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REVIEW

S100A6 protein: functional roles

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Abstract S100A6 protein belongs to the A group of the S100 protein family of Ca^{2+}-binding proteins. It is expressed in a limited number of cell types in adult normal tissues and in several tumor cell types. As an intracellular protein, S100A6 has been implicated in the regulation of several cellular functions, such as proliferation, apoptosis, the cytoskeleton dynamics, and the cellular response to different stress factors. S100A6 can be secreted/released by certain cell types which points to extracellular effects of the protein. RAGE (receptor for advanced glycation end-products) and integrin β1 transduce some extracellular S100A6's effects. Dosage of serum S100A6 might aid in diagnosis in oncology.

Keywords S100A6 protein · Proliferation · Migration/motility · Cancer · Invasion · Cytoskeleton · Receptor

Abbreviations

ALS	Amyotrophic lateral sclerosis
CacyBP/SIP	Calcyclin-binding protein/Siah-1-interacting protein
CDK	Cyclin-dependent kinase
EGF	Epidermal growth factor
Hsp	Heat shock protein
IL	Interleukin
MDM	Transformed mouse 3T3 cell double minute
NF-κB	Nuclear transcription factor κB
Nrf2	Nf-E2 related factor 2
PDGF	Platelet-derived growth factor
RAGE	Receptor for advanced glycation end product
ROS	Reactive oxygen species
SOD	Superoxide dismutase
Sp1	Specificity protein 1
TNF	Tumor necrosis factor
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
USF	Upstream transcription factor
VEFG	Vascular endothelial growth factor

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Introduction

S100A6 belongs to the S100 family of Ca^{2+}-binding proteins of the EF-hand type [1]. It is also known as 2A9, 5B10, CABP, Cacy, Calcyclin, growth factor-inducible protein 2A9, PRA—prolactin receptor associated protein, and S100 calcium binding protein A6, S100a6. As a member of the A group of S100 proteins, human S100A6 gene maps to chromosome 1q21 [2], a locus where frequent chromosomal rearrangements occur in neoplasia. S100A6 is expressed as an 89-amino-acid protein in mouse and rat and a 90-amino-acid protein in human and rabbit. Two chicken isoforms, A (92 amino acids) and B (91 amino acids), probably result from alternative mRNA splicing [3]. S100A6 from all these sources differs in only a few amino acids and in the length of the carboxy terminus. The

S100A6 gene was initially identified in growth-arrested rodent fibroblasts stimulated with serum [4] and suggested to have a role in cell-cycle progression as inferred by its upregulation in several tumors [5–7]. S100A6 was found to interact with calcyclin-binding protein/Siah-1-interacting protein (CacyBP/SIP) [8]. Because CacyBP/SIP is a component of the ubiquitin ligase complexes, S100A6 was suggested to be involved in the ubiquitination of β-catenin [9], thus supporting the possibility that S100A6 might play a role in the control of cell-cycle progression. S100A6's ability to inhibit the interaction between the heat shock proteins (Hsp70 and Hsp90) and Sgt1 [10] and Hop [11], suggested a potential role for S100A6 in the cellular response to different stress factors. In this respect, S100A6 was found to favor apoptosis in some cell types [12, 13], but to limit it in others [14]. The in vitro interaction of S100A6 with caldesmon [15], calponin [16], tropomyosin [17], and kinesin light chain [11] suggested that S100A6 might be involved in the regulation of cytoskeleton dynamics, particularly microfilament dynamics [18], and in vesicular transport. As an extracellular factor, S100A6 was shown to be involved in the release of lactogen II [19], insulin [20], and histamine [21]. By binding to the transmembrane receptor for advanced glycation endproducts (RAGE), S100A6 induced neuronal apoptosis by causing reactive oxygen species (ROS)-dependent activation of JNK and of caspases 3 and 7 [22]. RAGE transduces extracellular effects of several S100 proteins (23). Integrin β1 is another potential membrane protein transducing extracellular effects of S100A6 [24]. The present review seeks to critically summarize information about functional roles of S100A6 also in light of results of recent studies of S100A6 in cancer (Table 1).

Regulation of expression

Several factors have been shown to increase S100A6 mRNA and protein levels such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and serum [25], retinoic acid [26], estrogen [27], palmitate [28], vasopressin [29], and gastrin [30] (Fig. 1). S100A6 levels are also upregulated upon stress conditions such as ischemia [31], mechanical force [32], irradiation [33], and oxidative stress [34].

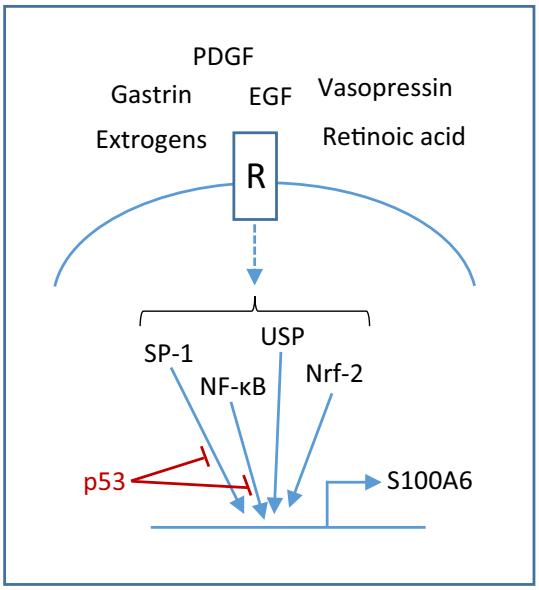

Fig. 1 Regulation of S100A6 expression. Several extracellular factors can upregulate S100A6 expression via the indicated transcription factors. The tumor suppressor, p53, decreases SP1 and NF-κB binding to the S100A6 promoter

In vivo, S100A6 protein levels are elevated in myocardial disease [35] and in many types of tumor cells (see below). However, the primary cause(s) of this increase remain(s) to be fully elucidated. A decrease in S100A6 levels was observed during the course of TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)- and etoposid-induced apoptosis in human breast cancer cells [36]. At the transcriptional level, USF (upstream transcription factor), NF-κB (nuclear transcription factor κB), Sp1 (specificity protein 1), and Nrf2 (Nf-E2-related factor 2) have been shown to activate the S100A6 gene promoter [13, 34, 37–39], whereas the tumor suppressor, p53, acts indirectly to suppress transcription via interference with Sp1 and NF-κB function on the *S100A6* promoter [40]. Insufficient suppression of S100A6 gene by p53 mutants might thus be responsible for S100A6 overexpression and cell-cycle deregulation in cancer.

Table 1 S100A6 in cancer

Role of S100A6	Cancer	References
S100A6 is overexpressed	Breast, stomach, pancreas and colon cancer, melanoma, thyroid carcinoma, clear cell renal cell carcinoma, mixed-lineage leukemia/AF4-positive acute lymphoblastic leukemia	[49–52, 54, 55, 81, 82]
S100A6 is underexpressed	Prostate and oral cancer	[49]
S100A6 is a diagnostic marker or prognostic factor	Pancreatic, gastric and prostate cancer, melanoma, non-small cell lung carcinoma, hepatocellular carcinoma	[50, 51]

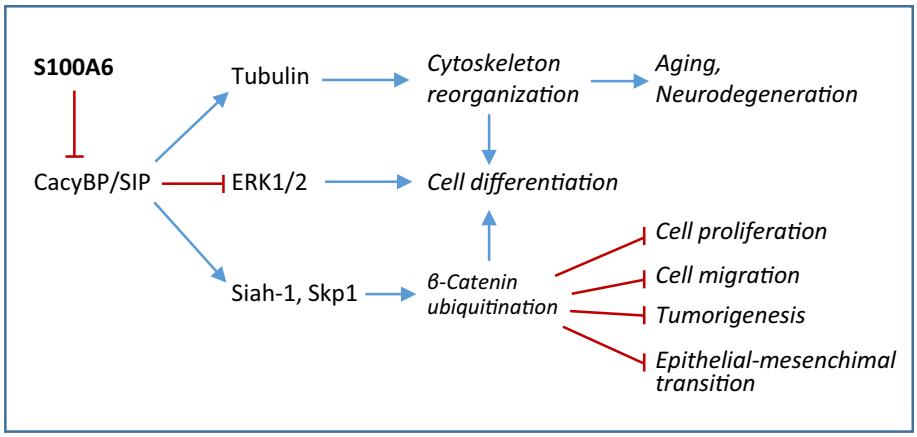

Fig. 2 Implications of S100A6 interaction with CacyBP/SIP. S100A6 inhibits CacyBP/SIP thereby stimulating cell proliferation and migration, tumorigenesis, and epithelial-mesenchymal transition via inhibition of β-catenin degradation, inhibiting cell differentiation, and participating in aging and neurodegeneration

Regulation of activity

Like other members of the S100 protein family (excepting S100G) [1], S100A6 exists within cells in the form of a homodimer in which the two subunits are arranged in an antiparallel fashion [41]. Each subunit consists of two EF-hand (helix–loop–helix) motifs tethered by a flexible hinge domain and a C-terminal tail [1, 42, 43]. Each S100A6 subunit binds two calcium ions. Ca^{2+}-binding induces conformational changes in the C-terminal half of each subunit of the S100A6 homodimer [41] as observed for other S100 proteins [1]. The Ca^{2+} binding causes hydrophobic residues of the hinge region, helices III and IV of each subunit to become exposed which enables S100A6 to interact with many target proteins such as glyceraldehyde-3-phosphate dehydrogenase, annexin II, annexin XI, annexin VI, and tropomyosin [44]. Additional intracellular interacting proteins are caldesmon, calponin and lysozyme, CacyBP/SIP, Sgt1, and melusin [44], p53 [13, 45], and the Hsp90/Hsp70-organizing protein (Hop) and kinesin light chain [10, 11, 43]. A Ca^{2+}- or Zn^{2+}-dependent S100A6/S100B heterodimer was identified in a yeast two-hybrid assay and confirmed in vivo [46, 47]. However, no functional correlates have been reported for these interactions with the exception of CacyBP/SIP (see subheading S100A6 and cell proliferation and cancer).

S100A6 also binds Zn^{2+} [48]. The binding of Zn^{2+} induces conformational changes in the S100A6 molecule that are different from those observed following Ca^{2+} binding. At present, there are no data showing a potential zinc-dependent activity of S100A6.

S100A6 and cell proliferation and cancer

S100A6 affects cell proliferation and cancer development by acting from within and from outside cells. S100A6 is overexpressed in breast, stomach, pancreas and colon cancer and in melanoma, whereas it is underexpressed in prostate and oral cancer [49]. It is considered a diagnostic marker or prognostic factor in pancreatic, gastric and prostate cancer, melanoma, non-small cell lung carcinoma, and hepatocellular carcinoma. S100A6 is also overexpressed in thyroid carcinoma [50, 51] and is suggested to play a key role in the progression and development of papillary thyroid carcinoma [52]. S100A6 affects murine models of cancer; however, its contribution to promoting a cancerous phenotype has only been examined in a limited number of model systems and the mechanistic basis for the observed effects on tumor progression has not been fully delineated [43]. In gastric cancer cells, S100A6 negatively regulates its partner-CacyBP/SIP-mediated inhibition of cell proliferation and tumorigenesis by affecting β-catenin degradation (Fig. 2) [53]. In addition, S100A6 enhanced migration and invasion of pancreatic ductal adenocarcinoma cells and promoted epithelial-mesenchymal transition via activation of β-catenin [54] (Fig. 2). The tumorigenic activity of overexpressed S100A6 was reported for clear cell renal cell carcinoma in which the protein inhibited the expression of the anti-tumor chemokine, CXCL14, and CXCL14-induced apoptosis [55]. It has been hypothesized that S100A6 may regulate CXCL14 through estrogen receptor 1 [55], but no experimental evidence for this has been presented. Additional evidence for S100A6-CacyBP/SIP interactions comes from the observation that S100A6 inhibits CacyBP/SIP phosphorylation by casein kinase II similar to the CacyBP/SIP phosphorylation inhibitor, DRB, which results in reduced phosphatase CacyBP/SIP activity towards the mitogen-activated protein kinases (MAPKs), ERK1/2 [56], which in turn might sustain cell proliferation and/or tumorigenesis.

S100A6 is reported to regulate endothelial cell cycle and senescence. In primary human endothelial cells, depletion of S100A6 caused increased cell-cycle arrest in G2/M phase. S100A6 depletion caused a decrease in both cyclin-dependent kinase 1 (CDK1), phosphorylated CDK1 levels,

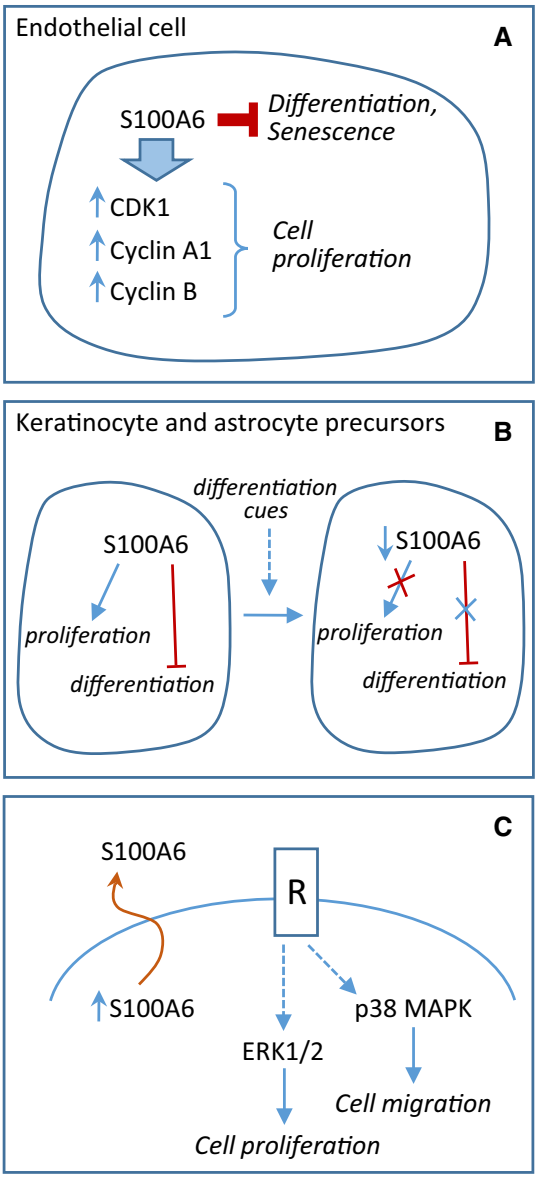

Fig. 3 Roles of S100A6 in cell proliferation and differentiation. **a** S100A6 is suggested to stimulate cell-cycle progression and to inhibit differentiation and senescence in endothelial cells. **b** S100A6 becomes downregulated at the beginning of keratinocyte and astrocyte differentiation, and S100A6 overexpression in these cells causes accelerated proliferation, enhanced adhesive properties, and reduced differentiation. **c** S100A6 is upregulated in and secreted by colorectal carcinoma cells. Secreted S100A6 stimulates cell proliferation and migration in a receptor-mediated manner

and cyclin A1 and cyclin B genes with effects on cell-cycle progression [57] likely via inhibition of antiproliferative signal transducers and activators of transcription (STAT) 1 signaling [58] (Fig. 3a). A role for S100A6 as an intracellular regulator of cell proliferation and differentiation is suggested by the finding that S100A6 becomes downregulated at the beginning of keratinocyte differentiation and that S100A6 overexpression in these cells causes accelerated proliferation, enhanced adhesive properties, and reduced differentiation [59] (Fig. 3b). Downregulation of S100A8 and S100A9 proteins upon differentiation of monocytes into mature macrophages has been reported [60, 61]. Transient downregulation has also been reported for S100B protein at the beginning of myoblast, neuronal, chondrocyte, and astrocyte differentiation and this event has been shown to be permissive for the differentiation of these cell types [62–67]. Whether transient downregulation at the beginning of cell differentiation is a general property of S100 proteins remains to be established.

Transfection with recombinant S100A6 of or administration of recombinant S100A6 to HCT116, a colorectal carcinoma cell line with relative low S100A6 expression, resulted in enhanced cell proliferation and migration, MAPK activation in vitro, and tumor growth in vivo. Conversely, RNAi-mediated knockdown of S100A6 in LoVo, a colorectal carcinoma cell line with relatively high S100A6 expression, resulted in reduced cell proliferation, migration, and MAPK activity. S100A6-induced proliferation was partially attenuated by an ERK1/2 inhibitor, while migration was suppressed by a p38 MAPK inhibitor [68] (Fig. 3c). These results suggest that S100A6 might act as an extracellular signaling molecule affecting cancer cells in a receptor-mediated manner. RAGE is a candidate receptor as it transduces certain effects of S100A6 on responsive cells [22, 69]. However, whether RAGE transduces S100A6 effects on colorectal carcinoma cells remains to be determined.

Regarding S100A6-RAGE interaction, one study reported that S100A6 binds the C1 and C2 domains of RAGE [22], whereas another study showed that S100A6 binds RAGE V domain similar to other S100 proteins [1, 70]. Recent work [71] suggests that the primary S100A6 binding site is formed by the RAGE C1 domain and that S100A6 adopts a dimeric conformation different from all known S100 dimers; the N-terminus of helix H1 from one S100A6 subunit inserts into the hydrophobic cleft formed between helices H3 and H4 from the opposite subunit in the presence of Ca^{2+}. Incidentally, this cleft binds RAGE [71] and CacyBP/SIP [72].

Contrasting effects have been reported regarding effects of S100A6 on cell proliferation. S100A6 increases adhesion and inhibits proliferation of mesenchymal stem cells isolated from Wharton's jelly of the umbilical cord [24]. Integrin β1 appears to be the membrane protein (receptor) transducing these S100A6 effects because neutralization of integrin β1, but not RAGE blunted them. On the other hand, exogenous expression of S100A6 in mesenchymal stem cells increased proliferation and inhibited osteogenic differentiation, and stimulated osteosarcoma growth in vivo [73]. Whether these latter S100A6's effects result

from intracellular regulatory activities, receptor-mediated mechanism(s), or both remains to be determined.

Interaction of certain S100 proteins with RAGE and with receptors other than RAGE is not unusual [1]. For example, S100A4, S100A8/S100A9, and S100B engage RAGE in several cell types but can act independently of RAGE on other cell types [1, 23]. Thus, S100A4 stimulates neurite outgrowth by binding to heparan sulphate proteoglycans and a putative Gαq-coupled receptor [74] and stimulates tumor progression by interacting with EGFR ligands [75]. S100A8 and S100A9 can activate toll-like receptor 4 in phagocytes [76], S100A12 activates a G-protein coupled receptor in mast cells and monocytes [77], and S100B binds bFGF and enhances bFGF/FGFR1 signaling and simultaneously blocks RAGE in high-density myoblast cultures thereby promoting cell proliferation [78].

S100A6 modulates RAGE-dependent survival of neuroblastoma cells by triggering apoptosis and generation of ROS through c-Jun NH2 terminal protein kinase activation [22]. S100A6 may regulate secretory processes in some cells. It stimulates secretion of lactogen II by trophoblasts [19] and insulin release from pancreatic islet cells [20], and may modulate allergic responses by inhibiting histamine release by mast cells [21, 79]. The receptor(s) transducing these effects remain(s) to be determined.

The role of S100A6 as an intracellular regulator of cell proliferation/apoptosis is further complicated by its effects on the anti-tumor, p53 [80], and by the finding that p53 acts indirectly to suppress S100A6 transcription [40] (Fig. 1). S100A6 competes with MDM2, an ubiquitin E3 ligase that degrades p53, for binding to p53, and with p300 acetyltransferase. Once acetylated, p53 loses the ability to bind S100A6, suggesting that high S100A6 concentrations might interfere with p53 acetylation, and thus, that S100A6 might protect p53 against untimely degradation and/or acetylation thus resulting in the promotion of p53 nuclear translocation and, likely, p53 transcriptional activity. In this perspective, S100A6 might aid in cell proliferation arrest and/or apoptosis. However, the opposite has also been observed in mixed-lineage leukemia/AF4-positive acute lymphoblastic leukemia, where IL-24-induced inhibition of S100A6 expression was shown to exert pro-apoptotic effects, which points to an anti-apoptotic, tumorigenic role of S100A6 in these cells [81, 82] (Fig. 4). For S100A6's anti-apoptotic effects, also see subheading S100A6 and stem cells in the following.

Other S100 proteins have been implicated in tumorigenesis and metastasis [1, 42, 43]. Intracellular S100A4 has pro-metastatic activity [83]. Once released by stromal/epithelial cancer cells, S100A4 stimulates cancer cell invasiveness [84], cooperates with the chemochine, RANTES (CCL5), in promoting tumor progression [85], and interacts with EGF receptor ligands, thereby enhancing

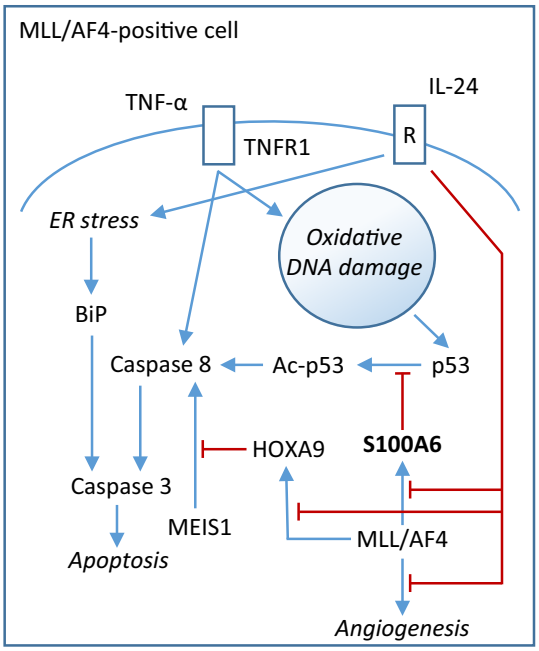

Fig. 4 S100A6 exerts anti-apoptotic effects in mixed-lineage leukemia (MLL)/AF4-positive leukemia cells. In MLL/AF4-positive acute lymphoblastic leukemia cells, IL-24-induced inhibition of S100A6 expression exerts pro-apoptotic effects, which points to an anti-apoptotic function of S100A6 in these cells

EGFR/ErbB2 receptor signaling and cell proliferation [74]. S100A7 overexpression is seen in invasive breast cancer [86] and enhances mammary tumorigenesis and breast cancer metastasis RAGE dependently [87, 88]. The S100A8/S100A9 heterodimer (calprotectin) facilitates tumor cell invasion [89, 90]. Overexpression of S100B is associated with and exerts a pathogenic role in malignant melanoma [91–93] and glioma [62, 94–96]. Thus, several S100 proteins have a role in tumor development and progression with a certain specificity in terms of mechanism of action and cell type.

S100A6 and cytoskeleton

Intracellular S100A6 has been functionally linked to changes in cellular motility and cytoskeletal reorganization [42, 79], but a clear mechanistic picture is still lacking. Knockdown of S100A6 in NIH-3T3 fibroblastic cells causes a reorganization of the actin cytoskeleton with an extensive cortical network of actin filaments and tropomyosin structures and increase in the number of focal adhesions at the cell periphery [18, 97]. Thus, S100A6 effects on actin filaments and tropomyosin structures might be responsible at least in part for the large increase in lamellipodia and possibly for the enhancement of cellular motility seen when S100A6 levels are reduced by siRNA

techniques [98]. The involvement of S100A6 in the motility of cancer cells has also been reported, albeit with contradictory outcomes. Down- or upregulating of S100A6 expression in osteosarcoma cells led to increased or decreased migration, respectively, suggesting a role for S100A6 as an inhibitor of cell motility in cultured cells [98, 99]. However, S100A6 has also been shown to promote cellular motility in pancreatic cancer cells [100, 101] by a mechanism that is dependent on the presence of annexin 2. Elevated levels of intracellular S100A6 have been shown to be associated with tumorigenesis (reviewed in [22]) and the ability of colorectal adenocarcinoma cells [102] and Ras-transformed NIH 3T3 cells [103] to metastasize to form secondary lesions. Yet, the molecular mechanisms underpinning S100A6's ability to regulate cell motility have remained elusive. Direct interaction between S100A6 and the tropomyosin–actin complex has been shown in vitro [17], but remains to be confirmed in vivo; the only current evidence suggests that S100A6 acts as a downregulator of tropomyosin expression [18]. S100A6 interacts in vitro with other components of the actin cytoskeletal architecture, such as the myosin ATPase inhibitors, caldesmon [104, 105], and calponin [16], but no mechanistic link to cell motility has been demonstrated. Other S100 proteins interact with the cytoskeleton. S100B binds to tubulin and inhibits its polymerization into microtubules [106, 107], associates with microtubules and intermediate filaments in cultured cells [108, 109], increases the Ca^{2+}-sensitivity of microtubules [110], and promotes stress fibers formation in and migration of proliferating astrocytes via a Src/PI3K/RhoA/ROCK pathway [65]. S100A1 interferes with the assembly of desmin intermediate filaments [111] and interacts with the giant sarcomeric protein, titin [112] thereby reducing sarcomeric passive tension before contraction [113]. Indeed, S100A1 gene delivery rescues failing myocardium [114]. Interaction with non-muscular myosin heavy chain IIA, tropomyosin, and actin is causally related to the pro-metastatic activity of intracellular S100A4 [42, 83, 115]. S100A8, S100A9, and the heterocomplex S100A8/S100A9 (also known as calprotectin) associate with vimentin intermediate filaments during Ca^{2+} transients in monocytes [116] and with keratin intermediate filaments in keratinocytes [117], and stimulate microtubule assembly during transendothelial migration of phagocytes [118]. Thus, regulation of the cytoskeleton and cytoskeleton-associated activities seems to be one intracellular function shared by several S100 proteins with each of them showing a preferential molecular target among cytoskeletal elements likely due to the unique length and primary sequence of the hinge region and C-terminal tail of individual S100 members and the cell type(s), where they are expressed.

S100A6 and stem cells

S100A6 was shown to be expressed in neural stem cells in the subgranular zone of the dentate gyrus in adult hippocampus [119]—a major neurogenic niche. These S100A6-expressing cells were recognized as astrocyte precursors. The finding that S100A6 was not detected in mature astrocytes suggested that S100A6 might play an important, yet unknown role during astrocytic differentiation of neural stem cells. Possibly, S100A6 has to be downregulated for astrocyte precursors to undergo differentiation, as observed for keratinocyte differentiation [59] (Fig. 3b) and with other S100 proteins [60–67]. S100A6 also marks glial precursor cells in neuroblastoma [120].

S100A6 expression is increased in the peri-infarct zone of rat heart postinfarction and functions as a global negative regulator of the induction of cardiac genes by trophic stimuli [35]. S100A6 is induced in cardiomyocytes by TNF-α via NF-κB activation and protects cardiomyocytes from TNF-α-induced apoptosis by associating with p53 and interfering with p53 phosphorylation [14] (Fig. 5). Similar to S100A6, S100B is induced in cardiomyocytes surviving an infarct, and can limit the hypertrophic response by inhibiting expression of α-actin and β-myosin [121]. However, extracellular S100B causes cardiomyocyte apoptosis in a RAGE-mediated manner [122] and induces myofibroblast proliferation in a RAGE-VEGF-mediated manner potentially contributing to the scar formation observed in infarcted myocardium [123]. At present, there is no information about potential extracellular effects of S100A6 in the context of cardiac infarction.

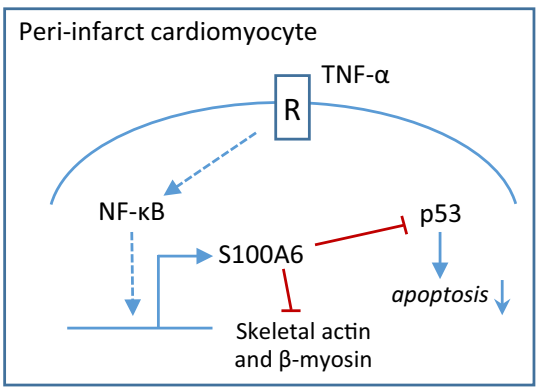

Fig. 5 Induction of S100A6 expression in peri-infarct cardiomyocytes. The TNF-α/NF-κB axis induces S100A6 in peri-infarct cardiomyocytes. Induced S100A6 reduces the cardiomyocyte hypertrophic response and inhibits the pro-apoptotic effect of p53

S100A6 and neurodegenerative diseases

In Alzheimer's disease mouse models, astrocytic S100A6 protein was shown to be homogeneously upregulated within the white matter, whereas within the grey matter, almost all S100A6 immunoreactivity was found to be concentrated in astrocytes surrounding the Aβ amyloid deposits of senile plaques [124]. S100A6 is also overexpressed in astrocytes located near impaired axons of motoneurons in amyotrophic lateral sclerosis (ALS) [125]. These findings suggest that S100A6 might participate in the pathophysiology of Alzheimer's disease and ALS, respectively. Mechanistically, S100A6 was shown to form oligomers and amyloid-like fibrils, an event negatively regulated by Ca^{2+}, and to potentiate in vitro the aggregation of superoxide dismutase-1 (SOD1) [126], that forms cytoplasmic aggregates in ALS-affected neurons. Although S100A6 oligomers but not fibrils proved toxic to neuronal cell in culture [126], there are no data to demonstrate that S100A6 plays a role in the promotion of SOD1 aggregates in ALS neurons. Other S100 proteins (e.g., S100B, S100A8, S100A9, and S100A12) are known to take part in the pathophysiology of neurodegenerative disorders by affecting neurons, astrocytes, and/or microglia mostly as extracellular signals [1, 127–140]. Likely, accumulation of S100 proteins, including S100A6, in the brain extracellular space might be a consequence rather than a cause of the underlying neurodegenerative disorder, and represents one molecular means by which astrocytes and microglia respond to noxious stimuli (such as disturbances of the local circulation, changes in the redox status, metabolic disorders, etc) to bring about a complex inflammatory response that cannot, however, progress through the canonical phases, i.e., an early proinflammatory, defense phase, and a late reparative phase, due to the persistence of the underlying noxious stimulus and the intervention of several membrane receptors. Overall, the available information about the involvement of several S100 proteins in the pathophysiology of neurodegenerative disorders [124, 127–140] suggests that targeting one single S100 protein might not be sufficient to reverse the pathology.

S100A6 as a serum marker of disease

Serum levels of S100A6 are significantly elevated in early stage non-small cell lung cancer [141], gastric cancer [142], urinary bladder urothelial carcinoma [143] and ovarian cancer [144] as well as in acute coronary syndrome and myocardial infarction [145]. Elevation of serum levels of other S100 proteins (e.g., S100B, S100A4, S100A7, S100A8, and S100A9) has been reported in several cancers [146–150]. However, pending additional work on larger cohorts of patients, usage of serum levels of S100A6 in diagnosis of the above tumors [141–144] is promising.

Conclusions

Studies of S100A6's interaction with and inhibition of its partner, CacyBP/SIP—an inhibitor of cell proliferation and tumorigenesis by virtue of its ability to promote degradation of β-catenin—support a role for S100A6 as a positive regulator of cell proliferation in the epidermis, endothelial cells, and tumor cells and as an anti-apoptotic factor in certain leukemias. In addition, upregulation of S100A6 in peri-infarct cardiomyocytes results in reduction of p53-induced apoptosis via interference with p53 phosphorylation and inhibition of induction of fetal genes responsible for cardiomyocyte hypertrophy. On the other hand, interaction with the tumor suppressor, p53, implicates S100A6 in apoptosis, with high concentrations of S100A6, as is typical of certain tumor cells, protecting p53 from inactivation by p300 acetyltransferase and degradation by MDM2. S100A6 can be secreted/released by certain cell types which points to extracellular effects of the protein. RAGE and integrin β1 might transduce extracellular S100A6's effects, but further analyses in physiological and pathological contexts are required. Finally, dosage of serum S100A6 might aid in diagnosis in oncology and acute coronary syndrome. The growing interest on S100A6 in cancer makes this protein a potential therapeutic target.

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