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The Roles of S100 Proteins and RAGE in Melanoma

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1. Introduction

The incidence of melanoma continues to rise worldwide and increases annually by 4% to 6% in the United States (Darrell and Rigel 2010). Once metastatic, invasive melanoma offers poor prognosis to patients (Bhatia, Tykodi and Thompson, 2009). The classic prognostic factors in melanoma include primary tumor thickness, patient gender, primary melanoma ulceration, mitotic activity and the presence of tumor infiltrating lymphocytes (Spatz et al. 2010). Besides these established prognostic markers, the S100 protein family member S100B has emerged in recent years as a new prognostic marker and is now incorporated into the American Joint Committee on Cancer (AJCC) melanoma staging system for stage IV melanoma patients (Balch et al. 2009; Chun et al. 2008; Gogas et al. 2009). High S100B serum concentration correlates with poor survival rate (Hauschild et al. 1999). Current studies are also analyzing the prognostic value of S100B in earlier melanoma stages (IIB-III) (Bouwhuis et al. 2010).

The role of S100B in the progression of melanoma is not clearly understood. For instance, although it is established that S100B is released from melanoma tumor cells, its role in tumor development, invasion and metastasis is currently under investigation. This chapter will discuss the role of S100B and other members of the S100 protein family in the biology of melanoma. We will focus on the relation between the S100 proteins and their common receptor, the receptor for advanced glycation endproducts (RAGE), in the context of melanoma.

2. Generalities about RAGE

RAGE is a multiligand receptor of the immunoglobulin superfamily and is involved in a large number of pathologies such as complications of diabetes, cardiovascular diseases, Alzheimer's disease, and cancer (Schmidt et al. 2000; Deane et al. 2003; Lue et al. 2009; Fang et al. 2010; Yan, Bierhaus et al. 2009; Bierhaus and Nawroth 2009; Sparvero et al. 2009).

RAGE is often described as a pattern recognition receptor and it is activated by structurally unrelated ligands. RAGE ligands include the advanced glycation endproducts (AGE) (Schmidt et al. 1992), the high mobility group box 1 protein (HMGB1 = amphoterin), amyloid forming peptides and proteins (amyloid β -peptide) and members of the S100 protein family (Heizmann, Ackermann, and Galichet 2007; Leclerc et al. 2009; Schmidt et al. 2000).

AGEs are the result of non-enzymatic modification of proteins or lipids by reducing carbohydrates and are therefore very heterogeneous in nature (reviewed in (Ahmed et al. 2005)). Due to poorly regulation of glucose concentration, AGEs are found elevated in patients suffering for diabetes but are also present at high concentration at sites of active inflammation (Yan et al. 2003). In addition, elevated concentration of AGEs have been found in melanoma tissue samples (Sander et al. 2003; Wondrak, Jacobson, and Jacobson 2006; Abe et al. 2004). Other ligands of RAGE include amyloid forming proteins or peptides such as A β peptide, responsible for Alzheimer's disease (Yan et al. 1996; Sturchler et al. 2008) or transthyretin, responsible for familial amyloid polyneuropathy or cardiomyopathy (Sousa et al. 2000).

The DNA binding protein HMGB1 is another RAGE ligand that plays important functions in neuronal development, inflammation, and cancer (Hori et al. 1995)(reviewed in (Sims et al. 2010; Rauvala and Rouhiainen 2010)). Interestingly, HMGB1 was shown to be secreted from melanoma cells following treatment with cytolytic lymphoid cells (Ito et al. 2007). Secreted HMGB1 could contribute to enhanced RAGE signaling in the tumor environment.

The S100 proteins constitute a large group of RAGE ligands with more than 20 members. S100 proteins are small calcium binding proteins that play diverse intra- and extracellular functions. These functions will be described in more details in the next chapter. S100A12 was the first member of the family to be identified as a RAGE ligand (Hofmann et al. 1999). Many other members of the family have since been identified as ligand (Donato 2007; Leclerc et al. 2009).

The physiological function of RAGE is not yet fully understood. Among human tissues, RAGE is expressed at the highest level in the lung where it is believed to exert a protective effect (Brett et al. 1993; Queisser et al. 2008; Ramsgaard et al. 2010; Buckley and Ehrhardt 2010). RAGE has also been suggested to have a beneficial function in peripheral nerve regeneration (Rong, Trojaborg et al. 2004; Rong, Yan et al. 2004), and in auditory stimuli in mice (Sakatani et al. 2009).

RAGE is expressed in different isoforms. The main two isoforms are the membrane bound and the soluble forms. The membrane bound full-length form of RAGE, is composed of an extracellular part (314 amino-acids), followed by a single transmembrane spanning helix (27 aa) and a short cytosolic domain (41 aa) (Figure 1) (Neeper et al. 1992). The extracellular part itself is composed of three Ig-like domains: a variable and two constant C1 and C2 domains. The structures of the V and VC1 domains of RAGE have been solved recently and showed similarities with other immunoglobulins (Matsumoto et al. 2008; Koch et al. 2010). RAGE is glycosylated *in vivo* and RAGE glycosylation has been shown to modulate the interaction of RAGE with AGEs, amphoterin and several S100 proteins (S100A8/A9, S100A12) (Neeper et al. 1992; Wilton et al. 2006; Osawa et al. 2007; Srikrishna et al. 2010).

The second important isoform of RAGE is soluble RAGE (sRAGE). sRAGE can be generated from splicing (RAGE_v1) or shedding by ADAM10 (Ohe et al. 2010; Hudson et al. 2008; Galichet, Weibel, and Heizmann 2008; Raucci et al. 2008; Zhang et al. 2008; Ding and Keller 2005; Yonekura et al. 2003). sRAGE is composed only of the extracellular part of receptor and is released in the extracellular space. sRAGE was suggested to play the role of decoy and to prevent RAGE activation by its ligands (Santilli et al. 2009). However, this role has been questioned due to the low concentration of sRAGE present in serum (Bierhaus and Nawroth 2009). Indeed, this concentration varies between 10pM and 50pM in normal conditions and might not be sufficient to counteract the effect of circulating RAGE ligands whose affinity towards RAGE are in the nanomolar range (Tesarova et al. 2007; Nakamura et al. 2008; Bierhaus and Nawroth 2009; Kislinger et al. 1999; Dattilo et al. 2007).

Fig. 1. RAGE and its ligands. RAGE is activated by structurally unrelated ligands. These ligands include the advanced glycation endproducts (AGE), amyloid β peptides, high mobility group box 1 protein and members of the S100 protein family. Recent evidences suggest that RAGE dimerize on the cell surface. Engagement of RAGE by its ligands triggers the formation of reactive oxygen species (ROS), the activation of members of the MAP kinase family (MAPK) and often leads to activation of NF- κ B. Since RAGE expression is under the control of NF- κ B, initial activation of RAGE leads to up-regulation of RAGE expression and sustained RAGE activation and inflammation. RAGE activation can also result in cell proliferation or cell death depending of the ligand and cell type. Soluble RAGE or sRAGE can also be generated by splicing or proteolytic shedding. sRAGE can counteract the activation of RAGE by its circulating ligands and serves as a decoy receptor

sRAGE has also been suggested to be a biomarker in certain pathologies such as Alzheimer's disease and diabetes (Emanuele et al. 2005; Nozaki et al. 2007; Nakamura et al. 2008; Yan, Ramasamy, and Schmidt 2010). However, many studies are contradictory and show either positive or negative correlation between the concentration of sRAGE and the stage of the disease (Bierhaus and Nawroth 2009; Humpert et al. 2007; Koyama, Yamamoto,

and Nishizawa 2007). We recently evaluated the change of transcript levels of the spliced form of RAGE (RAGE_v1) in 40 melanoma stage III and stage IV tissue samples. We showed that 90 % of those samples showed a significant reduction in the transcript level of RAGE_v1 (Leclerc, Heizmann, and Vetter 2009). However, further studies are necessary to demonstrate that the protein level of RAGE_v1 can be associated with distinct stages of melanoma.

The activation of RAGE by its ligands triggers the activation of multiple signaling pathways resulting in the production of reactive oxygen species, the activation of the extracellular signal regulated kinase (ERK1/2) and NF- κ B, leading to the initiation of inflammation (Bierhaus et al. 2005; Yan, Du Yan et al. 2009; Coughlan et al. 2009). Since the transcription of RAGE is under the control of NF- κ B itself and of other pro-inflammatory transcription factors such as SP-1, AP-2 and NF-IL6, RAGE activation by its ligands also result in sustained inflammation through a positive feedback loop (Schmidt et al. 2001; Bierhaus and Nawroth 2009). Other signaling pathways have been described and include RAC-1, NADPH-oxidase, p38, PI3K, JNK or JAK/STAT (Leclerc et al. 2007; Lin, Park, and Lakatta 2009; Bierhaus and Nawroth 2009; Donato 2007).

3. Generalities about S100 proteins

S100 proteins are small EF-hand calcium binding proteins that show tissue and cell specific expression (Donato 2003; Heizmann 2002). The cell expression specificity of some of the S100s has been suggested to be regulated by DNA methylation (reviewed in (Lesniak 2011)). 21 members have been described so far. Many of the genes coding for the S100 proteins identified as S100A1 to S100A16, are clustered onto one region of chromosome 1 (1q21), which is often prone to deletion and rearrangements, linking S100 proteins to cancer (Marenholz, Lovering, and Heizmann 2006). Binding of calcium to the S100 proteins occurs in the EF-hands (Fritz and Heizmann 2004). Most S100 proteins form dimers. Each S100 monomer contains two EF-hands: the C terminal EF-hand is present in all S100 proteins and is described as canonical. The N-terminal EF-hand is specific for each S100 protein. Binding of calcium to the C-terminal EF-hand is in average 100 times stronger than binding to the N-terminal site. Although most S100 proteins contain two functional EF-hands, some S100 protein present only one functional EF-hand (example). S100 proteins display a large range of calcium binding affinity ($K_D = 20\text{-}500\ \mu\text{M}$) (Heizmann, Ackermann, and Galichet 2007; Zimmer and Weber 2010). Certain S100 proteins possess additional metal binding sites for zinc and copper (Moroz, Wilson, and Bronstein 2010).

S100 proteins form a family of proteins with high similarities in amino-acid sequence and tri-dimensional structure (Fritz and Heizmann 2004; Heizmann, Fritz, and Schäfer 2002). For this reason, S100 proteins can share the same target proteins. For instance, fructose-1,6-biphosphate aldolase can be activated by both S100B and S100A1 (Zimmer and Van Eldik 1986). However, the slight differences in sequence and structure also explain that two S100 proteins can modulate the activity of the same target protein with different or opposite results. Indeed, whereas S100A1 activates phosphoglucomutase, S100B inhibits this enzyme (Landar et al. 1996). Similarly many members of the S100 protein family that include S100B, S100A1, S100A2, S100A4, S100A6 and S100A10 have been shown to interact in different manners to the tumor suppressor p53 protein (Baudier et al. 1992; Wilder et al. 2006; Mueller et al. 2005; Fernandez-Fernandez, Rutherford, and Fersht 2008; van Dieck, Teufel et al. 2009; van Dieck, Fernandez-Fernandez et al. 2009).

S100 proteins can exert both intra- and extracellular functions through the activation of their target proteins (Heizmann, Fritz, and Schäfer 2002; Donato 2003; Santamaria-Kisiel, Rintala-Dempsey, and Shaw 2006). Most of the S100 proteins exert their functions principally as dimers, but higher orders of oligomerisation have been observed. For example, functional tetramers of S100B and S100A8/A9, hexamers of S100A12 and oligomers of S100A4 have been described (Ostendorp et al. 2007; Vogl et al. 2006; Moroz et al. 2002; Kiryushko et al. 2006).

S100 proteins are found in many cell types constituting the epidermis (Eckert et al. 2004). S100B and S100A6 have been described in both melanocytes and Langerhan’s cells (Ito and Kizawa 2001; Boni, Burg et al. 1997; Ribe and McNutt 2003). S100A2, A7, A10, A11, A12 and S100A15 have been identified in basal keratinocytes (Ribe and McNutt 2003; Ito and Kizawa 2001; Boni, Burg et al. 1997; Zhang, Woods, and Elder 2002; Deshpande et al. 2000; Broome, Ryan, and Eckert 2003; Robinson et al. 2002; Mirmohammadsadegh et al. 2000). The role of these S100 proteins in normal skin is not fully understood. However, up-regulation of many S100 proteins has been described in inflamed keratinocytes and in melanoma (Broome, Ryan, and Eckert 2003; Eckert et al. 2004).

In this chapter we will discuss about the role of certain members of the S100 protein family that have been found to play a role in melanoma. These S100 proteins include S100B, S100A2, A4, A6 and S100A11 (Table 1).

S100 name	Expression	References
S100B	Melanoma	(Boni, Heizmann et al. 1997) (Harpio and Einarsson 2004) (Donato 2009) (Lin et al. 2010) (Hsieh et al. 2003) (Leclerc, Heizmann, and Vetter 2009)
S100A2	Keratinocytes Melanoma	(Ribe and McNutt 2003) (Boni, Burg et al. 1997) (Shrestha et al. 1998) (Leclerc, Heizmann, and Vetter 2009)
S100A4	Melanoma	(Hsieh et al. 2003) (Maelandsmo et al. 1997) (Andersen et al. 2004) (Leclerc, Heizmann, and Vetter 2009)
S100A6	Melanoma Keratinocytes Langerhans’ cells	(Ribe and McNutt 2003) (Maelandsmo et al. 1997) (Weterman et al. 1992) (Boni, Heizmann et al. 1997) (Hsieh et al. 2003) (Leclerc, Heizmann, and Vetter 2009)
S100A11	Keratinocytes Uveal melanoma	(Sakaguchi et al. 2008) (Van Ginkel et al. 1998)

Table 1. S100 proteins involved in melanoma

4. S100 proteins in melanoma

4.1 S100B

S100B is predominantly expressed in the brain (Moore 1965). It is mainly secreted by astrocytes and triggers neurotrophic or neurotoxic effects dependent of its concentration (reviewed in (Donato 2009)). S100B is also secreted by melanoma cells and is a biomarker for stage IV malignant melanoma: a high concentration of serum S100B correlates with poor prognosis (Balch et al. 2009; Ghanem et al. 2001; Harpio and Einarsson 2004). S100B binds two calcium ions with micromolar affinity (2-20 μM) (Baudier and Gerard 1986). Binding to calcium triggers large conformational changes in the C-terminal EF-hand leading to interaction with target proteins (Heizmann, Fritz, and Schäfer 2002). S100B also binds zinc and copper ions. It is important to note that binding of zinc to S100B is tighter ($K_D = 0.1\text{-}1 \mu\text{M}$) than binding of calcium. Binding of zinc to histidine and glutamic acid residues present at the dimer interface leads to major conformational changes within S100B resulting in modulation of the interaction with the target proteins (Wilder et al. 2005; Ostendorp et al. 2010).

S100B interacts with more than a dozen intracellular targets *in vitro* (Donato et al. 2009). Many of these targets have important functions in cancer and cell proliferation. For instance, S100B activates the glycolytic enzyme fructose-1,6-biphosphate aldolase, (Zimmer and Van Eldik 1986). S100B secreted by melanoma may therefore contribute to higher glycolysis of cancer cells. Cancer cells are known to have increased metabolism and glycolysis activity and inhibition of metabolism is currently a therapeutic approach to treat melanoma (Hersey et al. 2009; Xu et al. 2005). S100B may also contribute to cellular proliferation by interacting with many proteins of the cytoskeleton. As an example, S100B activates microtubule depolymerization in a calcium dependent manner (Donato 1988). S100B has been shown to directly interact with other constituents of the microtubules such as tubulin (Donato 1988), the microtubule associated tau protein (Baudier and Cole 1988), the actin binding protein caldesmon (Skripnikova and Gusev 1989) or the small GTPase Rac1 and cdc42 effector IQGAP1 (Mbele et al. 2002). S100B may also play a role in cellular division and proliferation through the activation of Nuclear Dbf2 related (ndr) kinase (Millward et al. 1998). S100B also binds to the giant phosphoprotein AHNAK/desmoyokin in a calcium dependent manner, resulting in the regulation of calcium homeostasis (Gentil et al. 2001). AHNAK is a protein of neuroectodermal origin and is present in melanoma cells (Shtivelman and Bishop 1993). Since changes in calcium homeostasis have been shown to play important roles in melanoma through the activation of protein kinase B/Akt, the interaction of S100B with AHNAK might be of high relevance in the disease (Fedida-Metula et al. 2008).

Among the intracellular proteins, the transcriptional factors p53 and its related factors p63 and p73 are also target proteins. Binding of S100B inhibits p53 phosphorylation and oligomerization resulting in inhibition of p53 apoptotic function (Lin et al. 2010).

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 may participate in the translocation of several S100s including S100B (Hsieh et al. 2004; Perrone, Peluso, and Melone 2008). The role of S100B, once secreted in the extracellular medium is currently unknown. Secreted S100B could act in an autocrine or paracrine manner through the activation of cell surface receptors. RAGE is among the potential candidates that could play the role of receptor.

4.2 S100A2

Although S100B is an established biomarker in melanoma, the role of S100A2 is not yet completely understood. S100A2 is expressed in many cells of the normal epidermis (Table 1) (Boni, Burg et al. 1997; Eckert et al. 2004; Maelandsmo et al. 1997). S100A2 is dimeric and binds both zinc ($K_D = 25$ nM) and calcium ($K_D = 470$ μ M) and binding to zinc reduces significantly the affinity for calcium (Franz et al. 1998; Koch et al. 2007).

S100A2 is mainly localized in the cell nucleus where it is believed to play the role of tumor suppressor (Glenney, Kindy, and Zokas 1989). In line with this hypothesis, S100A2 is found down-regulated in melanoma and other cancers that include prostate, oral, lung and breast cancers (Maelandsmo et al. 1997; Leclerc, Heizmann, and Vetter 2009; Gupta et al. 2003; Suzuki et al. 2005; Feng et al. 2001; Lee et al. 1992). However, recent studies also showed that S100A2 could be up-regulated in other cancers such as esophageal squamous carcinoma, gastric, and ovarian cancer (Imazawa et al. 2005; El-Rifai et al. 2002; Hough et al. 2001). Both down- and up-regulation of S100A2 have been found in different tumors of non-small cell lung cancer (NSCLC) (Smith et al. 2004; Strazisar, Mlakar, and Glavac 2009). In a mouse model of NSCLC over-expression of S100A2 correlated with strong metastasis (Bulk et al. 2009).

The expression pattern of S100A2 in melanoma is opposite to that of S100B. An earlier study showed that although most of benign nevi showed the presence of S100A2 mRNA, none of the metastatic tissue sample showed detectable levels of S100A2 mRNA (Maelandsmo et al. 1997). We recently confirmed this observation using a panel of 40 stage III and stage IV melanoma tissue samples and we showed a significant reduction in S100A2 mRNA level in both stage III and stage IV compared to the control samples (Leclerc, Heizmann, and Vetter 2009).

A role of S100A2 in uveal melanoma was also suggested by a recent study where co-treatment of uveal melanoma cells with decitabine and cell death inducing interferon- γ resulted in a dose-dependent increase in S100A2 expression, both at the transcription and protein level (Gollob and Sciambi 2007).

As mentioned earlier, S100A2 locates in the nucleus where its most evident target appears to be p53. Numerous studies have shown and characterized *in vitro* the interaction of S100A2 and p53. Binding of S100A2 with p53 results in increase of the transcriptional activity of the nuclear factor (Mueller et al. 2005; Fernandez-Fernandez, Rutherford, and Fersht 2008; van Dieck, Teufel et al. 2009). Binding of S100A2 to p53 is increased when p53 is phosphorylated (van Dieck, Teufel et al. 2009). A recent study shows that over-expression of S100A2 in nude mice resulted in the induction of metastatic melanoma (Bulk et al. 2009). The presence of S100A2 was also found to correlate with a favorable outcome in patients carrying p53 negative tumors (Matsubara et al. 2005).

The transcription of S100A2 itself has been shown to be under the control of p53 and of the p53 related factors p63 and p73 suggesting complex mechanisms of regulation of S100A2 and p53 (Tan et al. 1999; Kirschner et al. 2008).

S100A2 could also play a role in tumor suppression though the interaction with cyclophilin CyP40. Indeed S100A2 has been shown to interact with CyP40, resulting in inhibition of the complex formation between CyP40 and HsP90 and therefore resulting in alteration of protein folding (Shimamoto et al. 2010).

Although some mutations and polymorphisms within S100A2 have been reported in NSCLC, none have been reported in melanoma so far (Strazisar, Rott, and Glavac 2009).

We recently showed that S100A2 could interact with RAGE *in vitro* (Leclerc et al. 2009). However, the role of this interaction in melanoma or others pathologies has not yet been demonstrated.

4.3 S100A4

S100A4 is characterized by its involvement in cancer progression and metastasis (Boye and Maeldansmo 2010). S100A4 forms dimers, binds calcium and zinc and similarly to other S100 proteins, shows cell- and tissue-specific expression (Helfman et al. 2005; Garrett et al. 2006; Chen et al. 2009). In normal conditions, S100A4 is found in a large variety of cells that include fibroblasts, leukocytes, smooth muscle cells, and endothelial cells (Gibbs et al. 1995). It is also found in the brain where it is believed to play a role in neuronal plasticity (Kozlova and Lukanidin 2002).

The role of S100A4 in cancer was first suggested in mouse adenocarcinoma and later confirmed in many animal studies (Grum-Schwensen et al. 2005; Ambartsumian, Grigorian, and Lukanidin 2005). In one study, the injection of highly metastatic mouse mammary carcinoma did not generate metastasis in S100A4 knock-out mice whereas many metastases were found in the control animals (Grum-Schwensen et al. 2005).

The role of S100A4 in melanoma has not yet been clearly established. An earlier study aiming at measuring the mRNA levels of S100A4 in melanoma samples did not showed any significant difference in S100A4 mRNAs between melanoma samples and benign nevi (Maeldansmo et al. 1997). Our recent analysis of 40 samples of stage III and stage IV melanoma tissues showed a significantly reduction of S100A4 mRNA in stage IV tissue samples compared to control samples.

Although S100A4 might not possess the properties of prognostic marker for stage III and IV melanoma, it might predict the outcome of patients at earlier stages of the disease. Indeed, a study by Andersen et al. showed a positive correlation between the level of S100A4 and the depth of the primary nodular melanoma tumor, with a higher expression of S100A4 correlating with a decreased disease free survival rate (Andersen et al. 2004). Accordingly, loss of S100A4 expression was found in the metastatic tumors deriving from the nodular tumors (Andersen et al. 2004).

At the molecular level, S100A4 has been shown to interact with both intracellular (non-muscle myosin, tropomyosin) and extracellular targets (annexin II, plasminogen, EGFR ligands) (Kim and Helfman 2003; Takenaga et al. 1994; Ford et al. 1995; Li et al. 2003; Semov et al. 2005; Klingelhofer et al. 2009). The control of the interaction of S100A4 with its target proteins might involve S100A4 oligomerization, as suggested by recent studies with myosin-IIA (Malashkevich et al. 2010). In another study, self-association of S100A4 has been shown to be essential for S100A4 induced metastasis formation (Ismail et al. 2010). Importantly, as described for S100B and S100A2, S100A4 interacts with the tumor suppressor p53 protein, resulting in the inhibition of p53 oligomerization and its interaction with its target DNA (Grigorian et al. 2001; Fernandez-Fernandez, Rutherford, and Fersht 2008; van Dieck, Teufel et al. 2009; Berge and Maeldansmo 2010).

Both S100A4 dimers and oligomers have been found to interact with RAGE *in vitro* as demonstrated by biophysical studies (Kiryushko et al. 2006). *In vivo* the activation of RAGE by S100A4 appears to depend of the cell type. S100A4 has been shown to trigger RAGE dependent signaling in osteoarthritic cartilage and pulmonary artery smooth muscle cells but not in neurons (Yammani et al. 2006; Spiekerkoetter et al. 2009; Kiryushko et al. 2006).

4.4 S100A6

The gene of S100A6 was identified and cloned from human melanoma cells (Weterman et al. 1993). S100A6 is structurally very similar to S100B (Sastry et al. 1998; Otterbein et al. 2002) but is present in a larger number of tissues and cells than S100B. It is found in muscle tissues, lung, kidney, spleen, and brain (Kuznicki et al. 1989). S100A6 binds both calcium and zinc (Filipek, Heizmann, and Kuznicki 1990). S100A6 has been found in high levels in several cancers including colorectal cancer, pancreatic, hepato-cellular carcinoma, melanoma, lung cancer or gastric cancer and has been suggested to play a role in proliferation and tumorigenesis (Komatsu et al. 2000; Maelandsmo et al. 1997; Nedjadi et al. 2009; De Petris et al. 2009; Ohuchida et al. 2007; Yang et al. 2007; Lesniak, Slomnicki, and Filipek 2009; Vimalachandran et al. 2005).

S100A6 was identified by comparing metastatic melanoma samples with normal nevi (Weterman et al. 1993). An increase in S100A6 staining intensity correlated with the stage of the melanoma sample (Weterman et al. 1993). In a later study, Maelandsmo et al. confirmed that S100A6 mRNA expression was significantly higher in samples from patients with thick primary lesions and short survival time than in samples from patients with thin primary lesions and longer survival time (Maelandsmo et al. 1997). S100A6 over-expression has been described in ocular and non-ocular melanoma tissue samples (Van Ginkel et al. 1998; Hsieh et al. 2003). We recently examined by quantitative PCR a panel of 40 stage III and stage IV melanoma samples. Our study showed that 43% of stage III melanoma tissue samples presented significant over-expression of S100A6 mRNA (Leclerc, Heizmann, and Vetter 2009). Our results were in agreement with those of Ribe et al. where 33% of melanoma samples showed the expression of S100A6 at the protein level (Ribe and McNutt 2003).

At the molecular level, S100A6 interacts with the tumor suppressor p53. However, contrarily to the interaction of S100B or S100A2 with p53, binding of S100A6 to p53 does not affect p53 interaction with its target proteins (Fernandez-Fernandez, Rutherford, and Fersht 2008; Slomnicki, Nawrot, and Lesniak 2009). S100A6 also interacts with RAGE and triggers RAGE dependent intracellular signaling (Leclerc et al. 2007). We showed that S100A6 triggered cell death through the C2 domain of RAGE whereas on the same cells, S100B triggered cell proliferation through the V domain of the receptor (Leclerc et al. 2007).

4.5 S100A11

S100A11 shows 50% amino-acid homology with S100A2 (Kondo et al. 2002). It has a large tissue and cell distribution (Allen et al. 1996). S100A11 plays dual roles in cancer (reviewed in (He et al. 2009)). S100A11 was shown to promote tumor formation in prostate, breast, and pancreatic cancer (Rehman et al. 2004; Cross et al. 2005; Ohuchida et al. 2006). Surprisingly, it was also shown to play the role of tumor suppressor in bladder and renal carcinoma (Memon et al. 2005; Kondo et al. 2002). S100A11 has been found over-expressed in malignant melanoma of the uvea suggesting a role in this type of cancer as well (Van Ginkel et al. 1998).

At the molecular level, S100A11 interacts with a number of targets that have key functions in cell proliferation and repair mechanisms. For instance, S100A11 translocates from the cytoplasm to the nucleus where it regulates cell proliferation in response to DNA damage (Gorsler et al. 2010). S100A11 also interacts with annexin II which has been associated with many cancer (Diaz et al. 2004; Emoto et al. 2001; Esposito et al. 2006; Rintala-Dempsey et al. 2006). S100A11 binds to p53 and to the DNA repair protein Rad54B as well (Fernandez-Fernandez, Rutherford, and Fersht 2008; Murzik et al. 2008).

S100A11 has also been found to interact with RAGE and to trigger RAGE dependent intracellular signaling in osteoarthritis (OA) and in human keratinocytes (Cecil et al. 2005; Sakaguchi et al. 2008).

4.6 Other S100 proteins

The S100 proteins described above have been found in melanoma cells or tumor samples. However, melanoma tumors, like many solid tumors, are in constant communication with the tumor micro-environment through the activation of various signal transduction pathways. For instance, although S100A8/A9 are not over-expressed in melanoma tissue samples, the heterodimer was suggested to be released from the tumor environment and to participate in melanoma tumor growth through RAGE (Figure 2A, B) (Saha et al. 2010). S100A8 and S100A9 form heterodimers that are mainly expressed and secreted by monocytes and macrophages and were initially described as pro-inflammatory cytokines (Hsu et al. 2009). However, in recent years many studies have demonstrated that S100A8/A9 also play an increasing role in cancer (Ehrchen et al. 2009; Ghavami et al. 2009; Ang et al. 2010). Interestingly several studies have shown that S10A8/A9 may play a role in cancer through RAGE and the activation of MAPK and NF- κ B (Ghavami et al. 2008; Ang et al. 2010; Ichikawa et al. 2011).

S100A10 has also been suggested to play a role in melanoma and was found expressed at various levels in melanoma tumor samples and melanocytes (Petersson et al. 2009; Leclerc, Heizmann, and Vetter 2009).

5. Role of RAGE in melanoma and therapeutic approach

The role of RAGE in melanoma tumor growth and metastasis has been suggested by studies in mice (Huttunen et al. 2002; Abe et al. 2004). In the study by Huttunen et al., the metastatic activity of melanoma B16-F1 cells overexpressing either full-length RAGE (B16-F1 RAGE) or a truncated form of the receptor lacking the intracellular part (B16-F1 RAGE Δ cyto), were compared. The study showed that mice that received the B16-F1 RAGE Δ cyto cells developed about 70% less lung metastasis than the mice that were injected with B16-F1 RAGE cells (Huttunen et al. 2002). In a study by Abe et al., blockade of RAGE using anti-RAGE antibodies suppressed growth of melanoma tumors implanted in mice and originating from G361 melanoma cells (Abe et al. 2004). The presence of RAGE in melanoma tissue samples from human patients was demonstrated by Hsieh et al. (Hsieh et al. 2003) using tumor tissue microarrays. We have recently shown that the transcript levels of RAGE in melanoma patient tissue samples were significantly higher in stage IV than in stage III melanoma and that large variations were present between samples (>100 fold) (Leclerc, Heizmann, and Vetter 2009). A recent study also showed that the inhibition of proliferation of the melanoma cell line SK-MEL-28 following the treatment with the MK615 compound was accompanied with a decrease in the protein expression level of RAGE (Matsushita et al. 2010). In addition, Saha et al. demonstrated that in the uteroglobin-KO mouse model of pulmonary inflammation, RAGE expressing B16F10 melanoma cells were more prone to pulmonary metastatic colonization than in the control mice (Saha et al. 2010). More importantly, these authors demonstrated that metastatic melanoma cells were chemoattracted by S100A8 and S100A9 overproduced by the uteroglobin-KO mouse and that blocking RAGE with a specific antibody resulted in the inhibition of the chemotactic migration (Saha et al. 2010).

Fig. 2. a) Cells of the epidermis and dermis. In the epidermis, RAGE is expressed in skin fibroblasts, keratinocytes, endothelial cells and melanocytes (Lohwasser et al. 2006). In the dermis, RAGE is expressed on the surface of fibroblasts and endothelial cells. b) Invasion of melanocytes through the dermis. Melanocytes have invaded the dermis and have multiplied. Melanoma cells express RAGE and secrete S100B. Secreted S100B may activate other melanoma cells, fibroblasts or endothelial cells present in the environment through the interaction with RAGE, resulting in tumor growth. Other cells within the tumor environment produce S100A8/A9 and AGEs. Endothelial cells start forming new blood vessels. Activation of RAGE by its ligands results in up-regulation of RAGE and amplification of RAGE dependent signaling

There is currently no treatment that efficiently cures metastatic melanoma. For primary melanoma tumors, the therapeutic approach consists in the surgical removal of the lesion and the survival rate is very high (>90%). For metastatic melanoma, the FDA approved therapies include chemotherapy with alkylating agents (Dacarbazine) or immunotherapy with interleukin-2 (Atkins et al. 1999). However, even with these therapies, the survival rate of patients with advanced melanoma (stage III and IV) is only around 10%. There is therefore a need for new therapeutic targets.

RAGE appears to be a promising target and in two independent animal models, RAGE blockade resulted in decreased cell proliferation and tumor growth rate (Abe et al. 2004) as well as in the reduction of the number of metastasis (Huttunen et al. 2002). Due to the broad variety of its ligands, RAGE is at the crossroad of several pathways. The increased metabolic activity (glycolysis, mitochondrial oxidative stress) of tumor cells leads to the formation of reactive carbonyl species (RCS) that react with tumor proteins to form AGEs (Sander et al. 2003; Abe et al. 2004; Wondrak, Jacobson, and Jacobson 2006). AGEs react with RAGE and trigger proliferative signaling pathways. Blocking AGE formation through carbonyl scavengers have been tested in melanoma cell lines and showed encouraging results (Wondrak, Jacobson, and Jacobson 2006). Blocking RAGE activation by AGEs is another option. Blockade of RAGE/HMGB1 with an HMGB1 derived peptide was also shown to efficiently reduce the number of metastatic tumors generated by the melanoma cell line B16-F1 (Huttunen et al. 2002).

Blockage of RAGE/ligand might not be successful in each melanoma patient. As we recently showed, large variation in the transcript levels of RAGE exist between patients and blockade of RAGE might be efficient only in patients showing high expression of RAGE (Leclerc, Heizmann, and Vetter 2009).

6. Conclusion

The prevalence of metastatic melanoma is on the rise worldwide and new targets are urgently needed to treat this cancer. In recent years, S100 proteins have evolved from simple calcium binding proteins into proteins that participate actively in many diseases such as cancer. We have discussed in this chapter how S100 proteins could play important role in melanoma proliferation and metastasis through their interaction with key target proteins such as p53, tubulin associated protein, CyP40 or RAGE. In particular, RAGE appears to be a promising therapeutic target and efforts should be devoted to develop inhibitors of RAGE/S100 protein interaction.

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8. References

- Abe, R., T. Shimizu, H. Sugawara, H. Watanabe, H. Nakamura, H. Choei, N. Sasaki, S. Yamagishi, M. Takeuchi, and H. Shimizu. 2004. Regulation of human melanoma growth and metastasis by AGE-AGE receptor interactions. *J Invest Dermatol* 122 (2):461-7.

- Ahmed, N., U. Ahmed, P. J. Thornalley, K. Hager, G. Fleischer, and G. Munch. 2005. Protein glycation, oxidation and nitration adduct residues and free adducts of cerebrospinal fluid in Alzheimer's disease and link to cognitive impairment. *J Neurochem* 92 (2):255-63.
- Allen, B. G., I. Durussel, M. P. Walsh, and J. A. Cox. 1996. Characterization of the Ca^{2+} -binding properties of calgizzarin (S100C) isolated from chicken gizzard smooth muscle. *Biochem Cell Biol* 74 (5):687-94.
- Ambartsumian, N., M. Grigorian, and E. Lukanidin. 2005. Genetically modified mouse models to study the role of metastasis-promoting S100A4(mts1) protein in metastatic mammary cancer. *J Dairy Res* 72 Spec No:27-33.
- Andersen, K., J. M. Nesland, R. Holm, V. A. Florenes, O. Fodstad, and G. M. Maelandsmo. 2004. Expression of S100A4 combined with reduced E-cadherin expression predicts patient outcome in malignant melanoma. *Mod Pathol* 17 (8):990-7.
- Ang, C. W., T. Nedjadi, A. A. Sheikh, E. M. Tweedle, S. Tonack, S. Honap, R. E. Jenkins, B. K. Park, I. Schwarte-Waldhoff, I. Khattak, B. Azadeh, A. Dodson, H. Kalirai, J. P. Neoptolemos, P. S. Rooney, and E. Costello. 2010. Smad4 loss is associated with fewer S100A8-positive monocytes in colorectal tumors and attenuated response to S100A8 in colorectal and pancreatic cancer cells. *Carcinogenesis* 31 (9):1541-51.
- Atkins, M. B., M. T. Lotze, J. P. Dutcher, R. I. Fisher, G. Weiss, K. Margolin, J. Abrams, M. Sznol, D. Parkinson, M. Hawkins, C. Paradise, L. Kunkel, and S. A. Rosenberg. 1999. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 17 (7):2105-16.
- Balch, C. M., J. E. Gershenwald, S. J. Soong, J. F. Thompson, M. B. Atkins, D. R. Byrd, A. C. Buzaid, A. J. Cochran, D. G. Coit, S. Ding, A. M. Eggermont, K. T. Flaherty, P. A. Gimotty, J. M. Kirkwood, K. M. McMasters, M. C. Mihm, Jr., D. L. Morton, M. I. Ross, A. J. Sober, and V. K. Sondak. 2009. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 27 (36):6199-206.
- Baudier, J., and R. D. Cole. 1988. Interactions between the microtubule-associated tau proteins and S100B regulate tau phosphorylation by the Ca^{2+} /calmodulin-dependent protein kinase II. *J Biol Chem* 263 (12):5876-83.
- Baudier, J., C. Delphin, D. Grunwald, S. Khochbin, and J. J. Lawrence. 1992. Characterization of the tumor suppressor protein p53 as a protein kinase C substrate and a S100b-binding protein. *Proc Natl Acad Sci U S A* 89 (23):11627-31.
- Baudier, J., and D. Gerard. 1986. Ions binding to S100 proteins. II. Conformational studies and calcium-induced conformational changes in S100 alpha alpha protein: the effect of acidic pH and calcium incubation on subunit exchange in S100a (alpha beta) protein. *J Biol Chem* 261 (18):8204-12.
- Berge, G., and G. M. Maelandsmo. 2010. Evaluation of potential interactions between the metastasis-associated protein S100A4 and the tumor suppressor protein p53. *Amino Acids*: [Epub ahead of print].
- Bhatia, S., S. S. Tykodi, and J. A. Thompson. 2009. Treatment of metastatic melanoma: an overview. *Oncology (Williston Park)* 23 (6):488-96.
- Bierhaus, A., P. M. Humpert, M. Morcos, T. Wendt, T. Chavakis, B. Arnold, D. M. Stern, and P. P. Nawroth. 2005. Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med* 83 (11):876-86.

- Bierhaus, A., and P. P. Nawroth. 2009. 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* 52 (11):2251-63.
- Boni, R., G. Burg, A. Doguoglu, E. C. Ilg, B. W. Schafer, B. Muller, and C. W. Heizmann. 1997. Immunohistochemical localization of the Ca²⁺ binding S100 proteins in normal human skin and melanocytic lesions. *Br J Dermatol* 137 (1):39-43.
- Boni, R., C. W. Heizmann, A. Doguoglu, E. C. Ilg, B. W. Schafer, R. Dummer, and G. Burg. 1997. Ca(2+)-binding proteins S100A6 and S100B in primary cutaneous melanoma. *J Cutan Pathol* 24 (2):76-80.
- Bouwhuis, M. G., S. Suciu, W. Kruit, F. Sales, K. Stoitchkov, P. Patel, V. Cocquyt, J. Thomas, D. Lienard, A. M. Eggermont, and G. Ghanem. 2010. Prognostic value of serial blood S100B determinations in stage IIB-III melanoma patients: A corollary study to EORTC trial 18952. *Eur J Cancer* 47 (3):361-368.
- Boye, K., and G. M. Maelandsmo. 2010. S100A4 and metastasis: a small actor playing many roles. *Am J Pathol* 176 (2):528-35.
- Brett, J., A. M. Schmidt, S. D. Yan, Y. S. Zou, E. Weidman, D. Pinsky, R. Nowygrod, M. Neeper, C. Przysiecki, A. Shaw, and et al. 1993. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *Am J Pathol* 143 (6):1699-712.
- Broome, A. M., D. Ryan, and R. L. Eckert. 2003. S100 protein subcellular localization during epidermal differentiation and psoriasis. *Journal of Histochemistry & Cytochemistry* 51 (5):675-685.
- Buckley, S. T., and C. Ehrhardt. 2010. The receptor for advanced glycation end products (RAGE) and the lung. *J Biomed Biotechnol*:in press.
- Bulk, E., B. Sargin, U. Krug, A. Hascher, Y. Jun, M. Knop, C. Kerkhoff, V. Gerke, R. Liersch, R. M. Mesters, M. Hotfilder, A. Marra, S. Koschmieder, M. Dugas, W. E. Berdel, H. Serve, and C. Muller-Tidow. 2009. S100A2 induces metastasis in non-small cell lung cancer. *Clin Cancer Res* 15 (1):22-9.
- Cecil, D. L., K. Johnson, J. Rediske, M. Lotz, A. M. Schmidt, and R. Terkeltaub. 2005. Inflammation-induced chondrocyte hypertrophy is driven by receptor for advanced glycation end products. *J Immunol* 175 (12):8296-302.
- Chen, M., M. Sinha, B. A. Luxon, A. R. Bresnick, and K. L. O'Connor. 2009. Integrin alpha6beta4 controls the expression of genes associated with cell motility, invasion, and metastasis, including S100A4/metastasin. *J Biol Chem* 284 (3):1484-94.
- Chun, Y.S., Y. Wang, D.Y. Wang, D.M. McClain, A. Lucci, P.F. Mansfield, J.N. Cormier, M.I. Ross, J.E. Gershenwald, and J.E. Lee. 2008. Prognostic value of s100B levels and LDH levels in melanoma patients. *J Clin Oncol* 26:abstract 9002.
- Coughlan, M. T., D. R. Thorburn, S. A. Penfold, A. Laskowski, B. E. Harcourt, K. C. Sourris, A. L. Tan, K. Fukami, V. Thallas-Bonke, P. P. Nawroth, M. Brownlee, A. Bierhaus, M. E. Cooper, and J. M. Forbes. 2009. RAGE-induced cytosolic ROS promote mitochondrial superoxide generation in diabetes. *J Am Soc Nephrol* 20 (4):742-52.
- Cross, S. S., F. C. Hamdy, J. C. Deloulme, and I. Rehman. 2005. Expression of S100 proteins in normal human tissues and common cancers using tissue microarrays: S100A6, S100A8, S100A9 and S100A11 are all overexpressed in common cancers. *Histopathology* 46 (3):256-69.
- Darrell, S., and M.D. Rigel. 2010. Trends in Dermatology: Melanoma Incidence. *Archives in Dermatology* 146:318.

- Dattilo, B. M., G. Fritz, E. Leclerc, C. W. Kooi, C. W. Heizmann, and W. J. Chazin. 2007. The extracellular region of the receptor for advanced glycation end products is composed of two independent structural units. *Biochemistry* 46 (23):6957-70.
- De Petris, L., L. M. Orre, L. Kanter, M. Pernemalm, H. Koyi, R. Lewensohn, and J. Lehtio. 2009. Tumor expression of S100A6 correlates with survival of patients with stage I non-small-cell lung cancer. *Lung Cancer* 63:410-417.
- Deane, R., S. Du Yan, R. K. Subramanyam, B. LaRue, S. Jovanovic, E. Hogg, D. Welch, L. Manness, C. Lin, J. Yu, H. Zhu, J. Ghiso, B. Frangione, A. Stern, A. M. Schmidt, D. L. Armstrong, B. Arnold, B. Liliensiek, P. Nawroth, F. Hofman, M. Kindy, D. Stern, and B. Zlokovic. 2003. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med* 9 (7):907-13.
- Deshpande, R., T. L. Woods, J. Fu, T. Zhang, S. W. Stoll, and J. T. Elder. 2000. Biochemical characterization of S100A2 in human keratinocytes: subcellular localization, dimerization, and oxidative cross-linking. *J Invest Dermatol* 115 (3):477-85.
- Diaz, V. M., M. Hurtado, T. M. Thomson, J. Reventos, and R. Paciucci. 2004. Specific interaction of tissue-type plasminogen activator (t-PA) with annexin II on the membrane of pancreatic cancer cells activates plasminogen and promotes invasion in vitro. *Gut* 53 (7):993-1000.
- Ding, Q., and J. N. Keller. 2005. Splice variants of the receptor for advanced glycosylation end products (RAGE) in human brain. *Neurosci Lett* 373 (1):67-72.
- Donato, R. 1988. Calcium-independent, pH-regulated effects of S-100 proteins on assembly-disassembly of brain microtubule protein in vitro. *J Biol Chem* 263 (1):106-10.
2003. Intracellular and extracellular roles of S100 proteins. *Microsc Res Tech* 60 (6):540-51.
2007. RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. *Curr Mol Med* 7 (8):711-24.
2009. S100B's double life: intracellular and extracellular signal. *Biochimica Biophysica Acta: Molecular Cell Research* 1793 (6):1008-1022..
- Donato, R., G. Sorci, F. Riuizi, C. Arcuri, R. Bianchi, F. Brozzi, C. Tubaro, and I. Giambanco. 2009. S100B's double life: intracellular regulator and extracellular signal. *Biochim Biophys Acta* 1793 (6):1008-22.
- Eckert, R. L., A. M. Broome, M. Ruse, N. Robinson, D. Ryan, and K. Lee. 2004. S100 proteins in the epidermis. *Journal of Investigative Dermatology* 123 (1):23-33.
- Ehrchen, J. M., C. Sunderkotter, D. Foell, T. Vogl, and J. Roth. 2009. The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. *J Leukoc Biol* 86 (3):557-66.
- El-Rifai, W., C. A. Moskaluk, M. K. Abdrabbo, J. Harper, C. Yoshida, G. J. Riggins, H. F. Frierson, Jr., and S. M. Powell. 2002. Gastric cancers overexpress S100A calcium-binding proteins. *Cancer Res* 62 (23):6823-6.
- Emanuele, E., A. D'Angelo, C. Tomaino, G. Binetti, R. Ghidoni, P. Politi, L. Bernardi, R. Maletta, A. C. Bruni, and D. Geroldi. 2005. Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. *Arch Neurol* 62 (11):1734-6.
- Emoto, K., H. Sawada, Y. Yamada, H. Fujimoto, Y. Takahama, M. Ueno, T. Takayama, H. Uchida, K. Kamada, A. Naito, S. Hirao, and Y. Nakajima. 2001. Annexin II overexpression is correlated with poor prognosis in human gastric carcinoma. *Anticancer Res* 21 (2B):1339-45.

- Esposito, I., R. Penzel, M. Chaib-Harrireche, U. Barcena, F. Bergmann, S. Riedl, H. Kaye, N. Giese, J. Kleeff, H. Friess, and P. Schirmacher. 2006. Tenascin C and annexin II expression in the process of pancreatic carcinogenesis. *J Pathol* 208 (5):673-85.
- Fang, F., L. F. Lue, S. Yan, H. Xu, J. S. Luddy, D. Chen, D. G. Walker, D. M. Stern, A. M. Schmidt, J. X. Chen, and S. S. Yan. 2010. RAGE-dependent signaling in microglia contributes to neuroinflammation, Abeta accumulation, and impaired learning/memory in a mouse model of Alzheimer's disease. *FASEB J* 24 (4):1043-55.
- Fedida-Metula, S., S. Elhyany, S. Tsory, S. Segal, M. Hershfinkel, I. Sekler, and D. Fishman. 2008. Targeting lipid rafts inhibits protein kinase B by disrupting calcium homeostasis and attenuates malignant properties of melanoma cells. *Carcinogenesis* 29 (8):1546-54.
- Feng, G., X. Xu, E. M. Youssef, and R. Lotan. 2001. Diminished expression of S100A2, a putative tumor suppressor, at early stage of human lung carcinogenesis. *Cancer Res* 61 (21):7999-8004.
- Fernandez-Fernandez, M. R., T. J. Rutherford, and A. R. Fersht. 2008. Members of the S100 family bind p53 in two distinct ways. *Protein Sci* 17 (10):1663-70.
- Filipek, A., C. W. Heizmann, and J. Kuznicki. 1990. Calcyclin is a calcium and zinc binding protein. *FEBS Lett* 264 (2):263-6.
- Ford, H. L., M. M. Salim, R. Chakravarty, V. Aluiddin, and S. B. Zain. 1995. Expression of Mts1, a metastasis-associated gene, increases motility but not invasion of a nonmetastatic mouse mammary adenocarcinoma cell line. *Oncogene* 11 (10):2067-75.
- Franz, C., I. Durussel, J. A. Cox, B. W. Schafer, and C. W. Heizmann. 1998. Binding of Ca²⁺ and Zn²⁺ to human nuclear S100A2 and mutant proteins. *J Biol Chem* 273 (30):18826-34.
- Fritz, G., and C. W. Heizmann. 2004. 3D structures of the calcium and zinc binding S100 proteins. In *Handbook of Metalloproteins Vol. 3*, edited by A. Messerschmidt, W. Bode and M. Cygler. Chichester: Wiley.
- Galichet, A., M. Weibel, and C. W. Heizmann. 2008. Calcium-regulated intramembrane proteolysis of the RAGE receptor. *Biochem Biophys Res Commun* 370 (1):1-5.
- Garrett, S. C., K. M. Varney, D. J. Weber, and A. R. Bresnick. 2006. S100A4, a mediator of metastasis. *J Biol Chem* 281 (2):677-80.
- Gentil, B. J., C. Delphin, G. O. Mbele, J. C. Deloulme, M. Ferro, J. Garin, and J. Baudier. 2001. The giant protein AHNK is a specific target for the calcium- and zinc-binding S100B protein: potential implications for Ca²⁺ homeostasis regulation by S100B. *J Biol Chem* 276 (26):23253-61.
- Ghanem, G., B. Loir, R. Morandini, F. Sales, D. Lienard, A. Eggermont, and F. Lejeune. 2001. On the release and half-life of S100B protein in the peripheral blood of melanoma patients. *Int J Cancer* 94 (4):586-90.
- Ghavami, S., S. Chitayat, M. Hashemi, M. Eshraghi, W. J. Chazin, A. J. Halayko, and C. Kerkhoff. 2009. S100A8/A9: a Janus-faced molecule in cancer therapy and tumorigenesis. *Eur J Pharmacol* 625 (1-3):73-83.
- Ghavami, S., I. Rashedi, B. M. Dattilo, M. Eshraghi, W. J. Chazin, M. Hashemi, S. Wesselborg, C. Kerkhoff, and M. Los. 2008. S100A8/A9 at low concentration promotes tumor cell growth via RAGE ligation and MAP kinase-dependent pathway. *J Leukoc Biol* 83 (6):1484-92.
- Gibbs, F. E., R. Barraclough, A. Platt-Higgins, P. S. Rudland, M. C. Wilkinson, and E. W. Parry. 1995. Immunocytochemical distribution of the calcium-binding protein p9Ka

- in normal rat tissues: variation in the cellular location in different tissues. *J Histochem Cytochem* 43 (2):169-80.
- Glenney, J. R., Jr., M. S. Kindy, and L. Zokas. 1989. Isolation of a new member of the S100 protein family: amino acid sequence, tissue, and subcellular distribution. *J Cell Biol* 108 (2):569-78.
- Gogas, H., A. M. Eggermont, A. Hauschild, P. Hersey, P. Mohr, D. Schadendorf, A. Spatz, and R. Dummer. 2009. Biomarkers in melanoma. *Ann Oncol* 20 8-13.
- Gollob, J. A., and C. J. Sciambi. 2007. Decitabine up-regulates S100A2 expression and synergizes with IFN-gamma to kill uveal melanoma cells. *Clin Cancer Res* 13 (17):5219-25.
- Gorsler, T., U. Murzik, T. Ulbricht, J. Hentschel, P. Hemmerich, and C. Melle. 2010. DNA damage-induced translocation of S100A11 into the nucleus regulates cell proliferation. *BMC Cell Biol* 11:100.
- Grigorian, M., S. Andresen, E. Tulchinsky, M. Kriajevska, C. Carlberg, C. Kruse, M. Cohn, N. Ambartsumian, A. Christensen, G. Selivanova, and E. Lukanidin. 2001. Tumor suppressor p53 protein is a new target for the metastasis-associated Mts1/S100A4 protein: functional consequences of their interaction. *J Biol Chem* 276 (25):22699-708.
- Grum-Schwensen, B., J. Klingelhofer, C. H. Berg, C. El-Naaman, M. Grigorian, E. Lukanidin, and N. Ambartsumian. 2005. Suppression of tumor development and metastasis formation in mice lacking the S100A4(mts1) gene. *Cancer Res* 65 (9):3772-80.
- Gupta, S., T. Hussain, G. T. MacLennan, P. Fu, J. Patel, and H. Mukhtar. 2003. Differential expression of S100A2 and S100A4 during progression of human prostate adenocarcinoma. *J Clin Oncol* 21 (1):106-12.
- Harpio, R., and R. Einarsson. 2004. S100 proteins as cancer biomarkers with focus on S100B in malignant melanoma. *Clin Biochem* 37 (7):512-8.
- Hauschild, A., G. Engel, W. Brenner, R. Glaser, H. Monig, E. Henze, and E. Christophers. 1999. S100B protein detection in serum is a significant prognostic factor in metastatic melanoma. *Oncology* 56 (4):338-44.
- He, H., J. Li, S. Weng, M. Li, and Y. Yu. 2009. S100A11: diverse function and pathology corresponding to different target proteins. *Cell Biochem Biophys* 55 (3):117-26.
- Heizmann, C. W. 2002. The multifunctional S100 protein family. *Methods Mol Biol* 172:69-80.
- Heizmann, C. W., G. E. Ackermann, and A. Galichet. 2007. Pathologies involving the S100 proteins and RAGE. *Subcell Biochem* 45:93-138.
- Heizmann, C. W., G. Fritz, and B. W. Schäfer. 2002. S100 proteins: structure, functions and pathology. *Front Biosci* 7:d1356-68.
- Helfman, D.M., E.J. Kim, E. Lukanidin, and M. Grigorian. 2005. The metastasis associated protein S100A4: role in tumour progression and metastasis. *Br J Cancer* 92:1955-1958.
- Hersey, P., R. N. Watts, X. D. Zhang, and J. Hackett. 2009. Metabolic approaches to treatment of melanoma. *Clin Cancer Res* 15 (21):6490-4.
- Hofmann, M. A., S. Drury, C. Fu, W. Qu, A. Taguchi, Y. Lu, C. Avila, N. Kambham, A. Bierhaus, P. Nawroth, M. F. Neurath, T. Slattey, D. Beach, J. McClary, M. Nagashima, J. Morser, D. Stern, and A. M. Schmidt. 1999. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 97 (7):889-901.
- Hori, O., J. Brett, T. Slattey, R. Cao, J. Zhang, J. X. Chen, M. Nagashima, E. R. Lundh, S. Vijay, D. Nitecki, and et al. 1995. The receptor for advanced glycation end products

- (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. *J Biol Chem* 270 (43):25752-61.
- Hough, C. D., K. R. Cho, A. B. Zonderman, D. R. Schwartz, and P. J. Morin. 2001. Coordinately up-regulated genes in ovarian cancer. *Cancer Res* 61 (10):3869-76.
- Hsieh, H. L., B. W. Schafer, N. Sasaki, and C. W. Heizmann. 2003. Expression analysis of S100 proteins and RAGE in human tumors using tissue microarrays. *Biochem Biophys Res Commun* 307 (2):375-81.
- Hsieh, H. L., B. W. Schäfer, B. Weigle, and C. W. Heizmann. 2004. S100 protein translocation in response to extracellular S100 is mediated by receptor for advanced glycation endproducts in human endothelial cells. *Biochem Biophys Res Commun* 316 (3):949-59.
- Hsu, K., C. Champaiboon, B. D. Guenther, B. S. Sorenson, A. Khammanivong, K. F. Ross, C. L. Geczy, and M. C. Herzberg. 2009. Anti-Infective Protective Properties of S100 Calgranulins. *Antiinflamm Antiallergy Agents Med Chem* 8 (4):290-305.
- Hudson, B. I., A. M. Carter, E. Harja, A. Z. Kalea, M. Arriero, H. Yang, P. J. Grant, and A. M. Schmidt. 2008. Identification, classification, and expression of RAGE gene splice variants. *Faseb J* 22 (5):1572-80.
- Humpert, P. M., Z. Djuric, S. Kopf, G. Rudofsky, M. Morcos, P. P. Nawroth, and A. Bierhaus. 2007. Soluble RAGE but not endogenous secretory RAGE is associated with albuminuria in patients with type 2 diabetes. *Cardiovasc Diabetol* 6:9.
- Huttunen, H. J., C. Fages, J. Kuja-Panula, A. J. Ridley, and H. Rauvala. 2002. Receptor for advanced glycation end products-binding COOH-terminal motif of amphoterin inhibits invasive migration and metastasis. *Cancer Res* 62 (16):4805-11.
- Ichikawa, M., R. Williams, L. Wang, T. Vogl, and G. Srikrishna. 2011. S100A8/A9 activate key genes and pathways in colon tumor progression. *Mol Cancer Res* 9 (2):133-48.
- Imazawa, M., K. Hibi, S. Fujitake, Y. Kodera, K. Ito, S. Akiyama, and A. Nakao. 2005. S100A2 overexpression is frequently observed in esophageal squamous cell carcinoma. *Anticancer Res* 25:1247-1250.
- Ismail, T. M., S. Zhang, D. G. Fernig, S. Gross, M. L. Martin-Fernandez, V. See, K. Tozawa, C. J. Tynan, G. Wang, M. C. Wilkinson, P. S. Rudland, and R. Barraclough. 2010. Self-association of calcium-binding protein S100A4 and metastasis. *J Biol Chem* 285 (2):914-22.
- Ito, M., and K. Kizawa. 2001. 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* 116 (6):956-63.
- Ito, N., R. A. DeMarco, R. B. Mailliard, J. Han, H. Rabinowich, P. Kalinski, D. B. Stolz, H. J. Zeh, 3rd, and M. T. Lotze. 2007. Cytolytic cells induce HMGB1 release from melanoma cell lines. *J Leukoc Biol* 81 (1):75-83.
- Kim, E. J., and D. M. Helfman. 2003. Characterization of the metastasis-associated protein, S100A4. Roles of calcium binding and dimerization in cellular localization and interaction with myosin. *J Biol Chem* 278 (32):30063-73.
- Kirschner, R. D., K. Sanger, G. A. Muller, and K. Engeland. 2008. Transcriptional activation of the tumor suppressor and differentiation gene S100A2 by a novel p63-binding site. *Nucleic Acids Res* 36 (9):2969-80.

- Kiryushko, D., V. Novitskaya, V. Soroka, J. Klingelhofer, E. Lukanidin, V. Berezin, and E. Bock. 2006. Molecular mechanisms of Ca^{2+} signaling in neurons induced by the S100A4 protein. *Mol Cell Biol* 26 (9):3625-38.
- Kislinger, T., C. Fu, B. Huber, W. Qu, A. Taguchi, S. Du Yan, M. Hofmann, S. F. Yan, M. Pischetsrieder, D. Stern, and A. M. Schmidt. 1999. N(epsilon)-(carboxymethyl)lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. *J Biol Chem* 274 (44):31740-9.
- Klingelhofer, J., H. D. Moller, E. U. Sumer, C. H. Berg, M. Poulsen, D. Kiryushko, V. Soroka, N. Ambartsumian, M. Grigorian, and E. M. Lukanidin. 2009. Epidermal growth factor receptor ligands as new extracellular targets for the metastasis-promoting S100A4 protein. *FEBS J* 276 (20):5936-48.
- Koch, M., S. Bhattacharya, T. Kehl, M. Gimona, M. Vasak, W. Chazin, C. W. Heizmann, P. M. Kroneck, and G. Fritz. 2007. Implications on zinc binding to S100A2. *Biochim Biophys Acta* 1773 (3):457-70.
- Koch, M., S. Chitayat, B. M. Dattilo, A. Schiefner, J. Diez, W. J. Chazin, and G. Fritz. 2010. Structural Basis for Ligand Recognition and Activation of RAGE. *Structure* 18 (10):1342-52.
- Komatsu, K., A. Andoh, S. Ishiguro, N. Suzuki, H. Hunai, Y. Kobune-Fujiwara, M. Kameyama, J. Miyoshi, H. Akedo, and H. Nakamura. 2000. Increased expression of S100A6 (Calcyclin), a calcium-binding protein of the S100 family, in human colorectal adenocarcinomas. *Clin Cancer Res* 6 (1):172-7.
- Kondo, A., M. Sakaguchi, E. Makino, M. Namba, S. Okada, and N. H. Huh. 2002. Localization of S100C immunoreactivity in various human tissues. *Acta Med Okayama* 56 (1):31-4.
- Koyama, H., H. Yamamoto, and Y. Nishizawa. 2007. RAGE and soluble RAGE: potential therapeutic targets for cardiovascular diseases. *Mol Med* 13 (11-12):625-35.
- Kozlova, E. N., and E. Lukanidin. 2002. Mts1 protein expression in the central nervous system after injury. *Glia* 37 (4):337-48.
- Kuznicki, J., A. Filipek, P. Heimann, L. Kaczmarek, and B. Kaminska. 1989. Tissue specific distribution of calcyclin--10.5 kDa Ca^{2+} -binding protein. *FEBS Lett* 254 (1-2):141-4.
- Landar, A., G. Caddell, J. Chessher, and D. B. Zimmer. 1996. Identification of an S100A1/S100B target protein: phosphoglucomutase. *Cell Calcium* 20 (3):279-85.
- Leclerc, E., G. Fritz, S. W. Vetter, and C. W. Heizmann. 2009. Binding of S100 proteins to RAGE: an update. *Biochim Biophys Acta* 1793 (6):993-1007.
- Leclerc, E., G. Fritz, M. Weibel, C. W. Heizmann, and A. Galichet. 2007. S100B and S100A6 differentially modulate cell survival by interacting with distinct RAGE (receptor for advanced glycation end products) immunoglobulin domains. *J Biol Chem* 282 (43):31317-31.
- Leclerc, E., C. W. Heizmann, and S.W. Vetter. 2009. RAGE and S100 protein transcription levels are highly variable in human melanoma tumors and cells. *General Physiology and Biophysics* 28 (Focus Issue):F65-F75.
- Lee, S. W., C. Tomasetto, K. Swisshelm, K. Keyomarsi, and R. Sager. 1992. 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* 89 (6):2504-8.
- Lesniak, W. 2011. Epigenetic regulation of S100 protein expression. *Clinical Epigenetic*:DOI 10.1007/s13148-011-0023-9.

- Lesniak, W., L. P. Slomnicki, and A. Filipek. 2009. S100A6 - new facts and features. *Biochem Biophys Res Commun* 390 (4):1087-92.
- Li, Z. H., A. Spektor, O. Varlamova, and A. R. Bresnick. 2003. Mts1 regulates the assembly of nonmuscle myosin-IIA. *Biochemistry* 42 (48):14258-66.
- Lin, J., Q. Yang, P. T. Wilder, F. Carrier, and D. J. Weber. 2010. The calcium-binding protein S100B down-regulates p53 and apoptosis in malignant melanoma. *J Biol Chem* 285 (35):27487-98.
- Lin, L., S. Park, and E. G. Lakatta. 2009. RAGE signaling in inflammation and arterial aging. *Front Biosci* 14:1403-13.
- Lohwasser, C., D. Neureiter, B. Weigle, T. Kirchner, and D. Schuppan. 2006. The receptor for advanced glycation end products is highly expressed in the skin and upregulated by advanced glycation end products and tumor necrosis factor-alpha. *J Invest Dermatol* 126 (2):291-9.
- Lue, L. F., D. G. Walker, S. Jacobson, and M. Sabbagh. 2009. Receptor for advanced glycation end products: its role in Alzheimer's disease and other neurological diseases. *Future Neurol* 4 (2):167-177.
- Maelandsmo, G. M., V. A. Florenes, T. Mellingsaeter, E. Hovig, R. S. Kerbel, and O. Fodstad. 1997. Differential expression patterns of S100A2, S100A4 and S100A6 during progression of human malignant melanoma. *Int J Cancer* 74 (4):464-9.
- Malashkevich, V. N., N. G. Dulyaninova, U. A. Ramagopal, M. A. Liriano, K. M. Varney, D. Knight, M. Brenowitz, D. J. Weber, S. C. Almo, and A. R. Bresnick. 2010. Phenothiazines inhibit S100A4 function by inducing protein oligomerization. *Proc Natl Acad Sci U S A* 107 (19):8605-10.
- Marenholz, I., R. C. Lovering, and C. W. Heizmann. 2006. An update of the S100 nomenclature. *Biochim Biophys Acta* 1763 (11):1282-3.
- Matsubara, D., T. Niki, S. Ishikawa, A. Goto, E. Ohara, T. Yokomizo, C. W. Heizmann, H. Aburatani, S. Moriyama, H. Moriyama, Y. Nishimura, N. Funata, and M. Fukayama. 2005. Differential expression of S100A2 and S100A4 in lung adenocarcinomas: clinicopathological significance, relationship to p53 and identification of their target genes. *Cancer Sci* 96 (12):844-57.
- Matsumoto, S., T. Yoshida, H. Murata, S. Harada, S. Nakamura, Y. Yamamoto, T. Watanabe, H. Yonekura, H. Yamamoto, T. Ohkubo, and Y. Kobayashi. 2008. Solution Structure of the Variable-Type Domain of the Receptor for Advanced Glycation End Products: New Insight into AGE-RAGE Interaction(.). *Biochemistry* 47:12299-12311.
- Matsushita, S., K-I Tada, K-I Kawahara, K. Kawai, T. Hashiguchi, I. Maruyama, and T. Kanekura. 2010. Advanced malignant melanoma responds to Prunus mume Sieb. Et Zucc (Ume) extract: Case report and in vitro study. *Experimental and Therapeutic medicine* 1:569-574.
- Mbele, G. O., J. C. Deloulme, B. J. Gentil, C. Delphin, M. Ferro, J. Garin, M. Takahashi, and J. Baudier. 2002. The zinc- and calcium-binding S100B interacts and co-localizes with IQGAP1 during dynamic rearrangement of cell membranes. *J Biol Chem* 277 (51):49998-50007.
- Memon, A. A., B. S. Sorensen, P. Meldgaard, L. Fokdal, T. Thykjaer, and E. Nexø. 2005. Down-regulation of S100C is associated with bladder cancer progression and poor survival. *Clin Cancer Res* 11 (2 Pt 1):606-11.

- Millward, T. A., C. W. Heizmann, B. W. Schafer, and B. A. Hemmings. 1998. Calcium regulation of Ndr protein kinase mediated by S100 calcium-binding proteins. *Embo J* 17 (20):5913-22.
- Mirmohammadsadegh, A., E. Tschakarjan, A. Ljoljic, K. Böhner, G. Michel, T. Ruzicka, M. Goos, and U. R. Hengge. 2000. Calgranulin C is overexpressed in lesional psoriasis. *Journal of Investigative Dermatology* 114 (6):1207-1208.
- Moore, B. W. 1965. A soluble protein characteristic of the nervous system. *Biochem Biophys Res Commun* 19 (6):739-44.
- Moroz, O. V., A. A. Antson, E. J. Dodson, H. J. Burrell, S. J. Grist, R. M. Lloyd, N. J. Maitland, G. G. Dodson, K. S. Wilson, E. Lukanidin, and I. B. Bronstein. 2002. The structure of S100A12 in a hexameric form and its proposed role in receptor signalling. *Acta Crystallogr D Biol Crystallogr* 58 (Pt 3):407-13.
- Moroz, O. V., K. S. Wilson, and I. B. Bronstein. 2010. The role of zinc in the S100 proteins: insights from the X-ray structures. *Amino Acids* in press.
- Mueller, A., B. W. Schäfer, S. Ferrari, M. Weibel, M. Makek, M. Hochli, and C. W. Heizmann. 2005. The calcium-binding protein S100A2 interacts with p53 and modulates its transcriptional activity. *J Biol Chem* 280 (32):29186-93.
- Murzik, U., P. Hemmerich, S. Weidtkamp-Peters, T. Ulbricht, W. Bussen, J. Hentschel, F. von Eggeling, and C. Melle. 2008. Rad54B targeting to DNA double-strand break repair sites requires complex formation with S100A11. *Mol Biol Cell* 19 (7):2926-35.
- Nakamura, K., S. Yamagishi, H. Adachi, T. Matsui, Y. Kurita-Nakamura, M. Takeuchi, H. Inoue, and T. Imaizumi. 2008. Serum levels of soluble form of receptor for advanced glycation end products (sRAGE) are positively associated with circulating AGEs and soluble form of VCAM-1 in patients with type 2 diabetes. *Microvasc Res* 76 (1):52-6.
- Nedjadi, T., N. Kitteringham, F. Campbell, R. E. Jenkins, B. K. Park, P. Navarro, F. Ashcroft, A. Tepikin, J. P. Neoptolemos, and E. Costello. 2009. S100A6 binds to annexin 2 in pancreatic cancer cells and promotes pancreatic cancer cell motility. *Br J Cancer* 101 (7):1145-54.
- Neeper, M., A. M. Schmidt, J. Brett, S. D. Yan, F. Wang, Y. C. Pan, K. Elliston, D. Stern, and A. Shaw. 1992. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J Biol Chem* 267 (21):14998-5004.
- Nozaki, I., T. Watanabe, M. Kawaguchi, H. Akatsu, K. Tsuneyama, Y. Yamamoto, K. Ohe, H. Yonekura, M. Yamada, and H. Yamamoto. 2007. Reduced expression of endogenous secretory receptor for advanced glycation endproducts in hippocampal neurons of Alzheimer's disease brains. *Arch Histol Cytol* 70 (5):279-90.
- Ohe, K., T. Watanabe, S. Harada, S. Munesue, Y. Yamamoto, H. Yonekura, and H. Yamamoto. 2010. Regulation of alternative splicing of the receptor for advanced glycation endproducts (RAGE) through G-rich cis-elements and heterogenous nuclear ribonucleoprotein H. *J Biochem* 147 (5):651-9.
- Ohuchida, K., K. Mizumoto, S. Ohhashi, H. Yamaguchi, H. Konomi, E. Nagai, K. Yamaguchi, M. Tsuneyoshi, and M. Tanaka. 2006. S100A11, a putative tumor suppressor gene, is overexpressed in pancreatic carcinogenesis. *Clin Cancer Res* 12 (18):5417-22.
- Ohuchida, K., K. Mizumoto, J. Yu, H. Yamaguchi, H. Konomi, E. Nagai, K. Yamaguchi, M. Tsuneyoshi, and M. Tanaka. 2007. S100A6 is increased in a stepwise manner during

- pancreatic carcinogenesis: clinical value of expression analysis in 98 pancreatic juice samples. *Cancer Epidemiol Biomarkers Prev* 16 (4):649-54.
- Osawa, M., Y. Yamamoto, S. Munesue, N. Murakami, S. Sakurai, T. Watanabe, H. Yonekura, Y. Uchigata, Y. Iwamoto, and H. Yamamoto. 2007. De-N-glycosylation or G82S mutation of RAGE sensitizes its interaction with advanced glycation endproducts. *Biochim Biophys Acta* 1770 (10):1468-74.
- Ostendorp, T., J. Diez, C. W. Heizmann, and G. Fritz. 2010. The crystal structures of human S100B in the zinc- and calcium-loaded state at three pH values reveal zinc ligand swapping. *Biochim Biophys Acta*. in press
- Ostendorp, T., E. Leclerc, A. Galichet, M. Koch, N. Demling, B. Weigle, C. W. Heizmann, P. M. Kroneck, and G. Fritz. 2007. Structural and functional insights into RAGE activation by multimeric S100B. *Embo J* 26 (16):3868-78.
- Otterbein, L. R., J. Kordowska, C. Witte-Hoffmann, C. L. Wang, and R. Dominguez. 2002. Crystal structures of S100A6 in the Ca(2+)-free and Ca(2+)-bound states: the calcium sensor mechanism of S100 proteins revealed at atomic resolution. *Structure* 10 (4):557-67.
- Perrone, L., G. Peluso, and M. A. Melone. 2008. RAGE recycles at the plasma membrane in S100B secretory vesicles and promotes Schwann cells morphological changes. *J Cell Physiol* 217 (1):60-71.
- Petersson, S., E. Shubbar, L. Enerback, and C. Enerback. 2009. Expression patterns of S100 proteins in melanocytes and melanocytic lesions. *Melanoma Res* 19 (4):215-25.
- Queisser, M. A., F. M. Kouri, M. Konigshoff, M. Wygrecka, U. Schubert, O. Eickelberg, and K. T. Preissner. 2008. Loss of RAGE in pulmonary fibrosis: molecular relations to functional changes in pulmonary cell types. *Am J Respir Cell Mol Biol* 39 (3):337-45.
- Ramsgaard, L., J. M. Englert, J. Tobolewski, L. Tomai, C. L. Fattman, A. S. Leme, A. M. Kaynar, S. D. Shapiro, J. J. Enghild, and T. D. Oury. 2010. The role of the receptor for advanced glycation end-products in a murine model of silicosis. *PLoS One* 5 (3):e9604.
- Rauci, A., S. Cugusi, A. Antonelli, S. M. Barabino, L. Monti, A. Bierhaus, K. Reiss, P. Saftig, and M. E. Bianchi. 2008. 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* 22 (10):3716-27.
- Rauvala, H., and A. Rouhiainen. 2010. Physiological and pathophysiological outcomes of the interactions of HMGB1 with cell surface receptors. *Biochim Biophys Acta* 1799 (1-2):164-70.
- Rehman, I., A. R. Azzouzi, S. S. Cross, J. C. Deloulme, J. W. Catto, N. Wylde, S. Larre, J. Champigneulle, and F. C. Hamdy. 2004. Dysregulated expression of S100A11 (calgizzarin) in prostate cancer and precursor lesions. *Hum Pathol* 35 (11):1385-91.
- Ribe, A., and N. S. McNutt. 2003. S100A6 protein expression is different in Spitz nevi and melanomas. *Mod Pathol* 16 (5):505-11.
2003. S100A protein expression in the distinction between lentigo maligna and pigmented actinic keratosis. *Am J Dermatopathol* 25 (2):93-9.
- Rintala-Dempsey, A. C., L. Santamaria-Kisiel, Y. Liao, G. Lajoie, and G. S. Shaw. 2006. Insights into S100 target specificity examined by a new interaction between S100A11 and annexin A2. *Biochemistry* 45 (49):14695-705.

- Robinson, M. J., P. Tessier, R. Poulsom, and N. Hogg. 2002. The S100 family heterodimer, MRP-8/14, binds with high affinity to heparin and heparan sulfate glycosaminoglycans on endothelial cells. *J Biol Chem* 277 (5):3658-65.
- Rong, L. L., W. Trojaborg, W. Qu, K. Kostov, S. D. Yan, C. Gooch, M. Szabolcs, A. P. Hays, and A. M. Schmidt. 2004. Antagonism of RAGE suppresses peripheral nerve regeneration. *Faseb J* 18 (15):1812-7.
- Rong, L. L., S. F. Yan, T. Wendt, D. Hans, S. Pachydaki, L. G. Bucciarelli, A. Adebayo, W. Qu, Y. Lu, K. Kostov, E. Lalla, S. D. Yan, C. Gooch, M. Szabolcs, W. Trojaborg, A. P. Hays, and A. M. Schmidt. 2004. RAGE modulates peripheral nerve regeneration via recruitment of both inflammatory and axonal outgrowth pathways. *Faseb J* 18 (15):1818-25.
- Saha, A., Y. C. Lee, Z. J. Zhang, G. Chandra, S. B. Su, and A. B. Mukherjee. 2010. Lack of an Endogenous Anti-inflammatory Protein in Mice Enhances Colonization of B16F10 Melanoma Cells in the Lungs. *Journal of Biological Chemistry* 285 (14):10822-10831.
- Sakaguchi, M., H. Sonogawa, H. Murata, M. Kitazoe, J. Futami, K. Kataoka, H. Yamada, and N. H. Huh. 2008. S100A11, an Dual Mediator for Growth Regulation of Human Keratinocytes. *Mol Biol Cell* 19 (1):78-85.
- Sakatani, S., K. Yamada, C. Homma, S. Munesue, Y. Yamamoto, H. Yamamoto, and H. Hirase. 2009. Deletion of RAGE causes hyperactivity and increased sensitivity to auditory stimuli in mice. *PLoS One* 4 (12):e8309.
- Sander, C. S., F. Hamm, P. Elsner, and J. J. Thiele. 2003. Oxidative stress in malignant melanoma and non-melanoma skin cancer. *Br J Dermatol* 148 (5):913-22.
- Santamaria-Kisiel, L., A. C. Rintala-Dempsey, and G. S. Shaw. 2006. Calcium-dependent and -independent interactions of the S100 protein family. *Biochem J* 396 (2):201-14.
- Santilli, F., N. Vazzana, L. G. Bucciarelli, and G. Davi. 2009. Soluble forms of RAGE in human diseases: clinical and therapeutical implications. *Curr Med Chem* 16 (8):940-52.
- Sastry, M., R. R. Ketchum, O. Crescenzi, C. Weber, M. J. Lubinski, H. Hidaka, and W. J. Chazin. 1998. The three-dimensional structure of Ca(2+)-bound calyculin: implications for Ca(2+)-signal transduction by S100 proteins. *Structure* 6 (2):223-31.
- Schmidt, A. M., M. Vianna, M. Gerlach, J. Brett, J. Ryan, J. Kao, C. Esposito, H. Hegarty, W. Hurley, M. Clauss, and et al. 1992. 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* 267 (21):14987-97.
- Schmidt, A. M., S. D. Yan, S. F. Yan, and D. M. Stern. 2000. The biology of the receptor for advanced glycation end products and its ligands. *Biochim Biophys Acta* 1498 (2-3):99-111.
2001. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 108 (7):949-55.
- Semov, A., M. J. Moreno, A. Onichtchenko, A. Abulrob, M. Ball, I. Ekiel, G. Pietrzynski, D. Stanimirovic, and V. Alakhov. 2005. Metastasis-associated protein S100A4 induces angiogenesis through interaction with Annexin II and accelerated plasmin formation. *J Biol Chem* 280 (21):20833-41.
- Shimamoto, S., Y. Kubota, H. Tokumitsu, and R. Kobayashi. 2010. S100 proteins regulate the interaction of Hsp90 with Cyclophilin 40 and FKBP52 through their tetratricopeptide repeats. *FEBS Lett* 584 (6):1119-25.

- Shrestha, P., Y. Muramatsu, W. Kudeken, M. Mori, Y. Takai, E. C. Ilg, B. W. Schafer, and C. W. Heizmann. 1998. Localization of Ca(2+)-binding S100 proteins in epithelial tumours of the skin. *Virchows Arch* 432 (1):53-9.
- Shtivelman, E., and J. M. Bishop. 1993. The human gene AHNAK encodes a large phosphoprotein located primarily in the nucleus. *J Cell Biol* 120 (3):625-30.
- Sims, G.P., D.C. Rowe, S.T. Rietdijk, R. Herbst, and A.J. Coyle. 2010. HMGB1 and RAGE in Inflammation and Cancer. *Annual Review of Immunology* 28:367-388.
- Skripnikova, E. V., and N. B. Gusev. 1989. Interaction of smooth muscle caldesmon with S-100 protein. *FEBS Lett* 257 (2):380-2.
- Slomnicki, L. P., B. Nawrot, and W. Lesniak. 2009. S100A6 binds p53 and affects its activity. *Int J Biochem Cell Biol* 41 (4):784-90.
- Smith, S. L., M. Gugger, P. Hoban, D. Ratschiller, S. G. Watson, J. K. Field, D. C. Betticher, and J. Heighway. 2004. S100A2 is strongly expressed in airway basal cells, preneoplastic bronchial lesions and primary non-small cell lung carcinomas. *Br J Cancer* 91 (8):1515-24.
- Sousa, M. M., S. D. Yan, D. Stern, and M. J. Saraiva. 2000. Interaction of the receptor for advanced glycation end products (RAGE) with transthyretin triggers nuclear transcription factor kB (NF-kB) activation. *Lab Invest* 80 (7):1101-10.
- Sparvero, L. J., D. Asafu-Adjei, R. Kang, D. Tang, N. Amin, J. Im, R. Rutledge, B. Lin, A. A. Amoscato, H. J. Zeh, and M. T. Lotze. 2009. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. *J Transl Med* 7:17.
- Spatz, A., N. Stock, G. Batist, and L. C. van Kempen. 2010. The biology of melanoma prognostic factors. *Discov Med* 10 (50):87-93.
- Spiekerkoetter, E., C. Guignabert, V. de Jesus Perez, T. P. Alastalo, J. M. Powers, L. Wang, A. Lawrie, N. Ambartsumian, A. M. Schmidt, M. Berryman, R. H. Ashley, and M. Rabinovitch. 2009. 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* 105 (7):639-47.
- Srikrishna, G., J. Nayak, B. Weigle, A. Temme, D. Foell, L. Hazelwood, A. Olsson, N. Volkmann, D. Hanein, and H. H. Freeze. 2010. Carboxylated N-glycans on RAGE promote S100A12 binding and signaling. *J Cell Biochem* 110 (3):645-59.
- Strazisar, M., V. Mlakar, and D. Glavac. 2009. The expression of COX-2, hTERT, MDM2, LATS2 and S100A2 in different types of non-small cell lung cancer (NSCLC). *Cell Mol Biol Lett* 14 (3):442-56.
- Strazisar, M., T. Rott, and D. Glavac. 2009. Frequent polymorphic variations but rare tumour specific mutations of the S100A2 on 1q21 in non-small cell lung cancer. *Lung Cancer* 63 (3):354-9.
- Sturchler, E., A. Galichet, M. Weibel, E. Leclerc, and C. W. Heizmann. 2008. Site-specific blockade of RAGE-Vd prevents amyloid-beta oligomer neurotoxicity. *J Neurosci* 28 (20):5149-58.
- Suzuki, F., N. Oridate, A. Homma, Y. Nakamaru, T. Nagahashi, K. Yagi, S. Yamaguchi, Y. Furuta, and S. Fukuda. 2005. 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* 14 (6):1493-8.

- Takenaga, K., Y. Nakamura, S. Sakiyama, Y. Hasegawa, K. Sato, and H. Endo. 1994. Binding of pEL98 protein, an S100-related calcium-binding protein, to nonmuscle tropomyosin. *J Cell Biol* 124 (5):757-68.
- Tan, M., C. W. Heizmann, K. Guan, B. W. Schafer, and Y. Sun. 1999. Transcriptional activation of the human S100A2 promoter by wild-type p53. *FEBS Lett* 445 (2-3):265-8.
- Tesarova, P., M. Kalousova, M. Jachymova, O. Mestek, L. Petruzelka, and T. Zima. 2007. Receptor for advanced glycation end products (RAGE)--soluble form (sRAGE) and gene polymorphisms in patients with breast cancer. *Cancer Invest* 25 (8):720-5.
- van Dieck, J., M. R. Fernandez-Fernandez, D. B. Veprintsev, and A. R. Fersht. 2009. Modulation of the oligomerization state of p53 by differential binding of proteins of the S100 family to p53 monomers and tetramers. *J Biol Chem* 284 (20):13804-11.
- van Dieck, J., D. P. Teufel, A. M. Jaulent, M. R. Fernandez-Fernandez, T. J. Rutherford, A. Wyslouch-Cieszyńska, and A. R. Fersht. 2009. Posttranslational modifications affect the interaction of S100 proteins with tumor suppressor p53. *J Mol Biol* 394 (5):922-30.
- Van Ginkel, P. R., R. L. Gee, T. M. Walker, D. N. Hu, C. W. Heizmann, and A. S. Polans. 1998. The identification and differential expression of calcium-binding proteins associated with ocular melanoma. *Biochim Biophys Acta* 1448 (2):290-7.
- Vimalachandran, D., W. Greenhalf, C. Thompson, J. Luttges, W. Prime, F. Campbell, A. Dodson, R. Watson, T. Crnogorac-Jurcevic, N. Lemoine, J. Neoptolemos, and E. Costello. 2005. High nuclear S100A6 (Calcyclin) is significantly associated with poor survival in pancreatic cancer patients. *Cancer Res* 65 (8):3218-25.
- Vogl, T., N. Leukert, K. Barczyk, K. Strupat, and J. Roth. 2006. Biophysical characterization of S100A8 and S100A9 in the absence and presence of bivalent cations. *Biochim Biophys Acta* 1763 (11):1298-306.
- Weterman, M. A., G. M. Stoopen, G. N. van Muijen, J. Kuznicki, D. J. Ruiter, and H. P. Bloemers. 1992. Expression of calyculin in human melanoma cell lines correlates with metastatic behavior in nude mice. *Cancer Res* 52 (5):1291-6.
- Weterman, M. A., G. N. van Muijen, H. P. Bloemers, and D. J. Ruiter. 1993. Expression of calyculin in human melanocytic lesions. *Cancer Res* 53 (24):6061-6.
- Wilder, P. T., J. Lin, C. L. Bair, T. H. Charpentier, D. Yang, M. Liriano, K. M. Varney, A. Lee, A. B. Oppenheim, S. Adhya, F. Carrier, and D. J. Weber. 2006. Recognition of the tumor suppressor protein p53 and other protein targets by the calcium-binding protein S100B. *Biochim Biophys Acta* 1763 (11):1284-97.
- Wilder, P. T., K. M. Varney, M. B. Weiss, R. K. Gitti, and D. J. Weber. 2005. Solution structure of zinc- and calcium-bound rat S100B as determined by nuclear magnetic resonance spectroscopy. *Biochemistry* 44 (15):5690-702.
- Wilton, R., M. A. Yousef, P. Saxena, M. Szpunar, and F. J. Stevens. 2006. Expression and purification of recombinant human receptor for advanced glycation endproducts in *Escherichia coli*. *Protein Expr Purif* 47 (1):25-35.
- Wondrak, G. T., M. K. Jacobson, and E. L. Jacobson. 2006. Antimelanoma activity of apoptogenic carbonyl scavengers. *J Pharmacol Exp Ther* 316 (2):805-14.
- Xu, R. H., H. Pelicano, Y. Zhou, J. S. Carew, L. Feng, K. N. Bhalla, M. J. Keating, and P. Huang. 2005. Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. *Cancer Res* 65 (2):613-21.

- Yammani, R. R., C. S. Carlson, A. R. Bresnick, and R. F. Loeser. 2006. Increase in production of matrix metalloproteinase 13 by human articular chondrocytes due to stimulation with S100A4: Role of the receptor for advanced glycation end products. *Arthritis Rheum* 54 (9):2901-11.
- Yan, S. D., A. Bierhaus, P. P. Nawroth, and D. M. Stern. 2009. RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? *J Alzheimers Dis* 16 (4):833-43.
- Yan, S. D., X. Chen, J. Fu, M. Chen, H. Zhu, A. Roher, T. Slattery, L. Zhao, M. Nagashima, J. Morser, A. Migheli, P. Nawroth, D. Stern, and A. M. Schmidt. 1996. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 382 (6593):685-91.
- Yan, S. F., S. Du Yan, R. Ramasamy, and A. M. Schmidt. 2009. Tempering the wrath of RAGE: An emerging therapeutic strategy against diabetic complications, neurodegeneration, and inflammation. *Ann Med*:1-15.
- Yan, S. F., R. Ramasamy, Y. Naka, and A. M. Schmidt. 2003. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circ Res* 93 (12):1159-69.
- Yan, S. F., R. Ramasamy, and A. M. Schmidt. 2010. Soluble RAGE: therapy and biomarker in unraveling the RAGE axis in chronic disease and aging. *Biochem Pharmacol* 79 (10):1379-86.
- Yang, Y. Q., L. J. Zhang, H. Dong, C. L. Jiang, Z. G. Zhu, J. X. Wu, Y. L. Wu, J. S. Han, H. S. Xiao, H. J. Gao, and Q. H. Zhang. 2007. Upregulated expression of S100A6 in human gastric cancer. *J Dig Dis* 8 (4):186-93.
- Yonekura, H., Y. Yamamoto, S. Sakurai, R. G. Petrova, M. J. Abedin, H. Li, K. Yasui, M. Takeuchi, Z. Makita, S. Takasawa, H. Okamoto, T. Watanabe, and H. Yamamoto. 2003. 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* 370 (Pt 3):1097-109.
- Zhang, L., M. Bukulin, E. Kojro, A. Roth, V. V. Metz, F. Fahrenholz, P. P. Nawroth, A. Bierhaus, and R. Postina. 2008. Receptor for advanced glycation end products is subjected to protein ectodomain shedding by metalloproteinases. *J Biol Chem* 283 (51):35507-16.
- Zhang, T., T. L. Woods, and J. T. Elder. 2002. Differential responses of S100A2 to oxidative stress and increased intracellular calcium in normal, immortalized, and malignant human keratinocytes. *J Invest Dermatol* 119 (5):1196-201.
- Zimmer, D. B., and L. J. Van Eldik. 1986. Identification of a molecular target for the calcium-modulated protein S100. Fructose-1,6-bisphosphate aldolase. *J Biol Chem* 261 (24):11424-8.
- Zimmer, D. B., and D. J. Weber. 2010. The Calcium-Dependent Interaction of S100B with Its Protein Targets. *Cardiovasc Psychiatry Neurol* in press.

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Melanoma is considered to be one of the most aggressive forms of skin neoplasms. Despite aggressive researches towards finding treatments, no effective therapy exists to inhibit the metastatic spread of malignant melanoma. The 5-year survival rate of metastatic melanoma is still significantly low, and there has been an earnest need to develop more effective therapies with greater anti-melanoma activity. Through the accomplishment of over 100 distinguished and respected researchers from 19 different countries, this book covers a wide range of aspects from various standpoints and issues related to melanoma. These include the biology of melanoma, pigmentations, pathways, receptors and diagnosis, and the latest treatments and therapies to make potential new therapies. Not only will this be beneficial for readers, but it will also contribute to scientists making further breakthroughs in melanoma research.

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