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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 Aβ 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 conteract the effect of circulating RAGE ligands whose affinity towards RAGE are in the nanomolar RAGE (Tesarova et al. 2007; Nakamura et al. 2008; Bierhaus and Nawroth 2009; Kislinger et al. 1999; Dattilo et al. 2007).

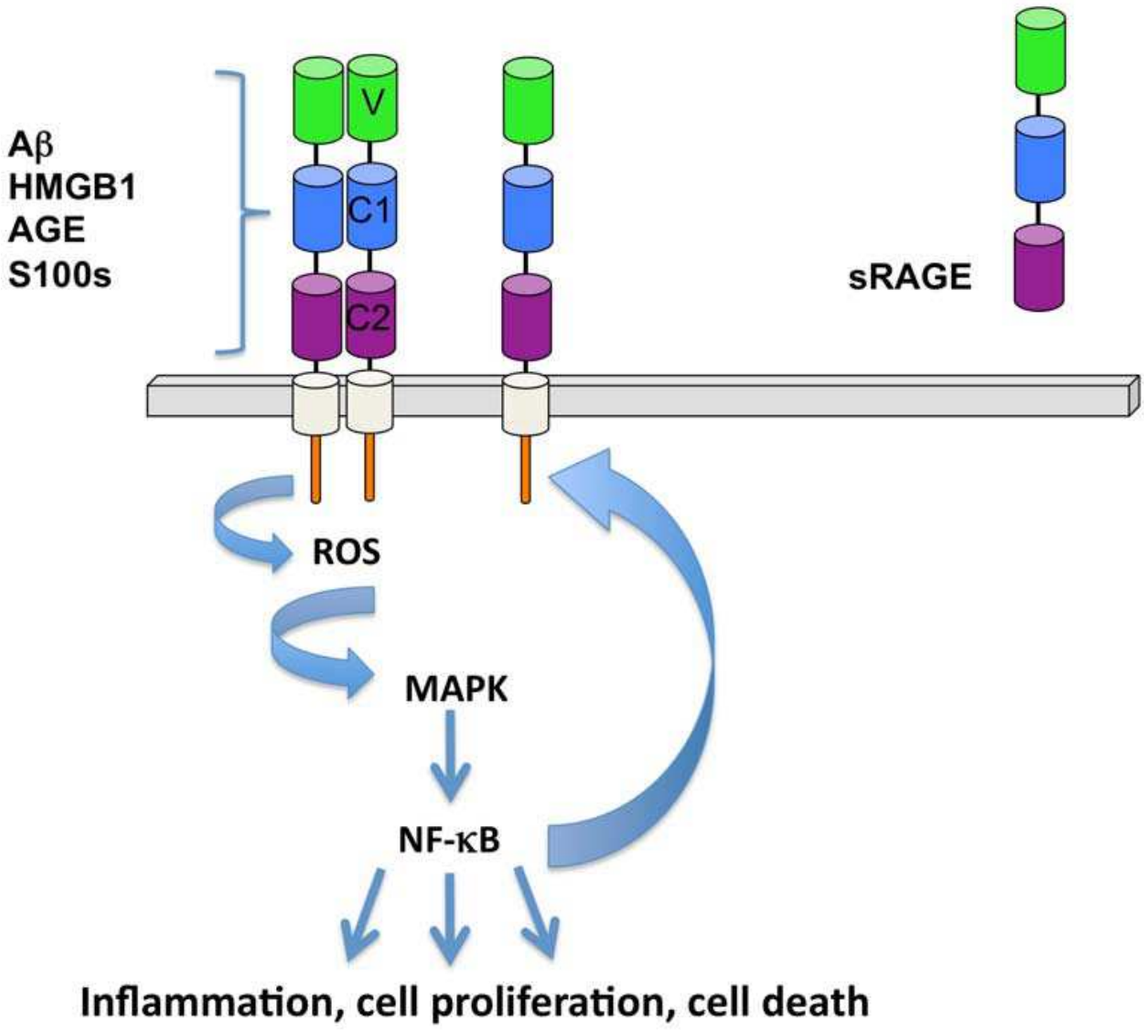

Fig. 1. RAGE and its ligands. RAGE is activated by structurally unrelated ligands. These ligands include the advanced glycation endproducts (AGE), amyloid β peptides, high mobility group box 1 protein and members of the S100 protein family. Recent evidences suggest that RAGE dimerize on the cell surface. 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-κB. Since RAGE expression is under the control of NF-κB, 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-κB, 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-kB 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 = 20-500 μM) (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 = 0.1-1 μM) that 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, ounce 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 μM) 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 Maelandsmo 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 (Maelandsmo 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 Maelandsmo 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 S1000A6 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 occular and non-occular 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-κB (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 RAGEΔcyto), were compared. The study showed that mice that received the B16-F1 RAGEΔcyto 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).

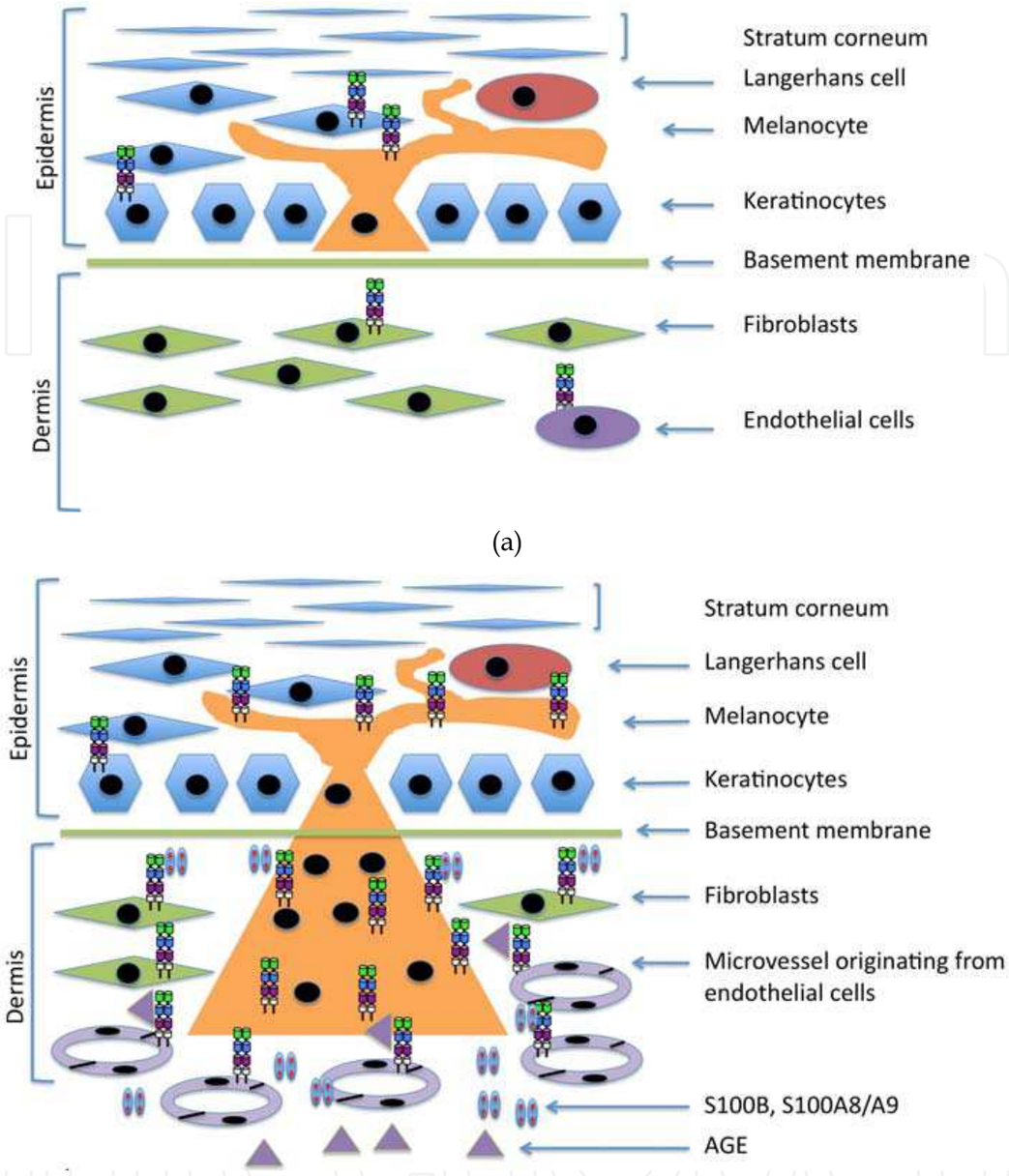

Fig. 2. a) Cells of the epidermis and dermis. In the epidermis, RAGE is expressed in skin fibroblasts, keratinocytes, endothelial cells and melanocytes (Lohwasser et al. 2006). In the dermis, RAGE is expressed on the surface of fibroblasts and endothelial cells. b) Invasion of melanocytes through the 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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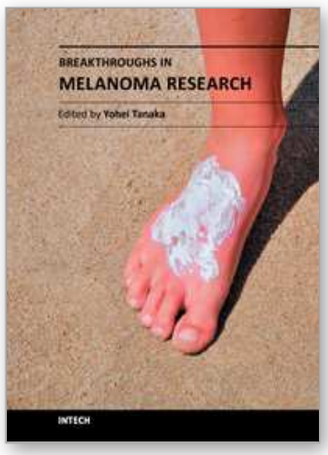

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Melanoma is considered to be one of the most aggressive forms of skin neoplasms. Despite aggressive researches towards finding treatments, no effective therapy exists to inhibit the metastatic spread of malignant melanoma. The 5-year survival rate 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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