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MINIREVIEW ARTICLE

S100A2 in cancerogenesis: a friend or a foe?

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Abstract Owing to the exceptional intracellular distribution and the heterogeneous expression pattern during transformation and metastasis in various tumors, the EF-hand calcium-binding protein S100A2 attracts increasing attention. Unlike the majority of S100 proteins, S100A2 expression is downregulated in many cancers and the loss in nuclear expression has been associated with poor prognosis. On the other hand, S100A2 is upregulated in some cancers. This mini review highlights the general characteristics of S100A2 and discusses recent findings on its putative functional implication as a suppressor or promoter in cancerogenesis.

Keywords Calcium-binding protein · EF-hand · p53 Protein family · Receptor for advanced glycation endproducts (RAGE) · Tumor promotor · Tumor suppressor

Introduction

In 1989, S100A2 was first isolated from bovine lung tissue. It has been identified as the seventh member of the S100 protein family and was termed S100L for lung (Glenney et al. 1989). Three years later, the human homologue of bovine S100L, CaN19 (S100A2) was identified by subtractive hybridization screening for tumor-suppressor genes in normal and tumor-derived human mammary epithelial cells (Lee et al. 1991). At this stage, 25 S100 proteins have been described, including S100A1 to S100A18, S100B, S100P, S100Z, calbindin 3 (S100G), trichohyalin, filaggrin, and repetin (Santamaria-Kisiel et al. 2006). The construction of phylogenetic trees revealed four major subgroups of S100 proteins in mammals. S100A2 belongs to a subgroup with S100A3, S100A4, S100A5, and S100A6, which have the tightest calculated phylogenetic distances throughout the S100 proteins, indicating that more recent gene duplication events led to the evolution of these proteins (Marenholz et al. 2004). The close relation to (rodent) S100A4 could be confirmed by sequence analysis. Both proteins share over 60% amino acid sequence identity (Glenney et al. 1989; Lee et al. 1992). The S100 proteins are small (9–13 kDa), acidic proteins and are solely present in vertebrates (Donato 2003). Phylogenetic analysis indicates no equivalent of S100A2 in the rat and the mouse genome (Ravasi et al. 2004). In this regard, Li et al. did not detect any S100A2 protein expression in mouse, rat and rabbit skin compared to S100A2 protein expression in human, frog, and pig skin. Furthermore, no S100A2 expression was found in cultured mouse keratinocytes (Li et al. 2009). Xia et al. (1997) showed a much higher S100A2 expression in human cultured keratinocytes compared to human skin. Moreover, human and mouse skin xeno(syn)grafts in SCID mice revealed no S100A2 expression at the mouse graft, but a strong signal for the human graft (Li et al. 2009). The existence of mouse S100A2 cannot be excluded since the prediction of mRNA/protein orthologes in mouse on chromosome 3 (public databases, XM 001478157.1/XP 001478207.1).

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Gene structure

The human S100A2 gene is located next to the S100A4 locus on chromosome 1q21.3 and within a cluster of S100

genes, which is part of the epidermal differentiation complex (EDC) (Elder and Zhao 2002; Engelkamp et al. 1993; Ravasi et al. 2004). The locus 1q21 is often rearranged (deletions, translocations, duplications) in human cancer/neoplasmas (Craig et al. 1994). Nucleotide sequence of human S100A2 cDNA and its genomic organization has been described in literature (Wicki et al. 1997). The S100A2 gene has a total length of 8,670 bp and seven splice variants, which can be categorized into five variants with protein product and two transcripts without an open-reading frame. From the five protein coding variants, there are four variants (S100A2-001, -002, -003, -201) which contain the three-exon-structure with the coding sequences in exon 2 and exon 3, and these variants share identical protein sequences. They only differ in their untranslated 5′ region. The variant S100A2-004 is completely different to the preceding variants. It contains four exons and exhibits a distinct protein sequence which resulted in a slightly bigger protein of 16 kDa. The mRNA size of S100A2, including the poly-adenylate stretch, is 970 bp (NM_005978.3). The S100A2 gene has an open-reading frame of 294 nucleotides encoding for a protein of 97 amino acid residues with a molecular mass of 11,117 kDa (NP_005969). Wicki et al. (1997) identified an enhancer element in the promoter region necessary for the transcription of the S100A2 gene. Stoll et al. (2001) described a sequence polymorphism 185A/G in the coding region of S100A2, which results in an amino acid change near the C-terminal EF-hand of S100A2 (Asn62Ser). Investigations on synchronized NMEC (normal mammary epithelial cells) cells showed that the S100A2 gene is cell cycle regulated. S100A2 expression is nearly absent in G_0 phase and increased in early G_1 and S phase of the cell cycle (Lee et al. 1992). The transcription of S100A2 can be induced by activation of the epidermal growth factor (EGF) receptor in human keratinocytes (Stoll et al. 1998).

Protein structure

The complete sequence of the human S100A2 protein is given in Fig. 1. Structural studies performed with multi-dimensional NMR analysis of the Zn^{2+}-bound protein revealed an equilibrium of at least two isoforms probably due to *cis–trans* isomerism of three prolines, which are located in the hinge region and in the C-terminus (Randazzo et al. 2001). In 2006, a first crystallization trial of S100A2-wildtype and a S100A2 variant lacking cysteine residues has been reported. Here, the cysteine residues are vulnerable to oxidation, which cause high-molecular-weight species due to the formation of intermolecular and/or intramolecular disulfide bonds (Koch et al. 2006). In 2008, the three-dimensional structure of the homodimeric S100A2 in the Ca^{2+}-free form could be exposed by X-ray crystallography at 1.6-Å resolution using S100A2 lacking the cysteine residues (Koch et al. 2008). The overall structure is similar to other S100 proteins. The two subunits or monomers form the homodimeric protein and each subunit is composed of two tandem Ca^{2+}-binding helix-loop-helix EF-hands. The three-dimensional structure of apo-S100A2 showed similarities with the structures of Ca^{2+}-free S100A3, S100A4 and S100A6 (Koch et al. 2008). Like other S100 proteins, S100A2 occurs as a homodimer in vitro and in vivo (Deshpande et al. 2000; Ilg et al. 1996). Furthermore, S100A2 is able to migrate as a monomer under reducing conditions but formed higher polymers under non-reducing conditions (Ilg et al. 1996). Yeast two-hybrid experiments showed S100A2 homodimerization without any additional proteins and the dimerization process does not require any disulfide bonds. In normal human keratinocytes, S100A2 seems to be capable of forming oxidized dimers cross-linked by intermolecular disulfide bonds. After H_2O_2 treatment (oxidative stress), S100A2 cross-linking is strongly promoted as well as its translocation from the nucleus to the cytoplasm (Deshpande et al. 2000; Zhang et al. 2002). Furthermore, concentrations of calcium and magnesium in the 10^{-4}–10^{-3} M range favor the formation of high molecular weight complexes of S100A2 (Deshpande et al. 2000). This is further supported by experiments on oxidation of S100A2 at physiological concentrations of copper with/without the presence of reducing agents in vitro showing rapid formation of covalently-bound S100A2 multimers. As a consequence, these multimers with higher affinity bind to one putative S100A2 receptor, the receptor for

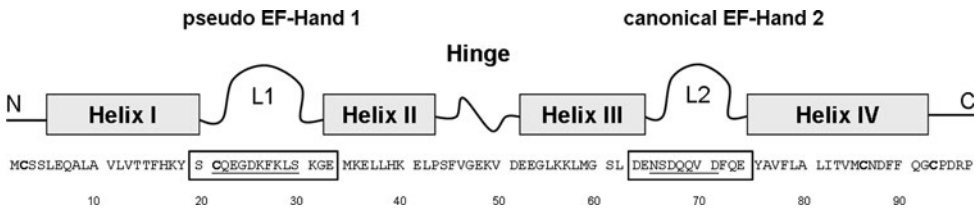

Fig. 1 Protein structure and amino acid sequence of human S100A2. The overall structure of S100 proteins includes four helices, two calcium-binding EF-hands (*underlined*, according to Koch et al. 2008; *boxes*, according to Eckert et al. 2004), a central hinge region of variable length and the C- and N-terminal variable domains (S100A2 sequence refers to Acc No. NP_005969). Cysteine residues are marked in *bold letters*, the cysteine in position 21 within the pseudo EF-hand is unique among the S100 proteins

advanced glycation endproducts (RAGE) (Haase-Kohn et al., unpublished results).

Ion binding properties

As a common characteristic of S100 proteins, one protein dimer binds through its four EF-hand motifs four Ca^{2+} ions. S100A2 binds Ca^{2+} ions with moderate affinity ($[Ca^{2+}]_{0.5} = 470$ μM) and with the highest positive cooperativity ($n_H = 2.04$) compared to S100A4, S100A6, S10011, etc. (Franz et al. 1998). Franz et al. supposed here that the C-terminal EF-hand 1 of S100A2 has a lower affinity for Ca^{2+} than in other S100 members, because the sequence CQ in the EF-hand 1 deviates strongly from the G(R/K) sequence encountered in the other members. Additionally, they revealed that the four Ca^{2+} binding sites form an allosteric unit and that binding of the first two Ca^{2+} ions overcomes an energetically expensive conformational change and leads to a facilitated binding of the next two Ca^{2+} (Franz et al. 1998). Anyway, S100A2 is also a Zn^{2+}-binding protein which has been examined thoroughly by different groups in the last decade (Heizmann and Cox 1989; Moroz et al., this issue). Franz et al. showed binding of two Zn^{2+} per S100A2 monomer with an affinity of 2×10^5 M^{-1}. Both binding of Ca^{2+} and Zn^{2+} to S100A2 induce conformational changes including a hydrophobic patch on the protein surface that may be essential for the interaction of S100A2 with nuclear targets (Franz et al. 1998). Stradal et al. supposed that the four cysteine residues (Cys2, Cys21, Cys 86, Cys93) in each subunit may be involved in Zn^{2+}-binding processes and used cysteine deficient mutants of S100A2. The substitution of all cysteine residues for serines completely abolishes Zn^{2+} binding but not the binding of Ca^{2+} suggesting that Ca^{2+} and Zn^{2+} affect different sites in the S100A2 protein. Most likely the S100A2 monomer consists of two separate Zn^{2+} binding sites with its own binding mechanism, but only the S100A2 dimer is able to bind Zn^{2+} completely. They also observed a fivefold increased affinity of wild type S100A2 for Zn^{2+} in the presence of Ca^{2+} (Stradal et al. 2000). Further NMR studies proposed two Zn^{2+} binding sites (His17-Cys21-Cys93 and Cys2-His39) in each subunit and Cys86 seems to be involved either in the first or the second binding site (Randazzo et al. 2001). Finally, Koch et. al determined the affinity of S100A2 for Zn^{2+} quantitatively ($K_D = 25$ nM) and supposed a stoichiometry of 2.5 Zn^{2+} per S100A2 homodimer (5 Zn^{2+} ions per S100A2 tetramer) using different mutated Cys residues (Cys → Ser). They identified two Cys–Zn site groups (Cys21 and Cys2) with different affinities (Koch et al. 2007). Furthermore, they found that Zn^{2+} at physiological concentrations reduces significantly the affinity of S100A2 for Ca^{2+} (ca. 300-fold), and thereby inhibits response to intracellular Ca^{2+} signals. The molecular mechanisms of Zn^{2+}-bound S100A2 inside the cell remains to be established. Very recently, the influence of Zn^{2+} and Ca^{2+} binding on folding and stability of S100A2 was investigated. Both ions regulate protein thermal stability in an opposite manner with Ca^{2+} being a stabilizer and Zn^{2+} being a destabilizer after thermal denaturation. Therefore, it has been suggested that Zn^{2+} binding causes destabilization of S100A2 and in turn leads to reduced Ca^{2+} affinity (Botelho et al. 2009).

Tissue and subcellular location

S100A2 protein is present in many organs or tissues, e.g., at high levels in bovine kidney and lung, low levels in brain and intestine, and intermediate levels in liver, cardiac muscle, and skeletal muscle (Glenney et al. 1989). In human tissues, S100A2 mRNA and protein are expressed in lung, kidney, prostate, skin and salivary and mammary gland (Ilg et al. 1996; Maelandsmo et al. 1997). In the normal skin, S100A2 was found to be specifically localized in the basal–parabasal cells of the epidermis, epithelial cells of the sebaceous glands, hair follicles and ductal epithelium of the sweat gland (Boni et al. 1997; Shrestha et al. 1998). S100A2 was also present in normal salivary ducts (Huang et al. 1996). In cell lines, S100A2 mRNA expression has been found also in normal mammary epithelial cells and keratinocytes (Andersen et al. 1996; Lee et al. 1992). The primary intracellular compartment of S100A2 is the nucleus compared to other members of the S100 protein family with a predominant cytosolic localization. This could be shown in the normal breast epithelial cell line HBL-100 and in smooth muscle cells (Ilg et al. 1996; Mandinova et al. 1998). Glenney et al. (1989) showed S100L expression throughout the nucleus and cytoplasm in bovine kidney cells (MDBK: Madin-Daby bovine kidney). Desphande and Zhang observed a diffuse cytoplasmic and strong nuclear expression in cultured normal human keratinocytes (Deshpande et al. 2000; Zhang et al. 2002). Different studies suppose a prolonged elevation of intracellular calcium to be responsible for the translocation of S100A2 to the cytoplasm (Mueller et al. 2005; Mandinova et al. 1998; Zhang et al. 2002). Additionally, the calcium ionophore A23187/Ca^{2+} induced translocation could be blocked by disulfide reducing agents, suggesting that disulfide-linked dimer formation is required for translocation (Zhang et al. 2002).

Binding/interacting partners

S100A2 (porcine/avian) interacts Ca^{2+}-dependently with recombinant tropomyosins in vitro in a one to one ratio

which proposed the involvement of S100A2 in the organization of the cytoskeleton (Gimona et al. 1997). Tan et al. (1999) demonstrated the binding and transcriptional activation of the S100A2 promotor by the tumor suppressor p53 (wild-type). Few years later, a direct interaction was displayed between endogenous S100A2 and the C-terminal domain of wildtype p53 in oral cancer cells in a Ca^{2+}-dependent manner (Mueller et al. 2005). Interactions were only measured at calcium concentrations higher than 0.5 mM in FaDu (squamous cell carcinoma of the hypopharynx) and higher than 2 mM in HBL-100 cells supposed to be due to a deregulated calcium homeostasis in human tumors. Furthermore, calcium binding of S100A2 resulted in an activation of p53 transcriptional activity (Mueller et al. 2005). Recently, Fernandez-Fernandez et al. found that S100A2 binds to the tetramerization domain (TET) and to the residues 367–393 of the C-terminal negative regulatory domain (NRD) of p53. Binding of S100 proteins to the TET domain of p53 seems to be a general property of the family, because it could also be shown for S100B, S100A4, S100A6, and S100A11 (Fernandez-Fernandez et al. 2008). The same group further investigated the interaction between S100A2 and p53 in more detail. Here, they demonstrated that the members of the S100 family including S100A2 bind to the residues 293–393 of the monomeric p53 fragment in a ratio of one S100 dimer binds to one p53 monomer. Additionally, S100A2 is able to bind the tetrameric form of p53 with a weak affinity. N-terminal phosphorylation of p53 increased the affinity for S100A2 more than threefold whereas acetylation and phosphorylation of the C-terminus decreased the affinity for S100A2. However, it should be mentioned that these results only describe the in vitro situation without respecting the intracellular concentrations of S100 proteins (van Dieck et al. 2009a, b).

Other members of the p53 family are p63 and p73, which exhibit strong similarity in DNA sequence and protein structure with p53. These proteins are transcription factors that activate target genes through DNA binding. There exist various isoforms of p63 and p73 because of alternative splicing procedures and two separate promotors in both genes (Yang et al. 2002). ΔNp63 is a transcript without the N-Terminal transactivation domain of p53. The exogenous expression of ΔNp63 in a human osteosarcoma cell line (Saos2) induced the S100A2 gene and promoter (Hibi et al. 2003). On the other site, Lapi et al. (2006) showed that S100A2 is a transcriptional target of different p73 and p63 isoforms (p73β and ΔNp63α) during keratinocyte differentiation of HaCaT (transformed human keratinocytes) cells. They found S100A2 gene and protein induction during keratinocyte differentiation besides the simultaneous upregulation of p73β and downregulation of ΔNp63α. Overexpression of additional isoforms (TAp63γ, TAp73α, TAp63α) resulted in a strong increase of S100A2 mRNA and protein due to transcriptional activation of the S100A2 promotor, which also implies tumor suppressor function of S100A2 (Kirschner et al. 2008). The biochemical characterization of the interaction between S100 proteins and p63/p73 revealed that S100A2 among others showed a higher affinity for the peptides p63TET and p73TET than for p53. Furthermore, S100A2 is able to bind monomeric, dimeric, and tetrameric p63 as well as dimeric and tetrameric p73 (van Dieck et al. 2010). The involvement of S100A2 in protein folding mechanisms could be shown by the interaction with the tetratricopeptide repeat (TPR) domains of hsp70/hsp90-organizing protein (Hop) and kinesin-light chain (KLC) in a Ca^{2+}-dependent manner (Shimamoto et al. 2008). Investigations about a receptor of S100A2 are rarely found so far. For several S100 proteins, the interaction with the receptor for advanced glycation endproducts (RAGE) has been proven, including S100B, S100A1, S100A6, S100A7, S100A8/A9, S100A11, and S100A12. Recently, a calcium-dependent interaction between immobilized GST-RAGE and S100A2 was reported measured by surface plasmon resonance with an affinity in the micromolar range. Additionally, the predominant interaction of S100A2 with the V-domain of RAGE was demonstrated (Leclerc et al. 2008). Moreover, S100A2 was found to negatively regulate the motility of human head and neck squamous cell carcinoma cell lines, which have an inverse correlation between RAGE and S100A2 mRNA expression (Nagy et al. 2001). Furthermore, S100A2 is chemotactic for eosinophils in vitro by an unknown mechanism (Komada et al. 1996). However, it is still unknown whether S100A2 is secreted or not and by which cell type.

The role of S100A2 in cancer

The identification of S100A2 (CaN19) by subtractive hybridization in 1992 as a markedly downregulated gene in tumor-derived mammary epithelial cell lines initiated the hypothesis that S100A2 (CaN19) acts as a tumor suppressor gene (Lee et al. 1991). Meanwhile, a downregulation of S100A2 has been described in many human cancers. On the other hand, it should be marked that there is an upregulation of S100A2 in some cancer types as well. A downregulated expression profile of S100A2 protein in skin, lung, kidney, and prostate tumors was already described by Ilg et al. (1996). Another study investigated the generality of CaN19 "underexpression" in malignant epithelial cell cultures and found reduced levels of CaN19 mRNA in the tumor-derived cell lines of bladder, skin, breast, and oral mucosa (Xia et al. 1997). Immunohistochemical characterization of S100A2 expression in 424

normal and tumoral tissues of diverse histological origin showed a very low expression in non-epithelial tissues compared to epithelials. Furthermore, S100A2 staining decreased in the epithelial specimens from normal to tumor stages (Nagy et al. 2002). In the following, the S100A2 expression pattern of different tumor entities and possible implication of S100A2 as a prognostic factor is described in more detail. For the malignant and desmoplastic melanoma, a general downregulation of S100A2 has been shown (Andersen et al. 1996; Boni et al. 1997; Ilg et al. 1996; Maelandsmo et al. 1997; Nonaka et al. 2008). The mRNA expression profile of S100A2 in some human melanoma cell lines of primary and metastatic origin is presented in Table 1 and shows different S100A2 expression levels. An upregulation of the S100A2 gene could be found after treating the amelanotic melanoma cell line A375(DRO) with PPARγ and RXR ligands. The nuclear hormone receptors RXR and PPARγ are used as therapeutic targets, for e.g., rexinoid (LGD1069) and thiazolidinediones (TZD), and cause inhibition of cell growth and increased apoptosis. These effects seem at least partially mediated by S100A2 (Klopper et al. 2010). Another upregulation was found in an in vitro model of uveal melanoma after treatment with IFN-γ and the methyltransferase inhibitor decitabine (Gollob and Sciambi 2007). Additionally, it has been shown that the antiproliferative activity of S100A2 requires the IFN-α or TGF-β signaling pathway (Foser et al. 2006). In bulk specimens of basal and squamous cell carcinomas (SCC) of the skin and oral cavity, including skin appendage tumors, S100A2 was strongly expressed (Shrestha et al. 1998; Xia et al. 1997). S100A2 protein was also found in squamous metaplastic cells of salivary tumors (Huang et al. 1996).

In oral cancer cell lines, S100A2 mRNA and protein was decreased compared to normal oral keratinocytes, especially in early-stage oral squamous cell carcinoma (OSCC) resulting in a shorter disease-free survival (Tsai et al. 2005). Another study found out that OSCC patients had a higher risk to get late cervical metastases when their tumors were S100A2 negative (Suzuki et al. 2005). Furthermore, patients with laryngeal squamous cell carcinoma (LSCC) and with S100A2-positive tumors had a better metastasis-free, relapse-free, and overall survival than patients with S100A2-negative tumors, which certified S100A2 expression as a prognostic marker (Almadori et al. 2009; Lauriola et al. 2000). Different studies indicated that in prostate cancer the S100A2 expression (protein, mRNA) decreased during tumor progression. In nonmalignant conditions as benign prostate hyperplasia (BPH) and prostatitis, the mRNA and protein levels of S100A2 are higher than in low-grade cancer, whereas its expression is lost in high-grade and metastatic cancer specimens. Therefore, S100A2 can be used as a potential predictor of prognosis in human prostate adenocarcinoma (Gupta et al. 2003; Rehman et al. 2005). The S100A2 expression in breast cancer has been investigated by different groups. In general, normal mammary epithelial cells showed a high S100A2 protein and mRNA expression, patient-derived primary mammary epithelial cells revealed weak expression of S100A2 and no S100A2 was found in tumor-derived mammary epithelial cells (Ilg et al. 1996; Lee et al. 1992; Liu et al. 2000; Mueller et al. 1999; Pedrocchi et al. 1994). A summary of the S100A2 expression profile in different breast cancer cell lines can be found in Table 1. Due to different investigations, it is proposed that S100A2 mRNA becomes downregulated during the formation of breast carcinoma cells and not at the earlier stage of development from normal epithelium to benign hyperplastic and neoplastic cells (Liu et al. 2000). Gene expression analysis of S100A2 in head and neck squamous cell carcinoma (HNSCC) showed contrary results: significantly overexpression on one site (Villaret et al. 2000) and reduced expression of S100A2 in metastatic cell lines compared to poorly metastatic parental cells on the other site (Chen et al. 2003). The same group found strong S100A2 protein staining in normal epithelial tissues and primary tumors some years later and due to their investigations, they predicted that S100A2 was significantly downregulated in lymph node metastasis compared with node-negative primary tumors (Zhang et al. 2007). The role of S100A2 expression in lung cancer also seems to be contradictory. Feng et al. showed the reduced S100A2 expression in different non-small cell lung cancer (NSCLC) cell lines derived from human squamous cell carcinomas and adenocarcinomas as well as in metaplastic lesions and in NSCLC cancer. The authors concluded that there is a stepwise suppression of S100A2 expression, a 25–50% decrease at the early stages of lung carcinogenesis and a complete loss of expression at later stages (Feng et al. 2001). However, Heighway et al. found that S100A2 is strongly expressed in NSCLC tumor samples compared to normal cells, which showed no predominant S100A2 expression (Heighway et al. 2002). Two years later, the same group confirmed their results and showed that S100A2 mRNA/protein was overexpressed in 76%/62% of NSCLC patients (Smith et al. 2004). Another group showed S100A2 overexpression in a small subset of metastasizing NSCLC tumors. Furthermore, the authors examined the migration behavior of cell cultures overexpressing S100A2 and revealed a significantly enhanced migratory phenotype of these cells suggesting an involvement of S100A2 in the metastatic process of early-stage NSCLC (Diederichs et al. 2004). Additionally, Wang et al. (2005) showed S100A2 overexpression in stage one NSCLC patients, and whose tumors had a positive S100A2 expression had a significantly lower overall survival and

Table 1 S100A2 expression profile in different human cell lines

Cancer/organ	Cell type/tissue origin	Cell line	S100A2 (mRNA)	S100A2 (protein)	References
Skin	Normal keratinocytes		+++		Andersen et al. 1996
	Normal fibroblasts		–		Andersen et al. 1996
	Normal melanocytes		–		Andersen et al. 1996
	Immortalized, nontumorigenic keratinocytes	HaCaT	++/+++		Xia et al. 1997
Malignant melanoma	Metastatic	SK-MEL 30	–		Andersen et al. 1996
		SK-MEL 75	–		
		SK-MEL 93	–		
		SK-MEL 113	–		
		SK-MEL 131	–		
		MeWo	–		
	Primary	WM1341B,	+		Maelandsmo et al. 1997
		WM902B	+		
		WM115	+		
		WM35	–		
		WM122	–		
		WM983A	–		
	Metastatic	WM239	+		
		WM9	±		
		WM45.1	±		
		SK-mel 28	–		
		MeWo	–		
		LOX	+++		
		THX	++		
		HHMSX	–		
		SESX	–		
		M14	±		
		FEMX	–		
Head and neck squamous cell carcinoma (HNSCC)	Metastatic, larynx	UM-HNSCC-22B	++		Xia et al. 1997
	Recurrent, larynx	UM-SCC-11B	±		
	Primary, larynx	UM-SCC-11A	++		
	Primary, tonsillar epitelium	UM-HNSCC-38	–		
	Hypopharynx	FADU	+	+++	Nagy et al. 2001
	Pharynx	Det-562	+	+	
	Nasal septum	RPMI	+	±	
	Tongue	SCC-9	+	±	
	Tongue	SCC-25	+	+	
	Primary, tongue	Tu686	+	++	Zhang et al. 2007
	Poorly metastatic	686LN	+	+	
	Lymph node metastasis of the primary tongue cancer (Tu686)				
	Highly metastatic	686LN-M3a2	±/–	±/–	
	Lymph node metastasis of a tongue cancer	686LN-M3a3	±/–	±/–	
		686LN-M3b2	±/–	±/–	
		686LN-M3b3	±/–	±/–	
	Primary, larynx	UPCI-15A		+	
		UPCI-37A		+++	
	Lymph node metastases of larynx carcinoma	UPCI-15B		+	
		UPCI-37B		+	
	Primary, hypopharynx	Tu212		++	
	Cervical lymph node metastases of a primary hypopharyngeal carcinoma	212LN		+++	

Table 1 continued

Cancer/organ	Cell type/tissue origin	Cell line	S100A2 (mRNA)	S100A2 (protein)	References
Oral mucosa	Normal oral keratinocytes	NOK	+++	+++	Tsai et al. 2005, 2006
	Dysplastic oral keratinocytes (tongue)	DOK	++		
Oral squamous cell carcinoma (OSCC)	Human tongue carcinoma with lymph node metastasis	KB	±		
		CAL-27	+/++		
		SCC-9	++		
		SCC-15	+		
		SCC25	++		
		OC-2	±		
		OEC-M1	±		
		OC-3	±		
		HSC-3	+		
Squamous cell carcinoma of the skin (SCC)	Highly tumorigenic	A431	++/+++		Xia et al. 1997
Transitional cell carcinoma of the bladder	Less differentiated	UM-UC2,3,6,9,13	±		
Papillary carcinoma of the bladder	Well differentiated	RT4	+		
Breast	Normal mammary epithelial cells (NMECs)	70 N	+++		Lee et al. 1992
		76 N	+++		
		81 N	+++		
	Papilloma virus-transformed	18-2P-1	+++		
	Epithelial cells, nontumorigenic	HBL-100	+		Pedrocchi et al. 1994
	Normal mammary epithelial cell line (from mammary gland, SV-40-virus-immortalized)	Huma 7	+		Liu et al. 2000
	Benign, mammary epithelial cell line	Huma 123	+++		
	Benign, mammary myo-epithelial-like cell line (derived from Huma 123)	Huma 109	+		
Breast cancer	From patients (primary tumors), mammary epithelial cells	21PT	±		Lee et al. 1992
		21NT	±		
	Metastatic, mammary epithelial cells	ZR75-1	–		
		T47D	–		
		HBL-100	–		
		MDA-MB-436	–		
		MDA-MB-468	–		
	Metastatic,epithelial cell line	MDA-MB-231		±	Ilg et al. 1996
	Adenocarcinoma	SK-Br-2/III	–		Pedrocchi et al. 1994
	Infiltrating ductal carcinoma	MCF-7	–		
	Infiltrating ductal carcinoma	BT-20	–		
	Infiltrating ductal carcinoma	BT-474	–		
	Infiltrating ductal carcinoma	BT-483	–		
	Infiltrating ductal carcinoma	T47-D	–		
	Infiltrating ductal carcinoma	ZR-75-1	–		
	Infiltrating ductal carcinoma	HS-578 T	–		
	Adenocarcinoma, metastatic, epithelial infiltrating ductal carcinoma	MDA-MB-231	+		
	Adenocarcinoma	MDA-MB-330	–		
		MDA-MB-361	–		
	Nontumorigenic highly tumorigenic	MCF-10A	+++		Xia et al. 1997
		MCF-7	–		
	Malignant, mammary epithelial cell line	MCF-7A	–		Liu et al. 2000
		T-47D	–		
		ZR-75	–		
		MDA-MB-231	–		

Table 1 continued

Cancer/organ	Cell type/tissue origin	Cell line	S100A2 (mRNA)	S100A2 (protein)	References
Prostate	Normal, epithelial cells	NHPE		+++	Gupta et al. 2003
	Virally transformed, epithelial cells	PZ-HPV-7		+++	
Prostate cancer		22Rv1		−	
		DU145		−	
		LNCaP		−	
		PC3		−	
		DU145	+	−	Rehman et al. 2005
		LNCaP	+	−	
		PC3	+	−	
Lung	Bronchial epithelial cells	NHBE	+++	+++	Feng et al. 2001, Matsubara et al. 2005, Bartling et al. 2007
	Small airway epithelial cells	SAEC	+++	+++	Matsubara et al. 2005
	Bronchiolo-alveolar (lung epithelial cell lines)	A549	+		Bartling et al. 2007
		H358	+		
		H358 (no Medium 10%FKS)	−		
	Bronchial epithelial cells, immortalized	BEAS-2B	+	+	Feng et al. 2001
		1799	+	+	
	Bronchial epithelial cells, transformed	1198	−	−	
	Bronchial epithelial cells, tumorigenic	1170-I	−	−	
Non-small cell lung cancer (NSCLC)		H460	−	−	Feng et al. 2001
		H1792	−	−	
		SK-MES-1	++/+++	+	
		Calu	−	−	
		H292	++	+	
		H157	−	−	
		H1944	−	−	
		H596	+/±	+	
		H522	−	−	
		A549	−	−	
		H226	−	−	
	Lung adenocarcinoma	A549	±		Matsubara et al. 2005
		H23	±		
		H522	±		
		H1395	±		
		H1648	++		
		H2009	±		
		H2347	±		
		LC-2/ad	−	−	
		ABC-1	−	−	
		H460	−	−	
		HLC1	±/+	±/+	
		H1299	−	−	
		PC3	−	−	
		VMRC-LCD	−	−	
		RERF-LC-KJ	−	−	

−, undetectable; ±, hardly detectable/low expression; +, present; ++, moderate expression; +++, high expression

disease-specific survival rate 5 years after surgery than patients with negative S100A2 expression. However, Matsubara et al. (2005) demonstrated a clear downregulation of S100A2 mRNA and protein in lung adenocarcinoma cell lines compared to the high expression in normal lung cells. Paradoxically, they found S100A2 protein staining in primary lung adenocarcinoma specimens, whereas it was absent in normal lung. In this study, the S100A2 expression

correlates significantly with lymphatic invasion (Matsubara et al. 2005). Another study also revealed an upregulation of S100A2 in NSCLC, which strongly depends on the histological subtype of this cancer entity. They found that early stages of squamous cell lung carcinomas strongly express S100A2 mRNA and protein, but not advanced tumor stages and lung adenocarcinomas (Bartling et al. 2007). From these and previous studies, it can be strongly assumed that S100A2 can be used as prognostic target to identify early-stage non-small cell lung carcinoma (Bartling et al. 2007; Zech et al. 2006). A further study described tumor specific genetic alterations in the S100A2 gene in 31.1% of non-small cell lung carcinoma samples. In general, they found that the S100A2 gene was downregulated in 32.8% and upregulated in 56.9% of the 90 NSCLC samples (Strazisar et al. 2009a). They also demonstrated a lower expression of the S100A2 gene in adenocarcinomas and a higher expression in squamous cell carcinomas of the lung (Strazisar et al. 2009b). In a recent publication, S100A2 has been identified as a prometastatic gene in patients with NSCLC, because high expression levels of S100A2 are closely associated with poor patient survival (60.4% of patients with high S100A2 expression died and 41.9% of the patients with low S100A2 expression died). Further investigations of the metastatic role revealed that the induced expression of S100A2 in NSCLC cell lines causes enhanced migration and transendothelial migration in vitro as well as a highly metastatic phenotype in a murine xenograft model. Repression of S100A2 inhibited the metastatic phenotype in vivo indicating that S100A2 is important in metastasis development (Bulk et al. 2009). In pancreatic cancer tissues and cell lines, S100A2 is expressed significantly higher than in normal pancreatic tissues. Therefore, S100A2 is suggested to be used as a marker of tumor progression or prognosis in patients with pancreatic cancer (Ohuchida et al. 2005, 2007). Recently, Biankin et al. demonstrated that moderate/high expression of S100A2 gene in pancreatic cancer is an independent marker of poor disease outcome even after pancreatectomy. Patients with low S100A2 expression levels had a survival benefit when the tumor was surgically removed even in the presence of lymph node metastases (Biankin et al. 2009). In gastric cancer, a gene expression analysis revealed that S100A2 is overexpressed in over 90% of the gastric tumors compared to normal gastric mucosa (El-Rifai et al. 2002; Liu et al. 2008). An overexpression of S100A2 mRNA and protein could be detected in lower esophageal, gastro-esophageal junction, and gastric adenocarcinomas (Lee et al. 2006). However, in esophageal squamous cell carcinoma (ESCC), S100A2 was found to be downregulated in early stages (T1), it reappeared in advanced and well-differentiated ESCCs and gradually increased following the size of the tumor. An explanation for this phenomenon could be that tumor cells surrounding tumor pearls were strongly stained for S100A2 or that genes which control S100A2 expression are dysregulated in the cancer cells and initiate a feedback enhanced expression of S100A2 in advanced tumors. They further demonstrated that the 5-year survival was 58% for the S100A2-negative group and 85% for the S100A2-positive group, which suggests that loss of S100A2 expression without lymph-node involvement predicts a poor survival (Kyriazanos et al. 2002). A significant downregulation of S100A2 in ESCC could also be verified by other groups (Ji et al. 2004; Cao et al. 2009). Moreover, they found a significant correlation between the gene expression of S100A2 and that of S100A8, S100A14, and S100P (Ji et al. 2004). Another study of esophageal cancer showed that 47% of the primary tumors revealed a higher S100A2 gene expression with a trend toward preferentially developing metastases. However, only two of the eight esophageal squamous carcinoma cell lines showed S100A2 gene overexpression (Imazawa et al. 2005). In thyroid carcinomas, S100A2 shows a unique immunohistochemical expression pattern because of its absence in follicular adenomas and carcinomas, and on the other hand, its upregulation in papillary and anaplastic carcinomas, which may at least provide S100A2 as a histological marker for distinguishing these two types of thyroid carcinoma (Ito et al. 2005). In summary, a downregulation of S100A2 could be verified for the following cancer entities: melanoma, prostate, oral, and breast. Some cancers did not show a clear down- or upregulation of S100A2: head and neck squamous cell carcinomas, lung cancer, laryngeal carcinoma, squamous cell carcinoma of the skin and esophageal carcinoma. Other cancers, including pancreas, gastric, and ovary exhibit an upregulation of S100A2 (Table 2). Several studies explained the loss of S100A2 expression in cancer with hypermethylation of the S100A2 promotor. In breast cancer, it could be shown that the S100A2 promotor was hypermethylated but unmethylated in normal breast epithelial cells (Wicki et al. 1997). In non-small cell lung cancer cell lines, the repression of the S100A2 transcription is caused in part by site-specific methylation of the S100A2 promotor region (Feng et al. 2001). Methylation of the S100A2 promotor has also been found in prostatic cancer, in high-grade prostatic intraepithelial neoplasia lesions (HG-PIN) and in adjacent non-malignant epithelium and benign prostatic hyperplasia (BPH). In the prostate cancer cell lines, there was no consistent methylation pattern. In some cell lines, the promoter region and exon 1 are hypermethylated, and in others, these regions showed no methylation (Jeronimo et al. 2004; Rehman et al. 2005). Therefore, the hypermethlyation of the S100A2 promotor seemed not to be responsible for the loss of S100A2 expression in prostate cancer. The tumor suppressor function of S100A2 has been

Table 2 S100A2 expression profile in human tumors

Cancer	S100A2 expression	References
Malignant melanoma Desmoplastic melanoma	↓	Andersen et al. 1996, Boni et al. 1997, Ilg et al. 1996, Maelandsmo et al. 1997, Nonaka et al. 2008
Oral squamous cell carcinoma (OSCC)	↓ + ↑	Suzuki et al. 2005, Tsai et al. 2005, Xia et al. 1997
Prostate cancer	↓	Gupta et al. 2003, Rehman et al. 2005
Breast cancer	↓	Ilg et al. 1996, Lee et al. 1992, Liu et al. 2000, Mueller et al. 1999, Pedrocchi et al. 1994
Head and neck squamous cell carcinoma (HNSCC)	↓ + ↑	Chen et al. 2003, Villaret et al. 2000, Zhang et al. 2007
Lung cancer (NSCLC)	↓ + ↑	Bartling et al. 2007, Bulk et al. 2009, Diederichs et al. 2004, Feng et al. 2001, Heighway et al. 2002, Matsubara et al. 2005, Smith et al. 2004, Strazisar et al. 2009a, Strazisar et al. 2009b, Wang et al. 2005, Zech et al. 2006
Pancreatic cancer	↑	Biankin et al. 2009, Ohuchida et al. 2005, Ohuchida et al. 2007
Gastric cancer	↑	El-Rifai et al. 2002, Lee et al. 2006, Liu et al. 2008
Esophageal squamous cell carcinoma (ESCC)	↓ + ↑	Kyriazanos et al. 2002, Ji et al. 2004, Imazawa et al. 2005, Cao et al. 2009
Epithelial ovarian cancer (EOC)	↑	Hough et al. 2001
Thyroid carcinoma	↓ + ↑	Ito et al. 2005

↑, upregulated; ↓, downregulated

shown in an in vitro and in vivo model. The ectopic overexpression of S100A2 in a squamous cell carcinoma cell line diminished growth properties, migratory and invasive behavior as well as the tumorigenicity in mice. Additionally, the overexpression of S100A2 negatively influences cyclooxygenase-2 (COX-2) expression, which may be, in part, responsible for the antitumor effect. Cox-2 upregulation is a common feature in many cancers (Tsai et al. 2006).

Subcellular S100A2 expression in cancer

Different immunolocalization studies revealed that in most cancer types, S100A2 protein is preferably located in the cytoplasm (Bartling et al. 2007; Lee et al. 2006; Mueller et al. 2005; Nagy et al. 2002; Suzuki et al. 2005; Wang et al. 2005; Zhang et al. 2007). However, in HeLa cells and tumorigenic epithelial cells of basal cell and squamous cell carcinoma of the skin, the S100A2 protein was mostly present in the cell nuclei (Mueller et al. 1999; Shrestha et al. 1998). In primary human lung adenocarcinoma specimens, S100A2 protein was found in both the cytoplasm and nucleus of the cancer cells as well as in basal cells of non-malignant and benign prostatic hyperplasia tissues (Matsubara et al. 2005; Rehman et al. 2005). Functional interrelations between S100A2 and other members of the S100 family have been reported. It is suggested that S100A4, which has the closest sequence identity to S100A2, may play an opposite role to S100A2 in cancer. For example, in human prostate adenocarcinoma, an inverse correlation between S100A2 (↓) and S100A4 (↑) protein expression has been found but without statistical significance (Gupta et al. 2003). In normal human bronchial epithelial cells and small airway epithelial cells, S100A2 mRNA and protein expression was high, whereas in lung adenocarcinoma cell lines, S100A2 was downregulated. S100A4 showed contrary results for these cells with low mRNA and protein content in the normal lung cells and an upregulated expression in the cancer cells (Matsubara et al. 2005). Also, bladder cancer specimens showed the inverse relationship between S100A2 and S100A4 protein expression. The combination of reduced S100A2 and increased S100A4 expression correlates with the pathological disease stage, tumor progression, and patient survival (Matsumoto et al. 2007).

Concluding remarks

This mini-review summarizes some important biochemical characteristics of S100A2 and highlights its controversial role in cancerogenesis. On the one hand, S100A2 acts as a tumor suppressor in some cancer entities and, on the other hand, as a tumor promotor, however, by mechanisms that are still poorly understood. The different patterns of S100A2 expression in distinct tumor types might be explained by the control through multiple factors with effects varying from tumor to tumor. From different studies concerning S100A2, alterations of both mRNA expression

and protein synthesis in human cancers, it is likely that S100A2 regulates tumorigenesis. However, controversy still exists about the role and clinical significance of S100A2 in progression, invasion, and metastasis of tumors. Further studies are needed to determine the exact mechanism underlying S100A2 abnormalities in human cancer.

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