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Deep Insight Section

S100 Protein Family and Tumorigenesis

Geetha Srikrishna, Hudson H Freeze

Sanford-Burnham Medical Research Institute, 10905 Road to the Cure, San Diego, CA 92121, USA (GS, HHF)

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1. Introduction

S100 proteins are a family of 25 homologous intracellular calcium-binding proteins characterized by EF hand motifs, low molecular weights (9-13 kDa), ability to form homodimers, heterodimers and oligomeric assemblies, and are characterized by tissue and cell-specific expression (Donato, 2001; Heizmann et al., 2002; Marenholz et al., 2004; Roth et al., 2003) (Figure 1). They are solely present in vertebrates (Donato, 2001). While human S100B, S100P, S100Z and S100G are located at 21q22, 4p16, 5q14 and Xp22 respectively, 21 of the human S100 genes (S100A1-S100A18, trichohyalin, filaggrin and repetin) are clustered at the chromosomal region 1q21, a region that is frequently deleted, translocated or duplicated in epithelial tumors and tumors of soft tissues (Craig et al., 1994; Donato, 2001; Gebhardt et al., 2006; Heizmann et al., 2002) (Figure 2). There is growing evidence that expression of S100 proteins is altered in many tumors, often in association with tumor progression, and they are therefore potentially important tumor biomarkers and therapeutic targets. However, their precise roles in tumor progression are not completely understood.

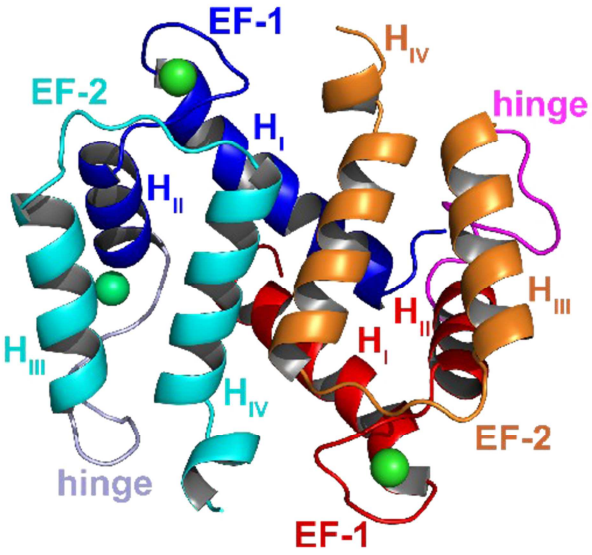

Figure 1. Dimer structure of S100 proteins. S100 proteins form a large multi-gene family of low molecular weight proteins that are characterized by calcium-binding EF hand motifs and exhibit remarkable tissue and cell-specific expression. They exist as homo and heterodimers, and oligomers. Each monomer consists of two EF-hands connected by a hinge region. (Reproduced from Heizmann CW, Fritz G, Schafer BW. Frontiers in Bioscience. 2002 May 1;7:d1356-68).

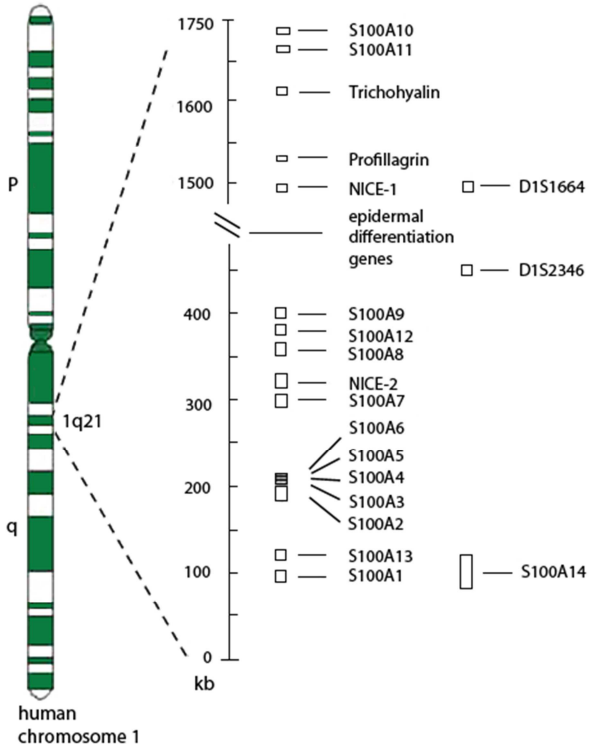

Figure 2. The S100 gene cluster on human chromosome 1q21. Most human S100 genes are located in the epidermal differentiation complex on chromosome 1q21, a region prone to rearrangements. Genes located in the cluster region are indicated, as well as two commonly used genomic markers (D1S1664 and D1S2346). p and q indicate the short and the long arm of the chromosome, respectively. Human S100B, S100P, S100Z and S100G are located on chromosomes 21q22, 4p16, 5q14 and Xp22 respectively. (Reproduced from Heizmann CW, Fritz G, Schafer BW. Frontiers in Bioscience. 2002 May 1;7:d1356-68).

2. Structure and functions of S100 proteins

S100 proteins have two distinct EF-hand (helix-loop-helix motif) calcium-binding domains connected by a hinge region (Fritz et al., 2010). The canonical C-terminal calcium-binding EF- hand is common to all EF-hand proteins, while the N-terminal EF-hand is non-canonical. There is variable degree of sequence identity among S100 proteins. S100 proteins exist as anti-parallel hetero and homodimers within cells. Calcium binding causes conformational changes that exposes binding sites for target proteins.

Intracellular functions of S100 proteins have been extensively studied. These include calcium homeostasis, cell cycle regulation, cell growth and migration, cytoskeletal interactions, membrane trafficking, protein phosphorylation, and regulation of transcriptional factors among others (Donato, 2001; Heizmann et al., 2002; Marenholz et al., 2004; Roth et al., 2003). S100 proteins can also be released into extracellular space in response to stimuli, or during cell damage, and they promote responses including neuronal survival and extension (S100B), apoptosis (S100A4 and S100A6), inflammation (S100B, S100A8/A9, S100A11 and S100A12), autoimmunity (S100A8/A9), chemotaxis (S100A8/A9) and cell proliferation and survival (S100P, S100A7), thus effectively functioning as paracrine and autocrine mediators. S100B, S100P, S100A4, S100A6, S100A8/A9, S100A11 and S100A12 are known to act via interaction with cell surface receptors, primarily the Receptor for Advanced Glycation End Products (RAGE) (Donato, 2007; Leclerc et al., 2009), while S100A8/A9 also bind Toll-like receptors or TLRs (Vogl et al., 2007). Multimeric forms of S100 proteins appear to be necessary for the extracellular functions of S100 proteins (Donato, 2007; Leukert et al., 2006). Multimeric assemblies have been reported for S100A12, S100A4, S100B and S100A8/A9 (Fritz et al., 2010). Elevated S100 protein levels are associated with chronic inflammation, neurodegeneration, cardiomyopathies, atherosclerosis and cancer (Pietzsch, 2010).

3. S100 proteins and tumorigenesis

A number of S100 proteins are up-regulated in tumors (Salama et al., 2008). With the identification of binding proteins and signaling pathways for at least a few of its family members, S100 proteins promise to offer both functional biomarkers and therapeutic targets in cancers, and the case for considering their importance is evolving rapidly (summarized in Table 1).

Table 1. Expression of S100 proteins in tumors*.

S100 proteins	Tumors in which expression is up-regulated	Tumors in which expression is down-regulated	Known functions / interactions / mechanism of action
S100A1	Renal, clear cell and papillary Endometriod subtype of ovarian and endometrial		Known RAGE ligand.
S100A2	Lung, non-small cell Pancreatic Gastric Thyroid, papillary and anaplastic	Oral squamous cell Prostate	Promotes p53 transcriptional activity and reduces expression of Cox-2.
S100A4	Breast		Promotes tumor migration, invasion and

	Colorectal Gastric Prostate Lung, non-small cell Ovarian Pancreatic Melanoma		angiogenesis. Regulates matrix metalloproteinases and interacts with p53 and inhibits p53 phosphorylation.
S100A6	Colorectal Pancreatic Gastric Hepatocellular Lung Melanoma		Known RAGE ligand.
S100A7	Breast, ER negative invasive, DCIS Bladder Skin		Possible interaction with Jab-1.
S100A8/A9	Gastric Colon Pancreatic Bladder Ovarian Thyroid Breast Skin		Interaction with RAGE and TLR4; promote tumor proliferation, and migration, accumulation of myeloid derived suppressor cells, activation of protumorigenic genes, and formation of premetastatic niches in distal organs.
S100A11	Uterine, smooth muscle Lymphoma, anaplastic large cell Pancreatic	Bladder Esophageal, squamous cell	
S100B	Melanoma (biomarker) Astrocytoma, anaplastic Glioblastomas		Interacts with p53 and down-regulates p53-mediated apoptosis in melanoma. Well known RAGE ligand.
S100P	Ovarian Pancreatic Breast Gastric Colorectal Prostate Lung		Activation of RAGE dependent signaling pathways.

* Relevant references are provided in the text.

3.1. S100A1

S100A1 is predominantly expressed in the heart, and to a lesser extent in the skeletal muscle (Heizmann et al., 2007; Leclerc et al., 2009). S100A1 is a key modulator of calcium homeostasis in the heart and targets several key regulators of sarcoplasmic reticulum including Ca^{2+} ATPase, ryanodine receptors and other targets, thereby enhancing cardiomyocyte performance. Dysregulation of cardiomyocyte S100A1 protein, and diminished levels following myocardial infarction contributes to cardiac hypertrophy and heart failure. Extracellularly, S100A1 exists as both a homodimer and heterodimer with S100B, S100A4 and S100P and interacts with RAGE (Leclerc et al., 2009). Besides cardiac and skeletal muscle, expression of S100A1 is low in most normal tissues, but up-regulated in cancers of the kidneys, skin and ovary. S100A1 expression helps to differentiate subtypes of renal carcinoma. S100A1 protein is expressed in renal oncocytomas, and in clear cell and papillary renal cell carcinomas but not in chromophobe renal cell carcinomas (Cossu-Rocca et al., 2009; Li et al., 2007). In addition, S100A1 is a specific and sensitive immunohistochemical marker to differentiate nephrogenic adenoma from prostatic adenocarcinoma where it is not expressed (Cossu-Rocca et al., 2009). S100A1 messenger RNA and protein are up-regulated in ovarian tumors and ovarian cancer metastasis compared with normal ovarian tissues. In the endometrioid subtype of ovarian and endometrial cancers, there is a negative correlation

between relapse-free survival and S100A1 expression, suggesting that S100A1 is a marker for poor prognosis of endometrioid subtypes of cancer (DeRycke et al., 2009).

3.2. S100A2

S100A2 protein is present in many organs or tissues, with high expression in lung and kidney. Unlike most other S100 proteins, S100A2 is markedly down-regulated in many tumors suggesting that it acts as a tumor suppressor gene. It promotes transcriptional activity of p53 (Mueller et al., 2005) and reduces expression of Cox-2 (Tsai et al., 2006). On the other hand, S100A2 is also up-regulated in some tumors (Salama et al., 2008; Wolf et al., 2010).

Loss of S100A2 expression has been associated with poor prognosis and shorter survival. S100A2 expression decreases in epithelial cells from normal to tumor stages, with the decrease more pronounced in glandular than in squamous epithelial tissue (Nagy et al., 2002). S100A2 expression is reduced in early-stage oral squamous cell carcinoma and is significantly associated with tumor recurrence and metastasis (Suzuki et al., 2005; Tsai et al., 2005). Patients with S100A2 positive laryngeal squamous cell carcinoma had a better relapse-free overall survival than patients with S100A2-negative tumors (Almadori et al., 2009). Benign prostate hyperplasia and prostatitis are characterized by higher levels of S100A2 than low-grade cancer, and expression is lost in high-grade and metastatic cancer specimens (Gupta et al., 2003).

S100A2 is up-regulated in some tumors such as non-small cell lung carcinoma (Smith et al., 2004), with higher expression found in early-stage carcinomas, associated with reduced overall survival, and higher propensity to metastasis (Bartling et al., 2007; Bulk et al., 2009; Feng et al., 2001; Wang et al., 2005; Zech et al., 2006). In pancreatic cancer tissues and cell lines, S100A2 expression is significantly higher than in normal pancreatic tissues, and higher expression co-related with poor disease outcome (Biankin et al., 2009; Ohuchida et al., 2007). S100A2 is also over-expressed in gastric tumors compared to normal gastric mucosa (Lee et al., 2006). Varied expression has been reported with oesophageal squamous carcinoma (Cao et al., 2009; Imazawa et al., 2005; Ji et al., 2004). In thyroid carcinomas, S100A2 is absent in follicular adenomas and carcinomas, but up-regulated in papillary and anaplastic carcinomas, providing a possible marker for distinguishing these two types of thyroid carcinoma (Ito et al., 2005).

3.3. S100A4

S100A4, also called Metastatin due to its well-established association with tumor metastasis (Tarabykina et al., 2007; Sherbet, 2009; Boye and Maelandsmo, 2010), is normally found in the nervous system and believed to be involved in neuritogenesis. S100A4 is also expressed at low levels in normal human fibroblasts, monocytes, macrophages, T cells, neutrophils, and endothelial cells. Although its expression is low in normal tissues, it is highly expressed in many tumors such as breast, colorectal, gastric, prostate and non-small cell lung cancer, ovarian and pancreatic cancers, and malignant melanoma (Boye and Maelandsmo, 2010; Sherbet, 2009). Expression is a significant predictor of patient survival and metastatic disease. S100A4 was first cloned from highly metastatic breast cancer cells, and since then its involvement in cancer metastasis has been substantiated by several studies (Boye and Maelandsmo, 2010; Sherbet, 2009; Tarabykina et al., 2007). Studies show that extracellular, intracellular, tumor-derived, and stroma-derived S100A4 all contribute to the metastatic process, and influence several steps in the metastatic cascade, including migration, invasion, and angiogenesis. Much of this metastatic potential has been linked to the ability of S100A4 to regulate matrix metalloproteinases, modulate cell motility, promote angiogenesis and epithelial mesenchymal transition, and the association of S100A4 expression with reduced expression of tumor suppressor genes such as p53 (Garrett et al., 2006; Salama et al., 2008). S100A4 interacts with p53 and inhibits p53-mediated tumor suppression by inhibiting its phosphorylation (Grigorian et al., 2001). The extensive association of S100A4 with tumor progression and metastasis has positioned it to be a target for novel therapeutic strategies.

3.4. S100A6

S100A6 is highly expressed in various organs, and on fibroblasts, epithelial and other cells (Leclerc et al., 2009; Lesniak et al., 2009). S100A6 is predominantly cytoplasmic protein but can translocate in the presence of Ca^{2+} to plasma membrane and the nuclear envelope. S100A6 expression can be up-regulated by platelet-derived growth factor, epidermal growth factor, tumor necrosis factor, retinoic acid and estrogen, and upon stress conditions, and at the transcriptional level by NF-κB. S100A6 interacts with many proteins including CacyBP/SIP, annexins II and XI, tropomycin and RAGE (Leclerc et al., 2009; Lesniak et al., 2009). S100A6 is overexpressed in many cancers including colorectal, pancreatic, gastric, hepatocellular and lung cancers, and melanoma. Expression in melanoma, pancreatic and colorectal cancers has been shown to correlate with tumor growth and metastatic progression suggesting a potential role for S100A6 in the development of malignancy (Lesniak et al., 2009; Salama et al., 2008). It is however down-regulated in prostate cancer and medulloblastoma.

3.5. S100A7

S100A7 was first identified in inflamed psoriatic skin, hence is also called psoriasin (Watson et al., 1998). It is released from keratinocytes around wounds and believed to exert cytokine and anti bacterial effects, and is also chemotactic for granulocyes, monocytes and lymphocytes (Eckert et al., 2004). Contrary to other S100 proteins, calcium binding does not induce large conformational changes in S100A7 (Streicher et al.,

2010). S100A7 is up regulated in breast, bladder and skin cancers (Salama et al., 2008). Increasing evidence show that S100A7 is up-regulated in ductal carcinoma in situ and ER negative invasive breast cancer and expression correlates with aggressive phenotype and patient survival (Emberley et al., 2004b). S100A7 interacts with Jab1 (c-jun activation domain binding protein 1) a protein with highly recognizable role in tumorigenesis to elicit functional effects in breast tumor progression (Emberley et al., 2004a).

3.6. S100A8/A9

S100A8 and S100A9 are expressed predominantly by myeloid cells, including granulocytes, monocytes, myeloid derived suppressor cells (MDSC) and other immature cells of myeloid lineage (Cheng et al., 2008; Goyette and Geczy, 2010; Roth et al., 2003; Sinha et al., 2008). Although the proteins are products of distinct genes, they are often co-expressed and function mainly as heterodimer of S100A8/A9 (calprotectin). Expression is down-regulated during macrophage and dendritic cell differentiation (Cheng et al., 2008; Lagasse and Clerc, 1988; Odink et al., 1987), but can be induced in epithelial cells, osteoclasts and keratinocytes (Gebhardt et al., 2006). S100A8/A9 released into the extracellular medium in response to cell damage or activation become danger signals (Damage Associated Molecular Pattern molecules or DAMP), which alert the host of danger by triggering immune responses and activating repair mechanisms through interaction with pattern recognition receptors (Donato, 2007; Ehrchen et al., 2009; Foell et al., 2007; Leclerc et al., 2009; Srikrishna and Freeze, 2009). Elevated S100A8/A9 is the hallmark of inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, cystic fibrosis and psoriasis (Foell et al., 2007; Roth et al., 2001; Roth et al., 2003). Critical roles for these proteins in endotoxin-induced lethality and systemic autoimmunity have recently been recognized (Loser et al., 2010; Vogl et al., 2007). In addition to expression within inflammatory milieu, strong up-regulation of these proteins has also been observed in many tumors, including gastric, colon, pancreatic, bladder, ovarian, thyroid, breast and skin cancers (Gebhardt et al., 2006; Salama et al., 2008).

S100A8/A9 exhibit concentration-dependent dichotomy of function in tumors. At high concentrations S100A8/A9 exert apoptotic effects on tumor cells (Ghavami et al., 2004), while at low concentrations promote tumor cell growth (Ghavami et al., 2008; Turovskaya et al., 2008). S100A8/A9 also stimulate tumor cell migration at low concentrations (Ang et al., 2010; Hermani et al., 2006; Hiratsuka et al., 2006; Moon et al., 2008; Saha et al., 2010). S100A8/A9 regulate the accumulation of MDSC (Cheng et al., 2008; Sinha et al., 2008), which are immature myeloid cells that expand during inflammation and in tumors, and are potent suppressors of T-cell mediated immune responses (Dolcetti et al., 2008; Gabrilovich and Nagaraj, 2009; Ostrand-Rosenberg and Sinha, 2009). Tumor derived factors promote sustained STAT3 dependent upregulation of S100A9 in myeloid precursors which results in inhibition of differentiation to DC and accumulation of MDSC (Cheng et al., 2008). S100A8/A9 are not only synthesized and secreted by MDSC, but they also have binding sites for S100A8/A9, and activate intracellular signaling that promote their migration (Sinha, et al., 2008), suggesting that S100A8/A9 support an autocrine feedback loop that sustains accumulation of MDSC in tumors (Ostrand-Rosenberg, 2008). They also bind to tumor cells and activate MAPK and NF-κB signaling pathways and specific downstream genes that promote tumorigenesis (Ghavami et al., 2009; Ichikawa et al., 2011). S100A8/A9 are involved in early metastatic processes. Expression of S100A8/A9 in myeloid and endothelial cells in premetastatic organs in response to soluble factors such as VEGF, TGFβ and TNFα expressed by distal primary tumors promotes homing of tumor cells to premetastatic niches (Hiratsuka et al., 2006). Recent studies argue for prominent roles for two pattern recognition receptors, TLR4 and RAGE, in S100A8/A9 mediated pathological effects (Gebhardt et al., 2008; Loser et al., 2010; Sinha et al., 2008; Turovskaya et al., 2008; Vogl et al., 2007).

3.7. S100A11

S100A11, also called S100C or calgizzarin, is expressed in many tissues including the placenta, heart, lung, and kidney (He et al., 2009; Inada et al., 1999; Salama et al., 2008). Expression levels are low in skeletal muscle and liver (Inada et al., 1999). S100A11 is overexpressed in uterine smooth muscle tumors (Kanamori et al., 2004), anaplastic large cell lymphomas (Rust et al., 2005), and pancreatic tumors (Ohuchida et al., 2006b), while significantly down-regulated in esophageal squamous cell (Ji et al., 2004) and bladder tumors (Memon et al., 2005). In bladder carcinoma, down-regulation of S100A11 is associated with poor prognosis and decreased survival, suggesting that S100A11 functions as a tumor suppressor (Memon et al., 2005). In pancreatic cancer, S100A11 is over-expressed in early stages and down-regulated in advanced tumors, again supporting a tumor-suppressor role and suggesting that S100A11 expression could be valuable in detecting early pancreatic tumors (Ohuchida et al., 2006b). On the other hand, S100A11 expression in prostate cancer is associated with advanced disease (Rehman et al., 2004), showing that S100A11 plays opposing roles depending on the tumor involved.

3.8. S100B

S100B is one of the best-studied proteins of the S100 family and its interaction with RAGE has been well characterized (Donato, 2007; Donato et al., 2008; Leclerc et al., 2009). S100B is particularly abundant in the brain and is highly expressed by astrocytes, oligodendrocytes and Schwann cells. It is considered as an intracellular regulator and extracellular signal,

exerting concentration-dependent trophic as well as toxic effects on neurons (Donato et al., 2008). It also activates microglia, and may have a role in the pathogenesis of neurodegenerative disorders. S100B is over-expressed in anaplastic astrocytomas and glioblastomas (Camby et al., 1999), and melanomas (Salama et al., 2008). S100B interacts with p53 in melanomas and down-regulates p53 mediated apopotosis (Lin et al., 2010). S100B is the best-studied biomarker for melanoma (Gogas et al., 2009; Salama et al., 2008). Serum levels of S100B increases in a stage-dependent manner in patients with melanoma, reflecting tumor load, with decline during therapy and remission, and correlate well with overall survival. Elevated levels following therapy has shown to correlate with melanoma recurrence. S100B is thus the first of the S100 proteins to be validated in a clinical setting.

3.9. S100P

S100P was first purified from placenta, but it is also expressed in many normal tissues including the GI tract, and in prostate and leukocytes (Arumugam and Logsdon, 2010; Leclerc et al., 2009). S100P is also expressed in many tumors, including ovarian, pancreatic, breast, gastric, colorectal, prostate, and lung carcinomas, and has been shown to be associated with poor clinical outcomes (Arumugam and Logsdon, 2010; Leclerc et al., 2009). Recent studies implicate DNA hypomethylation, bone morphogenic protein and non-steroidal anti-inflammatory drugs in the regulation of S100P expression in tumors (Hamada et al., 2009; Namba et al., 2009; Sato et al., 2004). S100P is expressed in pancreatic cancer cells, but not in pancreatic inflammation, and is also elevated early in preneoplastic cells, suggesting that S100P may be a useful biomarker for pancreatic cancer (Logsdon et al., 2003; Ohuchida et al., 2006a). S100P is absent in normal breast tissue but detected in hyperplasia, as well as in situ and invasive ductal carcinoma (Guerreiro Da Silva et al., 2000). Immunochemical studies show correlation between S100P and estrogen receptor expression, and with high-risk lesions and decreased survival (Schor et al., 2006). S100P has been shown to induce breast cancer metastasis (Wang et al., 2006). S100P is also up-regulated in colon cancer cells (Bertram et al., 1998; Fuentes et al., 2007), and in flat adenomas in the colon (Kita et al., 2006). S100P can be secreted, and interacts with RAGE on pancreatic and colon tumor cells (Arumugam et al., 2005; Fuentes et al., 2007), activating NF-κB and MAPK pathways (Fuentes et al., 2007). Efforts are therefore underway to develop small molecule inhibitors that block the interaction of S100P and RAGE.

Summary

There is growing evidence that many S100 proteins are altered in human tumors. Future studies are likely to reveal molecular mechanisms that define the multiple and specific roles that S100 proteins play in tumor progression and metastasis, providing novel therapeutic targets and biomarkers.

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