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Review Article

S100 protein family in human cancer

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Abstract: S100 protein family has been implicated in multiple stages of tumorigenesis and progression. Among the S100 genes, 22 are clustered at chromosome locus 1q21, a region frequently rearranged in cancers. S100 protein possesses a wide range of intracellular and extracellular functions such as regulation of calcium homeostasis, cell proliferation, apoptosis, cell invasion and motility, cytoskeleton interactions, protein phosphorylation, regulation of transcriptional factors, autoimmunity, chemotaxis, inflammation and pluripotency. Many lines of evidence suggest that altered expression of S100 proteins was associated with tumor progression and prognosis. Therefore, S100 proteins might also represent potential tumor biomarkers and therapeutic targets. In this review, we summarize the evidence connecting S100 protein family and cancer and discuss the mechanisms by which S100 exerts its diverse functions.

Keywords: S100 proteins, proliferation, apoptosis, invasion, migration, pluripotency, biomarker

Introduction

The S100 gene family is the largest subfamily of calcium binding proteins of EF-hand type [1]. To date, at least 25 distinct members of this subgroup have been described. Of these genes, 22 are clustered at chromosome locus 1q21. Interestingly, 14 of 22 members localized in the epidermal differentiation complex (EDC) on chromosome 1q21 [2]. S100 proteins form either homodimeric or heterodimeric complexes with one another [3, 4]. Upon calcium binding, most S100 proteins undergo a conformational change, thus allowing the protein to interact with the different protein targets, thereby exerting a broad range of intracellular and extracellular functions. Intracellular functions include regulation of calcium homeostasis, cell cycle, cell growth and migration, phosphorylation, cytoskeletal components and regulation of transcriptional factors. In contrast to intracellular function, extracellular S100 proteins act in a cytokine-like manner by binding to cell surface receptors such as the receptor for advanced glycation end products (RAGE) and Toll-like receptors (TLRs) [2, 5]. More recently, there is growing interest in the S100 proteins and their relationship with different cancers because of their involvement in a variety of biological events which are closely related to tumorigenesis and cancer progression. The association between S100 proteins and cancer can also be explained by several observations: firstly, most of S100 genes are clustered on human chromosome 1q21, a region prone to genomic rearrangements, supporting that S100 proteins may be implicated in tumor progression. Secondly, several S100 members show altered expression in various malignancies. Finally, a number of S100 proteins have been shown to interact with and to regulate various proteins involved in cancer and exert different effects on specific target proteins such as NF-κB, p53, and β-catenin. In this review we discuss the important roles of S100 proteins in tumorigenesis, cancer metastasis, tumor microenvironment, maintenance of pluripotency and their potential implications as biomarkers and prognostic factors. We also discuss the underlying mechanisms by which S100 proteins involved in tumorigenesis and cancer progression. Elucidating the mechanisms of S100 signaling in cancer will increase our understanding of tumorigenesis and may lead to the identification of new therapeutic targets.

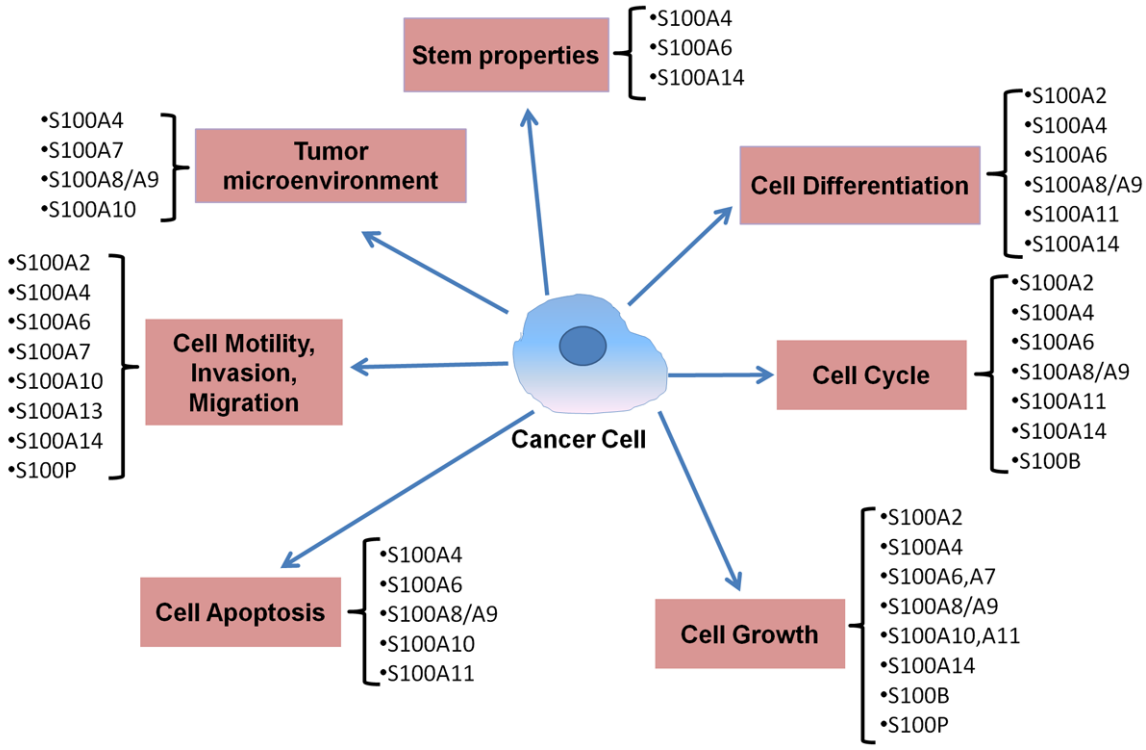

Figure 1. S100 proteins might have important roles during different steps of tumorigenic processes. S100 proteins are involved in many aspects of phenotypic features of cancer including regulation of cell differentiation, cell cycle progression, cell proliferation, cell apoptosis, cell motility, invasion and migration, tumor microenvironment and Cancer Stem Cells (CSCs) etc.

The functions of S100 protein family in cancer

Uncontrolled cell growth and invasion/metastasis are two characteristic features of cancer. Aberrant cell proliferation, perturbations of differentiation programs, loss of normal apoptosis, increase of angiogenesis/invasion/metastasis, and evasion of the immune system contribute to the malignant phenotype of cancer [6]. S100 proteins possess a wide range of biological functions that can alter and regulate the major phenotypic features of cancer. The functions of S100 proteins have been extensively studied and the functional modes of S100 proteins can be intracellular, extracellular, or a combination of both. Here, we mainly focus on several important and well-studied members of S100 protein family and summarize the key functions of S100 proteins including proliferation, apoptosis, metastasis, tumor microenvironment and cancer stem cells, which are central to S100 proteins with tumor development and progression (summarized in **Figure 1**). Furthermore, we identify key pathways in these functions and propose additional areas of study, which may be of particular importance for the less studied S100 family members and which may lead to new insights and discoveries for cancer diagnosis and treatment.

The association between S100 proteins and cancer cell differentiation

One of the hallmarks of many human cancers is disrupting the regulation of differentiation [7]. Most of S100 calcium-binding proteins are clustered at the chromosomal region 1q21, constituting important components of the epidermal differentiation complex (EDC) [8]. Therefore, S100 proteins are involved in the process of terminal differentiation of human epidermis and implicated in several disorders including cancer. On one hand, some S100 proteins expression levels correlate with tumor differentiation. For instance, high expression of S100A11 was associated with the histological differentiation of pancreatic adenocarcinoma (PAC) [9]. And downregulation or absence of S100A14 correlated with colorectal cancer (CRC) and esophageal squamous cell carcino-

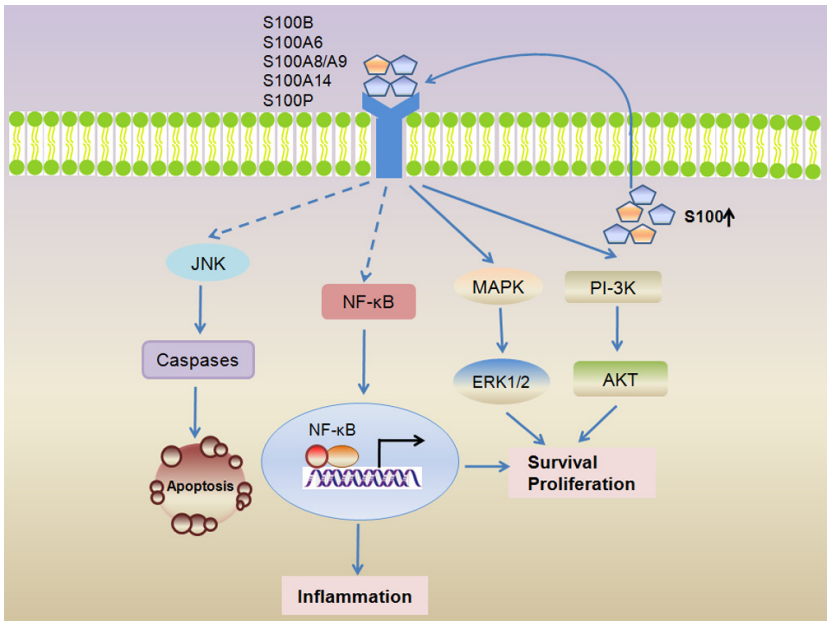

Figure 2. S100 proteins in RAGE signaling. S100 proteins can be secreted into the extracellular space, and crosslink with cell-surface receptor-RAGE and deliver signals inside the cell, thereby modulate cell survival, proliferation or apoptosis. Some S100 proteins (S100P, S100A8/A9, S100A12, S100A14, S100B) can interact with RAGE, subsequently activating the MAPK, PI-3K-AKT, and NF-κB signaling pathways, and thereby leading to the up-regulation of genes involved in cell survival and proliferation. In other cases, the apoptosis cascade is activated through the activation of JNK and caspases.

ma (ESCC) poor differentiation [10, 11]. On the other hand, some S100 proteins expression levels correlate with tumor dedifferentiation. For example, high levels expression of S100A4 is associated with poor differentiation in PAC and ESCC [12, 13]. And S100A6 can act as a poor-differentiation predictor in hepatocellular carcinoma (HCC) [14]. In addition, Some S100 proteins can even exhibit converse correlation with tumor differentiation dependent on cancer-type. For example, S100A2 protein underexpression was associated with poor tumor differentiation in laryngeal squamous cell carcinoma (LSCC) and ESCC [15, 16]. Conversely, expression levels of S100A2 are negatively associated with differentiation of pancreatic cancer cell lines [17]. Our previous study shows that loss of S100A8/S100A9 expression in ESCC correlates with poor differentiation [18]. In contrast, co-expression of S100A8/S100A9 correlates with poor tumor differentiation in breast invasive ductal carcinoma (IDC) [19]. And overexpression of S100A9 is also associated with the poor differentiation of pulmonary adenocarcinoma, IDC and liver carcinomas [20-22]. Taken together, these data suggest that S100 proteins expression correlates with tumor differentiation.

S100 proteins in cancer cell proliferation

S100 proteins in the cell cycle and cell proliferation

Cell cycle deregulation is fundamental alterations in the control of cell division, resulting in unstrained cell proliferation. Several S100 proteins have been implicated in the dysregulation of proliferation, particularly for S100A1, S100A4, S100A6, S100A8/A9 and S100A14, which are perhaps the most well-studied S100 proteins in human cancers. S100 proteins exert their actions through specific target proteins. In a few cases S100 proteins share their target proteins and, hence, contribute to identical activity. For example, extracellular S100 proteins can interact with RAGE that resulting in the activation of MAPK and NF-κB signaling. In addition, S100 proteins are also involved in the regulation of Epidermal Growth Factor (EGF) signaling. Intracellular S100 proteins can interact with p53, thereby affecting p53 transcriptional activity and p53-mediated cell cycle regulation and proliferation.

S100 proteins in RAGE signaling

Several lines of evidence show that certain S100 proteins are secreted into the extracellular space and exert their functions in an endocrine, paracrine and autocrine manner. One of the general receptors of S100 proteins is RAGE, which is a cell surface receptor implicated in multiple pathologies including inflammation and cancer [23]. S100 proteins including S100A1, S100A4, S100A6, S100A8/A9, S100A11, S100A12, S100A14, S100B, and S100P bind to RAGE and trigger RAGE-mediated cellular signaling which involves in MAP Kinase,

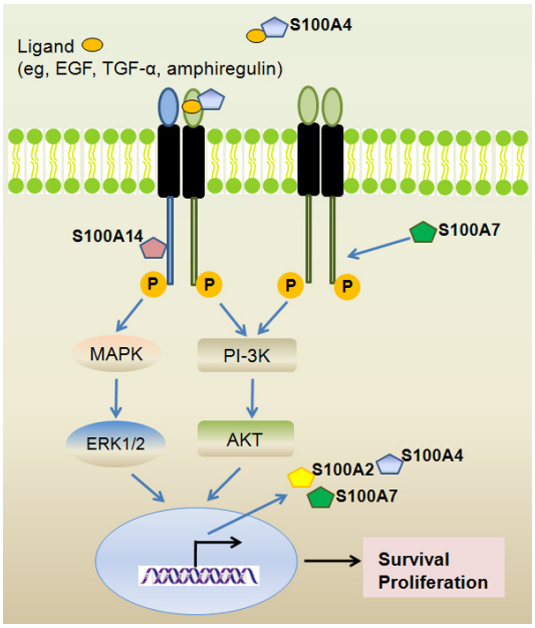

Figure 3. S100 proteins in EGF signaling. S100 proteins (S100A2, S100A4, S100A7) are induced by the activation of EGF/EGFR signaling. In turn, S100 proteins affect the activation of EGF/EGFR signaling and EGF/EGFR-mediated cell proliferation.

NF-κB, and phosphatidylinositol 3-kinase (PI-3K)/AKT signaling pathway. Therefore, S100 proteins are involved in the regulation of diverse cellular processes including inflammation and cancer [24-35]. Here, we summarized the effect of S100 proteins on cancer cell survival, proliferation or apoptosis via the interaction with RAGE (**Figure 2**). In neuroblastoma cells S100B modulates cell survival by recruiting PI-3K/AKT and NF-κB signaling pathway in a RAGE-dependent manner, whereas S100A6 inhibits cell survival and triggers cell apoptosis through the activation of JNK [31]. S100P increases colon cancer cell proliferation and stimulated both ERK1/2 phosphorylation and NF-κB activity via the interaction with RAGE, and antagonism of RAGE-cromolyn blocked the biological effects of S100P on cell proliferation [36]. Also, S100P regulates cell proliferation and survival of pancreatic cancer cells by activating RAGE [37]. S100A8/A9 at low concentration promotes tumor cell growth via activating MAP Kinase and NF-κB signaling pathway dependent on RAGE ligation. Accordingly, S100A8/A9-mediated cell growth can be blocked by RAGE specific siRNAs or antibody [32, 38]. Our published data suggest that extracellular S100A14 promotes cell proliferation at low concentrations via binding to the RAGE in ESCC cells [34].

S100 proteins in Epidermal Growth Factor (EGF) signaling

Several S100 family members are involved in EGF/EGFR signaling pathway (**Figure 3**). For instance, EGF receptor activation stimulates transcription of S100A2 in human keratinocytes [39]. And extracellular S100A4 was found to interact with a variety of EGFR ligands and have the highest affinity for amphiregulin and stimulate EGFR/ErbB2 receptor signaling and enhance the amphiregulin-mediated proliferation of mouse embryonic fibroblasts [40]. And levels of ErbB2 and S100A4 were tightly correlated in samples of primary medulloblastoma and ErbB2 overexpression up-regulated S100A4 expression in medulloblastoma cells [41]. Previous study also demonstrated that EGF treatment significantly induced S100A7 expression and S100A7 played a functional role in EGF-induced signaling pathway [42]. Further, S100A7 enhanced cell survival by binding to c-Jun activation domain-binding protein 1 (Jab1), thereby increasing activity of NF-κB and p-Akt, contaminant with EGFR signaling activation [43]. In addition, S100A14 can directly interact with ErbB2 and functions as a modulator of ErbB2 signaling. And S100A14 depletion significantly decreased HER2 phosphorylation, downstream signaling, and HER2-stimulated cell proliferation [44].

S100 proteins in p53 signaling

It's particularly intriguing that several S100 proteins may bind to p53. P53 and S100 proteins form autoregulatory feedback loop (**Figure 4**). P53 binds to the promoter of S100 proteins such as S100A2, S100A9, S100A14, and S100B and stimulates the expression of S100 proteins [45-48]. And as a direct p53 target gene, S100A9 induces p53-dependent cellular apoptosis and mediates the p53 apoptosis pathway [47]. In turn, S100 proteins can affect p53 function and interfering with p53 transcriptional activity. Hence, S100 proteins contribute to the regulation of cell cycle and cell growth via affecting p53 activity. S100A2 can interact with p53 in calcium-dependent manner and activate p53 transcriptional activity, presumably helping restore p53 function in cell arrest and apoptosis [49]. Overexpression of S100A4

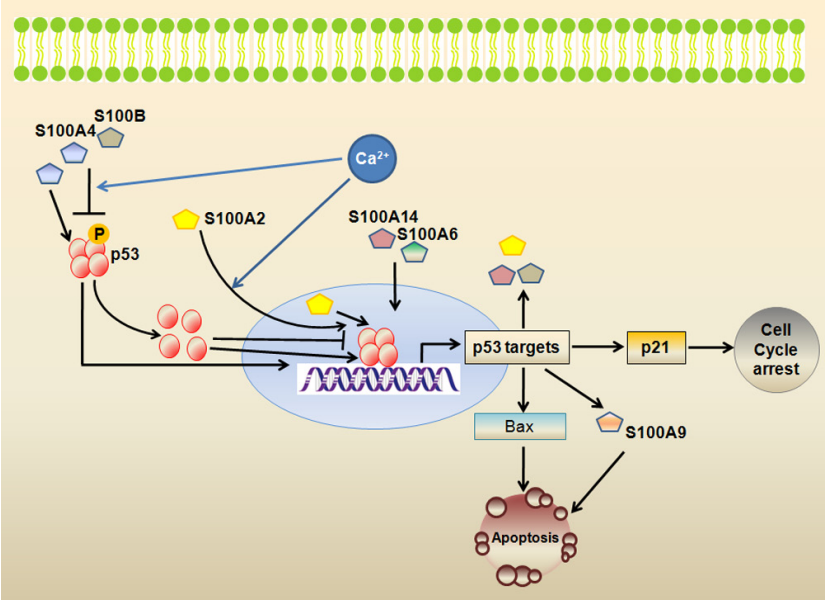

Figure 4. S100 proteins in p53 signaling. S100 proteins can be intracellularly located and regulate cell growth, cell-cycle progression and apoptosis by interacting with the relevant intracellular signal-regulation pathways. In particular, some S100 proteins can interact with p53 and affect p53 transcriptional activity, thereby resulting in the expression changes of p53 target genes involved in cell survival, proliferation and apoptosis.

drives cells into G2/M phase by sequestering p53 and upregulating the expression of p53 target gene-Stathmin [50]. Furthermore, S100A4 can interact with p53 and interfere with p53 transcriptional activity. For instance, S100A4 activates the p53 target genes such as p21/WAF1, thrombospondin-1, MDM2 in cells with wild-type p53. On the other hand, S100A4 interacts with p53 and inhibits the phosphorylation of p53. However, S100A4 exhibits a differential modulation of the p53 target gene. And expression of S100A4 resulted in the inhibition of the transcription of p21/WAF1. In contrast, S100A4 induced pro-apoptotic gene-Bax expression. Accordingly, S100A4 enhanced p53-dependent cell apoptosis. This observation implies that S100A4 may exert its function on tumor progression by p53 and enhancing p53-dependent apoptosis, which might accelerate the loss of p53 in tumors [51, 52]. S100A6 was also reported to interact with p53 in a calcium-dependent manner and enhance p53 transcriptional activity, thus facilitating the apoptotic action of p53 [53]. S100A14 inhibits cell proliferation by harboring p53 and inducing G1 arrest in oral squamous cell carcinomas (OSCC), this G1-arrest correlated with up-regulation of p21 [54]. S100B exerts dual regulatory effects on p53. In normal cells, S100B enhanced p53 nuclear translocation and accumulation via calcium-dependent signaling pathway, thereby promoting p53-mediated cell growth inhibition and apoptosis [55, 56]. In cancer cells, S100B interacts with p53, inhibits the phosphorylation of p53 and disrupts p53 tetramers, thus diminishing p53 ultimate function as a tumor suppressor [46, 57, 58].

In other cases different S100 members take part in the regulation of similar activity through different target proteins. Ectopic overexpression of S100A2 induced G1/S cell cycle arrest, thus attenuating cell growth both *in vitro* and *in vivo* partially by down-regulation of Cox-2 in oral cancer cells [59]. S100A6 has an important role in regulating endothelial cell cycle. In primary human endothelial cells, depletion of S100A6 caused increased cell-cycle arrest in the G2/M phase. Mechanistic investigation demonstrated that S100A6 depletion caused a decrease in both cyclin-dependent kinase (CDK1), phosphor-CDK1 levels, CDK1, cyclinA1 (CCNA1) and cyclin B (CCNB1) genes with effects on cell-cycle progression [60]. In gastric cancer cells, S100A6 protein negatively regulates its partner-CacyBP/SIP mediated inhibition of cell proliferation and tumorigenesis by affecting β-catenin degradation [61]. S100A7 may possess differential activities dependent on ER status. In ER-negative breast cancer cells, S100A7 increases cell growth *in vitro* and *in vivo* via the interaction with c-Jun activation domain-binding protein 1 (Jab1) [62]. Also, overexpression of S100A7 promoted MDA-MB-231 cell survival by increasing activity of NF-κB and phospho-Akt dependent on the interaction with Jab1 [43]. In contrast, in ER-positive breast cancer cells, S100A7 exhibits tumor suppressor capabilities through inhibition of the β-catenin/TCF4 pathway [63].

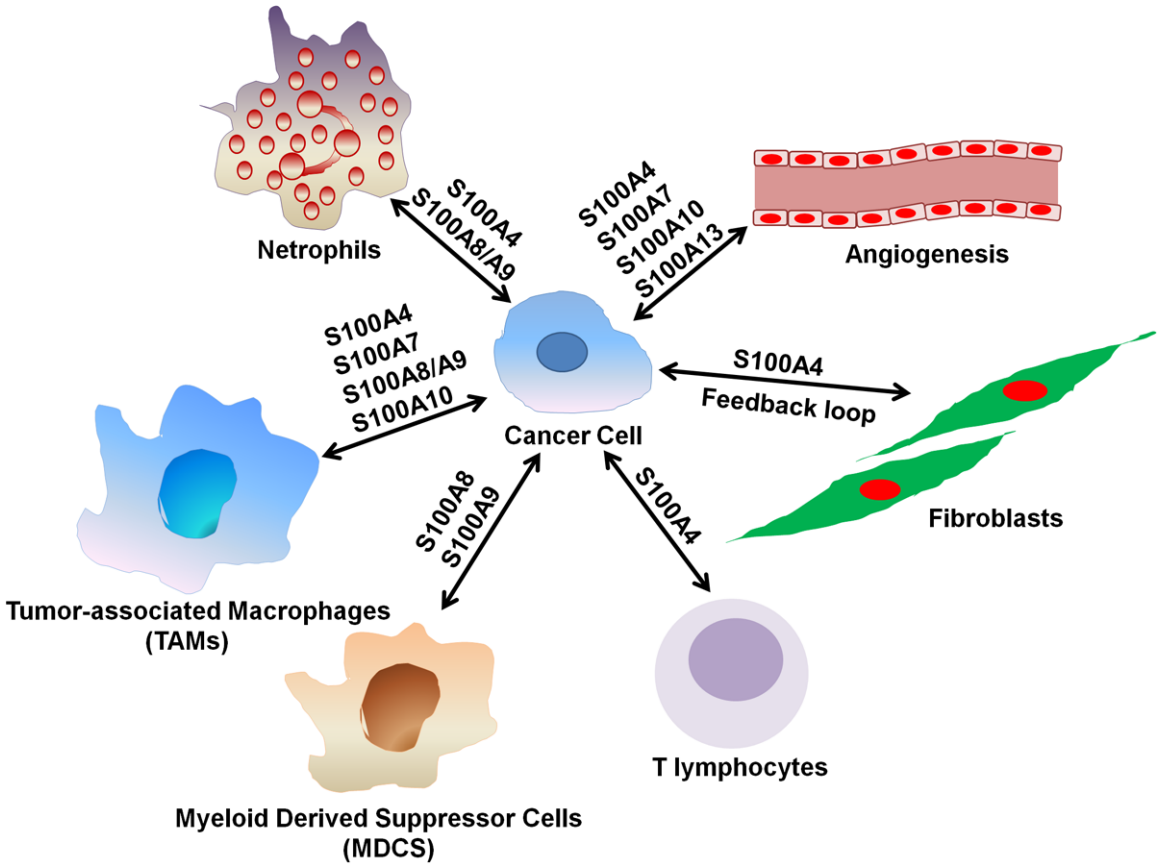

Figure 5. S100 proteins are involved in cancer-stromal interplay. Many of S100 proteins are implicated in the communication between cancer cells and stromal cells such as fibroblasts, endothelial cells, and inflammatory cells including Tumor-associated Macrophages (TAMs), Myeloid Derived Suppressor Cells (MDCS), T lymphocytes, and neutrophils.

Further, in squamous cell carcinoma of oral cavity (SCCOC), S100A7 inhibits cell growth by targeting β-catenin degradation [64]. S100A8/A9 is a crucial regulator of cell proliferation and inhibits growth of squamous cell carcinoma by negatively regulating G2/M cell cycle progression. S100A8/A9 increases PP2A phosphatase activity and p-Chk1 (ser345) phosphorylation, which represses phosphorylation of mitotic p-Cdc25C (ser216) and p-Cdc2 (Thr12/Tyr15) to inactivate the G2/M Cdc2/cyclinB1 complex. CyclinB1 expression then reduces and the cell cycle arrests at the G2/M checkpoint, thereby inhibiting cell division [65]. S100A10 positively regulates cell growth via the interaction with DLC1 in lung cancer [66]. S100A11 acts as a tumor suppressor and mediates growth inhibition by TGF-β1 via induction of p21/WAF1 [67]. Moreover, S100A11 suppresses the cell growth of squamous carcinoma cell lines via the interaction with Annexin A1 [68]. On the other hand, S100A11 could act as a tumor inducer and sustain the cell growth of lung adenocarcinoma cells [69]. There is also evidence that S100B is implicated in the regulation of cell division via targeting Ndr (a nuclear serine/threonine protein kinase) [70, 71]. In cultured glioma C6 cells, the accumulation of S100B correlates with contact-dependent inhibition [55]. In contrast, in human melanoma cells, overproduction of S100B protein in G1 phase is linked with cell cycle progression. These apparent contradictions suggest that alternative functions for intracellular S100B in negative and positive cell growth regulation might depend on other, as yet unidentified cellular cofactors.

S100 proteins in oncogenic transformation

S100 proteins function in proliferation and transformation via a variety of cellular receptors such as RAGE and TLR4. S100A2 overexpression in the human malignant squamous

cell carcinoma cell line KB decreases colony formation and *in vivo* tumor growth [59]. However, in lung cancer, overexpression of S100A2 promotes tumor growth [72]. S100A4 is involved in tumorigenesis in multiple cancers. For example, overexpression of S100A4 in melanoma cells promotes *in vivo* tumor growth, accordingly, S100A4 suppression decreases tumor growth. Further, suppression of S100A4 in the human pancreatic adenocarcinoma, osteosarcoma, and prostate cancer cells reduces tumor growth *in vivo* [27, 73, 74]. Heterozygously deleted S100A4 mice exhibit reduced prostate tumorigenesis contaminant with reduced NF-κB activity dependent on RAGE [75]. S100A6 overexpression in CRC enhances tumor growth *in vivo* [76]. Overexpression of human S100A7 or its murine homologue mS100a7a15 enhances mammary tumorigenesis [77]. S100A9 knock-out mice show reduced tumor incidence, growth and metastasis [38]. Also, the absence of S100A9 and S100A9 ligand TLR4 expression delays tumor incidence in a spontaneous prostate cancer model and influences growth of transplantable tumors in the EL-4 lymphoma model [78]. Accordingly, RAGE-deficient mice are resistant to DMBA/TPA-induced skin carcinogenesis, concomitant with loss of S100A8/A9 induction [79]. Downregulation of S100B in gliomas abrogates tumor growth *in vivo* [80]. S100P promotes pancreatic and prostate cancer growth [37, 81]. S100P-derived RAGE antagonistic peptide reduces tumor growth [82]. These findings suggest that S100 proteins might represent potential therapeutic targets in oncogenesis.

S100 proteins in cell apoptosis

Apoptosis is a tightly regulated cell suicide program, defects and evasion of cell apoptosis promote malignant transformation and have been recognized as a hallmark of cancer [6]. Accumulating evidence shows that several S100 proteins play central roles in the regulation of cell apoptosis. Knockdown of S100A4 induces cell apoptosis and enhances chemosensitivity through the induction of BNIP3 expression in pancreatic cancer [83]. In contrast, S100A4 sensitizes osteosarcoma cells to IFN-gamma-mediated induction of apoptosis in parallel with activating NF-κB [84]. S100A6 triggers cell apoptosis through activating JNK activity dependent on RAGE [31]. Further, upregulation of S100A6 (calcyclin) enhances cell apoptosis and decreases cell viability by affecting Caspase-3 activity in liver cancer cells [85]. Extracellular S100A8/A9 can inhibit growth of a variety of normal cell types (macrophages, bone marrow cells, lymphocytes, fibroblasts) and exhibit apoptosis-inducing activity in various tumor cells. In some cells, S100A8/A9 induces cell apoptosis through binding to the cell-surface receptor in a zinc-independent manner [86]. Another study suggests that S100A8/A9 exerts apoptotic activity by selective release of Smac/DIABLO and Omi/HtrA2 from mitochondria and modulation of anti-apoptotic protein Bcl-2 [87]. In addition, S100A8/A9 may also promote autophagy-like death by provoking the translocation of BNIP3 to mitochondria [88]. S100A10 may bind to Bcl-2-associated death promoter (BAD) protein, negatively affect BAD-induced apoptosis [89]. Synthetic N-terminal peptides of S100C/A11 induced cell apoptosis through partial translocation of apoptosis-inducing factor (AIF) from the cytoplasm to nuclei [90]. Our previous study showed that S100A14 can interact with RAGE and high dose S100A14 induces cell apoptosis is partially in a RAGE-dependent manner in esophageal cancer cells [34].

S100 proteins in tumor metastasis

Metastasis is a major cause of death for cancer patients. The process of metastasis involves a cascade of linked, sequential steps which include tumor invasion, migration, host immune escape, extravasation, angiogenesis, and tumor growth [91]. S100 proteins are involved in many steps of metastasis and some of them (i.e. S100A4) have been well recognized as metastasis markers. S100A4 is a direct target of β-catenin/TCF and it has been considered as an epithelial-mesenchymal transition (EMT) marker [92]. Enhanced S100A4 promotes a migratory phenotype, and in particular, promotes EMT [74, 93-95], whereas inhibition or loss of S100A4 decreased cell migration and abrogated EMT signatures [92, 95, 96]. Co-transfection of the human gene for S100A4 with pSV2neo induced the metastasis of Rama 37, a benign rat mammary cell line, suggesting that S100A4 possesses metastasis-inducing capability [97]. Furthermore, overexpression of S100A4 in MCF-7 cells induced hormone-independent cell growth *in vivo* and promoted cell invasiveness into surrounding tissues and

metastasized to regional lymph nodes and lungs [98]. Transgenic mice carrying S100A4 gene develop aggressive metastatic mammary tumors [99]. In contrast, mice lacking S100A4 gene suppresses the tumor development and metastasis [100]. The suppression of S100A4 reduced the metastasis of osteosarcoma cells, but has no effect on cell proliferation [101]. As a typical member of the S100 family, S100A4 protein exerts both intracellular and extracellular functions by specific target proteins. For instance, S100A4 regulates cell motility and adhesion by interacting with Nonmuscle Myosin IIA (NMIIA) and Ephrin-beta 1, thus contributing to the metastatic behavior of tumor cells [102-104]. S100A4 activates NF-κB by inducing phosphorylation of IKKalpha/beta, leading to increased ikappaBalpha phosphorylation [105]. Extracellular S100A4 activates the transcription factor NF-κB and induces a series of gene products including Ephrin-A1 and optineurin in a subset of human cancer cells, which represent possible candidates responsible for S100A4-mediated metastatic progression [106]. In addition to stimulating the motility of tumor cells, S100A4 may affect cell invasive properties through influencing the expression of matrix metalloproteinases (MMPs) and their endogenous inhibitors [107]. S100A4 binds to Smad3 and increases TGF-β-induced MMP-9 expression, thus enhancing the cell invasion ability [108]. S100A2 is regulated by TGF-β and involved in TGF-β-mediated cancer cell invasion and migration. Further, S100A2 interacts with Smad3, regulates TGF-β/Smad3 signaling and induces EMT in lung cancer [72]. Overexpression of S100A2 dramatically promotes non-small cell lung cancer (NSCLC) cell migration *in vitro* and enhances metastasis *in vivo*, whereas ablation of S100A2 inhibits tumor metastasis *in vivo*. These results indicate that S100A2 acts as a strong metastasis inducer in NSCLC [109]. Depletion of S100A6 has a profoundly negative effect on the invasion and motility of pancreatic cancer cells [110, 111]. Possible mechanism is that S100A6 facilitates Annexin II translocation to the cell membrane [111]. In contrast, overexpression of S100A6 in osteosarcoma cells decreases cell motility and anchorage independent growth on collagen gels [112]. S100A7 increases invasive capabilities of prostate cancer cells via a regulation of MMPs and promotes the migration and invasion of osteosarcoma cells via the interaction with RAGE [113, 114]. Another report shows that S100A7 inhibits β-catenin signaling by promoting β-catenin degradation. In turn, β-catenin signaling negatively regulates S100A7 expression. Thus, the reciprocal negative regulation contributes to their important roles in tumor progression [64]. S100A8/A9 promotes cell migration and invasion through p38 MAPK dependent NF-κB activation leading to an increase of MMP2 and MMP12 in gastric cancer [115]. S100A10 may bind to plasminogen and subsequently mediate its activation by plasminogen activators, facilitating the conversion of plasminogen to plasmin [116]. Subsequently, active plasmin further activates some members of MMP family [117, 118]. On the other hand, DLC1, a partner of S100A10, displaces Annexin II from S100A10, thereby enhancing the ubiquitin-dependent degradation of S100A10 [66]. Therefore, S100A10 was involved in the process of cell invasion and metastasis [66, 119-121]. Depletion of S100A13 inhibits invasiveness of lung cancer cell lines [122]. Our published data demonstrated that S100A14 acts as either an inducer or an inhibitor of cell invasion by regulating MMP2 transcription in a p53-dependent manner [123]. S100P acts as a metastasis inducer and knockdown of S100P decreased metastatic potential *in vivo* in pancreatic cancer cells, which is likely mediated by activating RAGE. Additionally, overexpression of S100P increases expression of S100A6 and Cathepsin D, both of which are involved in cellular invasion. Further study shows that S100P-induced invasive potential was at least partially due to the increase of cathepsin D [37, 124]. Also, S100P promotes the transendothelial migration of tumor cells through the interaction with ezrin in NSCLCs [125].

S100 proteins in the tumor microenvironment

S100 proteins in the communication between cancer cells and stromal cells

Accumulating evidence shows that the responses of the stromal cells in neoplastic tissues play central roles in tumor progression and cancer metastasis [126]. These cells include fibroblasts, vascular cells, infiltrating leukocytes, as well as bone marrow-derived myeloid cells (BMDCs) including macrophages, neutrophils, mast cells, myeloid cell-derived suppressor cells (MDSCs) and mesenchymal stem cells (MSCs) [127]. In addition to acting directly on

tumor cells, S100 proteins have also been implicated in many aspects of the communication between cancer cells and stromal cells. For example, S100 proteins are involved in the interaction between tumor cells and stromal fibroblasts, infiltration of leukocytes, recruitment of tumor-associated macrophages (TAMs), neutrophils and myeloid-derived suppressor cells (MDSCs), and regulation of angiogenesis, thereby participating in the cellular and molecular events necessary for invasion and metastasis (**Figure 5**).

S100A4 is considered as a marker of fibroblasts and a specific subset of inflammatory macrophages [128]. And S100A4 is expressed in a variety of cells such as in the tumor microenvironment (macrophages, fibroblasts, activated lymphocytes) and plays a crucial role in mediating tumor-stromal interplay [129, 130]. Recent studies found that MCF-7/S1 tumor cells can induce the expression of S100A4 in human mammary fibroblasts in co-culture experiments [131]. Accordingly, coinjecting $S100A4^{+/+}$ fibroblasts into the xenografts effectively rescued the metastatic inhibition of tumors in S100A4 knock-out mice [100]. In addition to stimulating S100A4 expression and affecting the metastatic phenotype by S100A4, tumor cells can also induce the release of S100A4 from stromal fibroblasts. In turn, extracellular S100A4 promotes metastatic capacity of tumor cells by increasing MMP-13 activity and modifying actin cytoskeleton and focal adhesions [130]. Mechanistic studies show that some cytokines, in particular RANTES (CCL5), a cytokine involved in tumor progression [132, 133] is necessary and sufficient for inducing the release of S100A4 from fibroblasts. Conversely, the secreted S100A4 activates the expression and secretion of RANTES. Thus, a positive feedback loop is formed, contributing to the formation of pre-metastatic niches [134]. These data suggest that the reciprocal regulation between RANTES expression and release of S100A4 plays a crucial role in metastatic formation. Recently, it has been demonstrated that ablation of S100A4 in stromal cells using transgenic mice significantly reduced metastatic colonization. Mechanistic investigation demonstrated that S100A4 exerts functions by regulating several extracellular matrix (ECM) molecules and growth factors, particularly matrix protein tenascin-C and growth factor VEGF-A, which are important for establishing an angiogenic microenvironment and protecting cancer cells from apoptotic stress [135]. Further, S100A4 plays a crucial role in neutrophil-promoting tumor progression and S100A4 depletion increases the effectiveness of anti-VEGF therapy in glioma [136]. Besides, S100A4 released into the tumor environment or $S100A4^{+/+}$ fibroblasts induce massive infiltration of T lymphocytes at the site of the growing tumor and release of specific proinflammatory cytokines including G-CSF and Eotaxin-2 (CCL24, MPIF-2), thus generating a favorable microenvironment for metastasis formation [137-139]. In addition to affecting the infiltration of T cells, S100A4 may also regulate the recruitment of macrophages. Genetic depletion of S100A4 impaired the recruitment of macrophages to sites of inflammation *in vivo*. Consistent with these observations, $S100A4^{-/-}$ primary bone marrow macrophages (BMMs) display defects in chemotactic motility [140].

S100A8 (calgranulin A, MRP8) and S100A9 (calgranulin B, MRP14) are abundantly expressed in cells of the myeloid lineage, including monocytes and neutrophils and early differentiation states of macrophages [141, 142]. Increased S100A8/A9 expression is found in tumor-infiltrating myeloid cells in many epithelial tumors [143, 144]. As mediators and cellular effectors of inflammation, S100A8/A9 proteins are important constituents of the tumor microenvironment that critically contributes to the development of tumors [145, 146]. S100A8/A9 proteins play essential roles in tumor-stromal interactions, leading to colitis-induced colon cancer [147]. S100A8/A9 regulates neutrophil cell survival by the MEK-ERK signaling pathway via TLR4 and the integrin CD11b/CD18 [148]. And in S100A9-deficient mice, the number of bone marrow neutrophils is decreased [149]. Further, the S100A8/A9 proteins stimulate infiltration of inflammatory lesions by activated myeloid cells, and are involved in neutrophil migration to the inflammatory sites [149-151]. Importantly, S100A9 expression has also been shown to be involved in Myeloid Derived Suppressor Cells (MDSC) function, which suppresses the adaptive immune response by blocking the functions of $CD4^+$ and $CD8^+$ T cells [127]. MDSC synthesize and secrete S100A8/A9 proteins. In turn, high levels of S100A9 inhibit the differentiation of dendritic cells (DCs) and induce accumulation of MDSCs in cancer [152]. Further, S100A8/A9

proteins bind to carboxylated N-glycan expressed on the receptor for advanced glycation end-products and other cell surface glycoprotein on MDCS, and promote MDCS migration to the tumor site through the activation of NF-κB and repress host-mediated anti-tumor immune response against cancer cells, thereby facilitating carcinogenesis and tumor progression [153]. Thus, the S100A8/A9 proteins serve as an autocrine feedback loop that sustains accumulation of MDSC and are sufficient to maintain the functionality of MDSC with the inflammatory tumor environment [38, 153-155]. Also, induced S100A8/A9 expression in the pre-metastatic lung creates an inflammation-like state and thereby promotes metastatic tumor spread [156, 157]. Together, S100A8/A9 promotes tumorigenesis by inducing inflammatory responses and creating a pro-inflammatory microenvironment. As inflammatory chemoattractants, S100A8/A9 proteins further mediate the recruitment of inflammatory cells to sites of tissue damage, thereby contributing to the tumorigenesis and cancer metastasis [158, 159]. In cancer cells, S100A8/A9 regulate inflammation through activation of MAPK and NF-κB signaling pathway via interaction with RAGE and carboxylated glycans, leading to inflammatory cell recruitment and tumor growth and metastasis [38, 147]. Also, a number of growth factors produced by tumor cells including TNF-α, TGF-β and VEGF-A can stimulate S100A8/A9 expression, thus serving to recruit myeloid cells into the pre-metastatic lung, contributing to the establishment of a "pre-metastatic niche", and thereby promoting metastasis formation [156]. Furthermore, S100A8/A9 induced by pre-metastatic lung promotes the expression and secretion of serum amyloid A3 (SAA3) protein which is involved in recruitment of myeloid cells and migration of tumor cells, hence, contribute to recruit the myeloid cells and enhance the migration of tumor cells by activation of TLR4 receptor and subsequent NF-κB signaling [157]. In addition, S100A8/A9 has been identified novel target genes in the well-established Mdr2 knockout mouse model of inflammation-associated liver carcinogenesis. And co-expression of S100A8 and S100A9 proteins promote malignant progression by activation of ROS-dependent signaling pathway and protection from cell death [160].

Other S100 proteins have been implicated in tumor microenvironment. For example, S100A7 is induced by the proinflammatory cytokines. And S100A7 may enhance breast cancer growth and metastasis through upregulating proinflammatory pathways and recruiting tumor-associated macrophages (TAMs) [77, 161]. In addition, S100A7 modulates a series of genes linked to the immune response including the multifunctional gene, CD74, suggesting that S100A7 may act by host conditions or stromal factors, thus contributing to the tumor progression [162]. S100A10 is also involved in the regulation of macrophage recruitment in response to inflammatory stimuli by binding to plasminogen, a key cell surface receptor of macrophages [163]. Further, S100A10-deficient mice show a decrease of macrophages and inhibition of growth of murine Lewis lung carcinomas or T241 fibrosarcomas, and the tumor growth deficit can be rescued by intraperitoneal injection of wild-type but not S100A10-deficient macrophages. These results demonstrated that S100A10 is essential for the migration of macrophages to the tumor site, which defines a rate-limiting step in tumor progression [164]. Mechanistic investigation demonstrated that DLC1, a Rho GTPase-activating protein (RhoGAP) competed with Annexin II for interaction with S100A10, promoting ubiquitin-dependent degradation, attenuating plasminogen activation and resulting in inhibition of *in vitro* cell migration, invasion and tumorigenicity of lung cancer cells [66]. Taken together, these data support the notion that S100 proteins drive chronic inflammation and thus promote tumor progression.

Angiogenesis

Angiogenesis is required for invasive tumor growth and metastasis and performs a critical role in the control of cancer progression [165]. Angiogenesis is controlled by equilibrium between angiogenic stimulators and inhibitors that are produced by tumor cells, surrounding stromal cells, and infiltrating leukocytes [166]. S100 proteins are involved in angiogenesis by affecting proangiogenic and antiangiogenic factors such as MMPs, TGF-β, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) etc. For example, S100A4 may induce angiogenesis through interaction with Annexin II and accelerate plasmin formation, thereby promoting tumor metastasis [167, 168]. Also, S100A4 may stimulate the degradation of ECM and promote angiogenesis by transcriptionally

Table 1. The altered expression and potentially clinical implications of S100 proteins in human cancer

Name	Gene expression (Tumor type)		Clinical implications	Reference
	Over-expression	Under-expression		
S100A1	Breast, Kidney, Ovary, Melanoma		A marker for poor prognosis ovarian and endometrial cancers; A specific and sensitive marker in distinguishing nephrogenic adenoma from prostatic adenocarcinoma.	[210-215]
S100A2	Esophagus, Breast, Colon, Stomach, Lung, Ovary Pancreas	Larynx Melanoma Prostate, Bladder	A poor prognostic marker for NSCLC and pancreatic cancer; A predictor of good prognosis and survival in OSCC, ESCC and LSCC; an independent prognostic marker for recurrence in oral cancer and CRC; A predictor of response pancreatectomy and a metastatic marker for pancreatic cancer.	[15, 17, 109, 176-178, 210, 214, 216-233]
S100A3	Stomach			[217]
S100A4	Breast Melanoma Stomach Bladder, Esophagus Kidney Lung Colon Bone Pancreas, Uterus Ovary Thyroid	Oral	A biomarker for progression/metastasis or prognosis in multiple cancers such as breast cancer, gastric cancer, bladder cancer, pancreatic cancer, ESCC, CRC, LSCC and NSCLC.	[10, 13, 83, 185-187, 210, 214, 217, 221, 229, 234-256]
S100A5	Brain			[204]
S100A6	Breast Melanoma Stomach Pancreas Colon	Prostate Oral	A diagnostic marker or prognostic factor in pancreatic cancer, gastric cancer, prostate cancer, melanoma, NSCLC and HCC;	[110, 210, 214, 249, 257-264]
S100A7	Stomach Head and neck Oral Ovary Skin Breast	Salivary gland	A predictor of poor prognosis in HNSCC and estrogen receptor-negative invasive breast cancer; Serum S100A7 may serve as a potentially diagnostic marker for lung cancer and ovarian cancer.	[192, 193, 195, 196, 217, 265-268]
S100A8	Breast Stomach Lung Oral Prostate	Oral cervix	A significant predictor of recurrence in bladder cancer; a poor prognostic marker for Non-Muscle-Invasive Bladder Cancer (NMIBC) and invasive ductal carcinoma of the breast (IDC).	[19, 182, 197, 210, 218, 249, 269-274]
S100A9	Breast, Stomach Lung Cervix Prostate	Esophagus	A poor prognostic marker in IDC and NSCLC; Serum S100A9 may serve as a useful marker to discriminate between prostate cancer and benign prostatic hyperplasia.	[19, 47, 181, 182, 210, 218, 269, 271, 272, 275]
S100A10	Breast Stomach Gallbladder Kidney		A predictor for recurrence of CRC; a potential molecular target for early gallbladder cancer diagnostics and therapeutic applications;	[210, 232, 276, 277]
S100A11	Breast, Stomach Pancreas Lung Colon Uterus		An unfavorable prognostic marker in PAC; Down-regulation of S100C is associated with bladder cancer progression and poor survival.	[9, 68, 183, 184, 210, 218, 278, 279]
S100A13	Melanoma		An angiogenic and prognostic marker in melanoma.	[280]
S100A14	Breast Ovary, Uterus	Oral Kidney, Rectum, Colon	Both S100A11 and S100A14 are significantly associated with breast cancer patient outcome.	[210, 249, 281]
S100A15	Breast			[282]
S100A16	Bladder, Lung, Thyroid gland, Pancreas, Ovary			[283]
S100B	Melanoma, Nerve Colon Bone		A poor prognostic marker for CRC and melanoma; Serum S100B has a clinically independent prognostic value in patients with melanoma and breast cancer.	[200-203, 214, 226, 284, 285]

S100P	Lung Breast Pancreas	S100P is potentially useful for molecular Diagnosis of NSCLCs; Elevated S100P level showed poorer overall survival in CRC and ovarian cancer patients.	[220, 223, 287-291]
S100Z	Breast		[287]

activating MMP-13 expression [169]. In addition, S100A4 and VEGF exerts a synergistic effect on Human Umbilical Vein Endothelial Cells (HUVECs) migration via the RAGE receptor by KDR expression and MMP-9 activity, and a neutralizing monoclonal antibody against S100A4 abolishes endothelial cell migration, tumor growth and angiogenesis [27]. S100A7 promotes angiogenesis by the dramatic regulation of MMP13 and VEGF [170]. S100A10 also plays an important role in angiogenesis *in vivo*, suggesting a critical role in endothelial cell function [171]. S100A13 affects the release of FGF-1 and contributes to angiogenesis [122]. Taken together, S100 proteins contribute to tumor metastasis through affecting the process of angiogenesis.

S100 proteins and cancer stem cells

Recent studies have linked cancer stem cells (CSCs), EMT and the tumor microenvironment (TME) in tumor metastasis. Major signaling pathways involved in EMT are from TME. Conversely, TME may induce the occurrence of EMT in tumor cells. In addition, CSCs may be the inducers of EMT in the tumor cells, and EMT could promote stem cell (SC) properties and further generate cells with the features of CSCs [172, 173]. As a typical member of the S100 family, S100A4 is not only involved in the interplay between EMT and TME, but also plays an important role in the establishment and/or maintenance of pluripotency. S100A4 is significantly upregulated in mouse glioma CSCs [174]. Also, S100A4 expression is highly enriched in head and neck cancer-initiating cells (HN-CIC). Knockdown of S100A4 markedly decreased tumor spheres and *in vivo* tumor formation. S100A4 depletion also significantly decreased the side population (SP) cells and ABCG2-positive cells in which high expression of ABCG2 possibly contributes to SP phenotype. In addition, S100A4 depletion dramatically decreased the enzymatic activity of aldehyde dehydrogenase (ALDH), which has been identified as a CSC marker, "cancer stemness" genes (Oct-4 and Nanog) expression and abrogated EMT signatures. Conversely, overexpression of S100A4 in head and neck squamous cell carcinomas cells enhanced their stemness and tumorigenic properties [95].

Other S100s have been implicated in CSCs, although their roles in the stemness properties are not well-studied. For example, S100A6 expression is upregulated in mouse glioma CSCs [174] and S100A14 is also identified as a potential novel marker of breast cancer cells with tumor-initiating features [175]. These data suggest that S100 proteins can play crucial roles in maintaining self-renewal or cancer stem-like properties.

The altered expression of S100 proteins and clinical interest for S100 proteins as putative biomarkers in cancers

Members of the S100 protein family display a unique pattern of tissue/cell type specific expression and exhibit distinct alterations in different types of cancers [4]. The complexity of different patterns of alterations implies S100 proteins might act as both friend and foe and exert both pro- and anti- tumorigenic actions. For instance, overexpression of several members of S100 proteins (i.e. S100A2, S100A3, S100A6, S100A8/A9, and S100A11) has been documented in several types of cancer. Conversely, underexpression of these proteins has been found in other types of cancer. Overexpression of S100A2 indicates poor prognosis in NSCLC and pancreatic cancer [17, 176, 177]. Conversely, loss of S100A2 expression has been reported to correlate with a poorer prognosis and shorter survival in OSCC and ESCC [178, 179]. And patients with S100A2 positive LSCC have a better relapse-free overall survival than patients with S100A2-negative tumors [15]. Moreover, S100A2 expression is a good predictor of response to pancreatectomy in pancreatic cancer [180]. S100A8 and S100A9 overexpression is considered as marker of poor prognosis in breast IDC and NSCLC [19, 181]. In contrast, the presence of S100A9-positive inflammatory cells in cancer tissues correlates with a better prognosis in patients

with gastric cancer [182]. S100A11 might be a significant tumor marker for pancreatic adenocarcinoma and high expression of S100A11 is an unfavorable predictor for prognosis of patients who have undergone surgical resection [9]. Conversely, low expression of S100A11 is associated with poor survival in patients with bladder cancer [183]. However, another report showed that overexpression of S100A11 predicts poor survival [184]. Therefore, these S100 proteins may be of value as a biomarker of cancer progression in some instances dependent on tumor type. In contrast, some S100 proteins (i.e. S100A4) exhibit similar expression patterns in most types of cancers. For example, S100A4 is universally overexpressed in multiple cancers and the enhanced expression of S100A4 proves to be independent marker for tumor progression, invasion, metastasis, poor survival and prognosis in several different types of cancer [12, 185-191]. Nuclear accumulation of S100A7 may serve as predictor of poor prognosis in head and neck cancer [192] and S100A7 expression is associated with a worse prognosis in estrogen receptor-negative invasive breast cancers [193].

More importantly, serum levels of some S100 proteins have been considered as biomarkers in cancer. For example, S100A6 in sera correlates with experimental burden and with clinical disease stage [194] and the level of S100A7 protein in serum may serve as a potential marker in lung cancer and ovarian cancer [195, 196]. Increased expression of S100A8/S100A9 in sera was associated with recurrence-free survival with bladder cancer [197]. Increasing serum S100B is an independent prognostic marker for melanoma relapse and mortality risk [198, 199]. And preoperative serum levels of S100B in breast cancer patients strongly predicted poor survival [200]. In melanoma, S100B is a strong independent prognostic factor for overall and long-term survival [201, 202]. Moreover, the overexpression of S100B has a significant correlation with postoperative relapse and poor prognosis in CRC patients [203]. Therefore, regulating S100-dependent biology means a better chance for a cure, especially in cancer. The most straightforward means in the clinic is to develop small molecule inhibitors directly inhibit the biological functions of S100 proteins. S100B inhibitors will likely have therapeutic value for treatment of some cancers such as malignant melanoma, astrocytomas [204], renal tumors [205], and some forms of leukemia [206], where S100B is elevated. Also, the antiallergy drug cromolyn binds S100P, prevents activation of RAGE and inhibits tumor growth and invasion in mouse model [207]. A S100A9-binding small molecule (ABR-215050) is presently in a clinical trial for the treatment of prostate cancer [208, 209]. Taken together, some S100 proteins are currently being explored in the clinic as potential diagnostic and prognostic markers or therapeutic targets of cancer [143]. This review summarizes these findings and evaluates their implications for human multiple cancers (Summarized in **Table 1**).

Future directions

S100 proteins play important roles in the development and progression of tumors due to their multifunctional properties involved in a variety of cellular and extracellular processes. Future studies are needed to further reveal molecular mechanisms and signaling pathways that define the multiple and specific roles that S100 proteins play in tumor progression and metastasis, providing novel therapeutic targets and biomarkers.

Recent studies show that communication between cancer cells and stromal cells which is often mediated by ECM components in the tumor microenvironment plays a central role in cancer metastasis. Many members of S100 proteins can be expressed by tumor cells and a variety of stromal cells. It is notable that a number of positive mutual feedback loops between these S100 proteins and growth factors, cytokines and SAA proteins that serve to increase their expression, secretion and activity during the interplay between tumor cells and stromal cells. Therefore, modulating S100 proteins is not limited to activities within the cell. Investigations of the tumor-stromal and stromal-stromal cross-talk involved in cellular migration in cancer may lead to the design of novel therapeutic strategies. Further studies are expected to investigate the role of S100 proteins in the communication between cancer cells and stromal cells and elucidate the underlying mechanism, which may facilitate not only S100-related cancer research, but also to the diagnosis, prevention, and treatment of cancer.

Finally, the clinical interest for S100 proteins will be continuously expanding. S100 proteins not only provide important diagnostic and prognostic tools for the management of cancer, but that inhibition of their activity may represent a possible means of controlling cancer development and progression.

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Disclosure of conflict of interest

We confirm that we have no conflict of interest to declare in the manuscript.

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