Chapter 13

RAGE and Its Ligands in Melanoma

Estelle Leclerc

Additional information is available at the end of the chapter

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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].

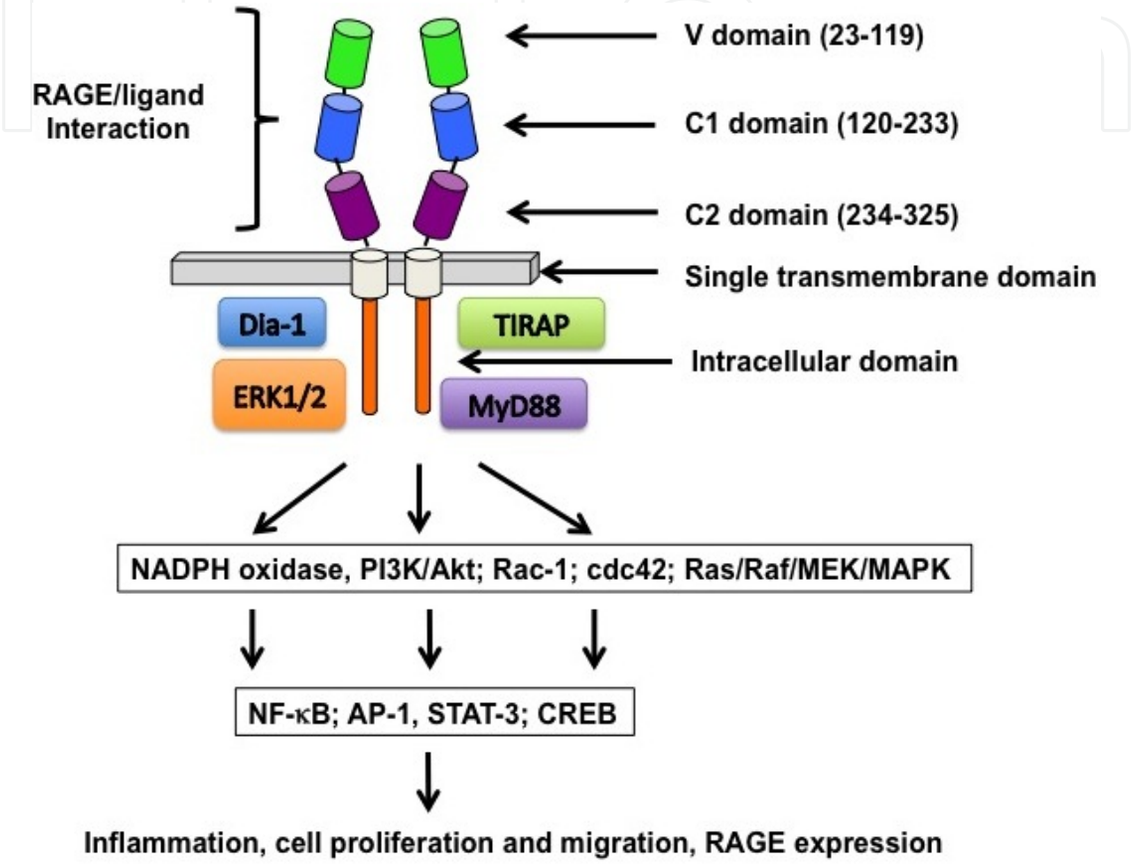

Figure 1. Schematic representation of RAGE. The extracellular part of RAGE is composed of three distinct immunoglobulin-like domains (V, C1 and C2). The V and C1 domains form a structural and functional unit [26]. Most ligands interact with the V-C1 domain. Four adaptor molecules have been suggested 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-κB, 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]
Phophatidylserine	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 significantly 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 a 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 S1006, 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-abondant 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 pyrraline [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 that 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-κB 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, β2 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 β2 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 β2 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 β2 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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Author details

Estelle Leclerc*

Address all correspondence to: Estelle.Leclerc@ndsu.edu

North Dakota State University/Department of Pharmaceutical Sciences, USA

References

[1] Howell PM, Jr., Liu S, Ren S, Behlen C, Fodstad O, Riker AI. Epigenetics in human melanoma. Cancer Control. 2009;16(3):200-18.

[2] Patino WD, Susa J. Epigenetics of cutaneous melanoma. Adv Dermatol. 2008;24:59-70.

[3] Palmieri G, Capone M, Ascierto ML, Gentilcore G, Stroncek DF, Casula M, et al. Main roads to melanoma. J Transl Med. 2009;7:86.

[4] Bhatia S, Tykodi SS, Thompson JA. Treatment of metastatic melanoma: an overview. Oncology (Williston Park). 2009;23(6):488-96.

[5] Eggermont AM, Robert C. Melanoma in 2011: A new paradigm tumor for drug development. Nat Rev Clin Oncol. 2012.

[6] Hodi FS, Oble DA, Drappatz J, Velazquez EF, Ramaiya N, Ramakrishna N, et al. CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS. Nat Clin Pract Oncol. 2008;5(9):557-61.

[7] Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Nat Rev Drug Discov. 2010;9(10):767-74.

[8] Robert C, Mateus C. [Anti-CTLA-4 monoclonal antibody: a major step in the treatment of metastatic melanoma]. Med Sci (Paris). 2011;27(10):850-8.

[9] Trinh VA, Hagen B. Ipilimumab for advanced melanoma: A pharmacologic perspective. J Oncol Pharm Pract. 2012.

[10] Wang T, Somasundaram R, Herlyn M. Combination therapy of immunocytokines with ipilimumab: a cure for melanoma? J Invest Dermatol. 2013;133(3):595-6.

[11] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16.

[12] Luke JJ, Hodi FS. Vemurafenib and BRAF inhibition: a new class of treatment for metastatic melanoma. Clin Cancer Res. 2012;18(1):9-14.

[13] Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363(9): 809-19.

[14] Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010;468(7326):973-7.

[15] Wagle N, Emery C, Berger MF, Davis MJ, Sawyer A, Pochanard P, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085-96.

[16] Poulikakos PI, Persaud Y, Janakiraman M, Kong X, Ng C, Moriceau G, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature. 2011;480(7377):387-90.

[17] Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155-64.

[18] Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423-37.

[19] Huttunen HJ, Fages C, Kuja-Panula J, Ridley AJ, Rauvala H. Receptor for advanced glycation end products-binding COOH-terminal motif of amphoterin inhibits invasive migration and metastasis. Cancer Res. 2002;62(16):4805-11.

[20] Hsieh HL, Schafer BW, Sasaki N, Heizmann CW. Expression analysis of S100 proteins and RAGE in human tumors using tissue microarrays. Biochem Biophys Res Commun. 2003;307(2):375-81.

[21] Abe R, Shimizu T, Sugawara H, Watanabe H, Nakamura H, Choei H, et al. Regulation of human melanoma growth and metastasis by AGE-AGE receptor interactions. J Invest Dermatol. 2004;122(2):461-7.

[22] Leclerc E, Heizmann CW, Vetter SW. RAGE and S100 protein transcription levels are highly variable in human melanoma tumors and cells. Gen Physiol Biophys. 2009;28 Spec No Focus:F65-75.

[23] Saha A, Lee YC, Zhang ZJ, Chandra G, Su SB, Mukherjee AB. Lack of an Endogenous Anti-inflammatory Protein in Mice Enhances Colonization of B16F10 Melanoma Cells in the Lungs. Journal of Biological Chemistry. 2010;285(14):10822-31.

[24] Meghnani V, Vetter SW, Leclerc E. RAGE overexpression confers a metastatic phenotype to the WM115 human primary melanoma cell line. Biochim Biophys Acta. 2014;1842(7):1017-27.

[25] Popa I, Ganea E, Petrescu SM. Expression and subcellular localization of RAGE in melanoma cells. Biochem Cell Biol. 2014;92(2):127-36.

[26] Dattilo BM, Fritz G, Leclerc E, Kooi CW, Heizmann CW, Chazin WJ. The extracellular region of the receptor for advanced glycation end products is composed of two independent structural units. Biochemistry. 2007;46(23):6957-70.

[27] Ishihara K, Tsutsumi K, Kawane S, Nakajima M, Kasaoka T. The receptor for advanced glycation end-products (RAGE) directly binds to ERK by a D-domain-like docking site. FEBS Lett. 2003;550(1-3):107-13.

[28] Hudson BI, Kalea AZ, Del Mar Arriero M, Harja E, Boulanger E, D'Agati V, et al. Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. J Biol Chem. 2008;283(49):34457-68.

[29] Sakaguchi M, Murata H, Yamamoto K, Ono T, Sakaguchi Y, Motoyama A, et al. TIRAP, an adaptor protein for TLR2/4, transduces a signal from RAGE phosphorylated upon ligand binding. PLoS One. 2011;6(8):e23132.

[30] Schmidt AM, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J Clin Invest. 2001;108(7):949-55.

[31] Schmidt AM, Yan SD, Yan SF, Stern DM. The biology of the receptor for advanced glycation end products and its ligands. Biochim Biophys Acta. 2000;1498(2-3):99-111.

[32] Yan SD, Bierhaus A, Nawroth PP, Stern DM. RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? J Alzheimers Dis. 2009;16(4):833-43.

[33] Bierhaus A, Nawroth PP. Multiple levels of regulation determine the role of the receptor for AGE (RAGE) as common soil in inflammation, immune responses and diabetes mellitus and its complications. Diabetologia. 2009;52(11):2251-63.

[34] Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, et al. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med. 2009;7:17.

[35] van Zoelen MA, Achouiti A, van der Poll T. RAGE during infectious diseases. Front Biosci (Schol Ed). 2011;3:1119-32.

[36] Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in Inflammation and Cancer. Annual Review of Immunology. 2010;28:367-88.

[37] Ramasamy R, Yan SF, Schmidt AM. Receptor for AGE (RAGE): signaling mechanisms in the pathogenesis of diabetes and its complications. Ann N Y Acad Sci. 2011;1243:88-102.

[38] Park S, Yoon SJ, Tae HJ, Shim CY. RAGE and cardiovascular disease. Front Biosci. 2011;16:486-97.

[39] Fritz G. RAGE: a single receptor fits multiple ligands. Trends Biochem Sci. 2011;36(12):625-32.

[40] Chavakis T, Bierhaus A, Al-Fakhri N, Schneider D, Witte S, Linn T, et al. The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. J Exp Med. 2003;198(10):1507-15.

[41] Lin L. RAGE on the Toll Road? Cellular & molecular immunology. 2006;3(5):351-8.

[42] Liliensiek B, Weigand MA, Bierhaus A, Nicklas W, Kasper M, Hofer S, et al. Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. J Clin Invest. 2004;113(11):1641-50.

[43] Rong LL, Trojaborg W, Qu W, Kostov K, Yan SD, Gooch C, et al. Antagonism of RAGE suppresses peripheral nerve regeneration. Faseb J. 2004;18(15):1812-7.

[44] Rong LL, Yan SF, Wendt T, Hans D, Pachydaki S, Bucciarelli LG, et al. RAGE modulates peripheral nerve regeneration via recruitment of both inflammatory and axonal outgrowth pathways. Faseb J. 2004;18(15):1818-25.

[45] Brett J, Schmidt AM, Yan SD, Zou YS, Weidman E, Pinsky D, et al. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. Am J Pathol. 1993;143(6):1699-712.

[46] Queisser MA, Kouri FM, Konigshoff M, Wygrecka M, Schubert U, Eickelberg O, et al. Loss of RAGE in pulmonary fibrosis: molecular relations to functional changes in pulmonary cell types. Am J Respir Cell Mol Biol. 2008;39(3):337-45.

[47] Ramsgaard L, Englert JM, Tobolewski J, Tomai L, Fattman CL, Leme AS, et al. The role of the receptor for advanced glycation end-products in a murine model of silicosis. PLoS One. 2010;5(3):e9604.

[48] Buckley ST, Ehrhardt C. The receptor for advanced glycation end products (RAGE) and the lung. J Biomed Biotechnol. 2010:in press.

[49] Sakatani S, Yamada K, Homma C, Munesue S, Yamamoto Y, Yamamoto H, et al. Deletion of RAGE causes hyperactivity and increased sensitivity to auditory stimuli in mice. PLoS One. 2009;4(12):e8309.

[50] Ohe K, Watanabe T, Harada S, Munesue S, Yamamoto Y, Yonekura H, et al. Regulation of alternative splicing of the receptor for advanced glycation endproducts (RAGE) through G-rich cis-elements and heterogenous nuclear ribonucleoprotein H. J Biochem. 2010;147(5):651-9.

[51] Hudson BI, Carter AM, Harja E, Kalea AZ, Arriero M, Yang H, et al. Identification, classification, and expression of RAGE gene splice variants. Faseb J. 2008;22(5): 1572-80.

[52] Galichet A, Weibel M, Heizmann CW. Calcium-regulated intramembrane proteolysis of the RAGE receptor. Biochem Biophys Res Commun. 2008;370(1):1-5.

[53] Raucci A, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, et al. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). Faseb J. 2008;22(10):3716-27.

[54] Zhang L, Bukulin M, Kojro E, Roth A, Metz VV, Fahrenholz F, et al. Receptor for advanced glycation end products is subjected to protein ectodomain shedding by metalloproteinases. J Biol Chem. 2008;283(51):35507-16.

[55] Ding Q, Keller JN. Splice variants of the receptor for advanced glycosylation end products (RAGE) in human brain. Neurosci Lett. 2005;373(1):67-72.

[56] Yonekura H, Yamamoto Y, Sakurai S, Petrova RG, Abedin MJ, Li H, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. Biochem J. 2003;370(Pt 3):1097-109.

[57] Park IH, Yeon SI, Youn JH, Choi JE, Sasaki N, Choi IH, et al. Expression of a novel secreted splice variant of the receptor for advanced glycation end products (RAGE) in human brain astrocytes and peripheral blood mononuclear cells. Mol Immunol. 2004;40(16):1203-11.

[58] Kalea AZ, Reiniger N, Yang H, Arriero M, Schmidt AM, Hudson BI. Alternative splicing of the murine receptor for advanced glycation end-products (RAGE) gene. FASEB J. 2009;23(6):1766-74.

[59] Jules J, Maiguel D, Hudson BI. Alternative splicing of the RAGE cytoplasmic domain regulates cell signaling and function. PLoS One. 2013;8(11):e78267.

[60] Deane R, Du Yan S, Submamaryan RK, LaRue B, Jovanovic S, Hogg E, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med. 2003;9(7):907-13.

[61] Park L, Raman KG, Lee KJ, Lu Y, Ferran LJ, Jr., Chow WS, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation end-products. Nat Med. 1998;4(9):1025-31.

[62] Yan SS, Wu ZY, Zhang HP, Furtado G, Chen X, Yan SF, et al. Suppression of experimental autoimmune encephalomyelitis by selective blockade of encephalitogenic T-cell infiltration of the central nervous system. Nat Med. 2003;9(3):287-93.

[63] Koch M, Chitayat S, Dattilo BM, Schiefner A, Diez J, Chazin WJ, et al. Structural basis for ligand recognition and activation of RAGE. Structure. 2010;18(10):1342-52.

[64] Emanuele E, D'Angelo A, Tomaino C, Binetti G, Ghidoni R, Politi P, et al. Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. Arch Neurol. 2005;62(11):1734-6.

[65] Nozaki I, Watanabe T, Kawaguchi M, Akatsu H, Tsuneyama K, Yamamoto Y, et al. Reduced expression of endogenous secretory receptor for advanced glycation end-products in hippocampal neurons of Alzheimer's disease brains. Arch Histol Cytol. 2007;70(5):279-90.

[66] Cheng DT, Kim DK, Cockayne DA, Belousov A, Bitter H, Cho MH, et al. Systemic soluble receptor for advanced glycation endproducts is a biomarker of emphysema and associated with AGER genetic variants in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188(8):948-57.

[67] Miniati M, Calugi S, Rucci P, Shear MK, Benvenuti A, Santoro D, et al. Predictors of response among patients with panic disorder treated with medications in a naturalistic follow-up: the role of adult separation anxiety. J Affect Disord. 2012;136(3):675-9.

[68] Yan SF, Ramasamy R, Schmidt AM. Soluble RAGE: therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. Biochem Pharmacol. 2010;79(10): 1379-86.

[69] Jing R, Cui M, Wang J, Wang H. Receptor for advanced glycation end products (RAGE) soluble form (sRAGE): a new biomarker for lung cancer. Neoplasma. 2010;57(1):55-61.

[70] Tesarova P, Kalousova M, Jachymova M, Mestek O, Petruzelka L, Zima T. Receptor for advanced glycation end products (RAGE)--soluble form (sRAGE) and gene polymorphisms in patients with breast cancer. Cancer Invest. 2007;25(8):720-5.

[71] Moy KA, Jiao L, Freedman ND, Weinstein SJ, Sinha R, Virtamo J, et al. Soluble receptor for advanced glycation end products and risk of liver cancer. Hepatology. 2013;57(6):2338-45.

[72] Jiao L, Weinstein SJ, Albanes D, Taylor PR, Graubard BI, Virtamo J, et al. Evidence that serum levels of the soluble receptor for advanced glycation end products are inversely associated with pancreatic cancer risk: a prospective study. Cancer Res. 2011;71(10):3582-9.

[73] Leclerc E, Heizmann CW, Vetter SW. RAGE and S100 protein transcription levels are highly variable in human melanoma tumors and cells. General Physiology and Biophysics. 2009;28(Focus Issue):F65-F75.

[74] Neeper M, Schmidt AM, Brett J, Yan SD, Wang F, Pan YC, et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J Biol Chem. 1992;267(21):14998-5004.

[75] Yatime L, Andersen GR. Structural insights into the oligomerization mode of the human receptor for advanced glycation end-products. FEBS J. 2013;280(24):6556-68.

[76] Zong H, Madden A, Ward M, Mooney MH, Elliott CT, Stitt AW. Homodimerization is essential for the receptor for advanced glycation end products (RAGE)-mediated signal transduction. J Biol Chem. 2010;285(30):23137-46.

[77] Xie J, Reverdatto S, Frolov A, Hoffmann R, Burz DS, Shekhtman A. Structural basis for pattern recognition by the receptor for advanced glycation end products (RAGE). J Biol Chem. 2008;283:27255-69.

[78] Xu D, Young JH, Krahn JM, Song D, Corbett KD, Chazin WJ, et al. Stable RAGE-Heparan Sulfate Complexes Are Essential for Signal Transduction. ACS Chem Biol. 2013;8(7):1611-20.

[79] Wei W, Lampe L, Park S, Vangara BS, Waldo GS, Cabantous S, et al. Disulfide bonds within the C2 domain of RAGE play key roles in its dimerization and biogenesis. PLoS One. 2012;7(12):e50736.

[80] Xu D, Young J, Song D, Esko JD. Heparan sulfate is essential for high mobility group protein 1 (HMGB1) signaling by the receptor for advanced glycation end products (RAGE). J Biol Chem. 2011;286(48):41736-44.

[81] Leclerc E, Fritz G, Weibel M, Heizmann CW, Galichet A. S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE (receptor for advanced glycation end products) immunoglobulin domains. J Biol Chem. 2007;282(43): 31317-31.

[82] Donato R. RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. Curr Mol Med. 2007;7(8):711-24.

[83] Logsdon CD, Fuentes MK, Huang EH, Arumugam T. RAGE and RAGE ligands in cancer. Curr Mol Med. 2007;7(8):777-89.

[84] Soman S, Raju R, Sandhya VK, Advani J, Khan AA, Harsha HC, et al. A multicellular signal transduction network of AGE/RAGE signaling. J Cell Commun Signal. 2013;7(1):19-23.

[85] Lander HM, Tauras JM, Ogiste JS, Hori O, Moss RA, Schmidt AM. Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. J Biol Chem. 1997;272(28):17810-4.

[86] Huttunen HJ, Fages C, Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem. 1999;274(28):19919-24.

[87] Brozzi F, Arcuri C, Giambanco I, Donato R. S100B Protein Regulates Astrocyte Shape and Migration via Interaction with Src Kinase: IMPLICATIONS FOR ASTROCYTE DEVELOPMENT, ACTIVATION, AND TUMOR GROWTH. J Biol Chem. 2009;284(13):8797-811.

[88] Bierhaus A, Stern DM, Nawroth PP. RAGE in inflammation: a new therapeutic target? Curr Opin Investig Drugs. 2006;7(11):985-91.

[89] Schmidt AM, Vianna M, Gerlach M, Brett J, Ryan J, Kao J, et al. Isolation and characterization of two binding proteins for advanced glycosylation end products from bovine lung which are present on the endothelial cell surface. J Biol Chem. 1992;267(21): 14987-97.

[90] Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res. 2004;63(4):582-92.

[91] Yan SF, Ramasamy R, Schmidt AM. The receptor for advanced glycation endproducts (RAGE) and cardiovascular disease. Expert Rev Mol Med. 2009;11:e9.

[92] Srikanth V, Maczurek A, Phan T, Steele M, Westcott B, Juskiw D, et al. Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease. Neurobiol Aging. 2011;32(5):763-77.

[93] Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell. 1999;97(7):889-901.

[94] Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, et al. Functions of S100 proteins. Curr Mol Med. 2013;13(1):24-57.

[95] Chen H, Xu C, Jin Q, Liu Z. S100 protein family in human cancer. Am J Cancer Res. 2014;4(2):89-115.

[96] Hori O, Brett J, Slattery T, Cao R, Zhang J, Chen JX, et al. The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. J Biol Chem. 1995;270(43):25752-61.

[97] Huttunen HJ, Rauvala H. Amphoterin as an extracellular regulator of cell motility: from discovery to disease. J Intern Med. 2004;255(3):351-66.

[98] Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. Nat Rev Immunol. 2005;5(4):331-42.

[99] Enokido Y, Yoshitake A, Ito H, Okazawa H. Age-dependent change of HMGB1 and DNA double-strand break accumulation in mouse brain. Biochem Biophys Res Commun. 2008;376(1):128-33.

[100] Sousa MM, Yan SD, Stern D, Saraiva MJ. Interaction of the receptor for advanced glycation end products (RAGE) with transthyretin triggers nuclear transcription factor kB (NF-kB) activation. Lab Invest. 2000;80(7):1101-10.

[101] Sasaki N, Takeuchi M, Chowei H, Kikuchi S, Hayashi Y, Nakano N, et al. Advanced glycation end products (AGE) and their receptor (RAGE) in the brain of patients with Creutzfeldt-Jakob disease with prion plaques. Neurosci Lett. 2002;326(2):117-20.

[102] Natale G, Ferrucci M, Lazzeri G, Paparelli A, Fornai F. Transmission of prions within the gut and towards the central nervous system. Prion. 2011;5(3):142-9.

[103] Bullard DC, Hu X, Schoeb TR, Axtell RC, Raman C, Barnum SR. Critical requirement of CD11b (Mac-1) on T cells and accessory cells for development of experimental autoimmune encephalomyelitis. J Immunol. 2005;175(10):6327-33.

[104] Ruan BH, Li X, Winkler AR, Cunningham KM, Kuai J, Greco RM, et al. Complement C3a, CpG oligos, and DNA/C3a complex stimulate IFN-alpha production in a receptor for advanced glycation end product-dependent manner. J Immunol. 2010;185(7):4213-22.

[105] Ma W, Rai V, Hudson BI, Song F, Schmidt AM, Barile GR. RAGE binds C1q and enhances C1q-mediated phagocytosis. Cell Immunol. 2012;274(1-2):72-82.

[106] He M, Kubo H, Morimoto K, Fujino N, Suzuki T, Takahasi T, et al. Receptor for advanced glycation end products binds to phosphatidylserine and assists in the clearance of apoptotic cells. EMBO Rep. 2011;12(4):358-64.

[107] Fischer U, Schulze-Osthoff K. New approaches and therapeutics targeting apoptosis in disease. Pharmacol Rev. 2005;57(2):187-215.

[108] Mizumoto S, Sugahara K. Glycosaminoglycans are functional ligands for receptor for advanced glycation end-products in tumors. FEBS J. 2013;280(10):2462-70.

[109] Lindahl U, Kjellen L. Pathophysiology of heparan sulphate: many diseases, few drugs. J Intern Med. 2013;273(6):555-71.

[110] Sirois CM, Jin T, Miller AL, Bertheloot D, Nakamura H, Horvath GL, et al. RAGE is a nucleic acid receptor that promotes inflammatory responses to DNA. J Exp Med. 2013;210(11):2447-63.

[111] Heizmann CW, Fritz G, Schäfer BW. S100 proteins: structure, functions and pathology. Front Biosci. 2002;7:d1356-68.

[112] Donato R. Intracellular and extracellular roles of S100 proteins. Microsc Res Tech. 2003;60(6):540-51.

[113] Marenholz I, Lovering RC, Heizmann CW. An update of the S100 nomenclature. Biochim Biophys Acta. 2006;1763(11):1282-3.

[114] Heizmann CW, Ackermann GE, Galichet A. Pathologies involving the S100 proteins and RAGE. Subcell Biochem. 2007;45:93-138.

[115] Zimmer DB, Weber DJ. The Calcium-Dependent Interaction of S100B with Its Protein Targets. Cardiovasc Psychiatry Neurol. 2010;2010.

[116] Moroz OV, Wilson KS, Bronstein IB. The role of zinc in the S100 proteins: insights from the X-ray structures. Amino Acids 2010:in press.

[117] Fritz G, Heizmann CW. 3D Structures of the Calcium and Zinc Binding S100 Proteins. In: Sons JW, editor. Encyclopedia of Inorganic and Bioinorganic Chemistry: Wiley Online Library; 2011.

[118] Nelson MR, Thulin E, Fagan PA, Forsen S, Chazin WJ. The EF-hand domain: a globally cooperative structural unit. Protein Sci. 2002;11(2):198-205.

[119] Leclerc E, Heizmann CW. The importance of Ca2+/Zn2+signaling S100 proteins and RAGE in translational medicine. Frontiers in Biosciences. 2011;S3:1232-62.

[120] Santamaria-Kisiel L, Rintala-Dempsey AC, Shaw GS. Calcium-dependent and-independent interactions of the S100 protein family. Biochem J. 2006;396(2):201-14.

[121] Baudier J, Delphin C, Grunwald D, Khochbin S, Lawrence JJ. Characterization of the tumor suppressor protein p53 as a protein kinase C substrate and a S100b-binding protein. Proc Natl Acad Sci U S A. 1992;89(23):11627-31.

[122] Wilder PT, Lin J, Bair CL, Charpentier TH, Yang D, Liriano M, et al. Recognition of the tumor suppressor protein p53 and other protein targets by the calcium-binding protein S100B. Biochim Biophys Acta. 2006;1763(11):1284-97.

[123] Mueller A, Schäfer BW, Ferrari S, Weibel M, Makek M, Hochli M, et al. The calcium-binding protein S100A2 interacts with p53 and modulates its transcriptional activity. J Biol Chem. 2005;280(32):29186-93.

[124] Fernandez-Fernandez MR, Rutherford TJ, Fersht AR. Members of the S100 family bind p53 in two distinct ways. Protein Sci. 2008;17(10):1663-70.

[125] van Dieck J, Teufel DP, Jaulent AM, Fernandez-Fernandez MR, Rutherford TJ, Wyslouch-Cieszynska A, et al. Posttranslational modifications affect the interaction of S100 proteins with tumor suppressor p53. J Mol Biol. 2009;394(5):922-30.

[126] van Dieck J, Fernandez-Fernandez MR, Veprintsev DB, Fersht AR. Modulation of the oligomerization state of p53 by differential binding of proteins of the S100 family to p53 monomers and tetramers. J Biol Chem. 2009;284(20):13804-11.

[127] Hsieh HL, Schäfer BW, Weigle B, Heizmann CW. S100 protein translocation in response to extracellular S100 is mediated by receptor for advanced glycation endproducts in human endothelial cells. Biochem Biophys Res Commun. 2004;316(3):949-59.

[128] Perrone L, Peluso G, Melone MA. RAGE recycles at the plasma membrane in S100B secretory vesicles and promotes Schwann cells morphological changes. J Cell Physiol. 2008;217(1):60-71.

[129] Leclerc E, Fritz G, Vetter SW, Heizmann CW. Binding of S100 proteins to RAGE: an update. Biochim Biophys Acta. 2009;1793(6):993-1007.

[130] Eckert RL, Broome AM, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. Journal of Investigative Dermatology. 2004;123(1):23-33.

[131] Ito M, Kizawa K. Expression of calcium-binding S100 proteins A4 and A6 in regions of the epithelial sac associated with the onset of hair follicle regeneration. J Invest Dermatol. 2001;116(6):956-63.

[132] Boni R, Burg G, Doguoglu A, Ilg EC, Schafer BW, Muller B, et al. Immunohistochemical localization of the Ca2+binding S100 proteins in normal human skin and melanocytic lesions. Br J Dermatol. 1997;137(1):39-43.

[133] Ribe A, McNutt NS. S100A6 protein expression is different in Spitz nevi and melanomas. Mod Pathol. 2003;16(5):505-11.

[134] Zhang T, Woods TL, Elder JT. Differential responses of S100A2 to oxidative stress and increased intracellular calcium in normal, immortalized, and malignant human keratinocytes. J Invest Dermatol. 2002;119(5):1196-201.

[135] Deshpande R, Woods TL, Fu J, Zhang T, Stoll SW, Elder JT. Biochemical characterization of S100A2 in human keratinocytes: subcellular localization, dimerization, and oxidative cross-linking. J Invest Dermatol. 2000;115(3):477-85.

[136] Broome AM, Ryan D, Eckert RL. S100 protein subcellular localization during epidermal differentiation and psoriasis. Journal of Histochemistry & Cytochemistry. 2003;51(5):675-85.

[137] Robinson MJ, Tessier P, Poulsom R, Hogg N. The S100 family heterodimer, MRP-8/14, binds with high affinity to heparin and heparan sulfate glycosaminoglycans on endothelial cells. J Biol Chem. 2002;277(5):3658-65.

[138] Mirmohammadsadegh A, Tschakarjan E, Ljoljic A, Bohner K, Michel G, Ruzicka T, et al. Calgranulin C is overexpressed in lesional psoriasis. Journal of Investigative Dermatology. 2000;114(6):1207-8.

[139] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36): 6199-206.

[140] Ghanem G, Loir B, Morandini R, Sales F, Lienard D, Eggermont A, et al. On the release and half-life of S100B protein in the peripheral blood of melanoma patients. Int J Cancer. 2001;94(4):586-90.

[141] Harpio R, Einarsson R. S100 proteins as cancer biomarkers with focus on S100B in malignant melanoma. Clin Biochem. 2004;37(7):512-8.

[142] Lin J, Blake M, Tang C, Zimmer D, Rustandi RR, Weber DJ, et al. Inhibition of p53 transcriptional activity by the S100B calcium-binding protein. J Biol Chem. 2001;276(37):35037-41.

[143] Lin J, Yang Q, Wilder PT, Carrier F, Weber DJ. The calcium-binding protein S100B down-regulates p53 and apoptosis in malignant melanoma. J Biol Chem. 2010;285(35):27487-98.

[144] Lin J, Yang Q, Yan Z, Markowitz J, Wilder PT, Carrier F, et al. Inhibiting S100B restores p53 levels in primary malignant melanoma cancer cells. J Biol Chem. 2004;279(32):34071-7.

[145] Cavalier M, Wilder PT, Coop A, MacKerell A, Weber DJ, editors. Inhibitors of S100B (SBiXs) in malignant melanoma. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2013; Boston, MA: Mol Cancer Ther.

[146] Zimmer DB, Van Eldik LJ. Identification of a molecular target for the calcium-modulated protein S100. Fructose-1,6-bisphosphate aldolase. J Biol Chem. 1986;261(24): 11424-8.

[147] Hersey P, Watts RN, Zhang XD, Hackett J. Metabolic approaches to treatment of melanoma. Clin Cancer Res. 2009;15(21):6490-4.

[148] Xu RH, Pelicano H, Zhou Y, Carew JS, Feng L, Bhalla KN, et al. Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. Cancer Res. 2005;65(2):613-21.

[149] Donato R. Calcium-independent, pH-regulated effects of S-100 proteins on assembly-disassembly of brain microtubule protein in vitro. J Biol Chem. 1988;263(1):106-10.

[150] Ferguson PL, Shaw GS. Human S100B protein interacts with the Escherichia coli division protein FtsZ in a calcium-sensitive manner. J Biol Chem. 2004;279(18):18806-13.

[151] Skripnikova EV, Gusev NB. Interaction of smooth muscle caldesmon with S-100 protein. FEBS Lett. 1989;257(2):380-2.

[152] Mbele GO, Deloulme JC, Gentil BJ, Delphin C, Ferro M, Garin J, et al. The zinc-and calcium-binding S100B interacts and co-localizes with IQGAP1 during dynamic rearrangement of cell membranes. J Biol Chem. 2002;277(51):49998-50007.

[153] Koganehira Y, Takeoka M, Ehara T, Sasaki K, Murata H, Saida T, et al. Reduced expression of actin-binding proteins, h-caldesmon and calponin h1, in the vascular smooth muscle inside melanoma lesions: an adverse prognostic factor for malignant melanoma. Br J Dermatol. 2003;148(5):971-80.

[154] Wang Z, Chen J, Wang J, Ahn S, Li CM, Lu Y, et al. Novel tubulin polymerization inhibitors overcome multidrug resistance and reduce melanoma lung metastasis. Pharm Res. 2012;29(11):3040-52.

[155] Jameson KL, Mazur PK, Zehnder AM, Zhang J, Zarnegar B, Sage J, et al. IQGAP1 scaffold-kinase interaction blockade selectively targets RAS-MAP kinase-driven tumors. Nat Med. 2013;19(5):626-30.

[156] Bhattacharya S, Large E, Heizmann CW, Hemmings B, Chazin WJ. Structure of the Ca2+/S100B/NDR kinase peptide complex: insights into S100 target specificity and activation of the kinase. Biochemistry. 2003;42(49):14416-26.

[157] Bichsel SJ, Tamaskovic R, Stegert MR, Hemmings BA. Mechanism of activation of NDR (nuclear Dbf2-related) protein kinase by the hMOB1 protein. J Biol Chem. 2004;279(34):35228-35.

[158] Millward TA, Heizmann CW, Schafer BW, Hemmings BA. Calcium regulation of Ndr protein kinase mediated by S100 calcium-binding proteins. Embo J. 1998;17(20): 5913-22.

[159] Gentil BJ, Delphin C, Mbele GO, Deloulme JC, Ferro M, Garin J, et al. The giant protein AHNAK is a specific target for the calcium-and zinc-binding S100B protein: po-

tential implications for Ca2+homeostasis regulation by S100B. J Biol Chem. 2001;276(26):23253-61.

[160] Shtivelman E, Bishop JM. The human gene AHNAK encodes a large phosphoprotein located primarily in the nucleus. J Cell Biol. 1993;120(3):625-30.

[161] Fedida-Metula S, Elhyany S, Tsory S, Segal S, Hershfinkel M, Sekler I, et al. Targeting lipid rafts inhibits protein kinase B by disrupting calcium homeostasis and attenuates malignant properties of melanoma cells. Carcinogenesis. 2008;29(8):1546-54.

[162] Donato R, Sorci G, Riuzzi F, Arcuri C, Bianchi R, Brozzi F, et al. S100B's double life: intracellular regulator and extracellular signal. Biochim Biophys Acta. 2009;1793(6): 1008-22.

[163] Ostendorp T, Leclerc E, Galichet A, Koch M, Demling N, Weigle B, et al. Structural and functional insights into RAGE activation by multimeric S100B. Embo J. 2007;26(16):3868-78.

[164] Glenney JR, Jr., Kindy MS, Zokas L. Isolation of a new member of the S100 protein family: amino acid sequence, tissue, and subcellular distribution. J Cell Biol. 1989;108(2):569-78.

[165] Maelandsmo GM, Florenes VA, Mellingsaeter T, Hovig E, Kerbel RS, Fodstad O. Differential expression patterns of S100A2, S100A4 and S100A6 during progression of human malignant melanoma. Int J Cancer. 1997;74(4):464-9.

[166] Gupta S, Hussain T, MacLennan GT, Fu P, Patel J, Mukhtar H. Differential expression of S100A2 and S100A4 during progression of human prostate adenocarcinoma. J Clin Oncol. 2003;21(1):106-12.

[167] Suzuki F, Oridate N, Homma A, Nakamaru Y, Nagahashi T, Yagi K, et al. S100A2 expression as a predictive marker for late cervical metastasis in stage I and II invasive squamous cell carcinoma of the oral cavity. Oncol Rep. 2005;14(6):1493-8.

[168] Feng G, Xu X, Youssef EM, Lotan R. Diminished expression of S100A2, a putative tumor suppressor, at early stage of human lung carcinogenesis. Cancer Res. 2001;61(21):7999-8004.

[169] Lee SW, Tomasetto C, Swisshelm K, Keyomarsi K, Sager R. Down-regulation of a member of the S100 gene family in mammary carcinoma cells and reexpression by azadeoxycytidine treatment. Proc Natl Acad Sci U S A. 1992;89(6):2504-8.

[170] Imazawa M, Hibi K, Fujitake S, Kodera Y, Ito K, Akiyama S, et al. S100A2 overexpression is frequently observed in esophageal squamous cell carcinoma. Anticancer Res. 2005;25:1247-50.

[171] El-Rifai W, Moskaluk CA, Abdrabbo MK, Harper J, Yoshida C, Riggins GJ, et al. Gastric cancers overexpress S100A calcium-binding proteins. Cancer Res. 2002;62(23): 6823-6.

[172] Hough CD, Cho KR, Zonderman AB, Schwartz DR, Morin PJ. Coordinately up-regulated genes in ovarian cancer. Cancer Res. 2001;61(10):3869-76.

[173] Smith SL, Gugger M, Hoban P, Ratschiller D, Watson SG, Field JK, et al. S100A2 is strongly expressed in airway basal cells, preneoplastic bronchial lesions and primary non-small cell lung carcinomas. Br J Cancer. 2004;91(8):1515-24.

[174] Strazisar M, Mlakar V, Glavac D. The expression of COX-2, hTERT, MDM2, LATS2 and S100A2 in different types of non-small cell lung cancer (NSCLC). Cell Mol Biol Lett. 2009;14(3):442-56.

[175] Bulk E, Sargin B, Krug U, Hascher A, Jun Y, Knop M, et al. S100A2 induces metastasis in non-small cell lung cancer. Clin Cancer Res. 2009;15(1):22-9.

[176] Nonaka D, Chiriboga L, Rubin BP. Differential expression of S100 protein subtypes in malignant melanoma, and benign and malignant peripheral nerve sheath tumors. J Cutan Pathol. 2008;35(11):1014-9.

[177] Gollob JA, Sciambi CJ. Decitabine up-regulates S100A2 expression and synergizes with IFN-gamma to kill uveal melanoma cells. Clin Cancer Res. 2007;13(17):5219-25.

[178] Klopper JP, Sharma V, Bissonnette R, Haugen BR. Combination PPARgamma and RXR Agonist Treatment in Melanoma Cells: Functional Importance of S100A2. PPAR Res. 2010;2010:729876.

[179] Tan M, Heizmann CW, Guan K, Schafer BW, Sun Y. Transcriptional activation of the human S100A2 promoter by wild-type p53. FEBS Lett. 1999;445(2-3):265-8.

[180] Lapi E, Iovino A, Fontemaggi G, Soliera AR, Iacovelli S, Sacchi A, et al. S100A2 gene is a direct transcriptional target of p53 homologues during keratinocyte differentiation. Oncogene. 2006;25(26):3628-37.

[181] Kirschner RD, Sanger K, Muller GA, Engeland K. Transcriptional activation of the tumor suppressor and differentiation gene S100A2 by a novel p63-binding site. Nucleic Acids Res. 2008;36(9):2969-80.

[182] Buckley NE, D'Costa Z, Kaminska M, Mullan PB. S100A2 is a BRCA1/p63 coregulated tumour suppressor gene with roles in the regulation of mutant p53 stability. Cell death & disease. 2014;5:e1070.

[183] Harbour JW, Onken MD, Roberson ED, Duan S, Cao L, Worley LA, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010;330(6009):1410-3.

[184] Carbone M, Ferris LK, Baumann F, Napolitano A, Lum CA, Flores EG, et al. BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITs. J Transl Med. 2012;10:179.

[185] Njauw CN, Kim I, Piris A, Gabree M, Taylor M, Lane AM, et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. PLoS One. 2012;7(4):e35295.

[186] Ebralidze A, Tulchinsky E, Grigorian M, Afanasyeva A, Senin V, Revazova E, et al. Isolation and characterization of a gene specifically expressed in different metastatic cells and whose deduced gene product has a high degree of homology to a Ca^{2+}-binding protein family. Genes Dev. 1989;3(7):1086-93.

[187] Takenaga K, Nakamura Y, Endo H, Sakiyama S. Involvement of S100-related calcium-binding protein pEL98 (or mts1) in cell motility and tumor cell invasion. Japanese journal of cancer research : Gann. 1994;85(8):831-9.

[188] Jenkinson SR, Barraclough R, West CR, Rudland PS. S100A4 regulates cell motility and invasion in an in vitro model for breast cancer metastasis. Br J Cancer. 2004;90(1): 253-62.

[189] Grum-Schwensen B, Klingelhofer J, Berg CH, El-Naaman C, Grigorian M, Lukanidin E, et al. Suppression of tumor development and metastasis formation in mice lacking the S100A4(mts1) gene. Cancer Res. 2005;65(9):3772-80.

[190] Ambartsumian N, Grigorian M, Lukanidin E. Genetically modified mouse models to study the role of metastasis-promoting S100A4(mts1) protein in metastatic mammary cancer. J Dairy Res. 2005;72 Spec No:27-33.

[191] Andersen K, Nesland JM, Holm R, Florenes VA, Fodstad O, Maelandsmo GM. Expression of S100A4 combined with reduced E-cadherin expression predicts patient outcome in malignant melanoma. Mod Pathol. 2004;17(8):990-7.

[192] Boye K, Maelandsmo GM. S100A4 and metastasis: a small actor playing many roles. Am J Pathol. 2010;176(2):528-35.

[193] Fernandez-Fernandez MR, Veprintsev DB, Fersht AR. Proteins of the S100 family regulate the oligomerization of p53 tumor suppressor. Proc Natl Acad Sci U S A. 2005;102(13):4735-40.

[194] Berge G, Maelandsmo GM. Evaluation of potential interactions between the metastasis-associated protein S100A4 and the tumor suppressor protein p53. Amino Acids. 2010:in press.

[195] Orre LM, Panizza E, Kaminskyy VO, Vernet E, Graslund T, Zhivotovsky B, et al. S100A4 interacts with p53 in the nucleus and promotes p53 degradation. Oncogene. 2013;32(49):5531-40.

[196] Ford HL, Zain SB. Interaction of metastasis associated Mts1 protein with nonmuscle myosin. Oncogene. 1995;10(8):1597-605.

[197] Takenaga K, Nakamura Y, Sakiyama S, Hasegawa Y, Sato K, Endo H. Binding of pEL98 protein, an S100-related calcium-binding protein, to nonmuscle tropomyosin. J Cell Biol. 1994;124(5):757-68.

[198] Li ZH, Bresnick AR. The S100A4 metastasis factor regulates cellular motility via a direct interaction with myosin-IIA. Cancer Res. 2006;66(10):5173-80.

[199] Kriajevska M, Bronstein IB, Scott DJ, Tarabykina S, Fischer-Larsen M, Issinger O, et al. Metastasis-associated protein Mts1 (S100A4) inhibits CK2-mediated phosphorylation and self-assembly of the heavy chain of nonmuscle myosin. Biochim Biophys Acta. 2000;1498(2-3):252-63.

[200] Cabezon T, Celis JE, Skibshoj I, Klingelhofer J, Grigorian M, Gromov P, et al. Expression of S100A4 by a variety of cell types present in the tumor microenvironment of human breast cancer. Int J Cancer. 2007;121(7):1433-44.

[201] Kikuchi N, Horiuchi A, Osada R, Imai T, Wang C, Chen X, et al. Nuclear expression of S100A4 is associated with aggressive behavior of epithelial ovarian carcinoma: an important autocrine/paracrine factor in tumor progression. Cancer Sci. 2006;97(10): 1061-9.

[202] Pedersen KB, Andersen K, Fodstad O, Maelandsmo GM. Sensitization of interferon-gamma induced apoptosis in human osteosarcoma cells by extracellular S100A4. BMC Cancer. 2004;4:52.

[203] Schmidt-Hansen B, Klingelhofer J, Grum-Schwensen B, Christensen A, Andresen S, Kruse C, et al. Functional significance of metastasis-inducing S100A4(Mts1) in tumor-stroma interplay. J Biol Chem. 2004;279(23):24498-504.

[204] Gibbs FE, Barraclough R, Platt-Higgins A, Rudland PS, Wilkinson MC, Parry EW. Immunocytochemical distribution of the calcium-binding protein p9Ka in normal rat tissues: variation in the cellular location in different tissues. J Histochem Cytochem. 1995;43(2):169-80.

[205] Ambartsumian N, Klingelhofer J, Grigorian M, Christensen C, Kriajevska M, Tulchinsky E, et al. The metastasis-associated Mts1(S100A4) protein could act as an angiogenic factor. Oncogene. 2001;20(34):4685-95.

[206] Ochiya T, Takenaga K, Endo H. Silencing of S100A4, a metastasis-associated protein, in endothelial cells inhibits tumor angiogenesis and growth. Angiogenesis. 2014;17(1):17-26.

[207] Schmidt-Hansen B, Ornas D, Grigorian M, Klingelhofer J, Tulchinsky E, Lukanidin E, et al. Extracellular S100A4(mts1) stimulates invasive growth of mouse endothelial cells and modulates MMP-13 matrix metalloproteinase activity. Oncogene. 2004;23(32):5487-95.

[208] Semov A, Moreno MJ, Onichtchenko A, Abulrob A, Ball M, Ekiel I, et al. Metastasis-associated protein S100A4 induces angiogenesis through interaction with Annexin II and accelerated plasmin formation. J Biol Chem. 2005;280(21):20833-41.

[209] Kiryushko D, Novitskaya V, Soroka V, Klingelhofer J, Lukanidin E, Berezin V, et al. Molecular mechanisms of Ca^{2+}signaling in neurons induced by the S100A4 protein. Mol Cell Biol. 2006;26(9):3625-38.

[210] Spiekerkoetter E, Guignabert C, de Jesus Perez V, Alastalo TP, Powers JM, Wang L, et al. S100A4 and bone morphogenetic protein-2 codependently induce vascular

smooth muscle cell migration via phospho-extracellular signal-regulated kinase and chloride intracellular channel 4. Circ Res. 2009;105(7):639-47, 13 p following 47.

[211] Dahlmann M, Okhrimenko A, Marcinkowski P, Osterland M, Herrmann P, Smith J, et al. RAGE mediates S100A4-induced cell motility via MAPK/ERK and hypoxia signaling and is a prognostic biomarker for human colorectal cancer metastasis. Oncotarget. 2014;5(10):3220-33.

[212] Siddique HR, Adhami VM, Parray A, Johnson JJ, Siddiqui IA, Shekhani MT, et al. The S100A4 Oncoprotein Promotes Prostate Tumorigenesis in a Transgenic Mouse Model: Regulating NFkappaB through the RAGE Receptor. Genes & cancer. 2013;4(5-6):224-34.

[213] Haase-Kohn C, Wolf S, Herwig N, Mosch B, Pietzsch J. Metastatic potential of B16-F10 melanoma cells is enhanced by extracellular S100A4 derived from RAW264.7 macrophages. Biochem Biophys Res Commun. 2014;446(1):143-8.

[214] Weterman MA, van Muijen GN, Bloemers HP, Ruiter DJ. Expression of calcyclin in human melanocytic lesions. Cancer Res. 1993;53(24):6061-6.

[215] Kuznicki J, Kordowska J, Puzianowska M, Wozniewicz BM. Calcyclin as a marker of human epithelial cells and fibroblasts. Exp Cell Res. 1992;200(2):425-30.

[216] Kuznicki J, Filipek A, Heimann P, Kaczmarek L, Kaminska B. Tissue specific distribution of calcyclin--10.5 kDa Ca2+-binding protein. FEBS Lett. 1989;254(1-2):141-4.

[217] Lesniak W, Slomnicki LP, Filipek A. S100A6-new facts and features. Biochem Biophys Res Commun. 2009;390(4):1087-92.

[218] Komatsu K, Andoh A, Ishiguro S, Suzuki N, Hunai H, Kobune-Fujiwara Y, et al. Increased expression of S100A6 (Calcyclin), a calcium-binding protein of the S100 family, in human colorectal adenocarcinomas. Clin Cancer Res. 2000;6(1):172-7.

[219] Nedjadi T, Kitteringham N, Campbell F, Jenkins RE, Park BK, Navarro P, et al. S100A6 binds to annexin 2 in pancreatic cancer cells and promotes pancreatic cancer cell motility. Br J Cancer. 2009;101(7):1145-54.

[220] De Petris L, Orre LM, Kanter L, Pernemalm M, Koyi H, Lewensohn R, et al. Tumor expression of S100A6 correlates with survival of patients with stage I non-small-cell lung cancer. Lung Cancer. 2009;63:410-7.

[221] Ohuchida K, Mizumoto K, Yu J, Yamaguchi H, Konomi H, Nagai E, et al. S100A6 is increased in a stepwise manner during pancreatic carcinogenesis: clinical value of expression analysis in 98 pancreatic juice samples. Cancer Epidemiol Biomarkers Prev. 2007;16(4):649-54.

[222] Yang YQ, Zhang LJ, Dong H, Jiang CL, Zhu ZG, Wu JX, et al. Upregulated expression of S100A6 in human gastric cancer. J Dig Dis. 2007;8(4):186-93.

[223] Vimalachandran D, Greenhalf W, Thompson C, Luttges J, Prime W, Campbell F, et al. High nuclear S100A6 (Calcyclin) is significantly associated with poor survival in pancreatic cancer patients. Cancer Res. 2005;65(8):3218-25.

[224] Li Z, Tang M, Ling B, Liu S, Zheng Y, Nie C, et al. Increased expression of S100A6 promotes cell proliferation and migration in human hepatocellular carcinoma. Journal of molecular medicine. 2014;92(3):291-303.

[225] Weterman MA, Stoopen GM, van Muijen GN, Kuznicki J, Ruiter DJ, Bloemers HP. Expression of calcyclin in human melanoma cell lines correlates with metastatic behavior in nude mice. Cancer Res. 1992;52(5):1291-6.

[226] Fullen DR, Garrisi AJ, Sanders D, Thomas D. Expression of S100A6 protein in a broad spectrum of cutaneous tumors using tissue microarrays. J Cutan Pathol. 2008;35 Suppl 2:28-34.

[227] Puri PK, Elston CA, Tyler WB, Ferringer TC, Elston DM. The staining pattern of pigmented spindle cell nevi with S100A6 protein. J Cutan Pathol. 2011;38(1):14-7.

[228] Slomnicki LP, Nawrot B, Lesniak W. S100A6 binds p53 and affects its activity. Int J Biochem Cell Biol. 2009;41(4):784-90.

[229] Streicher WW, Lopez MM, Makhatadze GI. Annexin I and annexin II N-terminal peptides binding to S100 protein family members: specificity and thermodynamic characterization. Biochemistry. 2009;48(12):2788-98.

[230] Mohan SK, Gupta AA, Yu C. Interaction of the S100A6 mutant (C3S) with the V domain of the receptor for advanced glycation end products (RAGE). Biochem Biophys Res Commun. 2013;434(2):328-33.

[231] Roth J, Vogl T, Sorg C, Sunderkotter C. Phagocyte-specific S100 proteins: a novel group of proinflammatory molecules. Trends Immunol. 2003;24(4):155-8.

[232] Yin C, Li H, Zhang B, Liu Y, Lu G, Lu S, et al. RAGE-binding S100A8/A9 promotes the migration and invasion of human breast cancer cells through actin polymerization and epithelial-mesenchymal transition. Breast Cancer Res Treat. 2013;142(2): 297-309.

[233] Grebhardt S, Muller-Decker K, Bestvater F, Hershfinkel M, Mayer D. Impact of S100A8/A9 expression on prostate cancer progression in vitro and in vivo. J Cell Physiol. 2014;229(5):661-71.

[234] Khammanivong A, Wang C, Sorenson BS, Ross KF, Herzberg MC. S100A8/A9 (calprotectin) negatively regulates G2/M cell cycle progression and growth of squamous cell carcinoma. PLoS One. 2013;8(7):e69395.

[235] Kwon CH, Moon HJ, Park HJ, Choi JH, Park do Y. S100A8 and S100A9 promotes invasion and migration through p38 mitogen-activated protein kinase-dependent NF-kappaB activation in gastric cancer cells. Mol Cells. 2013;35(3):226-34.

[236] Ehrchen JM, Sunderkotter C, Foell D, Vogl T, Roth J. The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. J Leukoc Biol. 2009;86(3):557-66.

[237] Ghavami S, Chitayat S, Hashemi M, Eshraghi M, Chazin WJ, Halayko AJ, et al. S100A8/A9: a Janus-faced molecule in cancer therapy and tumorgenesis. Eur J Pharmacol. 2009;625(1-3):73-83.

[238] Ang CW, Nedjadi T, Sheikh AA, Tweedle EM, Tonack S, Honap S, et al. Smad4 loss is associated with fewer S100A8-positive monocytes in colorectal tumors and attenuated response to S100A8 in colorectal and pancreatic cancer cells. Carcinogenesis. 2010;31(9):1541-51.

[239] Sinha P, Okoro C, Foell D, Freeze HH, Ostrand-Rosenberg S, Srikrishna G. Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. J Immunol. 2008;181(7):4666-75.

[240] Srikrishna G. S100A8 and S100A9: new insights into their roles in malignancy. Journal of innate immunity. 2012;4(1):31-40.

[241] Wang L, Chang EW, Wong SC, Ong SM, Chong DQ, Ling KL. Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage and plasma S100A8/A9 proinflammatory proteins. J Immunol. 2013;190(2):794-804.

[242] Basso D, Fogar P, Plebani M. The S100A8/A9 complex reduces CTLA4 expression by immature myeloid cells: Implications for pancreatic cancer-driven immunosuppression. Oncoimmunology. 2013;2(6):e24441.

[243] Burke M, Choksawangkarn W, Edwards N, Ostrand-Rosenberg S, Fenselau C. Exosomes from myeloid-derived suppressor cells carry biologically active proteins. J Proteome Res. 2014;13(2):836-43.

[244] Petersson S, Shubbar E, Enerback L, Enerback C. Expression patterns of S100 proteins in melanocytes and melanocytic lesions. Melanoma Res. 2009;19(4):215-25.

[245] Hibino T, Sakaguchi M, Miyamoto S, Yamamoto M, Motoyama A, Hosoi J, et al. S100A9 is a novel ligand of EMMPRIN that promotes melanoma metastasis. Cancer Res. 2013;73(1):172-83.

[246] Meyer C, Sevko A, Ramacher M, Bazhin AV, Falk CS, Osen W, et al. Chronic inflammation promotes myeloid-derived suppressor cell activation blocking antitumor immunity in transgenic mouse melanoma model. Proc Natl Acad Sci U S A. 2011;108(41):17111-6.

[247] Vogl T, Tenbrock K, Ludwig S, Leukert N, Ehrhardt C, van Zoelen MA, et al. MRP8 and MRP14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. Nat Med. 2007;13(9):1042-9.

[248] Ghavami S, Rashedi I, Dattilo BM, Eshraghi M, Chazin WJ, Hashemi M, et al. S100A8/A9 at low concentration promotes tumor cell growth via RAGE ligation and MAP kinase-dependent pathway. J Leukoc Biol. 2008;83(6):1484-92.

[249] Turovskaya O, Foell D, Sinha P, Vogl T, Newlin R, Nayak J, et al. RAGE, carboxylated glycans and S100A8/A9 play essential roles in colitis-associated carcinogenesis. Carcinogenesis. 2008;29:2035-43.

[250] Srikrishna G, Panneerselvam K, Westphal V, Abraham V, Varki A, Freeze HH. Two proteins modulating transendothelial migration of leukocytes recognize novel carboxylated glycans on endothelial cells. J Immunol. 2001;166(7):4678-88.

[251] Srikrishna G, Nayak J, Weigle B, Temme A, Foell D, Hazelwood L, et al. Carboxylated N-glycans on RAGE promote S100A12 binding and signaling. J Cell Biochem. 2010;110(3):645-59.

[252] Hagens G, Masouye I, Augsburger E, Hotz R, Saurat JH, Siegenthaler G. Calcium-binding protein S100A7 and epidermal-type fatty acid-binding protein are associated in the cytosol of human keratinocytes. Biochemical Journal. 1999;339:419-27.

[253] Semprini S, Capon F, Tacconelli A, Giardina E, Orecchia A, Mingarelli R, et al. Evidence for differential S100 gene over-expression in psoriatic patients from genetically heterogeneous pedigrees. Hum Genet. 2002;111(4-5):310-3.

[254] Brouard MC, Saurat JH, Ghanem G, Siegenthaler G. Urinary excretion of epidermal-type fatty acid-binding protein and S100A7 protein in patients with cutaneous melanoma. Melanoma Res. 2002;12(6):627-31.

[255] He H, Li J, Weng S, Li M, Yu Y. S100A11: diverse function and pathology corresponding to different target proteins. Cell Biochem Biophys. 2009;55(3):117-26.

[256] Van Ginkel PR, Gee RL, Walker TM, Hu DN, Heizmann CW, Polans AS. The identification and differential expression of calcium-binding proteins associated with ocular melanoma. Biochim Biophys Acta. 1998;1448(2):290-7.

[257] Reddy S, Bichler J, Wells-Knecht KJ, Thorpe SR, Baynes JW. N epsilon-(carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins. Biochemistry. 1995;34(34):10872-8.

[258] Thornalley PJ. Advances in glyoxalase research. Glyoxalase expression in malignancy, anti-proliferative effects of methylglyoxal, glyoxalase I inhibitor diesters and S-D-lactoylglutathione, and methylglyoxal-modified protein binding and endocytosis by the advanced glycation endproduct receptor. Crit Rev Oncol Hematol. 1995;20(1-2): 99-128.

[259] Wondrak GT, Jacobson MK, Jacobson EL. Antimelanoma activity of apoptogenic carbonyl scavengers. J Pharmacol Exp Ther. 2006;316(2):805-14.

[260] Sander CS, Hamm F, Elsner P, Thiele JJ. Oxidative stress in malignant melanoma and non-melanoma skin cancer. Br J Dermatol. 2003;148(5):913-22.

[261] Indurthi VS, Leclerc E, Vetter SW. Interaction between glycated serum albumin and AGE-receptors depends on structural changes and the glycation reagent. Arch Biochem Biophys. 2012;528(2):185-96.

[262] Bianchi ME, Beltrame M, Paonessa G. Specific recognition of cruciform DNA by nuclear protein HMG1. Science. 1989;243(4894 Pt 1):1056-9.

[263] Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science. 1999;285(5425):248-51.

[264] Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature. 2002;418(6894):191-5.

[265] Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H, et al. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol. 2007;8(5):487-96.

[266] Dong Xda E, Ito N, Lotze MT, Demarco RA, Popovic P, Shand SH, et al. High mobility group box I (HMGB1) release from tumor cells after treatment: implications for development of targeted chemoimmunotherapy. J Immunother. 2007;30(6):596-606.

[267] Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol. 2007;81(1):1-5.

[268] Tang D, Kang R, Zeh HJ, 3rd, Lotze MT. High-mobility group box 1 and cancer. Biochim Biophys Acta. 2010;1799(1-2):131-40.

[269] Ito N, DeMarco RA, Mailliard RB, Han J, Rabinowich H, Kalinski P, et al. Cytolytic cells induce HMGB1 release from melanoma cell lines. J Leukoc Biol. 2007;81(1): 75-83.

[270] Johnson KE, Wulff BC, Oberyszyn TM, Wilgus TA. Ultraviolet light exposure stimulates HMGB1 release by keratinocytes. Archives of dermatological research. 2013;305(9):805-15.

[271] Bald T, Quast T, Landsberg J, Rogava M, Glodde N, Lopez-Ramos D, et al. Ultraviolet-radiation-induced inflammation promotes angiotropism and metastasis in melanoma. Nature. 2014;507(7490):109-13.

[272] Tang Q, Li J, Zhu H, Li P, Zou Z, Xiao Y. Hmgb1-IL-23-IL-17-IL-6-Stat3 axis promotes tumor growth in murine models of melanoma. Mediators of inflammation. 2013;2013:713859.

[273] Li Q, Li J, Wen T, Zeng W, Peng C, Yan S, et al. Overexpression of HMGB1 in melanoma predicts patient survival and suppression of HMGB1 induces cell cycle arrest and senescence in association with p21 (Waf1/Cip1) up-regulation via a p53-independent, Sp1-dependent pathway. Oncotarget. 2014;5(15):6387-403.

[274] O'Connell MP, Weeraratna AT. A spoonful of sugar makes the melanoma go: the role of heparan sulfate proteoglycans in melanoma metastasis. Pigment Cell Melanoma Res. 2011;24(6):1133-47.

[275] Nikitovic D, Mytilinaiou M, Berdiaki A, Karamanos NK, Tzanakakis GN. Heparan sulfate proteoglycans and heparin regulate melanoma cell functions. Biochim Biophys Acta. 2014;1840(8):2471-81.

[276] Newton RA, Hogg N. The human S100 protein MRP-14 is a novel activator of the beta 2 integrin Mac-1 on neutrophils. J Immunol. 1998;160(3):1427-35.

[277] Carlos TM. Leukocyte recruitment at sites of tumor: dissonant orchestration. J Leukoc Biol. 2001;70(2):171-84.

[278] Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162-74.

[279] Mahnke K, Skorokhod A, Grabbe S, Enk AH. Opening a niche for therapy: local lymphodepletion helps the immune system to fight melanoma. J Invest Dermatol. 2014;134(7):1794-6.

[280] Najjar YG, Finke JH. Clinical perspectives on targeting of myeloid derived suppressor cells in the treatment of cancer. Frontiers in oncology. 2013;3:49.

[281] Riedl S, Rinner B, Asslaber M, Schaider H, Walzer S, Novak A, et al. In search of a novel target-phosphatidylserine exposed by non-apoptotic tumor cells and metastases of malignancies with poor treatment efficacy. Biochim Biophys Acta. 2011;1808(11):2638-45.

[282] Bro S, Flyvbjerg A, Binder CJ, Bang CA, Denner L, Olgaard K, et al. A neutralizing antibody against receptor for advanced glycation end products (RAGE) reduces atherosclerosis in uremic mice. Atherosclerosis. 2008;201(2):274-80.

[283] Taguchi A, Blood DC, del Toro G, Canet A, Lee DC, Qu W, et al. Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases. Nature. 2000;405(6784):354-60.

[284] Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, et al. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med. 2005;83(11):876-86.

[285] Hudson BI, Bucciarelli LG, Wendt T, Sakaguchi T, Lalla E, Qu W, et al. Blockade of receptor for advanced glycation endproducts: a new target for therapeutic intervention in diabetic complications and inflammatory disorders. Arch Biochem Biophys. 2003;419(1):80-8.

[286] Oldfield MD, Bach LA, Forbes JM, Nikolic-Paterson D, McRobert A, Thallas V, et al. Advanced glycation end products cause epithelial-myofibroblast transdifferentiation

via the receptor for advanced glycation end products (RAGE). J Clin Invest. 2001;108(12):1853-63.

[287] Deane R, Singh I, Sagare AP, Bell RD, Ross NT, LaRue B, et al. A multimodal RAGE-specific inhibitor reduces amyloid beta-mediated brain disorder in a mouse model of Alzheimer disease. J Clin Invest. 2012;122(4):1377-92.

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