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Chapter 3

S100A10: A Key Regulator of Fibrinolysis

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1. Introduction

Regulation of fibrinolytic activity can be achieved by several mechanisms, ranging from regulating the production and localization of the plasminogen activators and their inhibitors, the degradation and inactivation of plasmin via autoproteolysis, and the synthesis and localization of the cell surface receptors for plasminogen. Binding of the inactive zymogen plasminogen to its cell surface receptors has been shown to significantly increase the rate of its conversion to the active serine-protease plasmin by co-localizing plasminogen with its activators, the tissue-type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA) [1–3].One such cell surface plasminogen receptor is S100A10 (p11) [4]. S100A10, a member of the S100 protein family, was initially discovered as an annexin A2 (p36) binding partner [5–7]. S100A10 has also been found to interact with other cellular proteins including the Rho GTPase-activating protein DLC1 [8], cytosolic phospholipase A2 [9], the serotonin 1B receptor [10] and various ion channels, including the potassium channel TASK-1 [11], the sodium channel Na(V)1.8 [12] and the calcium channels TRPV5 and TRPV6 [13]. However, the major binding partners of S100A10 on the cell surface are tPA and plasminogen [14]. The focus of this review will be to discuss the role that extracellular S100A10 plays in regulating the conversion of plasminogen to plasmin and the physiological consequences of that process (Figure 1).

S100A10 is found on the cell surface as part of the annexin A2 heterotetramer complex (AIIt) [15]. AIIt is composed of two annexin A2 (p36) subunits along with two S100A10 subunits which form a $p36_2$ /$p11_2$ complex. Initially, annexin A2 was proposed to exist as a monomer on the cell surface where it functioned as a plasminogen receptor [16,17]. The possibility that S100A10 was present on the cell surface was ruled out by these investigators who reported that S100A10 was not present on the cell surface [18]. Subsequently, it was firmly established that S100A10 was present on the cell surface and this S100A10 was shown to exist as a complex with annexin A2 [15]. In view of this report, the proposed role of annexin A2 as a plasminogen

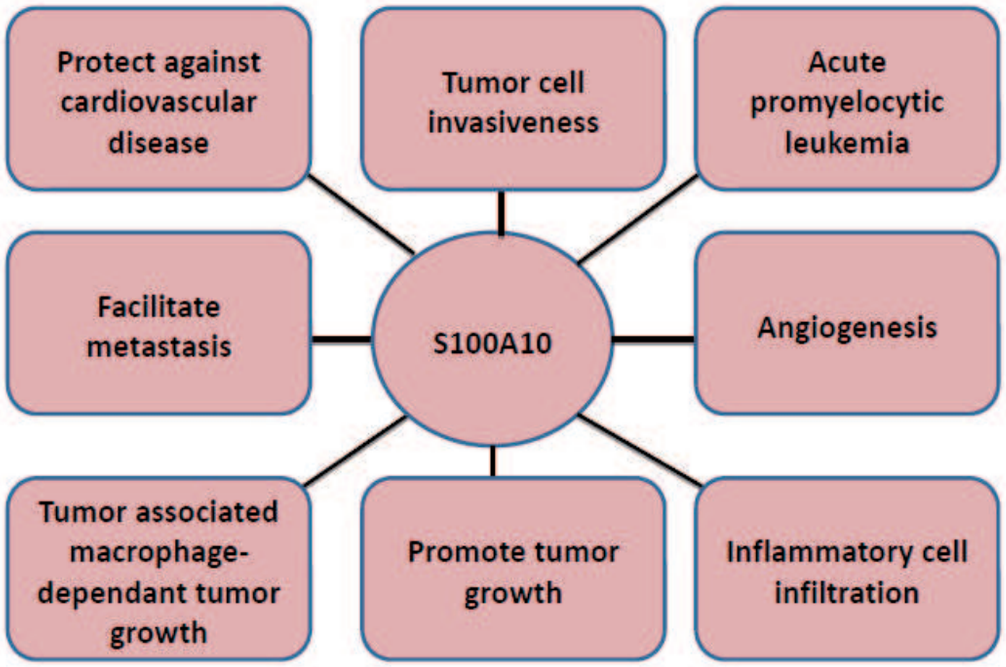

Figure 1. Roles of cell surface S100A10 in pathological processes. S100A10 on the cell surface participates in several pathological processes. S100A10 mediated fibrinolysis can have protective effects against cardiovascular disease and can participate in necessary inflammatory processes. Conversely, S100A10 mediated fibrinolysis may also participate in pathological inflammation and promote tumorigenesis through several mechanisms, including TAM infiltration, angiogenesis, tumor cell invasiveness and metastasis.

receptor was revised and it was reported that within the $p36_2p11_2$ complex, annexin A2 acted as the plasminogen receptor [19]. However, more rigorous studies have indicated that while annexin A2 does in fact anchor the $p36_2/p11_2$ complex to the cell surface in a calcium dependent fashion, S100A10 acts as the plasminogen receptor [14,15,20,21] (Figure 2).

Several cell surface proteins have been identified as plasminogen receptors, including histone 2B [22,23], integrin $\alpha_M\beta_2$ [24], α-enolase [25], cytokeratin-B [26,27] and Plg-R_{TK} [28]. All of these cell surface plasminogen receptors contain carboxyl-terminal lysines, which interact with the kringle domains of plasminogen [29–33]. Within the $p36_2/p11_2$ complex only S100A10 contains a carboxyl-terminal lysine. Binding studies using surface plasmon resonance demonstrated that S100A10 binds to plasminogen (K_d=1.81μM) while annexin A2 does not bind plasminogen. Interestingly, the $p36_2/p11_2$ complex binds plasminogen with higher affinity (K_d=0.11μM) than S100A10 alone, indicating that annexin A2 may induce a conformational change in S100A10 that facilitates the interaction of S100A10 with tPA or plasminogen. Treatment of both S100A10 and the $p36_2/p11_2$ complex with carboxypeptidase B, which removes carboxyl-terminal lysines, abolished plasminogen binding, indicating that plasminogen binding to the $p36_2/p11_2$ complex was dependent on the carboxyl-terminal lysine present on S100A10 [4,34]. S100A10 increased the rate of tPA dependent plasmin activation 46-fold while the $p36_2/p11_2$ complex increased the rate of activation 77-fold. Annexin A2, on the other hand, only increased the rate of activation 2-fold, indicating that S100A10 participates in plasminogen binding and subsequent generation of plasmin [21]. In the original studies in which purified annexin A2

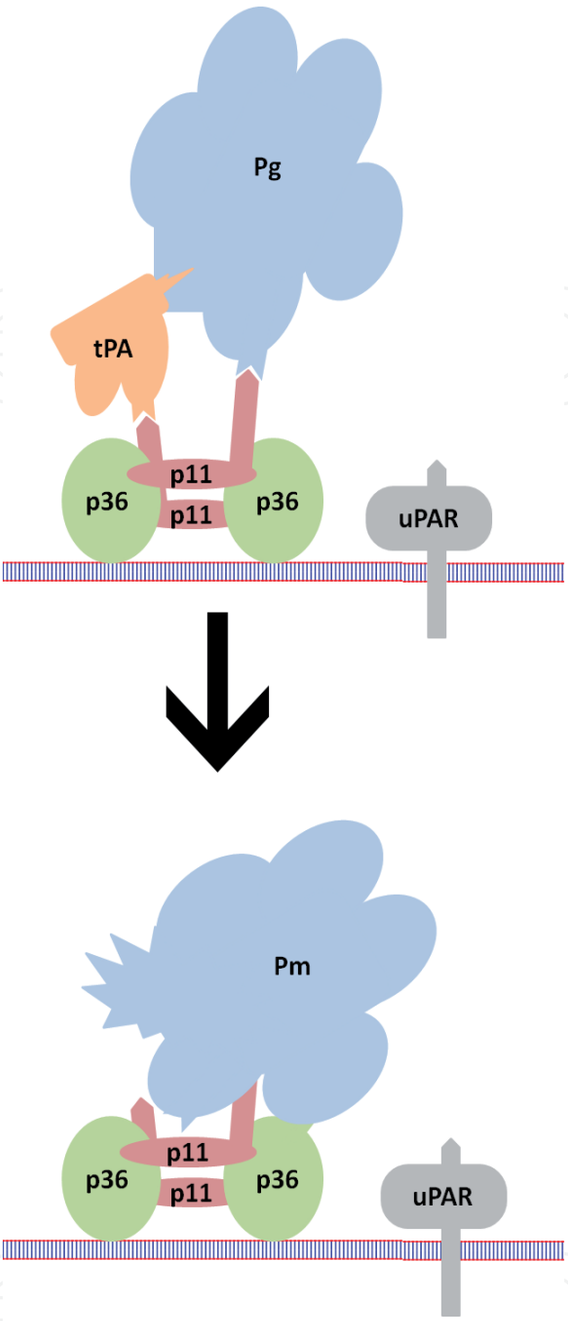

Figure 2. Model depicting AIIt dependant plasmin generation AIIt is composed of two annexin A2 (p36) monomers and two S100A10 (p11) monomers. Annexin A2 anchors AIIt to the cell membrane through phospholipid binding sites. Plasminogen (Pg) and tPA bind to S100A10 in a carboxyl-terminal lysine dependant fashion. AIIt also co-localizes with uPAR on the cell membrane. Binding of plasminogen to S100A10 therefore brings it into close proximity with the plasminogen activators tPA and uPA, accelerating proteolytic activation of plasminogen into the active serine protease plasmin (Pm). Plasmin binds to AIIt through annexin A2 and S100A10 in a non-carboxyl-terminal lysine dependant fashion.

was demonstrated to bind plasminogen, carboxypeptidase B treatment of this annexin A2 was observed to block plasminogen binding. Since annexin A2 does not possess a carboxyl-terminal lysine, a cleavage event at Lys307-Arg308 of annexin A2 was postulated to occur, thereby

exposing the prerequisite carboxyl-terminal lysine for plasminogen binding [35]. However, this cleavage event has never been demonstrated to occur *in vitro* or *in vivo.* In contrast, carboxyl-terminal lysines are present on S100A10 and therefore do not require post-translational modification. Furthermore, Plow's group demonstrated that an antibody generated against the K327-D338 region of annexin A2 inhibits plasmin generation, suggesting that the carboxyl-terminus of annexin A2 remains intact during plasmin generation and therefore that the putative cleavage event does not occur [36]. The crystal structure of annexin A2 has revealed that the amino- and carboxyl-terminal regions of annexin A2 are present in a cleft in the concave surface of annexin A2 in close proximity to S100A10. Surprisingly the possibility that the annexin A2 antibody might affect the conformation of S100A10 was not considered.

In addition to binding plasminogen, the carboxyl-terminal lysines of S100A10 form the binding site for tPA [21]. Since the $p36_2$ /$p11_2$ complex also co-localizes with the uPA receptor, uPAR, at the cell surface [15], binding of plasminogen to S100A10 brings plasminogen into close proximity to both plasminogen activators on the cell surface, thereby dramatically increasing the rate of conversion of plasminogen to plasmin.

2. Role of S100A10 in fibrinolysis

Conversion of plasminogen to plasmin contributes to the maintenance of vascular patency, as the serine-protease plasmin Is the principle enzyme responsible for degrading fibrin, the main protein component of blood clots. Cell surface plasminogen receptors, which play a critical role in the activation of plasminogen, therefore participate in the clearance of potentially dangerous blood clots. The advent of annexin A2 (annexin A2−/−) and S100A10 knock-out (S100A10−/−) mice have provided valuable tools to investigate the *in vivo* role of the $p36_2$ / $p11_2$ complex in fibrinolysis. As discussed, previous reports had suggested that annexin A2 was responsible for the generation of plasmin and subsequent fibrinolysis [16,35,37]. However, since annexin A2 is responsible for stabilization of S100A10 levels [38], loss of annexin A2 can be regarded as loss of both annexin A2 and S100A10. For example, studies conducted with the annexin A2 knockout mouse and with shRNA knockdown of annexin A2 in cultured cells have established that the S100A10 levels are uniquely sensitive to the annexin A2 levels and that depletion of cellular annexin A2 results in the concomitant depletion of S100A10 [8,38,39]. It is therefore impossible to determine whether annexin A2 or S100A10 is responsible for plasmin generation in the annexin A2 knockout mouse model.

Since annexin A2 is present on the cell surface of S100A10−/− endothelial cells [39], we can conclude that alterations in plasminogen binding and plasmin activation in this model are due to loss of S100A10. The S100A10−/− mouse is therefore helpful in clarifying the mechanism by which the $p36_2$ /$p11_2$ complex participates in fibrinolysis and neoangiogenesis [39]. This model revealed a significant increase in fibrin deposits in the lung, liver, kidney and spleen of the S100A10−/− mouse [39]. S100A10 was also shown to play an important role in the clearance of microvascular thrombi as the S100A10-/- mouse had an impaired ability to clear blood clots induced by the thrombin-like enzyme batroxobin. Clots formed after the experimental

induction of vascular damage using the tail-clip assay were also more stable in the S100A10−/− mouse. Since the wild-type and S100A10−/− mice shared similar coagulation parameters, the observed reduction in bleeding time after tail clipping of the S100A10−/− mice was due to decreased fibrinolysis of the tail clip-induced blood clot. The time between cessation of bleeding and the initiation of subsequent episodes of bleeding, the rebleeding time, was of shorter duration and less frequent with the $S100A10^{-/-}$ mice, thus the clots formed by the S100A10−/− mice were more stable than the wild-type mice, again due to a decreased rate of fibrinolysis. S100A10 therefore plays a critical role in the fibrinolytic surveillance system which functions to maintain vascular patency. Failure of this system contributes to the pathogenesis of cardiovascular disease, including deep vein thrombosis, stroke, atherosclerosis and coronary heart disease.

Endothelial cells, which line the interior lumen of blood vessels, play a critical role in maintaining vascular patency by participating in the regulation of plasmin generation. Loss of S100A10 in endothelial cells results in a 40-50% decrease in plasminogen binding and activation, suggesting that endothelial cell S100A10 is crucial for vascular fibrinolysis and therefore plays a key role in the fibrinolytic surveillance system [39].

Other work using the S100A10−/− mouse demonstrated the role S100A10 plays in plasminogen-dependent macrophage invasion. Such invasion is critical in physiological and pathological inflammation as macrophages utilize proteases to remodel the extracellular matrix (ECM) in order to move through tissue barriers to reach sites of infection. Murine macrophages lacking S100A10 have an impaired ability to invade into the peritoneal cavity in response to inflammatory stimulation [40]. The presence of S100A10, but not annexin A2 alone, is associated with plasminogen dependent invasion by macrophages, providing further evidence that the S100A10 subunit of the $p36_2$ /$p11_2$ complex is responsible for plasmin generation.

3. Role of the $p36_2$ /$p11_2$ complex in hyperhomocysteinemia

Hyperhomocysteinemia, a condition where elevated levels of homocysteine are found in the blood, has been identified as an independent risk factor for cardiovascular disease [41–44]. Several groups have reported that elevated homocysteine levels results in endothelial cell dysfunction [45–49] and a hyperthrombotic state [41,50–52], which may provide a mechanism by which hyperhomocysteinemia contributes to cardiovascular disease. One mechanism by which homocysteine may promote a hyperthrombotic state is through an interaction with annexin A2 [42,52,53]. Homocysteine, a reactive thiol-containing amino acid produced during the conversion of methionine to cysteine [54], was postulated to form a disulfide bond with extracellular annexin A2 at Cys-8 [55]. This interaction was reported to interfere with tPA binding to annexin A2 [55], thus preventing tPA mediated plasmin generation and fibrinolysis, resulting in the accumulation of blood clots. The report of tPA forming a covalent bond with annexin A2 contradicts other reports that demonstrate tPA binding to the cell surface in a carboxyl-terminal lysine dependent fashion [56]. Results from our laboratory suggested that highly purified annexin A2 fails to bind to tPA [4]. A subsequent *in vivo* murine study by the

Hajjar group expanded on how homocysteine may target annexin A2 to inhibit fibrinolysis. They purified annexin A2 from control mice and mice on a hyperhomocysteinemic diet. A comparison of this purified annexin A2 revealed that the annexin A2 isolated from the mice on a hyperhomocysteinemic diet failed to stimulate tPA-dependent plasmin activation, ie. it was totally inactive. They concluded that elevated serum homocysteine formed a disulfide bond with extracellular annexin A2 resulting in inhibition of annexin A2-dependent plasmin generation [57]. The authors failed to note that 95% of annexin A2 is present intracellularly [17] and that only 5% of the total annexin A2 would be available to interact with homocysteine present in the blood. Thus even if all of the extracellular annexin A2 was modified by homocysteine, it is unclear how a population consisting of 5% extracellular homocysteine-modified annexin A2 and 95% unmodified intracellular annexin A2 could be completely inactive. Since the vast majority of the annexin A2 purified from murine lungs is intracellular, homocysteine would therefore have to label all or most of the intracellular annexin A2 in order to explain the *in vitro* results. Such labelling could also, theoretically, impact not only other annexin A2 functions but should also affect other redox-sensitive proteins and transcription factors which could contribute to endothelial cell dysfunction. It is also unclear how extracellular levels of homocysteine, which in the mouse model are unlikely to exceed 100 uM, could affect intracellular proteins since the intracellular levels of the homocysteine-reactive molecule, glutathione, is present intracellularly at levels of 10 mM. However, it seems implausible for homocysteine to label such a significant portion of intracellular annexin A2 as most homocysteine is bound to plasma proteins [58] and the effective free homocysteine concentration would be insufficient to label intracellular proteins to this extent. It therefore remains unclear how the reported interaction of annexin A2 with homocysteine may contribute to impaired fibrinolysis. Interestingly, a recent report appears to contradict the Hajjar model for homocysteinemia. The Lentz group investigated transgenic mice deficient for the cystathionine β-synthase (CBS), the enzyme responsible for metabolizing homocysteine to cystathionine. In humans, CBS deficiency causes severe hyperhomocysteinemia and this animal model is therefore representative of human disease. Loss of CBS did in fact result in endothelial dysfunction in these animals. However, CBS deficiency did not result in a prothrombotic phenotype. In fact the CBS-null animals displayed normal rates of fibrinolysis [59]. Since these authors were unable to reproduce the findings of the Hajjar study [57,60], they speculated that the prothrombotic phenotype observed in diet-induced hyperhomocysteinemia might not be due to elevated homocysteine but possibly due to other dietary metabolites.

The difficulty in reproducing the Hajjar study was recently discussed by Jakubowski [61]. He pointed out that if homocysteinylation of annexin A2 generates a prothrombotic phenotype, it should be observed in any model of hyperhomocysteinemia, regardless of whether the model is dietary or genetic. He proposed that annexin A2 homocysteinylation for an unknown reason did not occur in the genetic model of hyperhomocysteinemia. These data therefore suggest that annexin A2 does not play a physiologically relevant role in hyperhomocysteinemia in humans.

In humans, CBS deficiency results in severe hyperhomocysteinemia, where plasma homocysteine levels are in excess of 100μM. Treatment of these patients with B vitamins reduces plasma

homocysteine to 30-80μM, which is still higher than the normal 10μM, and reduces the risk of thrombotic events significantly [62]. Mild to moderate hyperhomocysteinemia, where plasma homocysteine levels vary from 16-100μM [63], is more common and can be influenced by diet and lifestyle. Treatment of mild to moderate hyperhomocysteinemia with B vitamins results in a decrease in serum homocysteine to normal levels. This decrease, however, does not correspond with decreased cardiovascular disease [64–68]. These human studies support the notion that hyperhomocysteinemia does not create a prothrombotic state and brings into question whether homocysteine targets annexin A2 in order to create a prothrombotic state. Therefore, the current evidence. The current evidence repudiates the theory that the pathological effects of hyperhomocysteinemia are due to targeting of cell surface annexin A2 and the subsequent loss of tPA binding potential resulting in impaired fibrinolysis.

4. Role of S100A10 in cancer

Alterations in fibrinolytic activity contribute to the pathogenesis of a wide variety of diseases. Excessive fibrinolytic activity has been associated with the pathogenesis of acute promyelocytic leukemia (APL) [69]. APL is caused by a chromosomal translocation that results in the presence of the PML-RAR-α fusion protein. Treatment with all-*trans* retinoic acid (ATRA) has greatly improved outcomes for patients with APL, in part by decreasing the hyper-fibrinolytic state associated with the disease. A role for annexin A2 in the pathogenesis of APL was proposed based on the discovery that annexin A2 levels increased as a result of this fusion protein and treatment with ATRA reduced annexin A2 levels, potentially resulting in reduced fibrinolytic activity [70,71]. Subsequent studies indicated that annexin A2 was actually present in a complex with S100A10 on the cell surface of most cells, that annexin A2 stabilized S100A10 protein levels [72] and that the S100A10 subunits of the $p36_2p11_2$ complex were responsible for plasminogen binding and activation [15,21], our group decided to explore if annexin A2 existed as a complex with S100A10 on the surface of APL cells and if so whether this S100A10 contributed to the hyper-fibrinolytic state presented in APL. We established the presence of S100A10 as a $p36_2p11_2$ complex on the surface of APL cells. Next, we showed that treatment of NB4 cells, an APL cell line, with ATRA resulted in decreased total and cell surface annexin A2 and S100A10 protein levels while mRNA levels were not affected. α-enolase and histone H2B, two other myeloid cell plasminogen receptors, were unaffected by ATRA treatment, providing further evidence that the $p36_2p11_2$ complex was the primary plasminogen receptor that contributed to hyperfibrinolysis in APL. Interestingly, the drop in S100A10 protein levels preceded that of annexin A2. This delay was observed in total protein levels as well as in cell surface protein levels, providing an opportunity to observe whether fibrinolyic activity decreased with loss of cell surface S100A10 alone or whether loss of the complete $p36_2p11_2$ complex was required to decrease fibrinolytic activity following ATRA treatment. Decreases in plasminogen binding, plasmin generation and plasminogen dependent cell invasion were not dependent on the loss of cell surface annexin A2, as these decreases only corresponded with loss of cell surface S100A10. Further evidence that S100A10 was responsible for increased fibrinolysis in APL cells was provided by silencing S100A10 expression using shRNA. Loss of

S100A10 following shRNA expression did not alter cell surface annexin A2 levels but significantly impacted plasminogen binding, plasmin generation and invasion. In order to further explore the relationship between PML-RAR-α and $p36_2p11_2$ complex levels, PML-RAR-α expression was induced in the U937/PR-9 cell line, a myeloid cell line with a $ZnSO_4$ inducible PML-RAR-α promoter. Induction of PML-RAR-α did in fact increase total and cell surface annexin A2 and S100A10 protein levels, yet this effect was not transcriptionally regulated as mRNA levels for each of these proteins were not impacted by PML-RAR-α expression. This increase in the $p36_2p11_2$ complex levels resulted in increased fibrinolytic activity. This provided a clear link between PML-RAR-α expression and increased levels of the $p36_2p11_2$ complex. Subsequent depletion of S100A10 by shRNA in these cells mimicked the previous results observed in the NB4 cells, as plasminogen binding, plasmin stimulation and invasion were decreased with the loss of S100A10 while cell surface annexin A2 levels were unaltered [69]. This study clarified how the $p36_2p11_2$ complex participates in APL hyperfibrinolyis and demonstrates how elevation in S100A10 contributed to the pathogenesis of APL.

Plasmin proteolytic activity has long been associated with tumorigenesis [73,74]. Plasmin mediated proteolysis remodels the tumor microenvironment to permit tumor growth and degrades the basement membrane to permit cancer cell invasion through the stroma and metastasis to other organs. Plasmin directly degrades basement membrane matrix components such as fibronectin [75] and laminin [76] while also activating other proteases, including matrix metalloproteinases (MMP) -1 and -9 [77–80], to trigger a proteolytic cascade necessary for invasion through the basement membrane. Expression of the uPA-uPAR system is considered a prognostic biomarker for several types of malignancies, including breast carcinoma [81], gastric cancer [82], prostate cancer [83] and lung cancer [84]. As components of the plasmin generating system, such as uPAR, are also associated with tumor progression, the key question has been whether the $p36_2p11_2$ complex mediates plasmin generation by cancer cells and if so, does plasmin generated by the $p36_2p11_2$ complex contribute to tumor growth, invasion and metastasis. Multiple reports demonstrated increased annexin A2 expression in a variety of malignancies, which was frequently associated with poor prognosis [85–88]. These reports, however, did not investigate whether S100A10 levels were also associated with these malignancies. As work demonstrating that the carboxyl-terminal lysine of S100A10 was responsible for plasminogen binding and plasmin generation emerged, studies were conducted to observe whether S100A10-dependent plasmin generation contributed to increased invasiveness and tumorigenesis of cancer cells. Our laboratory reported that loss of S100A10 decreased the ability of HT-1080 fibrosarcoma cells [89] and CCL-222 colorectal cancer [90] to invade through an extracellular matrix and that S100A10-depleted cells displayed decreased plasminogen binding, plasmin generation and plasminogen-dependent cellular invasion. In the study with HT-1080 cells, loss of S100A10 significantly decreased the ability of these cancer cells to form metastatic lung foci while over-expression of S100A10 in these same cells increased the metastatic potential, as demonstrated by increased development of metastatic lung foci. More recently, the Zimonjic group reported that DLC1, a Rho GTPase-activating protein and known tumor suppressor, interacted with S100A10 in non small cell lung carcinoma cell lines. DLC1 competed with S100A10 for a common binding site on annexin A2. The DLC1-S100A10 interaction resulted in depletion of S100A10 protein levels as DLC1 prevented the inhibition

of ubiquitin-dependent degradation of S100A10 by annexin A2. Depletion of S100A10 protein levels as a result of this interaction with DLC1 attenuated plasmin generation, migration, invasion through a matrigel extracellular matrix barrier and soft agar colony formation. Part of DLC1's tumor suppressor activity is therefore due to its role in decreasing S100A10 protein levels. Since DLC1-S100A10 interaction did not alter annexin A2 protein levels, this study provided further evidence that S100A10 dependent plasmin generation contributes to oncogenesis [8]. Tumor suppressor proteins such as DLC1 function by preventing normal cells from converting into cancer cells ie. they block the process of oncogenesis. Conceptually, this study was important because it linked the aberrant regulation of S100A10 protein levels with the process of oncogenesis.

In human studies, S100A10 has been identified as a tumor biomarker in several different malignancies. For example, S100A10 is associated with aggressive anaplastic carcinoma [91,92], as a marker for renal cell carcinoma [93], advanced diffuse large B-cell lymphoma [94], colorectal cancer [95], non-small cell lung carcinoma [96] and late stage aggressive gallbladder cancer [97]. Additionally, the S100A10 gene location has been identified as genomic region susceptible to epigenetic changes associated with cancer development, indicating the mechanisms associated with regulating S100A10 expression may be associated with malignancy [98]. Such associations between S100A10 levels and cancer development may correlate with cell culture and mouse studies suggesting S100A10 dependent plasmin generation facilitates tumor progression and metastasis.

Numerous studies have found associations between annexin A2 expression and tumorigenesis. These studies have proposed varying mechanisms by which annexin A2 may contribute to cancer development. Many groups maintain that annexin A2 directly interacts with plasminogen and this interaction leads to plasmin generation and subsequent plasmin mediated invasion and tumor growth. However, the majority of these studies fail to investigate whether S100A10 levels fluctuate with varying levels of annexin A2 [99–104], as would be expected by the reports demonstrating that annexin A2 protects S100A10 from ubiquitin dependent degradation [8]. Other studies have found that annexin A2 contributes to tumor progression by mechanisms other than increased plasmin generation. Annexin A2 regulates cell cycle progression by preventing G2 arrest in p53-dependent and -independent mechanisms in non-small cell lung cancer cells [105]. This provided a potential mechanism by which annexin A2 contributes to cell proliferation, which had been reported in several previous reports [102,106–109]. Annexin A2 may also contribute to tumorigenesis by protecting cancer cells from oxidative damage. Depletion of annexin A2 lead to increased levels of reactive oxygen species (ROS) and subsequent increased activation of ROS-induced proapoptotic kinases and cellular damage and resulting death. This study also demonstrated that annexin A2 increased cancer cell growth by preventing cellular protein oxidation, and elevations of reduced annexin A2 in human tumor samples correlated with reduced protein oxidation [110]. In addition to protein oxidation, ROS are also capable of mediating DNA damage [111]. Genotoxic agents, which are used in some chemotherapies, can cause DNA damage and subsequent cell death. Some genotoxic agents directly target and damage DNA, while other rely on the production of intracellular ROS that results from their metabolism [112]. Annexin

A2 levels increase in response to increased ROS [110]. Following increased ROS levels as a result of treatment with genotoxic agents, annexin A2 accumulates in the nucleus. Increased nuclear annexin A2 levels protected the cells from DNA damage following treatment with various genotoxic agents [113]. Elevated levels of annexin A2, through its redox functions, may therefore protect cancer cells from chemotherapeutic treatment. These studies demonstrate non-plasmin dependent mechanisms by which annexin A2 may directly contribute to tumor progression and poor prognosis (Figure 3).

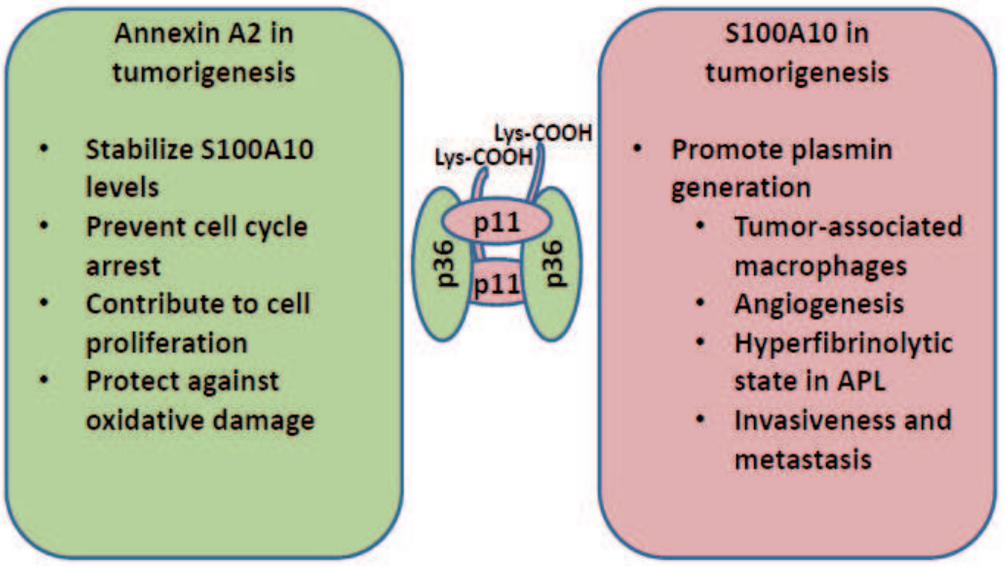

Figure 3. Roles of annexin A2 and S100A10 in tumorigenesis. Annexin A2 and S100A10 may promote tumorigenesis through several mechanisms. Annexin A2 contributes to tumorigenesis by stabilizing S100A10 levels, prevents cell cycle arrest, promotes cell proliferation and protects cancer cells from oxidative damage. S100A10 participates in tumorigenesis primarily by promoting plasmin generation, which contributes to TAM infiltration, angiogensis, invasiveness and metastasis and the hyperfibrinolytic state present in APL.

Tumor development and growth is a dynamic process that is dependent on stromal cells in addition to the cancer cells themselves. Tumor-associated macrophage (TAM) have been demonstrated to participate in tumor development [114], and increased TAM density within a solid tumor is associated with poor prognosis [115]. TAM infiltration into a growing tumor is dependent on the presence of S100A10 on the cell surface, presumably requiring the plasmin generated by the presence of S100A10 to remodel the ECM of the growing tumor and infiltrate into it. Tumor growth is impaired in S100A10−/− mice, and this impairment is due to an inability of TAM to invade into a growing tumor. Introduction of macrophages containing S100A10 into S100A10−/− mice rescued tumor growth, as did injection of S100A10 containing macrophages directly into growing tumors in S100A10−/− mice [116].

Angiogenesis, the process where a growing tumor is vascularized by endothelial cells in order to obtain a blood supply, has also been demonstrated to utilize the protease plasmin for proper angiogenesis associated ECM remodelling [117]. S100A10 dependent plasminogen activation promotes angiogenesis, as shown by decreased angiogenesis in tumors grown in the

S100A10−/− mouse and by a decreased ability of endothelial cells lacking S100A10 to invade through matrigel, an ECM substrate similar to that found in solid tumors [39]. These results clarify a previous study where annexin A2 dependent plasmin generation was postulated to contribute to angiogenesis [37]. Therefore, this study merely recapitulated the importance of annexin A2 in the regulation of S100A10 levels and how this function of annexin A2 often leads to the misassignment of S100A10-dependent functions to annexin A2.

Recently, both components of the $p36_2p11_2$ complex were demonstrated to mediate cell-cell interactions. S100A10 on the surface of endothelial cells was shown to bind to annexin A2 on the surface of breast cancer cells, indicating an additional mechanism by which these proteins may contribute to angiogenesis [118]. S100A10 dependent plasminogen binding and subsequent plasmin generation therefore contributes to tumor growth my a variety of different mechanisms, ranging from cancer cell remodelling of the tumor microenvironment to TAM and endothelial cell invasion into a growing tumor.

5. Conclusion

The involvement of S100A10 in the fibrinolytic surveillance system has been well documented. The recent demonstration of the regulation of S100A10 protein levels by oncogenes and tumor suppressor proteins suggest that S100A10 also plays a central role in cellular transformation. Since S100A10 is predominately an intracellular protein, proper spatio-temporal regulation of this protein is critical to the progression of pathological processes. Therefore, through its ability to bind plasminogen and tPA, S100A10 participates in hemostasis and oncogenesis and this makes S100A10 an attractive therapeutic target for diseases ranging from cancer to cardiovascular disease.

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