnani et al. 2014, *International Journal of Biochemistry and Cell Biology*, in press). The recent report of Popa et al. also suggests the presence of different oligomeric forms of RAGE with different roles and subcellular location during melanoma progression [25].

Studies in human melanoma tissue samples have shown that RAGE was not present in all melanoma samples but rather in a subset of samples. Hsieh et al. showed that only 20% tissue samples showed RAGE staining [20]. Our analysis of 40 samples of human melanoma tissue samples also showed large variations in RAGE transcripts levels, with up to 50-fold differences between samples [22].

Other studies have identified RAGE ligands as important elements in melanoma development. S100B has been studied in details and its role as a diagnostic marker for melanoma patients is well established (see section 3.1.1 on S100B). Abe et al. showed that AGEs could promote the proliferation of melanoma cells in culture [21]. Saha et al. showed that S100A8/A9 could attract B16F10 melanoma cells to a metastatic site, in a RAGE dependent manner [23]. In addition, our recent study showed a strong correlation between the expression of RAGE and that of its S100 protein ligands, in mouse xenograft melanoma tumors (Meghnani et al. 2014, *International Journal of Biochemistry and Cell Biology*, in press).

3. RAGE ligands

Since the identification of AGEs as ligands of RAGE, the list of RAGE ligands has grown to more than ten ligands or groups of ligands (Table 1). In this section, we will discuss the current knowledge on ligands that have been shown to play a role in melanoma progression, with a focus on S100 proteins.

RAGE ligand	Examples of disease where the ligand is involved	References
Advanced glycation end products	Inflammation, cancer, Alzheimer's disease, atherosclerosis, aging	[74, 89-92]
S100 proteins	Inflammation, cancer, aging, neurodegenerative disorders	[82, 93-95]
High mobility group box 1 (HMGB-1)	Cancer, inflammation, aging	[34, 96-99]
Alzheimer's β -peptide	Alzheimer's disease	[32, 60]
Transthyretin	Transthyretin amyloidosis	[100]
Prion	Prion's disease	[101, 102]
Mac-1	Diseases of the immune system	[40, 103]
Complement proteins C3a and C1q	Diseases of the immune system	[104, 105]
Phosphatidylserine	Diseases of apoptosis	[106, 107]
Heparan sulfate	Cancer, inflammation, developmental disorder	[78, 108, 109]
DNA, RNA	Infectious diseases, autoimmune disorders	[110]

Table 1. Non-exhaustive list of the different ligands of RAGE. The S100 proteins that are ligands of RAGE will be described in details in section 3.1

3.1. S100 proteins

Members of the S100 protein family have amino-acid sequence and structure similarities [111, 112]. They are small calcium binding proteins and belong to the superfamily of EF-hand proteins [111]. Restricted to vertebrates, S100 proteins show strong tissue and cell specificity [111, 113]. Most S100 genes (S100A1 to S100A16) are located on chromosome 1 in a region that is prone to chromosomal rearrangement, linking these S100 proteins to cancer [113]. The presence of EF-hands within the structure of S100 proteins enable them to bind calcium with moderate micromolar affinity [111, 112, 114, 115]. In addition to calcium, S100 proteins can also bind zinc and copper [116, 117]. For most S100 proteins, binding to calcium results in conformational rearrangements that allow the S100 proteins to interact with their targets [115, 117, 118]. Certain target proteins are S100 specific whereas others are shared among multiple S100s (Reviewed in [119]).

Most S100 target proteins are intracellular [111, 112, 120]. An example of such target that plays a role in cancer is the tumor suppressor p53 protein [121-126]. Several members of the S100 protein family (S100B, S100A1, S100A2, S100A4, S100A6 and S100A10) bind to p53 but the

outcome of this interaction differs depending of the S100 [121-126]. S100 proteins can also be secreted into the extracellular space through mechanisms that are not clearly understood [127, 128]. When secreted, many S100 proteins have been shown to interact with RAGE [82, 93, 129].

Many S100 proteins are found in cells constituting the epidermis [130]. S100B and S100A6 have been found in both melanocytes and Langerhan's cells [131-133]. S100A2, A7, A10, A11, A12 and S100A15 have been described in normal keratinocytes [131-138]. In pathophysiological conditions, such as in inflamed keratinocytes and melanoma, many S100 proteins have been found overexpressed [130, 136]. The next section will describe the role of these S100 proteins in melanoma.

3.1.1. S100B

S100B is used as a prognostic marker for stage IV malignant melanoma patients [139-141]. Serum concentration of S100B increases during the disease and high levels of S100B in the serum is indicative of a poor prognosis [139-141]. In melanoma tumors, melanoma cells are the main cells responsible for secreting S100B [141]. Within the cells, the role of S100B is not clearly understood but the main target of S100B appears to be the tumor suppressor p53 protein. Indeed, several studies from the group of Weber have shown that S100B interacts with p53 in melanoma cells and tumors, resulting in p53 inhibition and increased expression of S100B, in a negative feedback loop [142-144]. His group is currently investigating small interfering antisense RNA inhibitors of S100B as inhibitors of melanoma tumor growth [145].

Other intracellular target proteins of S100B could also contribute to increases in cellular proliferation and tumor growth in melanoma. For example, S100B interacts with and activates the glycolytic enzyme fructose-1,6-biphosphate aldolase, [146]. Consequences of this activation could be an increase in melanoma cell metabolism and glycolysis. Inhibiting melanoma cell metabolism and glycolysis is currently been considered in clinical trials [147, 148]. Inhibiting S100B/ fructose-1,6-biphosphate aldolase could be an approach to further reduce glycolytic activity in melanoma cells. S100B also interacts with many components of the cytoskeleton such as tubulin [149, 150], the actin binding protein caldesmon [151] or the small GTPase Rac1 and the cdc42 effector IQGAP1 [152]. All these proteins play important function in malignant melanoma [153-155] and increases in S100B levels could therefore favor increases in cell proliferation, migration and invasion through their modulation. S100B could also play a role in melanoma cell growth through the activation of the Nuclear Dbf2 related (ndr) kinase [156-158] and the interaction with the phosphoprotein AHNAK/desmoyokin [159-161].

As mentioned earlier, S100B is secreted from melanoma cells. The mechanisms of S100B secretion are still poorly understood but recent studies have suggested that RAGE participates in the translocation and secretion of several S100s including S100B [127, 128]. Similarly, the role of RAGE/S100B in melanoma is slowly being unraveled. S100B has been shown to signal through RAGE in a large number of diseases (reviewed in [162]) and we studied in details the *in vitro* interaction of RAGE with S100B [26, 81, 163]. For example, we showed that not only dimeric S100B but also tetrameric and hexameric S100B could interact with RAGE and signal in cells [163]. In addition, we recently showed that overexpression of RAGE, in human WM115 melanoma cells, was accompanied by the up-regulation of S100B in these cells [24], suggesting

a strong association between RAGE and S100B in melanoma. When the RAGE transfected WM115 cells were implanted in mice as xenografts, we also observed higher levels of S100B in the serum of these animals, compared to animals implanted with control WM115 cells (Meghnani et al. 2014, International Journal of Biochemistry and Cell Biology, in press).

3.1.2. S100A2

S100A2 is mainly located in the nuclei of cells [164]. The function of S100A2 in cancer is not clear. In certain cancers such as prostate, oral, lung and breast cancers, S100A2 has been shown to play the role of tumor suppressor [22, 165-169], whereas in other cancers such as esophageal squamous carcinoma, gastric, and ovarian cancer, studies indicate that it acts as tumor promoter [170-172]. In addition, in certain cancers, such as in non-small cell lung cancer (NSCLC), studies are contradictory since both down- and up-regulation of S100A2 have been reported [173-175].

In melanoma, most studies reported that S100A2 plays the role of tumor suppressor [130, 132, 165, 176]. We also showed a significant reduction in S100A2 mRNA level in both stage III and stage IV melanoma patients samples compared to control samples [22]. Additional evidences of a tumor suppressor effect of S100A2 comes from several studies that show positive correlations between the levels of S100A2 and anti-proliferative effects of chemotherapeutic agents in melanoma cells [177, 178]. However, our most recent study shows that xenograft melanoma tumors overexpressing RAGE, presented a growth advantage over control tumors, and exhibited significant higher levels of S100A2 than control tumors (Meghnani et al. 2014, International Journal of Biochemistry and Cell Biology, in press). We observed that S100A2 was up-regulated, both at the transcript and protein levels, in the RAGE overexpressing tumors (Meghnani et al. unpublished results). These data suggest a complex role of S100A2 in promoting or suppressing melanoma tumor growth.

As mentioned above, S100A2 is located in the nuclei of cells and has been shown to interact with the tumor suppressor p53, in two oral cancer cell lines (FADU and SCC-25), thereby modulating the transcriptional activity of p53 [123]. *In vitro* binding studies have confirmed the interaction between S100A2 and p53 and has shown differences in binding of p53 to S100B and S100A2; for example, although both S100B and S100A2 could bind to the monomeric form of p53, only S100B was able to disrupt the oligomerization of p53, suggesting different mode of transcriptional modulation of p53 by the S100 proteins [124, 126]. In addition to interacting with p53, S100A2 transcriptional activity is regulated by other members of the large p53 family, such as p63 and p73, suggesting an additional level of complexity of the S100A2/p53 regulation [179-181]. In breast cancer tissues and cells, it was shown that both the p53 homologue Np63, and BRCA1 were important for the transcriptional activity of S100A2 [182]. These recent data could have a large impact in understanding the molecular mechanism of melanoma because positive correlations have been found between the BRCA1 associated protein (BAP1) and malignant uveal and cutaneous melanoma [183-185].

We recently demonstrated that *in vitro*, S100A2 could interact with RAGE [22] and our recent study showed an association between RAGE overexpression and the levels of S100A2 in melanoma xenograft tumors (Meghnani et al. 2014, International Journal of Biochemistry and

Cell Biology, in press). However, a direct interaction of S100A2/RAGE in melanoma cells and tissue has yet to be demonstrated.

3.1.3. S100A4

S100A4 was initially identified from metastatic cells and was hence named metastasin [186]. Overexpression of S100A4 in multiple cell lines has been shown to increase cancer cell invasiveness and motility [187, 188]. The role of S100A4 in cancer was further demonstrated in S100A4^{-/-} mice that showed delayed tumor growth, compared to control mice, when implanted with highly metastatic mammary carcinoma cells [189, 190].

In melanoma, the role of S100A4 is complex and appears to vary during the progression of the disease. An early study showed no significant differences in S100A4 mRNA levels between melanoma tissue samples and control samples [165]. Our analysis of 40 samples of stage III and stage IV melanoma tissue samples showed a significant reduction of S100A4 mRNA in stage IV compared to control samples [22]. Another study also reported different correlation between the levels of S100A4 and patient survival rates during the progression of melanoma: high levels of S100A4 in primary melanoma tumors were associated with low patient survival rates whereas high S100A4 levels in metastatic tumors were not associated with differences in patient survival rates, suggesting a role of S100A4 at an early stage of the disease [191].

S100A4 exerts both intra- and extracellular functions (reviewed in [192]). Inside the cells, S100A4 can be found in the nuclei and cytoplasm [192]. S100A4 has been shown to interact with p53 and, as described for S100B, to disrupt p53 oligomerization [193, 194]. *In vivo*, interaction of S100A4 with p53 has been shown to promote degradation of p53, resulting in increases in tumor growth [195]. In the cytoplasm, S100A4 interacts with a large number of proteins of the cytoskeleton such as non-muscle myosin II [196] and tropomyosin [197], resulting in cytoskeletal reorganization, which occurs during cell migration and invasion [198, 199].

An important property of S100A4 is that it has been found secreted in the extracellular medium of cells and is present in the milieu of many tumor types such as breast cancer [200], ovarian carcinoma [201], osteosarcoma [202] or adenocarcinoma tumors [203]. Many cells from normal tissues and from tumors have been shown to release S100A4. These cells include fibroblasts, leukocytes, and endothelial cells [192, 204]. Extracellular S100A4 has been shown to promote tumor growth and metastasis [192], neovascularization and angiogenesis [205-207].

Two main targets of extracellular S100A4 with relevance to tumor growth and metastasis have been identified: Annexin II and RAGE [208, 209]. Interaction of S100A4 with annexin II has been associated with increased mechanisms of angiogenesis such as the formation of capillary-like tubes by endothelial cells [208]. S100A4 has been shown to enhance motility of pulmonary artery smooth muscle cells in a RAGE dependent manner [210]. Similarly, S100A4 was shown to promote prostate and colorectal cancer tumorigenesis and metastasis in a RAGE dependent manner [211, 212]. In melanoma, a recent study has demonstrated that S100A4 derived from macrophages could promote lung colonization of B16F10 melanoma cells in mice, in a RAGE dependent manner as well [213]. We have also observed that RAGE overexpression in the

WM115 melanoma cells resulted in the up-regulation of S100A4, by the melanoma cells, in xenograft tumors implanted in mice (Meghnani et al. 2014, International Journal of Biochemistry and Cell Biology, in press).

3.1.4. S100A6

S100A6 is another member of the S100 family with a link to cancer. S100A6 was identified from melanoma tissue samples by comparing melanocytic lesions from normal nevi [214]. S100A6 is most abundant in epithelial cells and fibroblasts but is also found, in smaller amounts, in other cell-types such as neurons, glial cells, smooth muscle cells, cardiac myocytes, platelets and lymphocytes [215, 216](reviewed in [217]). S100A6 has been found elevated in a large number of cancer types which include colorectal cancer, pancreatic, hepato-cellular carcinoma, melanoma, lung cancer and gastric cancer [165, 218-224](reviewed in [217]). In melanoma tumor samples, a positive correlation was found between the levels of S100A6 transcripts and the severity of the disease [165]. In animal models, S100A6 was found to correlate with the metastatic behavior of the melanoma cells [214, 225]. We also observed higher levels of S100A6, at the transcript level, in 43% of stage III melanoma samples examined, compared to control samples [22]. In agreement with our study, examination of another set of melanoma tissue samples showed that 33% of the samples stained positive for S100A6 [133]. However, examination of melanoma tumor biopsies by immunohistochemistry often shows that the expression of S100A6 is weak and patchy, and that other non-melanoma cutaneous lesions also stain positive for S100A6, making it difficult to use S100A6 as a diagnostic marker for melanoma [176, 226, 227].

S100A6 has been shown to interact with both nuclear and cytoplasmic proteins. S100A6 interacts with the tumor suppressor p53 but this interaction is different than the interaction of p53 with S100B, suggesting different regulation of the transcriptional activity of p53 by the two S100 proteins [124, 228]. S100A6 was shown to interact with a peptide derived from cell membrane associated annexin I, but the physiological relevance of this interaction has yet to be demonstrated [229]. We showed that S100A6 could interact with both the VC1 and the C2 domain of RAGE, but that in human neuroblastoma, signaling was transduced through the C2 domain [81]. The interaction of the C3S mutant form of S100A6 with the V domain of RAGE has recently been studied in details [230]. Similarly to what we observed with S100B, S100A2 and S100A4, RAGE overexpression in the WM115 melanoma cells resulted in the up-regulation of S100A6, by the melanoma cells, when the cells were forming xenograft tumors in nude mice, compared to control tumors (Meghnani et al. 2014, International Journal of Biochemistry and Cell Biology, in press).

3.1.5. S100A8/A9

S100A8 and S100A9 are mainly expressed by cells of myeloid origin such as monocytes and macrophages, and were first described as cytokine-like proteins for their up-regulation in inflamed tissues and inflammatory disorders [231]. Recent studies have also shown that they play significant roles in cancer where they promote tumor growth and metastasis in a large number of cancers such as in breast, prostate and pancreatic cancer [232-238]. In tumors, recent studies have shown that S100A8/A9 regulates the accumulation of myeloid-derived suppres-

sor cells (MDSC), and also promote the expansion of these cells, resulting in increased tumor growth [239-243].

Neither S100A8 nor S100A9 is present in significant amounts in the cells of a normal epidermis, including melanocytes [130, 244]. Although a study described that S100A8/A9 was absent from melanocytic lesions [244], other studies have suggested that they participate in melanoma progression. S100A9 has been shown to promote melanoma metastases formation in a mouse model [245]. In a different mouse model of melanoma, the levels of MDSCs correlated with the levels of S100A9, [246]. In addition, Saha et al. recently demonstrated that tail-vein injected B16F10 melanoma cells, that do not express S100A8 or S100A9, could migrate to S100A8/A9-abundant lungs of uteroglobin-knockout mice [23]. The migration of the B16F10 cells occurred along a concentration gradient of S100A8/A9, and resulted in the formation of secondary tumors in the lungs [23].

S100A8/A9 mediates their effect through the interaction with cell surface receptors or molecules. The two pattern recognition receptors, toll-like receptor 4 (TLR-4) and RAGE, have been shown to transmit RAGE signaling [23, 247, 248]. In certain conditions, signaling through RAGE has been shown to require carboxylated glycans that are covalently attached to RAGE [249, 250]. The importance of RAGE glycosylation for RAGE signaling has also been demonstrated for another member of the S100 protein family, S100A12 [251]. S100A8/A9 has been shown to interact with other glycans, such as heparin or heparin sulfate glycosaminoglycans [137]. In addition, S100A9 has also been shown to interact with and transmit signal through EMMPIRIN [245].

3.1.6. Other S100 proteins

Other S100 proteins are found in cells of the epidermis (reviewed by [130]), and their association with melanoma will be briefly described in this paragraph.

S100A7 or “psoriasin” has been linked to psoriasis because of its up-regulation in this disease [252, 253]. Although no direct role of S100A7 in melanoma has been described yet, in one study, significantly higher levels of S100A7 were found in the urine of melanoma patients compared to that of healthy patients [254].

S100A10 has been found expressed at various levels in melanoma tumor samples and melanocytes [22, 244]. Our recent study where we compared the levels of S100 proteins in WM115 xenografts, generated from either control WM115 cells or from RAGE overexpressing WM115 cells, showed that S100A10 was up-regulated in the RAGE overexpressing tumors (unpublished data). Comparison of the WM115-RAGE cells with control cells did not reveal any difference in S100A10 levels between the two cell lines, suggesting that RAGE overexpression was responsible for the up-regulation of S100A10 in the tumors. S100A10 could therefore play a role in melanoma progression.

S100A11 can either promote tumor growth or play the role of tumor suppressor, depending of the type of cancer (reviewed in [255]). S100A11 has been suggested to play a role in uveal melanoma, but has not yet been linked to cutaneous melanoma [256].

3.2. Other ligands of RAGE

3.2.1. Advanced Glycation End products (AGEs)

Among RAGE ligands, AGEs were the first group of ligands to be identified [89]. AGEs form a group of very heterogeneous compounds since they are the result of condensation and oxidation reactions between proteins and sugars [257]. Although the term AGE was initially reserved for brown, fluorescent and cross-linked structures that were produced during the Maillard reaction, such as those found in glycated collagen, it is now used to describe other types of modifications and AGEs now include proteins containing carboxymethyllysine, carboxymethyl hydroxylysine or pyrroline [257]. Since many types of sugars (glucose, ribose...) can modify many proteins, the number of different structures produced by glycation is very large. The large heterogeneity in AGE compounds renders the comparison among studies also very difficult. When comparing the results of studies involving AGEs, it is therefore important to know the type of AGEs used in the study.

Melanoma cells have been shown to produce high levels of reactive carbonyl species such as glyoxal, methylglyoxal and malondialdehyde, which all can lead to the glycation of proteins, and which have been implicated in melanoma cell proliferation and formation of metastases [258-260]. Abe et al. investigated the effects of different AGEs (glucose-derived AGE, glyceraldehyde-derived AGE, glycoaldehyde AGE, methylglyoxal-AGE, glyoxal-AGE and carboxymethyllysine-AGE) on melanoma cell proliferation, migration and invasion, and showed that all these AGEs were strongly present in human melanoma specimen whereas they were hardly detected in melanocytes [21]. However, the same authors showed that only certain types of AGE compounds (glyceraldehyde-derived AGE and glycoaldehyde AGE) could stimulate the proliferation, migration and invasion of G361 metastatic human melanoma cells *in vitro*. The role of RAGE in the *in vitro* AGE-dependent proliferation was demonstrated with anti-RAGE antibodies [21]. In addition, the authors showed that treatment of mice carrying G361 melanoma tumors, with anti-RAGE antibodies, resulted in reduced tumor growth and formation of lungs metastases [21]. These results strongly suggested a role of AGE/RAGE in the development of melanoma tumors by the G361 human melanoma cell line [21]. Our detailed study on melanoma cell proliferation of a panel of 20 glycated proteins showed that many factors influenced the proliferation, such as the extent of lysine modification, the percentage of β -sheet and the oligomerization state of the glycated proteins [261]. We showed that glycated proteins that demonstrated higher percentage of oligomeric forms, β -sheet content and modification of lysine, promoted stronger cell proliferation than proteins that contained lower levels of oligomers, β -sheet or lysine modification.

3.2.2. High Mobility Group Box 1 protein (HMGB1)

HMGB-1 is present in most eukaryotic cells (reviewed by [97]). It functions both as a nuclear protein, where it binds to DNA and assists in the transcription of multiple genes, and as an extracellular protein, where it binds to the pattern recognition receptors TLR-2, TLR-4 and TLR-9 as well as to RAGE, thereby promoting inflammation, mediating response to infection and injury as well as promoting cell proliferation, migration or invasion [98, 262-266]. HMGB-1

is also described as an alarmin or damage-associated molecular pattern [267]. HMGB-1 interacts directly with a large number of transcription factors that are relevant in cancer, and include the tumor suppressor p53, p73, the retinoblastoma protein (RB), the p50 subunit of NF- κ B and the estrogen receptor (reviewed by [268]). The release of HMGB-1 has been shown to be triggered by necrosis or apoptosis, such as following treatment of tumors with a chemotherapeutic agent [264, 266, 267].

HMGB-1 has also been shown to be released from necrotic or apoptotic melanoma cells [269]. A recent study showed that HMGB-1 could be released from keratinocytes in culture, or from murine skin, following exposure to UV light [270]. Using a genetically engineered mouse model of melanoma, Bald et al. showed that UV exposure also promoted metastasis and angiogenesis, through HMGB-1, and TLR-4 signaling [271]. In a different mouse model, Tang et al. showed the role of the HMGB-1/RAGE axis in promoting melanoma tumor growth [272]. In melanoma patients, HMGB-1 levels have also been shown to predict patient survival rates [273].

3.2.3. Glycosaminoglycans, β 2 integrin Mac-1 and phosphatidylserine

RAGE has been shown to interact with various glycosaminoglycans such as chondroitin sulfate, dermatan sulfate and heparin sulfate [108]. Many of these glycosaminoglycans are abundantly present in tumor stroma and have been shown to be key players of melanoma progression and metastasis formation [274, 275]. RAGE also interacts with β 2 integrin Mac-1 on leukocytes and has been shown to promote leukocyte recruitment at the site of inflammation [40]. The interaction between RAGE and Mac-1 is dependent of the presence of cations, and has been shown to be significantly augmented by the presence of S100B. In a different study, S100A9 has also been shown to activate β 2 integrin Mac-1 on neutrophils suggesting that other S100 proteins could also participate to the complex between Mac-1 and RAGE [276]. Leukocyte recruitment at tumor sites is an important process that allows cytotoxic T-cells to infiltrate tumors and to help in the elimination of cancer cells [277]. In melanoma, success of the therapy with interleukin-2 (IL-2) is based on the infiltration of cytotoxic T-cells to the interior of the tumor [277]. The involvement of S100 proteins and RAGE in leukocyte recruitment suggests that therapeutic approaches targeting RAGE should be carefully evaluated to avoid inhibiting the recruitment of cytotoxic T-cells at the site of melanoma tumors. On the other hand, targeting RAGE could also result in suppressing the recruitment of MDSCs, another form of leukocyte expressing β 2 integrin Mac-1 [278], at the tumor site, which would be beneficial for patients [279, 280].

RAGE has also been shown to interact with the negatively charged phospholipid phosphatidylserine (PS) [106]. This interaction has direct relevance in melanoma because PS has been shown to be exposed to the outer leaflet of the plasma membrane of cells forming melanoma metastases [281]. An association between malignancy of melanoma and PS exposure has also been described [281]. Further studies would be necessary to determine whether RAGE/PS could be targeted in melanoma.

4. Conclusion and therapeutic approaches

In the last two decades, RAGE has emerged as a new therapeutic target in a large number of diseases. Because of the large number of ligands of RAGE that are relevant in melanoma, targeting RAGE/ligand appears to be a promising approach. Several molecules could be used as inhibitors and include the soluble form of the receptor (sRAGE), antibodies against RAGE or small molecules. Both soluble RAGE and anti-RAGE antibodies have been used to demonstrate the role of RAGE in experimental models of a large number of diseases such as atherosclerosis, Alzheimer's disease or melanoma [21, 60, 282-286]. Two small molecule inhibitors of RAGE are currently available. One compound PFS-ZM1 has been recently used in an experimental model of Alzheimer's disease [287]. This inhibitor interacts with the V domain of RAGE and blocks the interaction of amyloid β -peptide with the receptor. The second compound (TPP488) has been evaluated for safety and efficacy, in a phase 2 study, in mild to moderate Alzheimer's disease patients. However, because of the large variation in the levels of RAGE observed in melanoma tumor samples, it is currently not known whether targeting RAGE would be efficacious in all melanoma tumors or only in the subset of tumors where it is overexpressed. Additional studies would be necessary to answer this important question.

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