The prognostic value of S100A10 expression in cancer (Review)

NORMASTUTI ADHINI TANTYO[1], AZRINA SARASWATI KARYADI[1], SITI ZULIMAS RASMAN[1], MARVELMARIO REGINALD GABRIEL SALIM[1], ASTRELLA DEVINA[1] and ANTON SUMARPO[2]

[1]Department of Biomedicine, Indonesia International Institute for Life Sciences, Jakarta Timur 13210; [2]Department of Biochemistry, Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta Utara 14440, Indonesia

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Abstract. S100A10, a member of the S100 protein family, commonly forms a heterotetrameric complex with Annexin A2. This is essential for the generation of cellular plasmin from plasminogen, which leads to a cascade of molecular events crucial for tumor progression. S100A10 upregulation has been reported in a number of cancers, suggesting that it may have potential as a prognostic biomarker, as well as predicting sensitivity to anticancer drugs. This review evaluates the direct and indirect relationships between S100A10 and cancer progression by investigating its role in cancer. Research papers published on PubMed and Google Scholar between 2007-2017 were collated and reviewed. We concluded that S100A10 affects the development of the hallmarks of cancer as explained by Hanahan and Weinberg in 2011, most notably by activating the invasion and metastasis of cancer cells. However, further studies are required to explore the underlying biological mechanisms of S100A10.

Contents

1. Introduction

Genomic analysis is an important tool used in the development of therapies against cancer. Current therapies for cancer often fail, which eventually leads to a high mortality rate. A study by Kim *et al* (2010) revealed that distinct subtypes of breast cancer exhibit different sensitivities to systemic chemotherapy (1). Causative gene mutations may also affect the sensitivity of cancer cells towards certain chemotherapeutic drugs (2), and so developing genomic biomarkers specific to each cancer subtype is essential for screening, diagnosis, predicting patient prognosis and selecting effective cancer treatments (2,3).

S100A10, a member of the S100 proteins family, forms a homodimer comprising two EF-hand motifs; an N-terminal S100-specific EF hand and a C-terminal canonical EF hand, linked by a hinge region known as the $Ca2^{+}$-binding loop (4). The function of the EF hand remains elusive due to limited knowledge regarding its structural effects on downstream targets, despite thorough studies of the interaction between the EF hand and Ca^{2+} (5). Genetic mutations, such as substitutions and deletions, have been identified in the calcium-binding residues of the EF hand, which render S100A10 unable to bind to calcium (6). S100A10 has been reported to interact with numerous ion channels, such as TRPV5 and TRPV6 for Ca^{2+} and Mg^{2+} transport, as well as the serotonin 5-HT1B receptor, which is involved in the regulation of serotonin signaling (7). Additionally, the expression of S100A10 in epithelial and stromal cells of the endometrium might promote embryo implantation (8). Furthermore, S100A10 upregulation is involved in the progression of angiogenesis of the embryo (9). Based on these reports, it appears that S100A10 is involved in a variety of normal functions in several tissues via interactions with various biomolecules.

Annexin 2 (ANXA2) is the most common ligand of S100A10, which, along with other ligands, forms a heterotetrameric complex known as AIIt (A2 heterotetramer). Several studies have reported that the ANXA2-S100A10 complex prevents ubiquitinylation of S100A10 (10,11). Allt is an essential regulator of cellular plasmin generation. Plasminogen circulates in the blood it its inactive form, and the conversion of S100A10-bound plasminogen to plasmin is mediated by tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) (11-13). Binding to Allt prevents inactivation of the plasmin, which may eventually contribute to cancer progression (14-18).

2. Tumor-promoting activities of S100A10 in cancer

It has been established that cancer cells undergo modifications that make them functionally different to normal cells.

Correspondence to: Dr Anton Sumarpo, Department of Biochemistry, Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, 2 Jl. Pluit Raya, Jakarta Utara 14440, Indonesia
E-mail: sumarpo01060715@gmail.com

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These modifications result in certain characteristics, known as the 'Hallmarks of Cancer'. In 2011, Hanahan and Weinberg reported the hallmarks of cancer as well as the enabling characteristics of cancer cells, which are: i) Sustained proliferative signaling; ii) resistance to cell death; iii) evasion of growth suppressors; iv) replicative immortality; v) tumor-promoting inflammation; vi) avoidance of immune destruction, vii) angiogenesis induction; viii) invasion and metastasis activation; ix) deregulation of cellular energetics and x) genome instability and mutations (19). In order to evaluate the role of S100A10 in cancer, the effects of S100A10 in the development of these hallmarks need to be investigated.

Sustained proliferative signaling, resistance to cell death, evasion of growth suppressors and replicative immortality. Tumor cells are considered to be persistent due to their ability to survive in unfavorable conditions, which is a result of the abovementioned modifications. This persistence be achieved by direct action via the release of their own growth factors, thus preserving autocrine signaling, or indirect action via interfering with the apoptotic pathway to inhibit apoptosis (19). The intrinsic apoptotic pathway, which involves the Bcl-2 family, regulates apoptosis through the mitochondria. Possible mechanisms by which Bcl-2 family proteins regulate apoptosis have been postulated (20), however these mechanisms have yet to be definitely elucidated. It has been reported that Bad, a pro-apoptotic member of the Bcl-2 family, induces cytochrome C release from the mitochondria, activating caspase 9 which in turn leads to the activation of caspase-3 and the initiation of apoptosis (20). However, S100A10 has been reported to interact with Bad and hinder its pro-apoptotic activity, suggesting that S100A10 may have anti-apoptotic effects in cancer cells (21,22). This may explain reports of increased caspase-3 expression following S100A10 downregulation *in vitro* (23) and in S100A10-knockout mice (24). Furthermore, S100A10 downregulation suppresses cell growth by reducing the expression of Cyclin D1 (24), which is the critical downstream effector protein of epidermal growth factor receptor (EGFR) signaling (25). It is important to note that S100A10 is overexpressed in patients with mutated EGFR in comparison to patients with normal EGFR, suggesting a correlation between the two (26). Reduced growth of murine Lewis lung carcinoma or T241 fibrosarcoma has also been reported in S100A10-deficient mice (12). In accordance with the *in vivo* evidence, the regulation of tumor cell proliferation by S100A10 has been observed in patients with a variety of cancers, including squamous cell carcinoma (27) and colorectal cancer (28), as well as in COLO201, COLO205, COLO320, DLD-1, HCT-15, HCT-116, HT29, LOVO, LS174T, SW480, SW620, SW1116 and WiDR colorectal cancer cell lines (22). Furthermore, reduced S100A10 expression caused by ANXA2 knockdown resulted in decreased tumor growth and proliferation in GL621 mouse glioma cells (29).

Tumor-promoting inflammation and avoidance of immune destruction. Inflammation is one of the critical traits that contributes to tumor progression and cancer development. Chronic inflammation is known to increase the incidence of cancer, primarily by causing DNA damage and inducing the inflammatory response, which give rise to a pro-tumorigenic microenvironment (30,31). When tumor growth reaches a certain point, tumors begin to produce pro-inflammatory factors, predominantly matrix metalloproteinases (MMPs), which induce further inflammation at the tumor site. This results in further recruitment of immune cells and cytokine production, which in turn promotes tumor progression (32). This recurrent positive loop of inflammation in tumorigenesis is integral to the rapid progression of cancer.

Tumor cells regulate inflammation via various mechanisms, and S100A10 has been identified to serve a pro-inflammatory role. As discussed, AIIt converts plasminogen into plasmin, which may lead to inflammation. The amino-terminal peptide is a byproduct of plasmin cleavage (33). AIIt-derived cell surface plasmin triggers the phosphorylation of PKC signaling molecules, which leads to ANXA2 cleavage, resulting in the activation of toll-like receptor 4 (TLR-4) and NFκB signaling (34). This pathway has been reported in hepatocellular carcinoma, in which activation of the Akt/NFκB signaling pathway promoted liver carcinogenesis. AIIt disassembly occurs after ANXA2 phosphorylation, following which tPA binds to the S100A10 subunit within the carboxyl-terminal lysine residue, to activate the CD11b-dependent integrin-linked kinase (ILK) pathway (13,35). Together with plasmin, ILK can induce nuclear translocation of NFκB, which promotes the production of pro-inflammatory factors, including IL-1, IL-6 and TNFα (13,33,36). Although AIIt-dependent macrophage activation may occur via the MAPK and NFκB pathways, TLR-4 knockdown inhibits AIIt-driven cytokine production (16); this suggests that TLR-4 serves an important role in AIIt-mediated inflammation. TLR-4 activation induces tumor-associated IL-6 expression in bladder cancer through p38 and Erk signaling (37), which is activated by JAK1/TYK2 and STAT3 stimulation. Inhibiting JAK, p38, and NFκB results in a significant reduction in IL-6 and TNF-α expression, suggesting that this pathway is important for releasing plasmin-dependent cytokines (38).

TLR-4 activation triggers AIIt to recruit and activate macrophages (16) via extravasation and migration within extravascular tumor tissues. The effects of S100A10 in cellular migration and invasion may significantly contribute to the recruitment of immune cells at the tumor inflammation site by inducing fibrinolysis. It has been hypothesized that S100A10 expression in macrophages induces the production of plasmin by cell surface plasminogen receptors, which allows for the migration of macrophages by facilitating the proteolysis of basement membrane and extracellular matrices (21). S100A10 has also been observed to have a direct effect in macrophage infiltration *in vivo*; $S100A10^{-/-}$ mice exhibited a significant reduction in macrophage recruitment compared with wild type mice (39). In addition, S100A10 indirectly stimulates the release of MCP-1 under hypoxic conditions (40), which might aid in the recruitment of monocytes in the tumor microenvironment via chemotaxis (33).

Prolonged inflammation at the tumor site suppresses the anti-tumoral activities of immune cells due to the secretion of tumor-promoting cytokines, including IL-1, IL-6 and TNF-α (41). The release of these cytokines and prostaglandin E_2 (PGE_2) stimulates the infiltration of myeloid derived suppressor cells (MDSCs) into the tumor microenvironment (42). Infiltrating MDSCs elicit immunosuppressive

effects via a number of mechanisms, such as inducing anergy in NK cells via membrane-bound TGF-β, STAT-5 activity and ARG-1. Furthermore, it can suppress the cytotoxicity of NK cells by inhibiting interferon-γ (IFN-γ) production (43) and downregulating NKG2D, as is observed in glioma (44). TGF-β also been reported to induce the activation of induced Treg (iTreg) cells by MDSC (45). Moreover, together with IL-6, TGF-β is able to stimulate Th17 and enhance the pro-tumoral effects of MDSC (41). The binding of TNF-α to its receptor on $CD11b^{+}Grl^{+}$ myeloid cells results in TGF-β release, which in turn suppresses the anti-tumoral activity of $CD8^{+}$ T cells (46), intensifying immunosuppression in the tumor microenvironment. S100A10's ability to release these pro-inflammatory cytokines indirectly facilitates immune-escape mechanisms by mitigating T cell cytotoxicity and evading immunosurveillance (36).

Angiogenesis induction. Due to its altered metabolism, the tumor microenvironment is hypoxic. This triggers the release of hypoxia inducible factor-1α (HIF-1α), which stimulates oxygen delivery to the hypoxic site by promoting angiogenesis by regulating pro-angiogenic genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and monocyte chemoattractant protein 1 (MCP-1) (40,47). This results in increases in vascular permeability, endothelial cell proliferation and sprouting, creating a vast tumor vasculature (47). However, tumor vessels typically function poorly due to their irregular and leaky structure (48). Inadequate tumor vessels leads to the stabilization of HIF-1α, which further promotes angiogenesis to generate a positive feedback loop (47). The feedback loop is exacerbated by HIF-1α-induced ANXA2 transcription, which occurs via binding to the hormone response element of ANXA2 gene (18,49). ANXA2 upregulation leads to the stabilization of S100A10 (10,18). Together, the heterotetrameric complex of ANXA2 and S100A10 enhances the generation of plasmin, which is able to activate a number of MMPs (50,51). Both plasmin and MMPs further promote angiogenesis via the extracellular matrix (ECM) -associated pro-angiogenic growth factors (36,52-54).

Studies have reported the significance of ANXA2 and S100A10 in the initiation and progression of angiogenesis. ANXA2-deficient mice exhibited decreased angiogenic activity (55,56). This disturbance in angiogenic activity may occur due to the impaired plasmin-MMP axis of angiogenesis. Inhibition of heterotetramer formation via competitive binding results in a substantial reduction in vascular branching (57). It can therefore be inferred that the ANXA2-S100A10 complex plays a pivotal role in the initiation and progression of angiogenesis.

Cell-cell interactions are mediated by interactions between cancer cells and opposing endothelial cells via Annexin 2 and S100A10. This has been observed in breast cancer, where interactions between Annexin 2 and S100A10 resulted in the generation of activated plasmin, promoting ECM proteolysis and initiating the release of ECM-sequestered VEGF via MMP-9 activation (13,58,59).

Activation of invasion and metastasis. Cancer malignancy is determined by its metastasis and invasion potential. This hallmark of cancer relies on the ability of cancer cells to modify ECM and induce epithelial to mesenchymal transition (EMT) (19). In order to invade and metastasize, cancer cells must cross the basement membrane. ECM is promoted by proteases, such as plasmin and MMPs (60). Plasmin proteolytic activity allows for the degradation of fibronectin and laminin within the basement membrane, simultaneously initiating a proteolytic cascade via the activation of proteases such as MMPs (61), which helps to remodel the ECM. An essential process in MMP regulation is the conversion of zymogen into active proteolytic enzyme, which is mediated by plasmin (62). S100A10 directly effects MMP regulation to influence plasmin generation. Following the binding of plasminogen to AIIt, the uPA-mediated generation and activation of plasmin upregulates MMP-1 via the Erk1/2, p38, cyclooxygenase-2 and PGE_2 pathways (51). Specifically, extracellular AIIt allows cancer cells to utilize plasmin, cathepsin B and MMPs to degrade cellular adhesion factors (21). Plasmin-dependent ECM proteolysis activates uPA, which binds to the uPA receptor (uPAR) to cleave and activate plasmin (21,63). Activated plasmin subsequently activates pro-uPA, generating a positive feedback loop once again (21).

The positive feedback loop is intensified by pathways regulated by oncogenic Ras. It has been reported that oncogenic HRas upregulates MMP-2 and MMP-9 via increasing the expression of uPAR, suggesting that invasion and metastasis may be Ras-dependent. Although oncogenic Ras is a key regulator of plasmin generation, S100A10 knockdown results in a significant reduction in Ras-dependent plasmin generation (64). This verifies the existence of a positive feedback loop between S100A10, plasmin generation and oncogenic Ras. S100A10 overexpression has been reported to induce invasion and metastasis in lung adenocarcinoma and is correlated with higher TNM stages (65), thyroid neoplasms (66) and acute promyelocytic leukemia (APL) (36). S100A10 overexpression is observed in the breast cancer cell line MDA-MB-435 (67) and colorectal cancer (28). S100A10 downregulation, on the other hand, reduces plasmin generation, which leads to a loss of invasiveness of cancer cells (67).

S100A10 is an independent prognostic biomarker for serous ovarian cancer. A previous study reported that high S100A10 mRNA levels and S100A10 cytoplasmic positivity was correlated with decreased overall patient survival and a 2-fold increase in ovarian cancer mortality (68). In APL patients, S100A10 overexpression and activation promotes the migration of cancerous leukemic cells as well as hyperfibrinolysis, often causing excessive bleeding (13). One study reported that the AIlt overexpression resulted in forced expression of leukemia/retinoic acid receptor a (PML/RARα) fusion protein, which led to a 27.6% increase in cell invasiveness, whereas antibodies inhibiting Allt reduced invasion and migration (36). It has been reported that the invasion of CCL-222 colorectal cells via ECM degradation was significantly reduced by a loss of S100A10 (69). S100A10 knockdown in HT-1080 cells results in the depletion of metastatic lung foci, whereas S100A10 upregulation increases the metastatic potential of these cells (61).

DLC-1, a Rho GTPase-activating protein, is a ligand that competitively binds wit S100A10 at the ANXA2 binding site. The coupling of S100A10 and DCL-1 prevents ANXA2 from

inhibiting the ubiquitin-dependent degradation of S100A10, resulting in a decrease in S100A10 and, consequently, reduced migration and invasion in non-small-cell lung cancer lines (A549 and H1395) (70). This confirms that plasmin generation and plasminogen-dependent cell invasion occurs due to the surface protein loss of S100A10, not ANXA2. However, ANXA2 expression has been reported to be an independent predictor of metastasis in clear-cell renal cell carcinoma. It was demonstrated that the 5-year metastasis-free rate is significantly lower in ANXA2-negative tumors compared with ANXA2-positive tumors (71). As ANXA2 expression is proportional to S100A10 expression (10,18,29), and S100A10 is highly expressed in renal cancer (72), it could be that renal cancer metastasis is initiated by the interaction between S100A10 and ANXA2. This has also been suggested in pancreatic (73) and gastric cancers (38,74,75). S100A10 expression is increased in advanced pancreatic tumors compared with benign pancreatic tumors (15) and, furthermore, is correlated with the proportion of lymph node metastases and the depth of gastric cancer (38). However, the exact mechanism of S100A10 in cancer invasiveness requires further investigation. ANXA2 has been found to have an invasion-promoting role in in pancreatic ductal adenocarcinoma, which is achieved via the initiation of hedgehog signaling, inducing the binding of tenascin C to ANXA2 (76).

Deregulating cellular energetics. One of the factors that allow cancer cells to survive in unfavorable conditions is their ability to alter metabolic processes (19). Altered metabolism in cancer cells occurs via upregulation of glucose transporter 1 (GLUT1), which results in an elevated glucose intake to support energy production (77-79). A direct role of S100A10 in altering cellular metabolism has not yet been identified; however, the aforementioned metabolism dysregulation is highly associated with oncogenic Ras and HIF-1α (77,78), suggesting an indirect effect of S100A10. As discussed above, S100A10 influences oncogenic Ras expression and HIF-1α stabilization, resulting in KRas mutations that cause GLUT1 upregulation and consequently increased glucose uptake (80). As well as S100A10-mediated HIF-1α stabilization, Ras activation also induces HIF-1α translation via the Ras/Raf/Mek/Erk kinase signaling cascade (81). HIF-1α then binds to hypoxia-response elements in the promoter region of the GLUT1 gene to increase GLUT1 expression (80).

In ovarian cancer, S100A10 has eight potential binding motifs for c-Myc transcriptional factor (82), which play an important role in the regulation of glycolysis via targeting the lactate dehydrogenase A (LDHA) (83). Overexpression and stabilization of c-Myc by S100A10 amplifies glycolysis, resulting in a persistent increase in the availability of nutrients necessary for cancer cell proliferation. There is a clear correlation between S100A10 expression and altered metabolism in tumor cells. However, further studies are required in order to explore the potential mechanisms by which S100A10 may directly affect tumor cellular energetics.

Genome instability and mutation. The hallmarks and characteristics of cancer develop via genetic or epigenetic modifications. Simply put, these modifications allow tumor cells to gain abilities that are beneficial for their growth. The underlying mechanism by which tumor cells obtain these characteristics is via mutations in caretaker genes. However, tumorigenesis may also be initiated by epigenetic changes that result in a downregulation of tumor suppressor genes (19). The location of the S100A10 gene is susceptible to epigenetic changes that may contribute to cancer development. These changes may affect the regulation of S100A10 expression, which corresponds to tumor malignancies (84).

No direct correlation between S100A10 and genomic changes has been identified. Nonetheless, its interaction with ANXA2 is associated with increased susceptibility to human papilloma virus (HPV) infection (85-87), in which integration of the viral genome into the host causes the degradation of p53 and Rb (88,89).

3. Conclusion and future studies

S100A10 is a novel gene that may have potential as a biomarker and treatment target due to its persistent overexpression in a variety of tumor cells, as well as its contribution to several key hallmarks of cancer. Recently, S100A10 expression has been recognized as a potential malignancy biomarker in colorectal cancer (28), renal cell carcinoma (72), non-small cell lung carcinoma (90) and gallbladder cancer (91).

It is thought that S100A10 might play role in cellular differentiation and cell cycle progression, making it a potent prognostic biomarker and a potential predictive marker of sensitivity to chemotherapeutic drugs. Oxaliplatin-based chemotherapy, which hinders the growth and proliferation of advanced cancer by activating certain apoptotic pathways, has been reported to be less effective in colorectal cancer with forced expression of S100A10 (47). Forced S100A10 expression significantly increases the 50% inhibitory concentration (IC50) of oxaliplatin (22). This suggests that S100A10 expression may be used to predict resistance to chemotherapeutic agents.

S100A10s is often expressed together with ANXA2, whose role in cancer has been well studied, as a heterotetramer complex localized in the intracellular cytoplasm and extracellular membrane of various cancer cells (13,16,49). Despite the observed correlation between S100A10 expression and cancer development, little is known with regard to the underlying biological mechanisms.

In summary, this review demonstrates that S100A10 interacts with a variety of proteins in different pathways to promote cancer development (Fig. 1). One of the persistent roles of S100A10 that contributes to the hallmarks of cancer is plasmin generation, which significantly remodels the ECM (13,61); this ECM modulation occurs in invasion, metastasis, inflammation, evasion of immune destruction, and angiogenesis. Furthermore, S100A10 appears to serve a greater role in the activation of invasion and metastasis compared with the other hallmarks of cancer (Table I). These findings may provide a basis for the development of effective treatment regimes for advanced cancer.

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Table I. Association between S100A10 expression and the hallmarks of cancer in different cancer types.

	Hallmarks of cancer					
Types of cancer	Apoptosis and proliferation	Immune escape and tumor-promoting inflammation	Angiogenesis	Invasion and metastasis	Cellular energetics deregulation	Genome instability and mutation[a]
Breast			√	√		
Colorectal	√			√		
Gastric				√		
Glioma	√	√				
Leukemia				√		
Liver		√				
Lung	√			√		
Ovarian				√	√	
Pancreas				√		
Renal				√		
SCC	√					
Thyroid				√		

SCC, squamous cell carcinoma. [a]There is no direct evidence that S100A10 protein is correlated with genomic modifications.

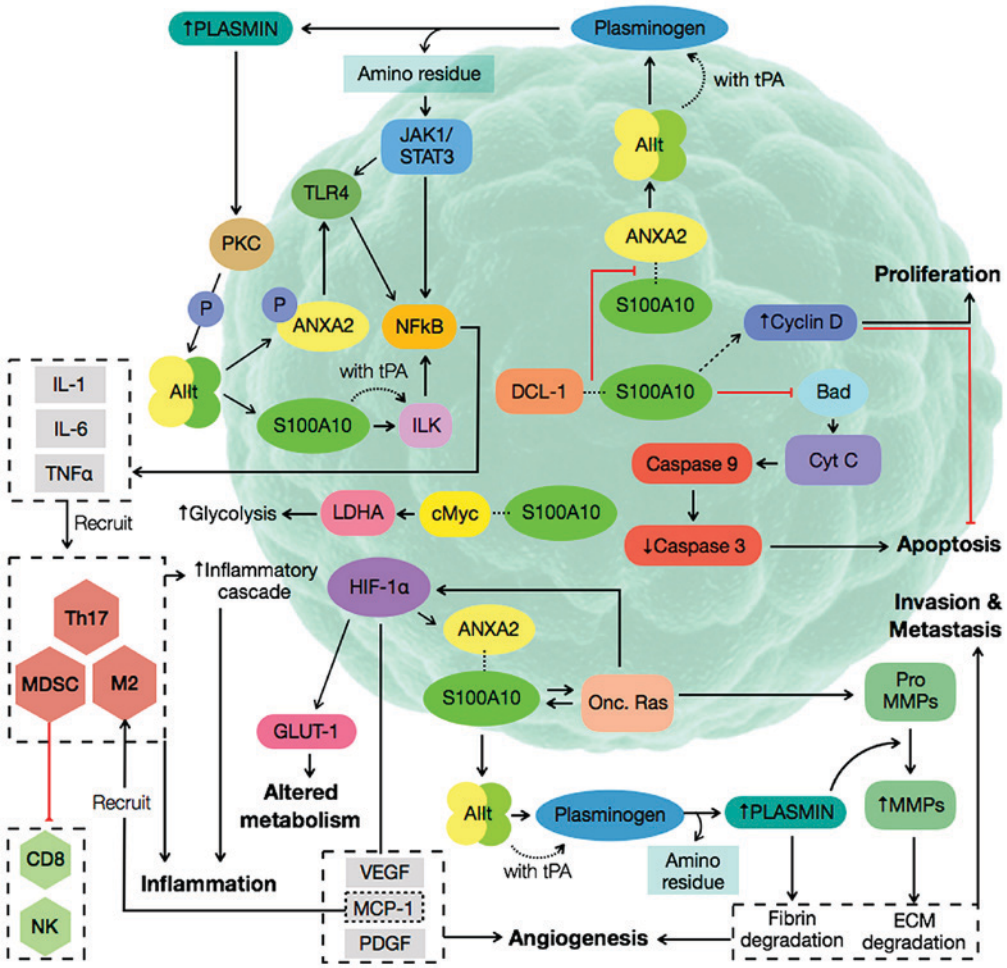

Figure 1. Cancer progression pathways involving S100A10. AIIt, Annexin A2 and S100A10 heterotetrameric complex; ANXA2, Annexin A2; CD8, $CD8^+$ T cells; Cyt C, Cytochrome C; c-Myc; HIF-1α, Hypoxia inducible factor-1α; IL-1, interleukin 1; IL-6, Interleukin 6; ILK, integrin-linked kinase; M2, type 2 macrophages; LDHA, lactate dehydrogenase A; MCP-1, monocyte chemoattractant protein 1; MDSC, myeloid-derived suppressor cells; MMPs, matrix metalloproteinases; NFκB, nuclear factor κB; NK, natural killer cells; Onc. Ras, oncogenic Ras; P, phosphate; PDGF, platelet derived growth factor; PKC, protein kinase C; Th17, T helper 17 cells; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor α; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

Availability of data and materials

Not applicable.

Authors' contributions

NAT and ASK devised the main conceptual ideas and proof outline. ASK designed the figures. NAT, ASK, SZR, MRGS and AD interpreted the results and drafted the manuscript. NAT took the lead in writing the manuscript. AS supervised the project, took part in the conceptualization of the whole manuscript and helped with the interpretations of the results obtained during the research process. In addition, AS also revised the manuscript thoroughly prior to submission and gave the final approval for its submission to be published.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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