S100A10 in Cancer Progression and Chemotherapy Resistance: A Novel Therapeutic Target against Ovarian Cancer

Tannith M Noye¹, Noor A Lokman¹ Martin K Oehler¹,² and Carmela Ricciardelli¹,*

¹ Discipline of Obstetrics and Gynaecology, Adelaide Medical School, Robinson Research Institute, The University of Adelaide, Adelaide, South Australia, Australia. emails: tannith.noye@adelaide.edu.au (T.M.N.); noor.lokman@adelaide.edu.au (N.A.L.); martin.oehler@adelaide.edu.au (M.K.O); carmela.ricciardelli@adelaide.edu.au (CR)

² Department of Gynaecological Oncology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

* Correspondence: carmela.ricciardelli@adelaide.edu.au; Tel.: +61-0883138255

Abstract: S100A10, which is also known as p11 is located in the plasma membrane and forms a heterotetramer with annexin A2. The heterotetramer, comprising of 2 subunits of annexin A2 and S100A10, activates the plasminogen activation pathway which is involved in cellular repair of normal tissues. Increased expression of annexin A2 and S100A10 in cancer cells leads to increased levels of plasmin which promote degradation of the extracellular matrix, increased angiogenesis and invasion of the surrounding organs. Although many studies have investigated the functional role of annexin A2 in cancer cells including ovarian cancer, S100A10 has been less studied. We recently demonstrated that high stromal annexin A2 and high cytoplasmic S100A10 expression is associated with a 3.4 fold increased risk of progression and 7.9 fold risk of death in ovarian cancer patients. Other studies have linked S100A10 with multidrug resistance in ovarian cancer, however, no functional studies to date have been performed in ovarian cancer cells. This article reviews the current understanding on S100A10 function in cancer with a particular focus on ovarian cancer.

Keywords: S100A10; annexin A2; plasmin; ovarian cancer; chemotherapy resistance.

1. Introduction

Ovarian cancer is the most lethal gynaecological malignancy with a 5-year survival rate of only about 46% [1]. It is estimated that there will be 1,580 new ovarian cancer cases for 2017 in Australia and the number of women that will succumb to their disease will be around 1047 [2]. The poor survival rate can be attributed to the fact that the cancer has non-specific symptoms and as a result is often diagnosed at stage 3 or 4. High recurrence rates following treatment and subsequent chemotherapy-resistance is another reason [3]. Epithelial ovarian cancers are the most common ovarian malignancies and of those 70% are high-grade serous carcinomas. High grade serous carcinomas have a high chemosensitivity following initial treatment with platinum-based therapies, but 75% of patients will relapse and ultimately die from chemoresistant disease [4]. The development of more effective molecularly targeted therapies to improve survival are therefore urgently needed. The aim of this review is to highlight the current understanding of S100A10 function in cancer cells with particular focus
on ovarian cancer and to discuss the potential for targeting S100A10 in ovarian cancer patients.

2. S100A10 Structure and Function

S100A10, which is also known as p11 belongs to the calcium binding S100 family, which is characterized by EF-hand calcium-binding motifs and consists of over 25 proteins with varying functions [5-7]. The five major functions are to (i) regulate the phosphorylation mediated by protein kinase; (ii) maintain cell shape and motility; (iii) promote calcium homeostasis; (iv) modulate enzyme-activity and (v) influence signaling transduction pathway [8]. All S100 family members, except S100A10 contain a Ca^{2+} binding motif [9]. S100A10 adopts a permanently open confirmation comparable to the Ca^{2+} bound confirmation observed with the other S100 proteins [9]. S100A10 in particular inhibits the phosphorylation of its binding protein annexin A2 [10]. S100A10 functionally acts as a linking protein with the ability to bind transmembrane proteins to annexin A2, thereby aiding the transportation of proteins to the plasma membrane [6].

3. S100A10 Interaction with Annexin A2

S100A10 is located in the plasma membrane, interacts with annexin A2 to form a heterotetramer consisting of 2 subunits of annexin A2 and S100A10 and activates the plasminogen activation pathway [11]. O’Connell and associates (2011) suggest that S100A10 rather than annexin A2 is the plasminogen receptor [12]. The interaction between S100A10 and annexin A2 is thought to protect S100A0 from degradation by the proteasome [9]. Normal endothelial cells utilize S100A10 in the plasminogen activation pathway to convert plasminogen to plasmin, which is vital for wound healing [13]. However, cancer cells produce increased levels of plasmin, which results in the degradation of the extracellular matrix, whilst increasing angiogenesis, and thereby enabling the invasion of surrounding organs or local vasculature [11,14,15]. Increased S100A10 has also been linked to chemotherapy resistance [16,17]. Several studies have suggested that the knockdown of annexin A2 concurrently results in the loss of S100A10 [13,17-20,21]. It is therefore not known if the effects observed in these studies were mediated by annexin A2 or S100A10.

4. S100A10 Expression in Cancers.

The expression of S100A10 in cancer has been widely studied and is summarised in Table 1. S100A10 is expressed in many cancers, such as those of the thyroid, stomach and bowel and the increased expression is generally associated with poorer prognosis and decreased overall survival [17,22,23]. S100A10 plays a significant role in the oncogenesis of lung, fibrosarcoma and colorectal cancers [13]. In kidney cancers S100A10 expression is 2.5 fold higher than in normal kidney tissue [24]. A prostate cancer study has revealed that S100A10 protein is absent in cancer cells yet interestingly prostate tissue cancer cells still express S100A10 mRNA [25]. Strong S100A10 staining is absent in the normal follicular thyroid.
tissue, however, increased levels of S100A10 are present in all anaplastic thyroid carcinomas, which are the most aggressive form of thyroid malignancy, suggesting that S100A10 plays a role in the progression of thyroid carcinomas [26]. Similarly, in colorectal carcinomas, high positive staining of S100A10 is associated with poorer prognosis and reduced overall survival [23]. Overexpression of S100A10 is also associated with poor prognosis in squamous cell carcinoma of the lung [27,28] and pancreatic cancer [29]. Increased S100A10 expression is independently associated with recurrence in colorectal cancer patients [30] and recently been identified as one of a three-gene expression signature to independently predict survival of lung adenocarcinoma patients [31].

Table 1: The expression of S100A10 in cancers.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>S100A10 expression</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>S100A10 is over-expressed in anaplastic thyroid carcinomas compared to normal tissue</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>S100A10 expression is reduced in follicular thyroid carcinomas</td>
<td>[26]</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Increased S100A10 expression is associated with poor prognosis and reduced overall survival in colorectal cancer</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>S100A10 gene expression is associated with tumour recurrence in colon cancer</td>
<td>[30]</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal cell carcinoma have a 2.5-fold higher expression of S100A10 than normal kidney tissue</td>
<td>[24]</td>
</tr>
<tr>
<td>Gastric</td>
<td>S100A10 is overexpressed in gastric cancers</td>
<td>[22]</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>S100A10 is over-expressed in anaplastic large cell lymphoma</td>
<td>[33]</td>
</tr>
<tr>
<td>Prostate</td>
<td>S100A10 expression is lost in prostate cancer tissues</td>
<td>[25]</td>
</tr>
<tr>
<td>Lung</td>
<td>Over-expression of S100A10 is associated with poor prognosis in lung squamous cell carcinoma.</td>
<td>[27,28]</td>
</tr>
<tr>
<td></td>
<td>S100A10 is one a three-gene expression signature to independently predict lung adenocarcinoma survival</td>
<td>[31]</td>
</tr>
</tbody>
</table>
Pancreas  
*S100A10* mRNA and protein is over expressed in pancreatic cancer and predicts patient outcome [29]

5. Functional Role of *S100A10* in Cancer

*S100A10* plays a pro-tumorigenic role by regulating proliferation, cell adhesion, migration, invasion, metastasis and chemotherapy resistance in various malignancies as summarized in Table 2.

5.1 Proliferation

*S100A10* has been linked to proliferation in cancer. Increased cell proliferation of basal-type breast cancer cells is linked to an up-regulation of *S100A10* in those cells compared to non-basal type cells [34]. The knockdown of annexin A2 and concurrent loss of *S100A10* decreased the proliferation of invasive breast cancer cells [21]. *S100A10* has also been shown to be associated with growth of tumours in a knockout mice model [35]. The displacement of *S100A10* from annexin A2 attenuates plasminogen activation, impairing colony formation and growth of lung cancer cells [36].

5.2 Adhesion

Myrvang and coworkers (2013) were able to show that cell surface *S100A10* promotes the adhesion of breast cancer cells to endothelial cells *in vitro* [37]. *S100A10* has also been shown to regulate adhesion of leukemia cells to osteoblasts [16].

5.3 Migration

*S100A10* plays a role in promoting migration of lung cancer cells [36]. Several studies also suggest a direct link between *S100A10* expression and the recruitment and migration of macrophages [34,35,38].

5.4 Invasion

Several studies have shown that *S100A10* plays a role in promoting invasion of cancer cells. *S100A10* was crucial for promoting plasmin production and the invasiveness of colon cancer and fibrosarcoma cells [39,40]. A study by Phipps et al (2011) has also demonstrated that tumour cells of *S100A10* null mice were unable to grow and invade due to the inability to recruit macrophages to the tumour site [35]. The macrophages from *S100A10* knockout mice have been shown to exhibit reduced plasmin dependent invasion [38]. When *S100A10* is displaced from annexin A2 the attenuation of plasminogen activation impairs the invasion of lung cancer cells [36]. The depletion of *S100A10* in kidney (HEK293) and fibroblast (NIH-3T3) cell lines resulted in reduced invasiveness and loss of plasmin production [41]. Acute promyelocytic leukemic cells invasion has recently shown to be inhibited by *S100A10* antibody treatment [42].
5.5 Angiogenesis

The process of forming new blood vessels depends on the presence of S100A10. Phipps et al. (2011) showed that in the S100A10-null mouse model density of blood vessels is decreased by over 50% compared to the control wild-type [35].

5.6 Metastasis

As the hallmark of disease progression, metastasis has been shown to be promoted by the presence of S100A10. S100A10 plays an important role in this process, as overexpression of S100A10 was shown to increase the metastatic burden in HT1080 fibrosarcoma mice [40], whilst the loss of S100A10 reduced the metastatic burden in the HT1080 fibrosarcoma mice [40].

5.7 Therapy resistance

Treatment with inhibitors of the S100A10-annexin A2 interaction, anti-annexin A2 antibodies or knockdown of S100A10 contributes to the increase in sensitivity of leukaemia cancer cells receiving combination treatment of corticosteroids and the chemotherapy drug vincristine [16]. Colorectal cancer cells that overexpressed S100A10 showed reduced sensitivity to oxaplatin [17]. Spijkers-Hagelstein et al. (2013) were able to show that to improve the treatment success of glucocorticoid therapy, the phosphorylation of annexin A2 is required, additionally; this phosphorylation required the binding partner S100A10 and the absence of both annexin A2 and S100A10 reduced the resistance to treatment [43].

Table 2. The functional roles of S100A10 on cancer cells.

<table>
<thead>
<tr>
<th>Function</th>
<th>Observation</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>S100A10 is upregulated in basal-type breast cancer cells compared to the non-basal type cells</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Lewis Lung carcinoma and T241 sarcoma tumours proliferation is inhibited in S100A10 knockout mice</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>S100A10 is downregulated by a knockdown of annexin A2, which decreases the proliferation of breast cancer cell lines</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>The displacement of S100A10 from annexin A2 attenuates plasminogen activation, impairing colony formation and growth of lung cancer cells</td>
<td>[36]</td>
</tr>
<tr>
<td>Adhesion</td>
<td>Surface S100A10 promotes in vitro adhesion of breast cancer cells to endothelial cells</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>S100A10 regulates adhesion of leukaemia cells to osteoblasts.</td>
<td>[16]</td>
</tr>
<tr>
<td><strong>Migration</strong></td>
<td>The displacement of S100A10 from annexin A2 attenuates plasminogen activation and impairs migration of lung cancer cells.</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>· S100A10 expression is associated with the recruitment and migration of macrophages</td>
<td>[34,35,38]</td>
<td></td>
</tr>
<tr>
<td><strong>Invasion</strong></td>
<td>S100A10 in colon cancer cells is crucial for promoting plasmin production and cell invasiveness</td>
<td></td>
</tr>
<tr>
<td>· S100A10 antibodies inhibited invasion of acute promyelocytic leukemia cells</td>
<td>[42]</td>
<td></td>
</tr>
<tr>
<td>· S100A10 expression in fibrosarcoma cells increases plasmin production and the invasiveness of fibrosarcoma cells</td>
<td>[40]</td>
<td></td>
</tr>
<tr>
<td>· The displacement of S100A10 from annexin A2 attenuates plasminogen activation and impairs invasion of lung cancer cells.</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>· Macrophages from S100A10 knockout mice have reduced plasmin dependent invasion</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td><strong>Angiogenesis</strong></td>
<td>S100A10-null mice have reduced blood vessel density compared to wild-type mice.</td>
<td></td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Loss of S100A10 reduces metastatic burden in HT1080 fibrosarcoma mouse model.</td>
<td></td>
</tr>
<tr>
<td>· Overexpression of S100A10 increases metastatic burden in the HT1080 fibrosarcoma mouse model.</td>
<td>[40]</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy resistance</strong></td>
<td>Disruption of both annexin A2 and S100A10 interactions sensitize leukaemia cells to chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>
Overexpression of S100A10 reduces the sensitivity of colorectal cancer cells to oxaliplatin. [17]

Knockdown of S100A10 inhibits annexin a2 phosphorylation and increases sensitivity of acute lymphoblastic leukaemia cells to prednisolone. [43]

6. Role of S100A10 in Ovarian Cancer and Chemotherapy Resistance

To date there have been only three studies which investigated the expression of S100A10 in ovarian cancer. The study by Gillet et al. (2012) including 80 patients treated with carboplatin and paclitaxel, found S100A10 to be one of 11 signature genes whose expression is involved in multidrug resistance [18]. Nymoen et al (2015) found that S100A10 protein expression was related to poor chemotherapy response and associated with shorter overall and progression free survival [44]. Lokman et al. (2016) used 13 publicly available ovarian cancer microarray datasets including 722 serous ovarian cancer patients who had received single platinum treatment and 468 patients with combined platinum-taxane treatment [45]. They showed that high mRNA levels of S100A10 predict reduced overall survival and that high cytoplasmic S100A10 expression was significantly associated with reduced overall survival [45]. Our preliminary immunohistochemistry studies show increased S100A10 expression in chemotherapy resistant disease (Figure 1). Together these findings suggest S100A10 plays an important role in the progression of serous ovarian cancer and chemotherapy resistance. However to date no studies have investigated the functional role of S100A10 in ovarian cancer.

Figure 1. S100A10 immunostaining in matching tissues from serous ovarian cancer patient at diagnosis (a) and recurrence with chemotherapy resistant disease (b). S100A10 antibody (1/1000, BD Biosciences). Scale bar=100µm

7. Summary and Conclusion

In conclusion, S100A10 has been shown to play an important role in promoting protumorigenic behavior in a wide range of cancers. The interaction between S100A10 and its binding partner annexin A2 mediate the production of plasmin, and facilitate the degradation of the extracellular matrix and the invasion into surrounding organs. S100A10 may also play
a key role in development of chemotherapy resistance however the mechanisms involved are poorly understood. A greater understanding of the functional role of S100A10 in ovarian cancer cells could lead to the development of effective strategies to target S100A10 and its interactions with annexin A2, and inhibit progression and chemotherapy resistance in serous ovarian cancer patients.

References
2. AIHW. Summary pages for selected cancers 2017.


treated with 5'fluoruracil-based adjuvant chemotherapy. *Int J Cancer* 2013, 132, 1090-1097.


35. Phipps, K.D.; Surette, A.P.; O’Connell, P.A.; Waisman, D.M. Plasminogen receptor s100a10 is essential for the migration of tumor-promoting macrophages into tumor sites. *Cancer Res* 2011, 71, 6676-6683.


42. Spijkers-Hagelstein, J.A.; Mimoso Pinhancos, S.; Schneider, P.; Pieters, R.; Stam, R.W. Src kinase-induced phosphorylation of annexin a2 mediates glucocorticoid


45. Lokman, N.A.; Pyragius, C.E.; Ruszkiewicz, A.; Oehler, M.K.; Ricciardelli, C. Annexin a2 and s100a10 are independent predictors of serous ovarian cancer outcome. *Transl Res* 2016, 171, 83-95 e81-82.