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REVIEW ARTICLE

S100P: a novel therapeutic target for cancer

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Abstract S100P expression is described in many different cancers, and its expression is associated with drug resistance, metastasis, and poor clinical outcome. S100P is member of the S100 family of small calcium-binding proteins that have been reported to have either intracellular or extracellular functions, or both. Extracellular S100P can bind with the receptor for advanced glycation end products (RAGE) and activate cellular signaling. Through RAGE, S100P has been shown to mediate tumor growth, drug resistance, and metastasis. S100P is specifically expressed in cancer cells in the adult. Therefore, S100P is a useful marker for differentiating cancer cells from normal cells, and can aid in the diagnosis of cancer by cytological examination. The expression of S100P in cancer cells has been related to hypomethylation of the gene. Multiple studies have confirmed the beneficial effects of blocking S100P/RAGE in cancer cells, and different blockers are being developed including small molecules and antagonist peptides. This review summarizes the role and significance of S100P in different cancers.

Keywords S100P · RAGE · Calcium-binding protein · Cancer · Cromolyn

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Introduction

S100P is a 95-amino acid member of the S100 family of protein, purified and characterized from placenta by Becker et al. (1992). The term "S100" was coined to indicate a group of proteins soluble in a 100% saturated ammonium sulfate solution (Moore 1965). The designation "P" was coined to indicate that it was purified first from placenta (Becker et al. 1992). S100P is a member of the large family of S100 calcium-binding proteins which possess consecutive EF hands, where the loop between two α-helices provides the Ca^{2+}-binding site (Zhang et al. 2003). The carboxyl-terminal EF hand has high affinity for Ca^{2+}, whereas the amino-terminal EF hand has low Ca^{2+}-binding affinity (Brodersen et al. 1998; Donato 1999; Réty et al. 1999, 2000). Calcium introduces a conformational change in the S100 molecules, and exposes a hydrophobic surface that is thought to be responsible for binding to target proteins (Schäfer et al. 1995). S100s can act as both intracellular and extracellular signaling molecules (Arumugam et al. 2004; Austermann et al. 2008). Interestingly, the gene for S100P is uniquely located on human chromosome 4q16, while all other S100 genes are localized on human chromosome 1 (Schäfer et al. 1995).

There is increasing evidence suggesting that S100P has a significant role in cancer. This gene has been found to be expressed in several forms of the disease, including pancreas, breast, colon, prostate, and lung, and has been shown to be associated with poor clinical outcomes (Logsdon et al. 2003; Guerreiro Da Silva et al. 2000; Wang et al. 2006; Fuentes et al. 2007; Mousses et al. 2002; Diederichs et al. 2004). The functional role of S100P in different cancer models will be the subject of this review. We will also discuss the potential benefit of developing new therapeutic agents to block the function of S100P on cancer tissue.

S100P in different cancers

Pancreatic cancer

Pancreatic adenocarcinoma (PDA) is arguably the most virulent of all cancers, as more than 95% of patients diagnosed with this disease will die from it, more than half of them within 6 months of diagnosis (Jemal et al. 2008). Radio- and chemo-therapies do not have major effects on pancreatic cancer patient survival. Therefore, efforts have been made to identify novel therapeutic targets. S100P was found to be expressed highly in pancreatic cancer in microarray analysis of gene expression (Logsdon et al. 2003; Crnogorac-Jurcevic et al. 2003; Sato et al. 2004; Missiaglia et al. 2004; Fukushima et al. 2004; Ohuchida et al. 2006). Expression of S100P was observed to be specific to pancreatic cancer cells and was not found in samples of chronic pancreatitis, an inflammatory disease with similar abundant desmoplastic features (Logsdon et al. 2003). The specificity for cancer cells was further confirmed in microdissected pancreatic cancer tissues and isolated primary cultures of cancer and stromal cells (Ohuchida et al. 2006). In fact, S100P expression is one of the most common genetic alterations in pancreatic cancer. The specificity of S100P expression in cancer suggested that it would be a useful histological marker for the disease, and several studies support this concept (Logsdon et al. 2003; Crnogorac-Jurcevic et al. 2003; Sato et al. 2004; Missiaglia et al. 2004; Fukushima et al. 2004; Ohuchida et al. 2006). Of particular significance, recent studies indicated that staining of fine needle aspiration biopsy (FNAB) specimens with an S100P antibody were highly diagnostic for pancreatic cancer (Deng et al. 2008). In this study, S100P positivity was able to confirm the diagnosis of PDA in specimens that had suspicious diagnosis. Thus, S100P may have utility as a histological biomarker for pancreatic cancer.

S100P is also a marker of pre-malignancy. S100P expression is first observed in early stage preneoplastic epithelial neoplasms (PanIN) lesions and levels increase during pancreatic cancer progression from precursor PanIN lesions to invasive adenocarcinoma (Dowen et al. 2005). The presence of S100P in early pancreatic samples, combined with the fact that it is a secreted molecule (Arumugam et al. 2004, 2005), suggests that S100P may be a useful blood biomarker for early detection of pancreatic cancer. However, to date, there are no data available about serum level of S100P in various disease conditions. This is likely due to the lack of a sufficiently sensitive and specific assay. Efforts directed at developing such an assay are currently underway.

The mechanisms responsible for the emergence of S100P gene expression during tumorigenesis are only partially understood. Expression of S100P in pancreatic cancer has been suggested to involve hypomethylation of its gene in pancreatic cancer (Sato et al. 2004). Recently it was reported that S100P expression can be regulated by bone morphogenetic protein (BMP4) in pancreatic duct epithelial cell lines (Hamada et al. 2009). Other studies have suggested that S100P expression is elevated by treatments that reduce Cox-2 activity (Namba et al. 2009). Further studies are warranted to understand the regulation of S100P expression which will aid in developing preventative and therapeutic treatments.

The mechanism, whereby S100P increases the aggressiveness of pancreatic cancer cells, has been the subject of investigation. S100P is secreted from pancreatic cancer cell lines, and extracellular S100P was found to act extracellularly through the receptor of advanced glycation end products (RAGE) (Arumugam et al. 2004, 2005). RAGE is a member of the immunoglobulin superfamily of cell surface molecules that is activated by multiple ligands (Logsdon et al. 2007; Sparvero et al. 2009). RAGE was originally identified based on its ability to bind advanced glycation end-products, which are adducts formed by glycoxidation (Logsdon et al. 2007; Sparvero et al. 2009). Subsequently, it has been observed that RAGE can be activated by a number of ligands including amphoterin, amyloid-β peptide, and members of the S100 family. RAGE activation plays important roles in a variety of disease states, including inflammation, diabetes, Alzheimer's disease, and cancer (Logsdon et al. 2007; Sparvero et al. 2009). Acting through RAGE, S100P was shown to activate MAPkinase and NFκB pathways in pancreatic cancer cell lines. These two pathways are constitutively active in most pancreatic cancer cell lines, and are thought to influence tumor growth and chemotherapeutic drug resistance (Rayet and Gélinas 1999; Mebratu and Tesfaigzi 2009). We found that inhibiting S100P RAGE interactions significantly reduced basal levels of NFκB activation (Arumugam et al. 2006). These data suggest that an autocrine loop involving S100P and RAGE is at least partially responsible for the high level of constitutive NFκB activity observed in pancreatic cancer (Wang et al. 1999).

S100P ectopic expression increased tumor growth and metastasis, and stable silencing of S100P resulted in the reduction of the tumor growth and secondary metastatic volume in models of pancreatic cancer (Arumugam et al. 2005). Silencing of S100P also sensitized the cancer cells to chemotherapeutic drugs (Arumugam et al. 2005, 2006). Thus, the S100P-RAGE autocrine loop appears contributes to drug resistance in some pancreatic cancer cell lines (Arumugam et al. 2005). Efforts to inhibit the interaction of S100P and RAGE as a basis of novel therapies for pancreatic cancer using small molecules (Arumugam et al. 2006) and antagonist peptides (unpublished data) are ongoing.

Breast cancer

Breast cancer is the most common cancer among women, and comprises 26% of all cancers diagnosed in women in the USA (Dizdar and Altundag 2009). S100P was absent in normal breast tissue but detected in hyperplasia, both typical and atypical, as well as in situ and invasive ductal carcinoma (Guerreiro Da Silva et al. 2000). These data indicated that this protein exhibits a strong link with tumor progression in breast cancer. Following this study, others suggested that activation of ERBB2 increases expression of S100P in breast cancer cells (Mackay et al. 2003). As in pancreatic cancer, hypomethylation has been suggested to be involved in the expression of S100P in breast cancer tissue (Sato et al. 2004).

Benign breast diseases represent the vast majority of diagnosis in breast pathology, but only high risk proliferative lesions are the risk to progress into malignant tumor. To date, there is no strong and clear cytological marker available to differentiate patients at risk for this progression. The presence of S100P in the very early stages of breast carcinogenesis (Guerreiro Da Silva et al. 2000) suggest that S100P could be used as a marker to differentiate lesions at high risk of malignant evolution. S100P immunohistochemistry in 155 samples showed a positive association between estrogen receptor (ER) and S100P expression, as well as a clear positive association between S100P and high-risk lesions. The strong association between S100P and ER expression highlights the hypothesis that S100P is involved in the very early stages of breast carcinogenesis (Schor et al. 2006).

Metastasis is a significant problem and creates more mortalities than do primary tumors. Therefore, identifying a metastasis inducer is of prime importance in cancer biology research. Strong evidence supports the role of S100P as an inducer of breast cancer metastasis. Transfection of a vector expressing S100P into a benign, non-metastatic rat mammary cell line caused a threefold increase in local muscle invasion and a significant induction of metastasis in up to 75% of tumor-bearing animals (Wang et al. 2006). S100P immunohistochemistry in 303 breast cancer patients clearly indicated that survival of patients with S100P-positive carcinomas is significantly worse by about sevenfold than for those with negatively stained carcinomas. There is also a significant correlation between intensity of immunohistochemical staining of the carcinoma cells for S100P and decreased survival (Wang et al. 2006). Interestingly, Fos-related antigen 2 (Fra-2), which is known to be involved in the regulation of breast cancer invasion and metastasis, up-regulated the expression of S100P and increased the invasive potential of breast cancer cells (Milde-Langosch et al. 2008).

Prostate cancer

Prostate cancer is a major public health problem, affecting 186,000 men in USA and causing 29,000 deaths each year (Jemal et al. 2008). The frequency of S100P expression in prostate cancer is currently controversial. In one study, S100P staining of a tissue microarray showed that S100P levels were frequently elevated in prostate cancer and strongly correlate with progression to metastatic disease (Mousses et al. 2002). In contrast, in a separate study, Higgins et al. (2007) reported only 2% (256 cases) of prostate carcinoma expressed S100P. Despite the uncertainty of the frequency of S100P expression in prostate tumors, there has developed a strong association between S100P expression and prostate tumor progression and metastasis. Basu et al. (2008), recently reported that over-expression of S100P in PC3 cells promoted cell growth, increased the percentage of S-phase cells, decreased basal apoptosis rate and promoted anchorage independent growth in soft agar and protected against camptothecin-induced apoptosis. They also reported that silencing of S100P in 22Rv1 cells resulted in a prominent cytostatic effect. Furthermore, S100P-overexpressing PC3 cells had a dramatically increased tumor formation compared to controls. This study confirms the oncogenic nature of S100P in prostate cancer and suggests that S100P protein may directly confer resistance to chemotherapy.

The growth and function of normal prostate is dependent on the presence of androgen. As prostate tumors progress there is a loss of androgen-dependent cell growth and the identification of the genes that are regulated by androgens may be of pathological and clinical significance. Based on this idea, a study analyzing gene expression in androgen-dependent and -independent cell lines revealed that S100P is regulated by androgen in prostate cancer cells (Averboukh et al. 1996). Treatment of metastatic prostate cancer with androgen-ablation often elicits dramatic tumor regressions, but the response is rarely complete, making clinical recurrence inevitable with time (Oesterling et al. 1997). Amler et al. (2000) reported that S100P was decreased following androgen-deprivation in androgen-dependant tumors and was subsequently re-expressed in androgen-independent tumors on treatment with androgens. Therefore, in prostate cancer there appears to be a direct relationship between androgens and S100P. Whether these effects of adrogens on S100P expression are restricted to this tissue is currently unknown.

Colon cancer

S100P was found to be up-regulated in doxorubicin resistant colon cancer cells (Bertram et al. 1998). In other studies, S100P was identified as being expressed in flat adenomas in the colon (Kita et al. 2006). Flat adenomas

are associated with a relatively higher potential for malignancy. In another study, S100P was reported to be specifically expressed in colon cancer tissue (Fuentes et al. 2007). In this study, S100P was found to bind with RAGE and activate key signaling pathways, including ERK1/2 and NFκB activity, similar to what was reported in the pancreas (Arumugam et al. 2004, 2005). Thus, it appears that S100P is present in colon cancer, and this may be another site where S100P-based therapy would be useful.

Lung cancer

Distant metastasis is the predominant cause of death in early-stage of non-small cell lung cancer (NSCLC). A comparison of gene expression profiles between early-stage NSCLC patients and those whose cancer ultimately did or did not metastasize during the course of their disease showed that S100P was specifically over-expressed in metastatic tissue. Furthermore, the level of S100P in metastasizing lung tumors correlated with poor patient survival (Diederichs et al. 2004; Kim et al. 2007; Bartling et al. 2007). However, in another study, Rehbein et al. (2008) reported that S100P was up-regulated only in early stages and not in advanced stages of lung adenocarcinoma. Therefore, there is again some disagreement about the expression of S100P in patient samples. In a mouse model of lung cancer, Bulk et al. (2008) reported that over-expression of S100P increased angiogenesis. They found that silencing of S100P by shRNA delivery to the growing tumor drastically reduced the angiogenesis and metastasis (Bulk et al. 2008). Therefore, the bulk of the data support a role of S100P in lung cancer and particularly in metastasis of this disease.

Other cancers

S100P was also reported to be expressed in ovarian tumor (Surowiak et al. 2007), and its expression correlated with un-favorable prognostic outcome (Surowiak et al. 2007). S100P also expressed in leukemia (Tsumura et al. 2009) with unknown functions. In oral cavity squamous cell carcinoma expression of S100P was associated with anoikis resistance (Kupferman et al. 2007). Interestingly, S100P mRNA can be measured in saliva, and aids in the diagnosis of oral cancer (Li et al. 2004). S100P is also expressed in gastric cancer (Shyu et al. 2003; Liang et al. 2007) and appears to function to increase the growth and invasion of the cancer cells (Namba et al. 2009).

S100P: a potential target for cancer treatment

Despite recent advances in understanding the biology of cancer and molecular alterations in tumor pathogenesis, cancer remains a challenge for overall human health (Jemal et al. 2008). Chemo- and radiotherapies are the two most commonly available treatment regimens for most of the cancer apart from surgery. Because of the poor response to these standard forms of therapy, recent efforts have focused on the application of novel, biologically targeted agents aimed at well-known cancer mechanisms. Examples of these approaches include compounds that target vascular endothelial growth factor receptors, e.g., bevacizumab; the epidermal growth factor receptor (EGFR), e.g., cetuximab; the EGFR-activating tyrosine kinase, e.g., erlotinib and gefitinib; and K-ras, e.g., farnesyol transferase inhibitor tipifarnib (Pliarchopoulou and Pectasides 2009). However, most of the early clinical trials with these agents have shown very modest survival advantage compared with standard chemotherapy treatment (Mesa 2006; Grothey and Galanis 2009; Martinelli et al. 2009; Hartmann et al. 2009). Clearly, new targets and therapeutic approaches are needed for this disease. Therapeutic target development requires identification of novel molecules, validation of their functional importance, understanding their mechanisms of action, and strategies for intervention. As reviewed here, S100P has been found to be expressed in a number of important cancers (Logsdon et al. 2003; Guerreiro Da Silva et al. 2000; Wang et al. 2006; Fuentes et al. 2007; Mousses et al. 2002; Diederichs et al. 2004). In nearly all cases, the evidence suggests that S100P increases tumor growth and metastasis and decreases patient survival. Thus, blocking S100P function might be expected to improve responses to therapeutic treatments.

The primary mechanism of action of S100P, at least in the case of pancreatic and colon cancer, is through activation of the cell surface receptor RAGE (Arumugam et al. 2004). RAGE can be activated by a number of ligands, including advanced glycation end-products (AGEs), specific S100 molecules (S100B, S100A12, and S100P), amyloid, and amphoterin (Logsdon et al. 2007; Sparvero et al. 2009). RAGE participates in a number of important pathologic processes besides cancer, including Alzheimer's disease, diabetes, and inflammation (Logsdon et al. 2007; Sparvero et al. 2009). Activation of RAGE by S100P stimulates cellular signaling pathways, including the mitogen-activated protein (MAP) kinase and nuclear factor-B (NFκB) pathways (Arumugam et al. 2004). NFκB signaling may be of particular importance, because elevated NFκB activity is associated with increased resistance to therapies in different cancers (Arlt et al. 2001; Karin et al. 2002). Therefore, interventions that block the ability of S100P to activate RAGE may provide therapeutic benefit.

Recently, the small molecule cromolyn, which is widely used to treat allergic symptoms, was shown to bind with S100P and prevent its activation of RAGE (Arumugam

et al. 2006). Cromolyn also binds to other S100 molecules (Shishibori et al. 1999; Okada et al. 2002). Cromolyn inhibited pancreatic cancer cell function and pancreatic tumor formation in animal models (Arumugam et al. 2006). Cromolyn has been used in humans for many years. However, cromolyn has low oral bioavailability (Leone-Bay et al. 1996). Other anti-allergy drugs have also been reported to bind to members of the S100 family of RAGE ligands (Shishibori et al. 1999; Okada et al. 2002). Epidemiological studies have revealed that prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of cancer. But, in some models up-regulated S100P after celecoxib (NSAIDs) treatment blocks the celecoxib effect. A recent study on gastric cancer cells, either silencing of S100P or cromolyn treatment both improved the effect of celecoxib and supports the concept that cromolyn has clinical value for cancer treatment (Namba et al. 2009).

In recent study, several breast cancer cell lines were found to be completely resistant to the standard chemotherapeutic drug cisplatin in vitro. However, the combination of cisplatin with S100 inhibitors phenothiazine, chlorpromazine or W7 sensitized the drug resistant cell lines to apoptosis (Dairkee et al. 2009). Furthermore, overexpression of S100P was reported to reverse the responses to these drugs. Therefore, the authors suggested that this was due to the ability of these treatments to block S100P function. However, these treatments may have multiple targets, and these types of drug studies can be difficult to interpret. Nonetheless, these data generally suggest S100P as a therapeutic target.

Previously a peptide antagonist for RAGE developed from a COOH-terminal motif in amphoterin that was found to block S100P-mediated function in pancreatic cancer cells (Arumugam et al. 2005). Recently, a number of specific short peptides (10–12 mers) derived from S100P were examined, and some were found to bind with RAGE and block activation of this receptor by several of its ligands (unpublished observation). These peptides are currently being developed as another approach based to block RAGE in cancer.

Conclusion

Existing literature strongly supports the significant role of S100P during the development and progression of different cancers. S100P can be secreted and act through RAGE. What we learned from published studies strongly supports the idea that blocking S100P/RAGE interaction is clinically beneficial; so future studies on clinical trials using S100P/RAGE blockers are necessary to determine whether the experimental evidence can be translated into patient benefit.

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