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REVIEW ARTICLE

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Multiple functions of S100A10, an important cancer promoter

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Abbreviations:
ANXA2, annexin A2; APL, acute promyelocytic leukemia; DIC, disseminated intravascular coagulation; ECM, extracellular matrix; HIF, hypoxia inducible factor; MMP, matrix metalloproteinase; OS, overall survival; Sp1, specificity protein 1; STAT1, signal transducer and activator of transcription 1; TAM, tumor-associated macrophage; t-PA, tissue plasminogen activator; TYK, tyrosine kinase; u-PA, urokinase-type plasminogen activator

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The S100 group of calcium binding proteins is composed of 21 members that exhibit tissue/cell specific expressions. These S100 proteins bind a diverse range of targets and regulate multiple cellular processes, including proliferation, migration and differentiation. S100A10, also known as p11, binds mainly to annexin A2 and mediates the conversion of plasminogen to an active protease, plasmin. Higher S100A10 expression has been reported to link to worse outcome and/or chemoresistance in a number of cancer types in lung, breast, ovary, pancreas, gall bladder and colorectum and leukemia although some discrepancy was reported. In this review, we focused on the roles of the S100A10 in cancer. We summarized its biological functions, role in cancer progression, prognostic value and targeting of S100A10 for cancer therapy.

KEYWORDS
annexin A2, ANXA2, cancer invasion, metastasis, p11, plasminogen receptor, S100A10

INTRODUCTION

The nomenclature of S100 was first used in 1965: it was a soluble fraction isolated from bovine brain in 100% saturated ammonium sulfate.[1] This fraction has two family members, S100A1 and S100B, which have molecular weights of approximately 10 kDa.[2,3] Additional proteins have been classified to this family based on sequence homology and similar structural properties. There are 21 S100 proteins encoded by individual genes in the human genome.[4] Localizations of these S100 genes along with seven pseudogenes are summarized in Table 1: most of the *S100A* family members are encoded on 1q21.3, called the epidermal differentiation complex[5] and others, *S100B* is on 21q22.3, *S100G* is on Xp22.2, *S100P* is on 4p16.1 and *S100Z* is on 5q13.3. S100 proteins typically form homodimers with the exception that S100A8/S100A9 forms a heterodimer.[6] Each S100 subunit contains an N-terminal and a C-terminal EF-hand Ca^{2+}-binding motif separated by a linker region, which exhibits the most sequence divergence and is critical for interactions with numerous proteins.[7] The target protein binding is typically Ca^{2+}-dependent. These Ca^{2+}-dependent interactions enable S100 proteins to act as calcium sensors that transduce changes in calcium concentrations in response to biological responses. The S100 proteins are expressed in a cell

Table 1 Chromosomal localization of S100 genes

Gene	Localization	Comment
S100A1	1q21.3	
S100A2	1q21.3	
S100A3	1q21.3	
S100A4	1q21.3	
S100A5	1q21.3	
S100A6	1q21.3	
S100A7	1q21.3	
S100A7A	1q21.3	
S100A7L2	1q21.3	
S100A7P1	1q21.3	Pseudogene
S100A7P2	1q21.3	Pseudogene
S100A8	1q21.3	
S100A9	1q21.3	
S100A10	1q21.3	
S100A11	1q21.3	
S100A11P1	7q22.1	Pseudogene
S100A11P2	7p14.2	Pseudogene
S100A11P3	11q13.4	Pseudogene
S100A11P4	12q14.2	Pseudogene
S100A12	1q21.3	
S100A13	1q21.3	
S100A14	1q21.3	
S100A15A	1q21.3	Pseudogene
S100A16	1q21.3	
S100B	21q22.3	
S100G	Xp22.2	
S100P	4p16.1	
S100Z	5q13.3	

and tissue specific manner in vertebrates and have non-redundant roles in multiple biological processes.[6]

S100A10 was first isolated as a potential substrate for the epidermal growth factor receptor (EGF)-receptor tyrosine kinase, initially called p11 or calpactin light chain.[8] S100A10 is expressed ubiquitously in most tissues and is highest in lung, kidney, and intestine. S100A10 has also been observed in various other cell types, including endothelial cells,[9] macrophages,[10] fibroblasts,[11] epithelial cells,[12] and various cancer cell lines.[13] The promoter region of *S100A10* contains binding sites for the transcription factors STAT1[14] and Sp1[12] and for glucocorticoid response elements. S100A10 expression may be induced by transforming growth factor,[15] epidermal growth factor,[16] and basic fibroblast growth factor.

FUNCTIONS OF ANXA2-S100A10 COMPLEX

S100A10 contains four α helical domains. In contrast to other S100 proteins, their EF-hands do not bind to Ca^{2+} and remain in a permanently active state. The S100A10 protein has a tight association with membrane-binding protein annexin A2 (ANXA2), which is a member of the annexin family (Fig. 1). This group is characterized by a conserved C-terminal core domain comprised of 70 amino acid repeated segments that harbor Ca^{2+}-dependent binding sites for acidic phospholipids. The variable N-terminal domains are accessible for cytosolic factors in their membrane-bound state, and, in some cases, such interacting partners are S100 family proteins.[17] ANXA2 is linked to many membrane-related events, such as trafficking, microdomain formation, membrane-cytoskeleton linkages and membrane fusion.[18–20] ANXA2 can exist in two physical states: monomeric ANXA2, mainly localized in the cytosol, and a heterotetrameric complex comprising two molecules of ANXA2 and two of S100A10.[21] S100A10 binding is required for ANXA2 to localize to the extracellular cell surface.[22] Although ANXA2 itself can associate with the cellular membrane, S100A10 depletion disrupts such membrane association.[23] Monomeric ANXA2 can be localized to the nucleus, and sequestration of ANXA2 by S100A10 in the cytosol prevents such nuclear localization.[24] Loss of S100A10 has been observed to affect the level of ANXA2. In *S100a10* knockout mice, the Anxa2 levels are decreased in spleen, kidney, lungs and liver, but not affected in intestine.[13] In most reports, interfering with the expression of ANXA2 affects the levels of S100A10. In complex with S100A10, ANXA2 may protect S100A10 from polyubiquitination and degradation.[25]

Early research revealed that the ANXA2-S100A10 complex binds and bundles F-actin.[26] The ANXA2-S100A10 complex is important for the organization of F-actin at lipid rafts and for the regulation and remodeling of the actin cytoskeleton.[27]

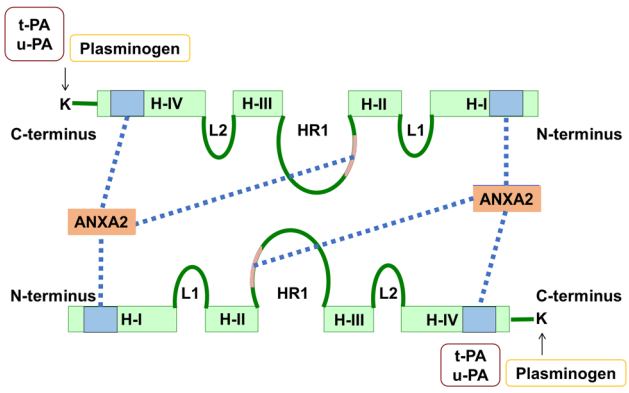

Figure 1 Structure of S100A10 associated with annexin A2 (ANXA2), t-PA, u-PA and plasminogen. Each S100A10 monomer contains α helical domains H-I, H-II, H-III, and H-IV. There are two helical loops: L1 separates H-I and H-II, L2 separates H-III and H-IV. The H-II and H-III domains are connected by a Hinge region (HR1). ANXA2 interacting domains are indicated by purple color, and C-terminal K residue associates with t-PA, u-PA and plasminogen.

The ANXA2-S100A10 complex also acts as a plasminogen receptor. Its C-terminal lysine residue in S100A10 forms a binding site for plasminogen activators and plasminogen and is involved in the plasminogen system. Plasminogen is a 90-kDa glycoprotein, a precursor of plasmin, which regulates extracellular proteolytic events. It is activated by various proteases, including tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), to cause plasmin activation. Plasmin is a serine protease involved in proteolysis; it contributes to both physiological and pathological processes such as tissue remodeling and embryogenesis, inflammation, cancer invasion and metastasis.

The ANXA2-S100A10 complex has also been shown to function as a receptor in plasmin-induced signaling. A chemotactic response to plasmin in monocytes and stimulation of the JAK1/TYK2 signaling pathway through ANXA2 and S100A10 has been observed.[28,29]

S100A10 functions not only as a scaffold protein connecting the two ANXA2 molecules, but also achieves protein interaction itself in the absence of ANXA2. Several molecules were identified by a two-hybrid screen. S100A10 can interact with TASK-1, a potassium channel, and 5-HT_{1B}, a serotonin receptor, involving the regulation of the traffic of these proteins.[30,31]

THE ROLE OF S100A10 AS A PLASMINOGEN RECEPTOR IN CANCER

As mentioned above, the ANXA2-S100A10 complex acts as a plasminogen receptor, which seems to be the most important role for S100A10 in cancer progression, including migration, and metastasis. Plasminogen receptors on cell surfaces of tumors initiate the conversion of plasminogen to plasmin, followed by the activation of pro-matrix metalloproteinases (pro-MMPs), extracellular matrix (ECM) degradation and reduced cellular interaction (Fig. 2a). Previous reports have suggested that cancer cells overexpress the ANXA2-S100A10 complex, which causes an increase in the formation of plasmin, thus enhancing ECM degradation.[32] ECM degradation provides carving out space for cancer cells to gain access to the circulation. Once cancer cells enter the circulation system, they can utilize proteolytic activity to enter and form stable metastatic foci into other tissues.[32] Several studies have shown that S100A10 plays an important role in tumor invasion and metastasis. Mice injected with S100A10-depleted fibrosarcoma cells showed a threefold reduction of metastatic foci in the lungs compared to mice injected with control cells.[33] Another study showed that siRNA mediated downregulation of *S100A10* using colorectal cancer cells without expression of ANXA2

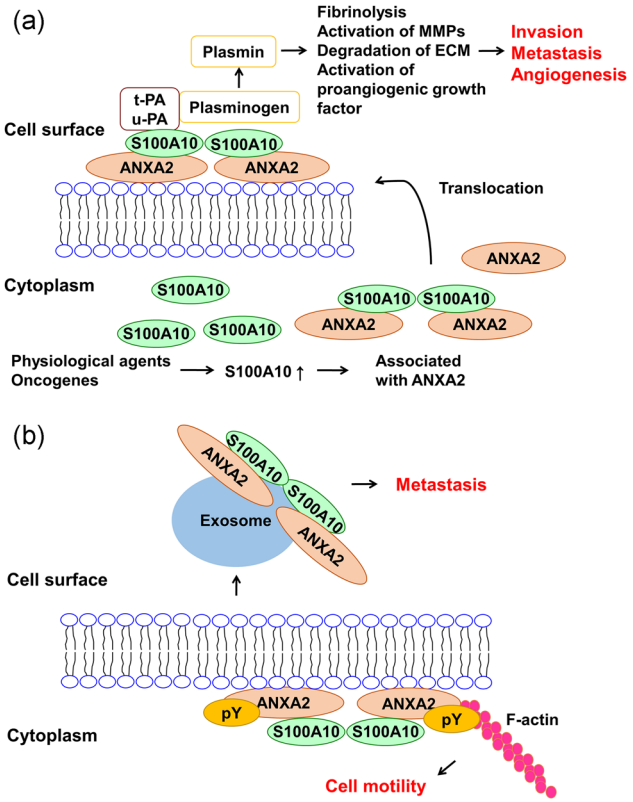

Figure 2 (**a**) Schematic representation of the plasminogen-dependent functions of S100A10 in cancer cells. Many physiological (EGF, interferon-γ, TGFα and TGFβ1) and pathological (PML-RARα and K-RAS) molecules, in combination, stimulate the upregulation of the S100A10 protein level. The association with annexin A2 (ANXA2) promotes translocation of the ANXA2-S100A10 complex to the cell membrane; then this complex activates plasminogen *via* tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), increasing the production of plasmin. Plasmin leads to activation of metalloproteinases (MMPs) and the degradation of the extracellular matrix (ECM) proteins, leading to promotion of tumor progression. (**b**) Plasminogen independent functions of S100A10 in cancer cells. Tyr23 phosphorylated (pY) ANXA2 associates with S100A10 and triggers F-actin rearrangement, leading to profound effects on cell shape and motility. ANXA2-S100A10 complex is captured by the exosomes which create a favorable microenvironment for metastasis.

abolished the plasminogen-dependent invasiveness of the cells through a matrigel barrier.[34] These results suggest that the invasiveness of these cells is independent of ANXA2. Collectively, these studies establish a role for S100A10 in metastasis and invasiveness.

The ANXA2-S100A10 complex has a significant role in induction of angiogenesis of cancer stroma, most likely through direct profibrinolytic activity. The hypoxic environment within a tumor triggers hypoxia inducible factor-1α (HIF-1α), which promotes angiogenesis. HIF-1α induces transcription of ANXA2 by binding to the hormone response element of the ANXA2 gene.[35] ANXA2 upregulation leads to the stabilization of S100A10 and activation of MMPs, which

further promote angiogenesis via extracellular matrix (ECM)-associated proangiogenic growth factors.[36] Anxa2-deficient mice exhibited decreased angiogenesis due to the impaired plasmin-MMP axis of angiogenesis.[9] The competitive inhibitor of ANXA2-S100A10 complex formation reduces vascular branching.[37] S100a10 null mice showed a defective vascularization compared to wild type mice, and S100a10-depleted endothelial cells had a significantly decreased ability to migrate through matrigel. These results establish that S100a10 plays an important role in angiogenesis *in vivo*.[9]

Recently, Bydoun *et al.*[38] revealed the involvement of S100A10 in a novel mechanism of plasminogen activation during the epithelial-to-mesenchymal transition (EMT). Although it had been shown that EMT is often coupled with enhanced proteolytic activity, the mechanism by which cells undergoing EMT regulate plasminogen activation was not understood. They found that the cells undergoing EMT reciprocally modulate plasminogen activation in part by regulating S100A10 and the plasminogen activation inhibitor (PAI-1). S100A10 was shown to be upregulated through a SMAD4-dependent TGFβ1 signaling pathway.[38]

THE ROLE OF S100A10 IN CANCER INDEPENDENT OF PLASMINOGEN ACTIVATION

ANXA2 is originally identified as a major substrate of v-Src, the major transforming protein of Rous sarcoma virus.[39] Cell transformation by v-Src involves rearrangement of the actin cytoskeleton, disassembly of focal adhesions and the development of anchorage-independent growth. ANXA2 is shown to be indispensable for v-Src transformation and has been shown to have a dual role as a regulator of v-Src trafficking and targeting and a v-Src effector in reorganization of actin[40] Downregulation of S100A10 in A431 cells, human epithelial squamous cell carcinoma cell line, by small interfering RNA (siRNA) induced a disorganization of F-actin structures without reduction of the total cellular actin concentration. Cell lacking S100A10 showed impaired migration activity and were unable to close a scratched wound.[41] These data suggest that the ANXA2-S100A10 complex functions as a regulator of actin polymerization and cell motility processes in the cancer cells (Fig. 2b).

ANXA2 is one of the most highly expressed proteins in tumor-derived exosomes, which are membranous vesicles, 40–10 nm in diameter, secreted from the cells under both physiological and pathological conditions. Tumor-derived exosomes contribute to the establishment of a niche and generate suitable microenvironments in metastatic sites by stimulating angiogenesis, modulating stromal cells, and remodeling extracellular matrix.[42] Maji *et al.*[43] demonstrated that exosomal ANXA2 promoted angiogenesis *in vitro* and *in vivo* and created favorable microenvironments for brain and lung metastasis of breast cancer cells *in vivo*. Fang *et al.*[44] observed that S100A10-dependent surface translocation of ANXA2 was associated with the exosomal secretion pathway, and that IFN-gamma-induced ANXA2 in the exosomes was blocked in S100A10-silenced cells. These results suggest the indispensable contribution of S100A10 to functional tumor-derived exosomes.

ASSOCIATION OF S100A10 WITH STROMAL MACROPHAGES IN CANCER PROGRESSION

Tumor-associated macrophages (TAMs) also require proteolytic activity to migrate into the tumor stroma. A role for S100A10 in the migration of TAMs has been reported. TAMs promote tumor growth by mediating inflammation and angiogenesis, suppressing antitumor immunity and remodeling matrix.[45] Several studies have suggested that macrophages mobilize a number of plasminogen receptors to generate plasmin to migrate to the tumor site. S100A10 was shown to play a significant role in mediating plasmin generation at the surface of macrophages.[46] Moreover, tumors grown in S100a10 null mice injected with Lewis lung carcinoma cells reached maximum size after 7 days, whereas tumors in their wild type counterparts continued to grow exponentially. Immunohistochemical analysis revealed that macrophage recruitment was impaired in the S100a10 null mice.[10] These studies demonstrate that expression of S100a10 on the surface of macrophages plays a significant role in their ability to associate with the tumor microenvironment and promote tumor growth. The proteolytic activity of S100a10 is used by both cancer cells and tumor-associated cells.

THE PROGNOSTIC VALUE OF S100A10 FOR CANCER

S100A10 upregulation has been reported in a number of cancers and is generally associated with a poor prognosis. High S100A10 expression in gall bladder carcinoma is shown to be associated with poor prognosis.[47] Overexpression of S100A10 is also associated with poor prognosis in lung adenocarcinoma[48] and pancreatic ductal adenocarcinoma.[49] For lung squamous cell carcinoma, membranous immunopositivity was found (Fig. 3). Even among those with such positive cases, strong membranous immunopositivity in contact with the stroma is associated with higher pathological TNM stage, tumor size, lymphatic invasion, lymph node metastasis and poor prognosis.[50] Lockman *et al.*[51] analyzed publicly available microarray datasets of 1190 serous ovarian cancer patients who received single or combined platinum treatments and showed that high messengerRNA levels of S100A10 predict reduced overall survival.

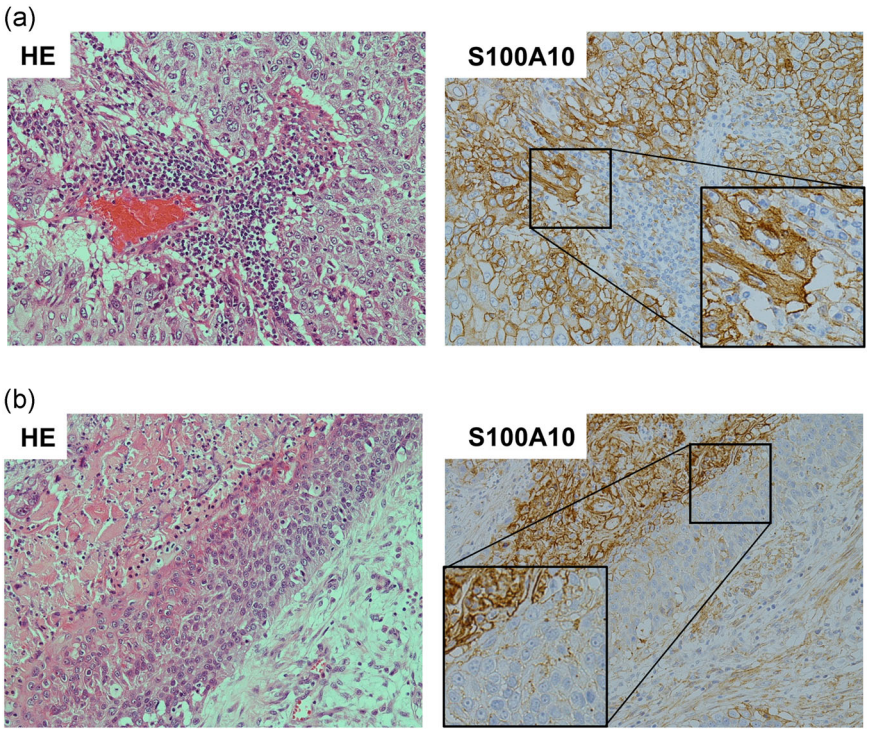

Figure 3 Immunohistochemical staining of S100A10 protein of lung squamous cell carcinoma specimens. (**a**) S100A10-positive case. Distinct membranous-immunoreactivity of S100A10 is observed mainly in the cancer islands. Strong S100A10-positivity is found in cancer-cell surface in contact with the stroma. Original magnification: ×100, inlet ×400. (**b**) S100A10-negative case. Only keratin material shows immunoreactivity. Original magnification: ×100, inlet ×400.

Similarly, in colorectal carcinomas, increased S100A10 expression is associated with poor prognosis.[52] These results suggest a role for S100A10 as the prognostic marker and potential therapeutic target in cancers. These results are summarized in Table 2.

S100A10 FUNCTIONS IN THERAPEUTIC BURDEN

Shang *et al.*[52] showed that knockdown of S100A10 by siRNA significantly reduced the proliferation, migration and invasion capacity of colorectal cancer cell lines. In our study,

Table 2 Clinicopathological significance of S100A10 expression by cancer types

Organ	Histologic Type	Method	Cases	Poorer Differentiation	Late Staged Disease	Vascular Invasion	Nodal Involvement / Lymphatic Invasion	Shorter Survival	Reference
Lung	Adenocarcinoma	ICH	202	$P = 0.015$	$P = 0.004$	$P = 0.001$	$P = 0.054$ / $P = 0.05$	$P = 0.030$	[49]
Lung	Squamous cell carcinoma	ICH	120		$P = 0.0119$	no link	$P = 0.0006$ / $P = 0.0005$	$P = 0.0064$	[51]
Gall bladder	Adenocarcinoma	ICH	50		$P = 0.015$		$P = 0.02$ / NA	$P = 0.02$	[48]
Pancreas	Adenocarcinoma	mRNA	178					$P = 0.007$	[50]
Colorectal	Adenocarcinoma	ICH	882	$P = 0.0012$	$P = 0.003$			$P = 0.0012$	[53]
Ovary	Serous adenocarcinoma	ICH	123					$P = 0.027$	[52]

The *P*-value of 0.05 or less was used to determine the significance.
Abbreviation: ICH, immnochistochemistry.

Table 3 The correlation between S100A10 expression and drug resistance

Organ	Histologic type	Drug	Material	Method	S100A10 status and characteristics	Reference
Leukemia	Acute lymphoblastic	Vincristine	Primary culture cells	S100A10 inhibitor	Down regulation induced sensitization	[54]
Breast	Adenocarcinoma	Tamoxifen	Resistant cell line (MCF7)	Quantitiative MS	Upregulation in resistant cells	[55]
Breast	Adenocarcinoma	Tamoxifen	Primary tumor	Quantitiative MS	Downregulation in relapse group	[56]
Colorectal	Adenocarcinoma	Oxaliplatin	Cell lines	Quantitiative MS, WB	Upregulation in poor responder ($R^2 = 0.27$, $P = 0.02$)	[57]
Ovary	Serous adenocarcinoma	Carboplatin/ paclitaxel	Primary tumor	Microarray	Upregulation in poor responder ($P = 0.0013$)	[58]
Ovary	Serous adenocarcinoma	Carboplatin/ paclitaxel	Primary and metastatic tumor	Quantitaitive RT-PCR	Upregulation in poor responder ($P = 0.029$)	[59]

The *P*-value of 0.05 or less was used to determine the significance.
Abbreviations: MS, mass spectrometry; WB, western blotting.

S100A10 depleted lung cancer cell lines, including adenocarcinoma and squamous cell carcinoma, showed significant slow growth (unpublished data). In an *in vivo* study, Bydoun M *et al.* reported that the growth of Panc-1, S100A10 depleted, in NOD/SCIS mice was hindered showing significant reduction in expression of VEGF and cyclin D1, compared to the scramble control. However, it should be noted that S100A10-depleted panc-1 cells have similar proliferation rates compared to the control *in vitro*.[49] It still remains controversial and unclear whether the reduced tumor growth is plasminogen-dependent or -independent. Further research is needed.

S100A10 may also be linked to drug resistance. Inhibition of ANXA2-S100A10 complex formation or the knockdown of S100A10 can increase the sensitivity of leukemia cells to vincristine.[53] Increased S100A10 expression has been shown to be associated with tamoxifen resistance in breast cancer cells[54] and breast cancer tissue.[55] Forced expression of S100A10 reduces sensitivity to oxaliplatin in colorectal cancer cells.[56] Gillet *et al.*[57] found S100A10 to be one of the 11 signature genes whose expression is involved in multidrug resistance of ovarian serous cancer. Nymoan *et al.*[58] found that high S100A10 expression is related to poor chemotherapeutic responses. The mechanism by which S100A10 regulates drug resistance is poorly understood and requires further investigation. These results are summarized in Table 3.

Some oncogenes are reported to regulate S100A10. Acute promyelocytic leukemia (APL), characterized by PML-RARα fusion protein, is commonly accompanied by disseminated intravascular coagulation (DIC), which is thought to be a result of increased production of plasmin. RNAi mediated depletion of S100A10 in APL cells resulted in marked loss in plasminogen binding and plasmin generation. Forced expression of PML-RARα in U937, a monocyte cell line, resulted in a rapid upregulation of S100A10 and a subsequent increase in plasminogen binding and fibrinolytic activity, suggesting that the regulation of S100A10 by PML-RARα is direct.[59] Oncogenic K-RAS was also shown to induce S100A10. Disruption of the oncogenic K-RAS results in a dramatic decrease in S100A10 protein level, suggesting a role for S100A10 in Ras-dependent plasmin activation.[60]

TARGETING S100A10 FOR CANCER THERAPY

S100A10 could be an excellent target for cancer treatment, because mouse models suggest that genetic deletion has minimal effects on normal physiology. Different therapeutic strategies have been used to target S100A10, including peptides, neutralizing antibodies, small molecule inhibitors, and all-trans retinoic acid (ATRA).[5] An ANXA2 peptide which interferes with ANXA2-S100A10 complex formation prevents binding of prostate cancer cells and multiple myeloma cells to osteoblasts.[61,62] S100A10 antibodies are effective in reducing leukemia cell homing to the bone marrow *in vivo*.[53] A number of small molecules that inhibit the formation of the complex have been identified.[5] One of these inhibitors, 5-benzyl-4-methyl-2-(toluene-4-sulfonylamino)-thiophene-3-carbocylic acid amide, has been shown to inhibit the adhesion of leukemic cells to osteoblasts *in vivo*.[53]

As mentioned above, S100A10 is upregulated by the expression of PML-RARα fusion protein. The treatment of an APL cell line with ATRA causes the rapid loss of S100A10 protein. However, the mechanism of that regulation has not yet been well understood. Holloway *et al.*[63] found that ATRA treatment of breast cancer cells promotes the proteasomal degradation of S100A10, but does not affect ANXA2

transcript and protein levels, indicating that ATRA can regulate S100A10 levels independently of PML-RARα and ANXA. This study highlights S100A10 regulation by retinoid signaling and challenges the hypothesis that ubiquitin-mediated proteasomal degradation of S100A10 represents a universal mechanism of regulation of this protein.[63]

Targeting S100A10 has the potential risk of a thromboembolic event. It will be important to monitor patients treated with anti-S100A10 therapies and consider antithrombotic prophylaxis.

CONCLUSIONS

S100A10 has been shown to play an important role in cancer progression. The ANXA2-S100A10 complex mediates the conversion of plasminogen to plasmin, which facilitates ECM degradation, MMP activation, and angiogenesis, leading to increased cancer cell migration, invasion and metastasis. A greater understanding of the molecular mechanisms of S100A10 function is leading to the development of effective strategies to target the ANXA2-S100A10 complex.

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DISCLOSURE STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

YS: conception and design of the review, drafting the manuscript, figure, and tables. AH: conception and design of the review, drafting the manuscript, figure, and tables.

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