S100 family signaling network and related proteins in pancreatic cancer (Review)

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Abstract. The occurrence and development of pancreatic cancer is a complex process convoluted by multi-pathogenies, multi-stages and multi-factors. S100 proteins are members of the S100 family that regulate multiple cellular pathways related to pancreatic cancer progression and metastasis. S100 proteins have a broad range of intracellular and extracellular functions, including the regulation of protein phosphorylation and enzyme activity, calcium homeostasis and the regulation of cytoskeletal components and transcriptional factors. S100 proteins interact with receptor for advanced glycation end-products (RAGE), p53 and p21, which play a role in the degradation of the extracellular matrix (ECM) and metastasis, and also interact with cytoskeletal proteins and the plasma membrane in pancreatic cancer progression and metastasis. S100A11 and S100P are significant tumor markers for pancreatic cancer and unfavorable predictors for the prognosis of patients who have undergone surgical resection. Recently, S100A2 has been suggested to be a negative prognostic biomarker in pancreatic cancer, and the expression of S100A6 may be an independent prognostic impact factor. The expression of S100A4 and S100P is associated with drug resistance, differentiation, metastasis and clinical outcome. This review summarizes the role and significance of the S100 family signaling network and related proteins in pancreatic cancer.

Contents

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1. Introduction

The prevention and treatment of pancreatic cancer is a difficult issue worldwide, as pancreatic cancer is associated with higher malignancy and metastatic rates from the early stage of disease (1). More than 95% of patients diagnosed with pancreatic cancer succumb to the disease and half of these patients within six months after diagnosis (2,3). Radio- and chemotherapy do not have major effects on the survival of pancreatic cancer patients (2,4); thus, surgery remains the optimal treatment method. Prognosis mainly depends on early diagnosis and treatment. Therefore, it is of great importance to identify novel diagnostic markers and to explore related proteins involved in signaling pathways associated with the occurence, development and metastasis of pancreatic cancer. S100 proteins interact with multiple molecular targets in both a calcium-dependent and -independent manner (5,6). They regulate multiple cellular pathways that play key roles in pancreatic cancer progression and metastasis (7,8). S100 proteins may thus be early diagnostic biomarkers.

2. The S100 family

The S100 protein family, a multigene calcium-binding family, comprises more than 20 members, each encoded by a separate gene. At least 16 of these genes cluster on chromosome 1q21 (6), known as the epidermal differentiation complex (7,9). In 1965, the first member of the S100 family was purified from bovine brain by Moore (10). Due to its solubility in a 100% saturated solution at neutral pH with ammonium sulfate (11,12), it was termed the 'S100' protein. The S100 protein family is an acidic calcium-modulated protein family of low molecular weight (10-12 kDa), mainly expressed in vertebrates. It shares homology with calmodulin and other EF-hand type calcium-modulated proteins (11). Since then the expression of S100 proteins has been demonstrated in a diverse spectrum of tissues (5).

Structure of S100 proteins. S100 proteins belong to the calcium-binding EF-hand motif superfamily and have the

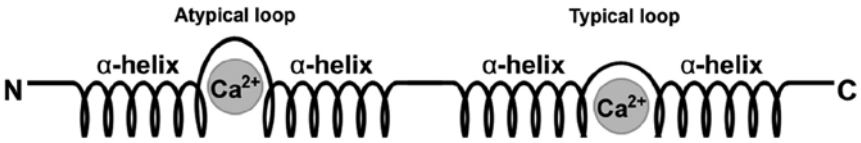

Figure 1. Schematic representation of the secondary structure of an S100 protein.

ability to form homodimers, heterodimers and oligomers (6). Each S100 protein is characterized by the presence of two Ca^{2+}-modulated motifs of the EF-hand type interconnected by an intermediate region which is often referred to as the hinge region, resulting in a helix-loop-helix arrangement (8,11,12) (Fig. 1). S100 proteins have two distinct EF-hands, one common to all EF-hand proteins on the C-terminal portion and the other specific to the family located at the N-terminus. Subsequent to the C-terminal EF-hand region is a stretch of amino acids referred to as the C-terminal extension. Between the two EF-hand domains is the area known as the hinge (7,9). It is the C-terminal extension and hinge areas that have the most variability among the different proteins and hence they are responsible for their specific biological properties (9).

Biological functions of S100 proteins. It is well documented that S100 proteins have a broad range of intracellular and extracellular functions (9). Intracellular functions include the regulation of enzyme activity and protein phosphorylation, calcium homeostasis, the regulation of cytoskeletal components and the regulation of transcriptional factors (7,9,12) (Fig. 2).

Intracellular activities of S100 proteins. S100 proteins play a wide range of roles in cells. The extracellular (9) and intracellular activities of S100 proteins include the regulation of adjusting key enzymes, calcium balance, the composition of the cytoskeleton, protein phosphorylation and dephosphorylation, as well as the regulation of energy metabolism (13,14), cell differentiation and the cell cycle (8,15). Members of the S100 family interact with p53 and these interactions with p53 produce differential effects, depending on the activity of the protein involved (9) (Fig. 3). Both S100A4 and S100B are thought to inhibit p53 phosphorylation, leading to the inhibition of its transcriptional activity, thereby compromising p53 tumor-suppressor activity (12). By contrast, S100A2 promotes p53 transcriptional activity (7). Thus the balanced actions of different S100 proteins within a cell determine its function. Many of the S100 family members are involved in modulating cytoskeletal dynamics. Again they display remarkable diversity of function, exhibiting direct interaction with tubulins, intermediate filaments, actin, myosin and tropomyosin. Some of these proteins have been implicated in mediating metastasis (8), such as S100A1 and S100A11. S100 protein members also play a role in regulating proliferation. In addition, most of the genes of the human S100 proteins are located on human chromosome lq21 (7,9). Once a tumor develops, the genes in this area are easily reorganized and can interfere with the gene expression of S100 (9). Therefore, it is often observed that S100 proteins are accompanied by an abnormal expression in advanced cancer and metastasis. Thus, S100 proteins are closely related to the development and metastasis of a variety of tumors (9).

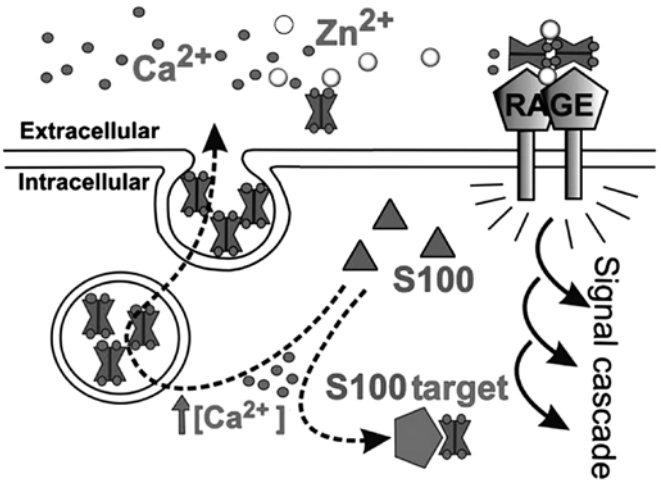

Figure 2. Intra- and extracellular functions of S100 proteins. S100 proteins act as Ca^{2+} sensor proteins in the cell and transmit a signal by Ca^{2+}-dependent binding to a target protein, regulating its biological activity. Furthermore, several S100 proteins are secreted upon a Ca^{2+} signal. Extracellularly in the presence of high concentrations of Ca^{2+} and Zn^{2+}, S100 proteins can form polymers and bind to the receptor, RAGE.

Extracellular roles of S100 proteins. S100 proteins are involved in the extracellular stimulation of neuronal survival, differentiation and astrocyte proliferation, resulting in neuronal death via apoptosis, and stimulate (in some cases) or inhibit (in other cases) the activity of inflammatory cells (9,16). S100 proteins are closely related to a variety of human diseases, such as neurological disorders, cancer, inflammation and heart disease (15).

3. S100 proteins as molecular targets in pancreatic cancer

S100 proteins interact with multiple molecular targets in pancreatic cancer. The key multiple molecular targets include the following:

Extracellular S100 proteins: interaction with receptor for advanced glycation end-products (RAGE). S100 proteins form heterodimers. These complexes display different affinities to target proteins, depending on their oligomerization state (17). This has been demonstrated for p53 and RAGE (8,9,18). Structural analysis of receptor-ligand interaction has indicated that RAGE recognizes three-dimensional structures: one 'V-type' domain and two 'C-type' domains; a short transmembrane domain and a 43-amino acid cytoplasmic tail (19,20). The V-type domain has been found to confer ligand binding. The cytoplasmic tail is required for intracellular signaling, and the V-type domain is responsible for ligand binding. Multiple

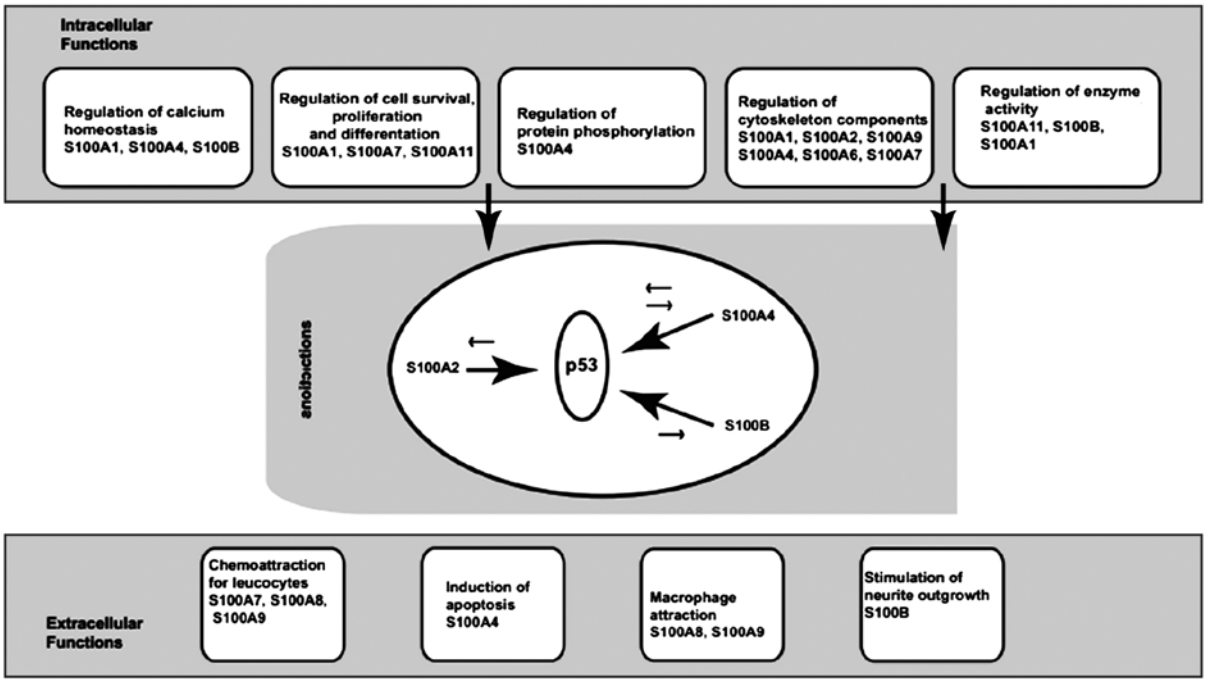

Figure 3. S100 proteins and their functions.

pathways downstream of RAGE have been identified, such as mitogen-activated protein (MAP) kinases, phosphatidylinositol 3-kinase (PI3K), Rho GTPases, nuclear factor (NF)-κB and JAK/STAT (8,21,22). RAGE has been shown to transduce the extracellular effects of S100B (22), S100A4, S100A6 (22), S100A8/A9 (23), S100A11 (24), S100A12, S100A13 and S100P (19,20,25). The activation of RAGE by S100P stimulates cellular signaling pathways, including the MAP kinase and NF-κB pathways (19,22,26). Certain studies have indicated that inhibiting S100P-RAGE interactions significantly reduces the basal levels of NF-κB activity in pancreatic cancer and supports the existence of an autocrine loop involving RAGE ligands and RAGE in pancreatic cancer (2,25,26). S100B and S100A6 have been shown not only to interact with distinct RAGE immunoglobulin domains, but also to exert opposite effects on cell survival (27,28). At similar concentrations, S100B increases cellular proliferation (26), whereas S100A6 triggers apoptosis (29,30). In addition, both S100 proteins induce the formation of reactive oxygen species (ROS); however, S100B recruits PI3K/AKT and NF-κB (31,32), whereas S100A6 activates JNK (30). The study by Arumugam *et al* also showed that S100A4 binding to RAGE was blocked by RAP (25). It has been reported that S100A4 may influence the resistance of pancreatic cancer cells to therapy (16,33).

S100 proteins bind with cytoskeletal proteins and plasma membrane, thereby increasing cell migration. S100 proteins regulate all three major constituents of the cytoplasmic cytoskeleton, i.e. microtubules (MTs), intermediate filaments (IFs) and microfilaments (MFs) (22,34), as well as tropomyosin and myosin (8,35). S100 proteins can exert their effects depending on their interactions with cytoskeletal proteins and the membrane resulting in an enhancement of cell migration (8,9). For example, S100B and S100A1 disassemble cytoplasmic MTs and induce the aggregation of vimentin IFs as a result of *in situ* MT disassembly in triton-cytoskeletons from several cell lines (20). The consequent sequence potentially implicated in S100B binding has been identified in helix H8 of the central portion of tubulin and in its C-terminus, regions considered important for protofilament formation and, hence, for the MT assembly (8,34,36). S100A4 interacts with cytoskeletal elements, such as actin, tubulin and non-muscle tropomyosin, establishing a direct role of S100A4 in regulating cell motility and cytoskeletal rearrangement (16). This suggests that S100A4 plays a possible mechanistic role in cell shape, motility and thus, invasion (12,16). Other studies reported that S100A11 can associate with actin, β-tubulin, IFs and actin organization and Annexin I (37,38). S100A6 interacts with tropomyosin β, Annexin 11 and 2, and the novel binding protein, lamin B1, in pancreatic cancer cells. Hayes *et al* demonstrated that Annexin 2 was concentrated in the dynamic actin-rich protrusions of motile cells and that the siRNA-mediated depletion of Annexin 2 led to loss of protrusive and retractile activity (39). De Graauw *et al* pointed out that the phosphorylation of Annexin 2 was a key event in the remodelling of the actin cytoskeleton during cell spreading (40).

Interaction with p53. p53 is subjected to complex regulation. The biochemical activity of p53 as a transcription factor is adjusted by phosphorylation and acetylation, as well as modulation of protein stability, the degree of oligomerization, nuclear translocation and interactions with other components of the transcriptional machinery (12). The tumor suppressor protein, p53, plays a pivotal role in the maintenance and regulation of normal cellular functions through the induction of cell cycle arrest, DNA repair, or apoptosis in response to a

variety of cellular stress signals and DNA damage (8,12). In response to stress, p53 prevents tumorigenic transformation through the induction of cell cycle arrest or apoptosis (22,41). p53 interacts with other components of the transcriptional machinery (22,42). In unstressed cells, the expression level of p53 tumor suppressor is low (43,44); however, upon stress challenge, p53 is activated by post-translational modifications that increase its stability (45,46). The regulation of protein stability is one of the most effective mechanisms for controlling the function of p53 (9,45). The key to this process is mouse double minute 2 (MDM2), an E3 ligase that targets p53 for ubiquitination. Several S100 proteins, such as S100B (46), S100A1, S100A2 (47), S100A4 (48), S100A6, S100A11 (24,32) and S100A14 (49) have been shown to interact with MDM2. Direct protein-protein interactions between S100 proteins and MDM2 promote the degradation of p53, as has been demonstrated for S100B and S100A4 (12,48,50). This results in the loss of p53-dependent tumor suppressor activities. Elucidating the consequences of the metastasis-promoting activities of S100 proteins on p53-mediated functions, is of great importance in understanding cancer development and metastasis (8,51). It is noteworthy that potential p53-binding sites have been identified in the promoter sequences of several S100 genes, indicating that the metastasis-promoting properties of S100 proteins are not as clear-cut as has been previously suggested. This is due to their interaction with p53-dependent apoptosis (22). This fact may explain why some members of the S100 family are markedly downregulated in malignant cells, in comparison to normal cells (22). Both S100A4 and S100B are thought to inhibit p53 phosphorylation, leading to the inhibition of its transcriptional activity, thereby compromising p53 tumor-suppressor activity (16,41). By contrast, S100A2 promotes p53 transcriptional activity and of note, S100A4 has also been documented to enhance p53-dependent apoptosis (16,47,50). Thus, the balance of actions of different S100 proteins within a cell can determine function (8).

Interaction with p21. p21/WAF1 is also known as cyclin-dependent kinase (CDK) inhibitor 1 or CDK-interacting protein 1. p21/WAF1 is a cell cycle checkpoint, where cells either set about repairing themselves or commit suicide through apoptosis (52,53). The p21/WAF1 protein functions as a regulator of cell cycle progression at the G1 phase by inhibiting cyclin-CDK2 or -CDK1 activity (52,54,55). The expression of its gene is tightly controlled by p53, through which the p21/WAF1 protein mediates p53-dependent cell cycle G1 phase arrest, in response to a variety of stress stimuli (24,55). For example, S100A11 has been shown to be involved since TGF-β induces S100A11 gene expression and translocation into the nucleus, where it interacts with p21/WaF1 (56,57). S100A4 target genes comprise p21/WAF, Bax, thrombospondin-1 and MDM2 (16,58,59).

S100 proteins: role in the degradation of the extracellular matrix (ECM) and metastasis. Angiogenesis is a crucial step in cancer progression, as it supplies the proliferating tumor cells with necessary nutrients and oxygen and at the same time, it provides an escape route for invading tumor cells (60). Matrix metalloproteinases (MMPs) promote metastasis both by degrading the ECM and promoting and maintaining angiogenic characteristics (16). An important factor affecting the motility of cancer cells is the degradation of the ECM (22). S100 proteins have a variety of molecular mechanisms. For example, the metastatic function of S100A4 is associated with its ability to upregulate the expression of several MMPs. S100A4 gene suppression significantly decreases the expression of MMP-9, while the overexpression of the S100A4 gene significantly increases MMP-9 expression (12,16,18). Extracellular S100A4 binds to RAGE, and upregulates MMP-13, MMP-2 and MMP-9 gene expression (19,61), allowing cell invasion and thus promoting metastasis (1,16). Intracellular S100A14 promotes cell motility and invasiveness by regulating the expression and function of MMP-2 in a p53-dependent manner (22,62). p53 transrepresses MMP-2 gene expression and thus enables intracellular S100A14 to effect p53 transactivity and stability, resulting in an enhancement of MMP2 gene expression (22). S100A8/A9 overexpression can also induce the upregulation of MMP-9 in HaCaT keratinocytes. MMP9 gene induction depends on NF-κB activation and intracellular S100A8/A9 has been shown to promote epithelial NADPH oxidases and subsequently, NF-κB activation (63). S100P induces the expression of cathepsin D, an aspartyl protease, which takes part in the proteolytic degradation of the ECM. Hence it increases the invasive potential of the tumor (2,22).

4. S100 protein expression in pancreatic cancer

Multiple proteins of the S100 protein family are closely related to pancreatic cancer, including the following proteins:

S100A2. The S100A2 gene is located on the long arm of Area 2 of chromosome 1. The chromosomal stability of this section is poor, and closely related to tumor development (47,64). S100A2 is often expressed in normal cells and regulated by cell cycle progression and the tumor suppressor gene, p53 (47). The lack of S100A2 has been proven to be associated with the development of numerous human tumors. Since it is absent in the majority of tumor types, S100A2 is very important in normal tissue growth and differentiation (65). Studies have demonstrated that the lack of S100A2 functionality may be due to the selective hypermethylation in the promoter region. In tumor cells, a transcription factor binds to S100A2 promoter, which leads to hypermethylation and, consequently, to the transcriptional silencing of S100A2, thereby rendering it non-reactive with most tumor suppressor genes (65). Ohuchida *et al* microdissected invasive ductal carcinoma (IDC), pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), pancreatitis-affected epithelial (PAE) and normal ductal cells and then studied S100A2 expression by quantitative reverse transcription PCR (qRT-PCR) (27). The analyses revealed that IDC cells expressed higher levels of S100A2 than did IPMN, PAE or normal cells (27). Cell lines from metastatic sites expressed higher levels of S100A2 than those from primary sites. PanIN cells expressed higher levels of S100A2 than normal cells. IDC cells associated with poorly differentiated adenocarcinoma expressed higher levels of S100A2 than did IDC cells without poorly differentiated adenocarcinoma (27). Analyses of formalin-fixed paraffin-embedded (FFPE) samples revealed that the expression levels of S100A2 were higher in samples from patients who survived <1,000 days after surgery

than in those from patients who survived >1,000 days (27). S100A2 may be a marker of tumor progression or prognosis in pancreatic carcinogenesis and pancreatic cancer (65,66). Moreover, S100A2 has recently been suggested to be a negative prognostic biomarker in pancreatic cancer. Biankin *et al* (67) demonstrated that patients with S100A2-negative tumors had a significant survival benefit from pancreatectomy even in the presence of involved surgical margins or lymph node metastasis. S100A2 expression is a good predictor of the response to pancreatectomy for pancreatic cancer. Data suggest that a high S100A2 expression may be a marker of a metastatic phenotype (67,68). The prospective measurement of S100A2 expression in diagnostic biopsy samples has potential clinical utility as a predictive biomarker of response to pancreatectomy and other therapies that target locoregional disease (67,68). These data demonstrate that S100A2 is associated with tumor progression in pancreatic cancer and is a negative prognostic biomarker in pancreatic cancer.

S100A4. The S100A4 protein consists of 101 amino acids, it is an 11-kDa molecular weight protein and exists as non-covalent dimers in the cell and as covalent dimers in the extracellular domain (16,69). In normal lung, kidney, breast, thyroid, pancreas and colon tissue cells, the expression of the S100A4 protein is absent. Studies have shown that the expression of S100A4 protein in pancreatic cancer is significantly higher than in adjacent normal pancreatic tissue, and that the expression of S100A4 in poorly differentiated pancreatic tissue and metastatic pancreatic cancer tissue (66) is significantly higher than that in well-differentiated and non-metastatic pancreatic cancer tissue (16,70). The overexpression of S100A4 protein is associated with hypomethylation of the first intron of the corresponding gene, leading to poor differentiation of pancreatic cancer (71). S100A4 protein overexpression also plays an important role in pancreatic cancer invasion and in the metastasis process (71). Another study demonstrated that S100A4-silenced cells exhibited a marked decrease in migration and invasiveness and increased adhesion, whereas overall proliferation and apoptosis were not overtly altered (1). S100A4 and its downstream factors play important roles in pancreatic cancer invasion. A100A4 silencing can significantly restrain the invasiveness of pancreatic cancer (1). Studies have suggested that the S100A4 protein is an independent prognostic factor of pancreatic cancer which can differentiate pancreatic cancer from lymph node metastasis (68,72,73).

S100A6. The S100A6 gene is a single-copy gene, located on human chromosome lq21, adjacent to ski proto-oncogene (74). S100A6 consists of 90 amino acids. The S100A6 protein may be relevant to pancreatic cancer prognosis (30). Ohuchida *et al* (75,76) analyzed the secretion of S100A6 protein expression in normal pancreatic tissue, PanIN and IDC of the pancreas, and found that the level of S100A6 expression in pancreatic cancer was significantly higher than that in non-cancerous tissue. S100A6 protein expression in cancerous pancreatic juice was significantly higher than that in normal pancreatic juice (35). Vimalachandran *et al* (77) showed that the expression of S100A6 in pancreatic cancer cell nuclei was significantly higher compared with the cytoplasm. Patients with high S100A6 protein expression levels in the nucleus presented with poor prognosis (77). However, the expression level of cytoplasmic S100A6 had no clear association with prognosis. An absence of S100A6 expression was observed during PanIN period. However, as PanIN levels increased, S100A6 protein expression levels gradually increased as well, particularly in the nucleus (77). This indicated that even though S100A6 protein expression in pancreatic cancer is an early event, it is the expression of S100A6 in the nucleus that can be used as an independent prognostic factor. Its high expression levels often precede a poor prognosis. However, there is no evidence to date to support a correlation between S100A6 and the occurrence, differentiation and metastasis of pancreatic cancer (75,76,77).

S100P. S100P is a 95-amino-acid protein whose gene is located on chromosome 4pl6 (42). S100P protein monomers have shown a positive correlation with calcium-dependent binding; whereas the dissociation rate constant was independent of calcium (2). The dimer contact surface and the core area of the hydrophobic amino acid mutation S100P proteins affect polymerization. S100P and its ligand, S100P BPR, coexist in the nucleus. *In situ* hybridization has confirmed the presence of the S100P BPR transcription product in normal pancreatic islet cells and pancreatic ductal adenocarcinoma, which was not expressed in normal pancreatic duct cells (78,79). As shown by qRT-PCR, S100P and S100PBPR were observed in PanIN and pancreatic cancer tissue specimens. These results suggest that S100P and S100PBPR play a role in early pancreatic cancer occurrence (78,79). The expression level of S100P is positively associated with PanIN. The gradual increase in S100P concentration is expressed as PanlN-1, PanIN-2 and PanIN-3. This indicates that S100P plays an important role in the progression from PanIN to invasive ductal adenocarcinoma in the pancreas (78,79). Ohuchida *et al* (80), as well as others examined the expression levels of S100P in various other pancreatic diseases. According to organizational analyses it was found that pancreatic cancer and IPMN tissue expressed significantly higher levels of S100P than did tissue from non-neoplastic pancreas (80,81). Microdissection analyses revealed that IPMN tissue expressed significantly higher levels of S100P than did pancreatic cancer and PanIN tissue (80,81). There was no significant difference between the expression levels of pancreatic cancer and PanIN. In pancreatic juice analyses, S100P expression levels in patients with pancreatic cancer and IPMN were significantly higher than those in patients with pancreatitis (80,81). Thus, neoplastic disease can be effectively distinguished from chronic pancreatitis. S100P has been shown to mediate tumor growth, drug resistance and metastasis through RAGE (26,42,80). Arumugam *et al* (90) demonstrated that elevated expression levels of S100P in mice accelerated the growth rate of pancreatic cancer cells, contrary to its decreased expression levels which delayed cancer cell growth. These studies demonstrate that the S100P protein plays an important role in the incidence of pancreatic cancer. S100P favors the early diagnosis of pancreatic cancer (82). It can be used as an early diagnostic biomarker for pancreatic cancer by detecting its expression levels in the pancreatic juice of the patient. The expression of S100P has been shown to be associated with drug resistance, metastasis and poor clinical outcome (2,83).

S100A11. S100A11 also known as S100C (55), is a member of the family of S100 proteins, and was first discovered in 1989 (55). The S100A11 protein consists of 99 amino acids, with a molecular weight of 11 kDa. Its gene is located on chromosome 1q21 (55,56). The detection of S100A11 RNA expression levels in different tissues has indicated that the highest expression levels are present in the placenta, heart, kidneys and lungs, whereas moderate expression levels are present in skeletal muscle tissues and the lowest in the brain tissue (55,84). Higher levels of S100A11 protein are expressed in duct cells of different tissues, while lower levels are detected in the epithelial cells of the digestive tract. The S100A11 protein is mainly distributed in the nucleus, and the remaining S100A11 protein is distributed in the cytoplasm (55,85). Sakaguchi *et al* (53) reported that S100A11 increases the transcription of p21, a negative regulator of cell growth (66,85). In addition, the expression of several known tumor suppressor genes, including p53 and p16INK4 (86), has been reported to be increased in premalignant lesions; S100A11 expression is elevated in non-invasive neoplasms, such as IPMA and PanIN, but decreased in invasive cancer, such as IDC (87,88). The expression of S100A11 protein has been shown to be significantly decreased within human fibroblasts that have undergone malignant transformation (57). The enforced expression of S100A11 protein has been shown to significantly inhibit the growth of malignant cells. Data suggest that S100A11 may be a tumor suppressor gene (56). Ohuchida *et al* also showed that S100A11 expression increased during the early stages of pancreatic cancer and then decreased as cancer progressed (57). Previous studies have also shown that S100A11 functions as a dual cell growth mediator as it is highly expressed in pancreatic tissue, and its high expression in pancreatic cancer is associated with tumor differentiation and lymph node metastasis (56,84). S100A11 is a significant tumor marker for pancreatic cancer and an unfavorable predictor for the prognosis of patients who have undergone surgical resection (84,89). We consider S100A11 relevant with the occurrence and development of pancreatic cancer. In conclusion, S100A11 is a putative tumor suppressor gene. It can be used as an independent prognostic indicator of pancreatic cancer, particularly for the early diagnosis of pancreatic cancer. S100A11 analysis in pancreatic juice may allow the early detection of pancreatic cancer and the effective screening of patients with high-risk lesions that may progress to pancreatic cancer, such as patients who have a family history of pancreatic cancer or who have chronic pancreatitis (57).

5. Conclusion

S100 proteins interact with RAGE, p53 and p21, play a role in the degradation of the ECM and metastasis, and bind with cytoskeletal proteins and the plasma membrane in pancreatic cancer progression and metastasis. S100A11 and S100P are significant tumor markers for pancreatic cancer and unfavorable predictors for the prognosis of patients who have undergone surgical resection. S100A2 has recently been suggested to be a negative prognostic biomarker in pancreatic cancer. The expression of S100A6 in the nucleus may used as an independent prognostic pancreatic factor. The expression of S100A4 and S100P is associated with drug resistance, differentiation, metastasis and clinical outcome. The data presented in this review suggest that S100 proteins may be used as molecular markers for the early diagnosis, treatment and prognosis of pancreatic cancer.

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