Biochimica et Biophysica Acta 1852 (2015) 2706–2711

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

The role of S100 proteins and their receptor RAGE in pancreatic cancer

Estelle Leclerc *, Stefan W. Vetter

Department of Pharmaceutical Sciences, North Dakota State University, PO Box 6050, Department 2665, Fargo, ND 58108-6050, USA

ARTICLE INFO

Article history:
Received 12 June 2015
Received in revised form 23 September 2015
Accepted 25 September 2015
Available online 3 October 2015

Keywords:
RAGE
S100 proteins
Pancreatic ductal adenocarcinoma

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with low survival rates. Current therapeutic treatments have very poor response rates due to the high inherent chemoresistance of the pancreatic-cancer cells. Recent studies have suggested that the receptor for advanced glycation end products (RAGE) and its S100 protein ligands play important roles in the progression of PDAC. We will discuss the potential role of S100 proteins and their receptor, RAGE, in the development and progression of pancreatic cancer.

© 2015 Elsevier B.V. All rights reserved.

1. Pancreatic ductal adenocarcinoma

Pancreatic cancer is the fourth leading cause of cancer death in the United States with fewer than 6% of patients surviving more than 5 years. Among all pancreatic cancers, the most frequent (85%) one is pancreatic ductal adenocarcinoma (PDAC). PDAC arises from epithelial cells in small pancreatic ducts which alter their morphologies and progress into cells with invasive properties. Several important steps have been identified during disease progression (Fig. 1). The first step is the formation of pancreatic intraepithelial neoplasia (PanIN), or lesions, which progresses from stages 1A, 1B and 2 to stage 3, based on the degree of architectural and nuclear atypia, before reaching an invasive stage (Fig. 1). The lesions that progress to the invasive stage are the sites of multiple genetic and epigenetic alterations. For example, mutations in the *KRAS* gene have been suggested to drive early events in the formation of PanIN, whereas mutations in the $P16^{INK4a}$, *P53* and *SMAD4* genes have been associated with later events and the acquisition of invasiveness (Fig. 1) [1].

For many years, pancreatic-cancer patients with metastatic disease only had one chemotherapeutic option, a monotherapy with gemcitabine, which was the first drug to be FDA-approved for the treatment of pancreatic cancer. However, new combination therapies have recently been tested in clinical trials and have led to improved overall survival rates. These new treatment options include a combination of gemcitabine with the mitotic inhibitor paclitaxel, which is formulated as albumin-based nanoparticles. Another option consists of a multi-drug combination called folfirinox, which includes two cytotoxic drugs, 5-fluorouracil and oxaliplatin; the topoisomerase inhibitor irinotecan; and an adjuvant drug, folinic acid [1]. Despite showing improved overall response rates, these new combinations are also accompanied with toxic adverse effects, such as severe cytopenias, diarrhea and neutropenic fevers, which can limit their usage in patients [1].

Despite the recent advances with combination-drug therapies, pancreatic cancer still remains difficult to treat because of the pancreatic tumors' high chemoresistance, resulting from molecular mechanisms, such as deficiencies in nucleoside transporters or deoxycytidine kinase activity, as well as from mechanical properties caused by strong desmoplasia, poor vascularization and high interstitial fluid pressure in the tumor [1]. To overcome the chemoresistance problem, novel therapeutic strategies are currently being tested in pre-clinical and clinical trials; these studies focus on improving the drug delivery to and specific targeting of both the tumor cells and the tumor's micro-environment [1].

Recent studies suggest that the receptor for advanced glycation end products (RAGE) could be a key player in the progression of pancreatic cancer and could be a potential therapeutic target (Fig. 1) [2]. Among other ligands, RAGE can be activated by several members of the S100 protein family [3]. We will discuss evidence supporting a role for RAGE and its S100 protein ligands in the progression of pancreatic ductal adenocarcinoma.

2. The receptor for advanced glycation end products (RAGE)

2.1. The physiological role of RAGE

RAGE is a cell-surface receptor from the large family of immunoglobulin-like receptors. Although RAGE is not essential for life, *in vivo* studies suggest that RAGE contributes to auditory sensitivity in mice; RAGE plays a role in certain types of pulmonary fibrosis, innate

* Corresponding author.
E-mail address: Estelle.Leclerc@ndsu.edu (E. Leclerc).

http://dx.doi.org/10.1016/j.bbadis.2015.09.022
0925-4439/© 2015 Elsevier B.V. All rights reserved.

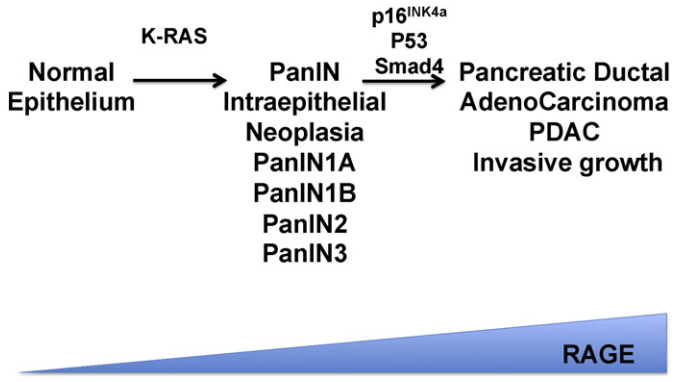

Fig. 1. Important stages in the development of pancreatic ductal adenocarcinoma (PDAC). PDAC arises from genetic and epigenetic changes in epithelial cells of pancreatic ducts. Four main stages (1A, 1B, 2 and 3) of intraepithelial neoplasia (PanIN), or lesions, have been described. These lesions can progress into invasive PDAC. Studies have identified important genes (KRAS, *P16I*^{NK4A}, *P53* and *SMAD4*) that are responsible for the phenotypic changes with PDAC. Recent studies have also shown that RAGE expression increases significantly during PDAC progression [2].

immune responses, peripheral nerve regeneration, osteoclast maturation and myogenesis following acute skeletal muscle injury. The role of RAGE on the pancreas' homeostasis is still poorly understood, however, increasing evidence suggests that RAGE contributes to the progression of pancreatic ductal adenocarcinoma.

2.2. Ligands of RAGE

RAGE was first identified as a receptor for a class of compounds named advanced glycation end products (AGEs). AGEs are formed as a result of the reaction between carbonyl groups of carbohydrates and amino groups of proteins. AGEs are found in multiple types of disease tissues, such as cancer tissues, the brain of Alzheimer's disease patients or the vasculatures of diabetic patients [4].

Besides AGEs, RAGE also binds to other structurally unrelated ligands, such as amyloid-forming peptides and proteins, the high mobility group box 1 protein (HMGB1), the complement receptor macrophage-1 antigen (Mac-1) and S100 proteins [3]. In recent years, new types of RAGE ligands, including the C3a and C1q complement proteins, phosphatidylserine, heparan sulfate, and DNA and RNAs, have been identified.

2.3. RAGE isoforms

Structurally, RAGE belongs to the immunoglobulin receptor superfamily, with the extracellular part containing three immunoglobulin-like domains: one variable-like (V) and two constant-like (C) domains. In addition to this extracellular VC1C2 part, the full-length RAGE isoform also possesses a short 35-residue-long transmembrane domain that anchors the receptor to the cell and an intracellular domain (40 amino acids) that is responsible for signal transduction [5].

Besides full-length RAGE, other isoforms of RAGE that lack specific domains, such as the V, transmembrane or intracellular domains, have been described [6]. An important isoform is the soluble form of RAGE (sRAGE). sRAGE can be generated through two mechanisms, splicing events or shedding by proteases [6]. The physiological function of these non-full-length RAGE isoforms is being debated. The soluble form of RAGE has been suggested to play the role of a decoy receptor and to bind to RAGE ligands. However, RAGE is present at picomolar concentrations in the circulation; this concentration does not allow RAGE to form complexes with all potential RAGE ligands that may be present at nanomolar concentrations. Recently, it was suggested that the soluble form of RAGE could act through the formation of a non-functional complex with a full-length RAGE isoform [5].

2.4. RAGE structure and signaling

At the cell surface, in the absence of ligands, RAGE has been shown to exist as a homodimer. Binding the ligand to RAGE has been suggested to trigger the formation of larger oligomeric forms, and several models for the RAGE/ligand complexes have been proposed [5].

When RAGE is engaged by its ligands, multiple signaling pathways may be activated in a ligand-dependent manner. These signaling pathways include the PI3K/Akt pathway; several mitogen-activated protein kinase (MAPK) pathways involving Erk1/2, p38, and JNK; and other pathways involving small GTPases, such as p21-Ras, Rac-1, or cdc42. RAGE engagement by its ligands often leads to the activation of several transcription factors, such as NF-κB, AP-1, STAT-3 and CREB. Because the RAGE gene is under the control of NF-κB, the engagement of RAGE by its ligands results in amplified RAGE activation in a positive feedback loop [4].

2.5. RAGE in pancreatic cancer

Growing evidence suggests that RAGE participates in the progression of pancreatic cancer. Early studies showed a positive correlation between the RAGE level and the metastatic properties of several pancreatic-cancer cells. Later, independent gene-profiling studies of human pancreatic-tumor tissues showed that two RAGE ligands, S100P and S100A6, were strongly expressed in tumor samples when compared with the control-tissue samples. Epigenetic modifications, such as aberrant gene hypomethylation, of S100P were also associated with increased tumor progression in pancreatic-tumor tissues. In a series of studies, the Logdson group demonstrated that blocking the RAGE/S100P interaction with either a S100P-derived antagonistic peptide or the small molecule S100P-binding drug cromolyn resulted in reduced growth, invasiveness and viability for the pancreatic-cancer cell lines as well as reduced tumor growth and metastasis formation in orthotopic mouse models of pancreatic cancer [7]. The role of RAGE in PDAC was also strongly supported by the observation that, in a *KRAS* mouse model of PDAC, animals lacking RAGE (Pdx1-Cre; LSL-Kras (G12D/+); RAGE (−/−)) experienced significant reductions in the number of early pancreatic PanIN lesions and in pancreatic-cancer tumor growth, and exhibited longer median survivals compared to the control mice [2]. At the molecular level, Kang et al. showed that RAGE promoted cell survival through increased autophagy and reduced apoptosis (Fig. 2A). In a different study, these authors demonstrated that RAGE contributed significantly to resistance to chemo- and radiotherapy through the release of HMGB1 by dying cells, resulting in sustained activation of RAGE and cell survival through a positive feedback loop involving NF-κB (Fig. 2A). The HMGB1 −/RAGE axis was also shown to control the bioenergetics of pancreatic-cancer cells [8].

RAGE signaling from stromal cells could significantly contribute to tumor development. Indeed, RAGE is expressed in many cells that form the tumor environment, such as endothelial cells, fibroblasts, myofibroblasts, T cells and myeloid-derived suppressor cells [4]. Among these cells, tumor-associated myofibroblasts have been shown to be responsible for the desmoplastic reactions that are characteristic of pancreatic tumors. Because of its expression in both cancer and stromal cells, RAGE appears to be a promising therapeutic target for pancreatic cancer.

3. S100 proteins

Calcium plays important roles in many cellular processes, such as cell proliferation and cell death, and alterations in the calcium levels and signaling have been observed in cancer cells. Inside the cells, calcium-level differences can result from changes in the calcium spikes within the cells due to variations in calcium influx, efflux and release from the intracellular stores. In many cell types, the store-operated calcium channels (SOC), ORAI1 and STIM1, play major roles in regulating

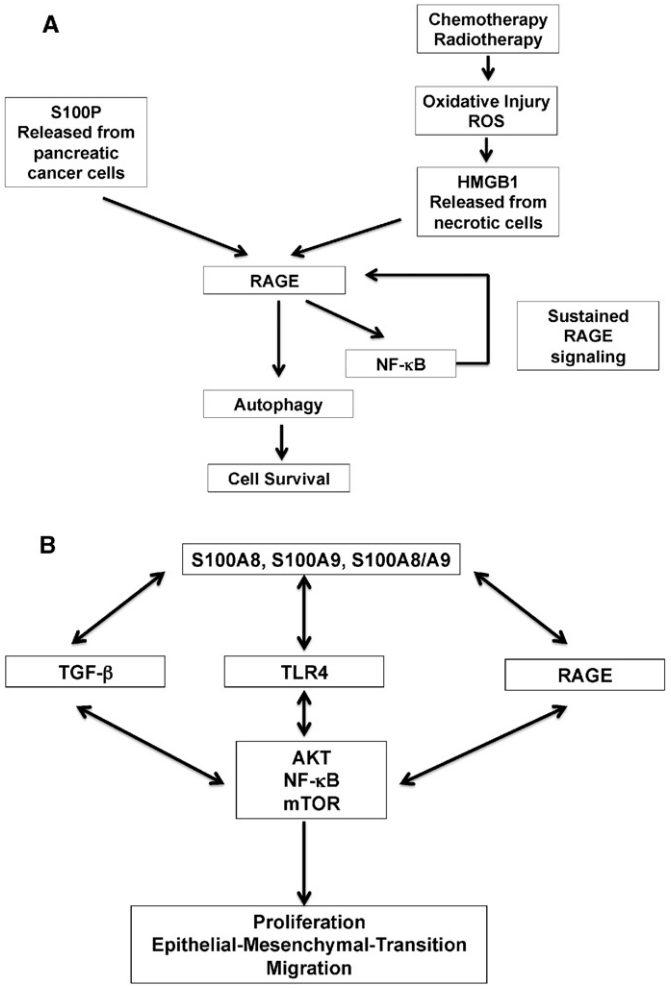

Fig. 2. A: RAGE signaling in pancreatic cancer. In pancreatic-cancer cells, RAGE promotes autophagy, resulting in higher cell survival and sustained RAGE activation through a NF-κB dependent, positive feedback loop. RAGE can be activated by several ligands, including S100P, which is produced by pancreatic-cancer cells, and HMGB1, which is released from dying pancreatic cells following chemo- or radiotherapy. B: Proposed signaling mechanisms of S100A8/A9 in pancreatic-cancer cells. S100A8/A9 could interact with RAGE, leading to the activation of MAP kinases and NF-κB signaling. Depending on the status of Smad4 in the cells, S100A8/A9 has been shown to activate differentially AKT, NF-κB and the mTOR signaling pathway. S100A9 may form a heterocomplex with TGF-β, resulting in modulating the TGF-β signaling pathway. S100A9 could also promote tumor growth through the engagement of TLR4, as demonstrated in prostate tumors.

calcium spikes. In pancreatic adenocarcinoma cell lines, Kondratska et al. recently showed that ORAI1 and STIM1 possessed additional pro-survival and anti-apoptotic roles, and were up-regulated following treatments with the cytotoxic drugs gemcitabine and 5-fluorouracil [9].

Inside cells, changes in the calcium levels are sensed by calcium-binding proteins, such as S100 proteins. These proteins form a family that currently has 24 members [3]. The S100 genes of the A series (*S100A1* to *S100A16*) are located in a region of chromosome 1 which is prone to rearrangements, linking these S100 proteins with cancer [3]. The S100 proteins bind calcium with moderate micromolar affinity (Kd), and certain S100 proteins also bind zinc and copper [3]. Because of these moderate calcium-binding affinities, in resting intracellular conditions, S100 proteins are in the inactive conformation. However, following calcium spikes, the intracellular calcium concentration increases sufficiently to chelate the S100 proteins, resulting in conformational rearrangements that allow them to interact with their target proteins. These targets can be S100 specific or shared with other S100 proteins [10].

In recent years, there has been a growing interest to understand how S100 proteins contribute to the progression of human cancers (see the following reviews [11,12]). In this mini-review, we focus on S100 proteins with extracellular functions, thus we specifically examine how S100A2, S100A4, S100A6, S100A8/A9, S100A11 and S100P contribute to the progression of pancreatic cancer.

3.1. S100A2

Although S100A2 is mainly a nuclear protein, it translocates to the cytoplasm and has been shown to be secreted into the extracellular milieu by kidney's epithelial cells. We therefore briefly discuss the role of S100A2 as a potential extracellular RAGE ligand in pancreatic cancer. S100A2 appears to have a complex role in cancer with either a tumor-suppressor role, such as in prostate, oral, lung and breast cancers, or as a tumor promoter in others, including esophageal squamous carcinoma, gastric and ovarian cancer [3,11,12].

In several studies, S100A2 has been reported to be up-regulated in pancreatic-cancer tissues, and recent clinical data suggest S100A2 to be a predictive biomarker for pancreatic-cancer patients undergoing a pancreatectomy or being treated with adjuvant therapy [13,14]. For patients treated with adjuvant therapy, high levels of S100A2 correlated with high overall survival [13], whereas for patients who had a pancreatectomy, low levels of S100A2 were shown to be predictive of better overall survival rates after surgery, suggesting the complex roles of S100A2 in cancer progression.

Despite the fact that S100A2 possesses mainly nuclear targets, such as the tumor-suppressor p53 protein [3,11,12], we recently showed that, *in vitro*, S100A2 can interact with RAGE [15]. This interaction still needs to be confirmed *in vivo*. Depending upon the signaling pathways activated by S100A2/RAGE in pancreatic-cancer cells, S100A2 could act as either a tumor promoter or a tumor suppressor.

3.2. S100A4

S100A4 was identified from a highly metastatic mammary carcinoma cell line and was, hence, named metastasin. Later studies showed that, when S100A4 was overexpressed in cancer-cell lines, the cells exhibited increased invasiveness and motility [3]. In addition, highly metastatic mammary carcinoma cells showed delayed tumor growth when implanted in S100A4 (−/−) mice, compared to their growth in wild-type mice, further supporting the important role of S100A4 for tumor growth. In a mouse model, S100A4 was shown to participate in the homing of breast-cancer cells to the animal's bones [16]. Strong correlations were found between the level of S100A4 and the prognosis for patients carrying tumors of esophageal squamous cell carcinoma, non-small cell lung and gastric cancers, melanoma, prostate adenocarcinoma and bladder cancer [3,11,12].

In pancreatic cancer, S100A4 was overexpressed in a panel of 21 pancreatic-cancer cells with levels of S100A4 varying by about 1000-fold among cell lines. In cell lines (AsPC-1 and MIA PaCa-2) expressing the highest levels of S100A4, suppressing the S100A4 expression resulted in cell apoptosis and decreased motility [17]. For the two cell lines expressing the lowest level of S100A4 (PCI-35 and -43), forced expression of this S100 protein resulted in increased cell motility without changing the proliferation or invasion properties [17]. Increased S100A4 levels were also associated with chemoresistance and radioresistance in pancreatic-cancer cell lines [18].

Several clinical studies have found a correlation among the expression level of S100A4, the invasive properties of the pancreatic tumors and the patients' prognosis [19,20]. Although performed with small patient cohorts, these studies suggest that S100A4 could become a useful prognostic marker for pancreatic-cancer patients.

S100A4 can exert intracellular and extracellular functions, all relevant to cancer progression. The intracellular targets of S100A4 include p53, non-muscle myosin, F-actin and tropomyosin [3,11,12]. Extracellular

S100A4 has been found to interact with at least two targets: annexin II and RAGE. The interaction of S100A4 with annexin II has been associated with enhanced mechanisms of angiogenesis, such as the formation of capillary-like tubes by endothelial cells. Angiogenesis is an important part of tumor development, and other studies also support the role of S100A4 in this process [3,11,12]. S100A4 has also been shown to interact with RAGE *in vitro* [15] as well as to enhance the cells' motility, metastases formation and tumorigenesis in a RAGE-dependent manner in a variety of cells and tissues, including colon- and prostate-cancer cells as well as melanoma tissues [21–23]. It has not been demonstrated that S100A4 triggers RAGE-dependent signaling in pancreatic-cancer cells or tumors. At the molecular level, S100A4 expression has been shown to be regulated by the sonic hedgehog–GLi1 signaling pathway (Fig. 3) [24], which plays an important role in pancreatic ductal adenocarcinoma, and by the dual Src–FAK signaling pathway [25].

3.3. S100A6

S100A6 is another member of the S100 family with a relevance to cancer. S100A6 was initially identified from fibroblasts and has since been found to be abundant in many other cell types, including epithelial cells, neurons, glial cells, smooth-muscle cells, cardiac myocytes, platelets and lymphocytes [3,11,12]. S100A6 is up-regulated in a large number of cancer tissues that include colorectal cancer, hepatocellular carcinoma, melanoma as well as lung, gastric and pancreatic cancer [3,11,12].

Two early comprehensive gene-profiling studies about pancreatic adenocarcinoma and pancreatitis tissues showed several genes specifically up-regulated in pancreatic-cancer tissue; these genes included S100A6 and S100P. In recent studies, S100A6 was shown to be a potential diagnostic marker of pancreatic ductal adenocarcinoma [26]. In Panc-1 cells, the overexpression of S100A6 was shown to result in increased migration and invasion in a β-catenin-dependent manner, thereby influencing the epithelial to mesenchymal transition processes [27].

S100A6 possesses both intracellular and extracellular targets. The intracellular targets have been reviewed elsewhere [3,11,12]. As an extracellular ligand, S100A6 has been shown to interact with and signal through RAGE [15,28] and to interact with the integrin beta 1 receptor [29]. Whether the effects of S100A6 in PDAC are mediated by RAGE is currently unknown.

3.4. S100P

S100P was initially identified from placental tissue, hence its name [3]. Besides the placenta, S100P is also found in significant levels in epithelial cells of the stomach [3]. Its expression significantly increases in many solid tumors, including ovarian, prostate, gastric, colorectal, breast and pancreatic carcinomas [3,30]. S100P is clinically used as a diagnostic marker of pancreatic ductal adenocarcinoma [31,32].

S100P interacts with several intracellular and extracellular target proteins. Intracellular targets include ezrin, the Ras GTPase activating-like protein1 (IQGAP1) and a protein named the S100P binding protein (S100PBP), all relevant with pancreatic cancer [3,11,12].

Extracellular S100P was shown to bind to RAGE [33] and to stimulate cell-growth survival and invasion (Fig. 2A) [30]. As a result, several RAGE/S100P inhibitors were developed and used to block RAGE-dependent, pancreatic-cancer cell or tumor growth [7,30,34–37]. A S100P-derived peptide, which blocks the RAGE/S100P interaction, inhibited pancreatic-tumor growth and metastasis formation in a pancreatic ductal adenocarcinoma mouse model [30,34]. Different forms of cromolyn, 5-methyl cromolyn and cromolyn encapsulated into liposomes [35], were shown to reduce pancreatic-tumor growth in mice [7,36]. Recently, Dakhel et al. showed that monoclonal antibodies against S100P could also reduce pancreatic-cancer cell growth and metastasis formation in a xenograft mouse model [37].

3.5. S100A8 and S100A9

S100A8 and S100A9 are mainly expressed as S100A8/A9 heterodimers [3]. S100A8/A9 are often referred to as cytokines because, in certain inflammatory conditions, they are abundantly secreted by immune cells, specifically neutrophils [3]. S100A8/A9 have also been shown to be expressed by tumor and non-tumor cells in cancer tissues and to modulate tumor growth and metastasis [3].

Extracellular S100A8 and S100A9 homodimers or S100A8/A9 heterodimers have been shown to interact with several cell-surface molecules, including TLR-4; EMMPRIN; the scavenging receptor, CD36; and

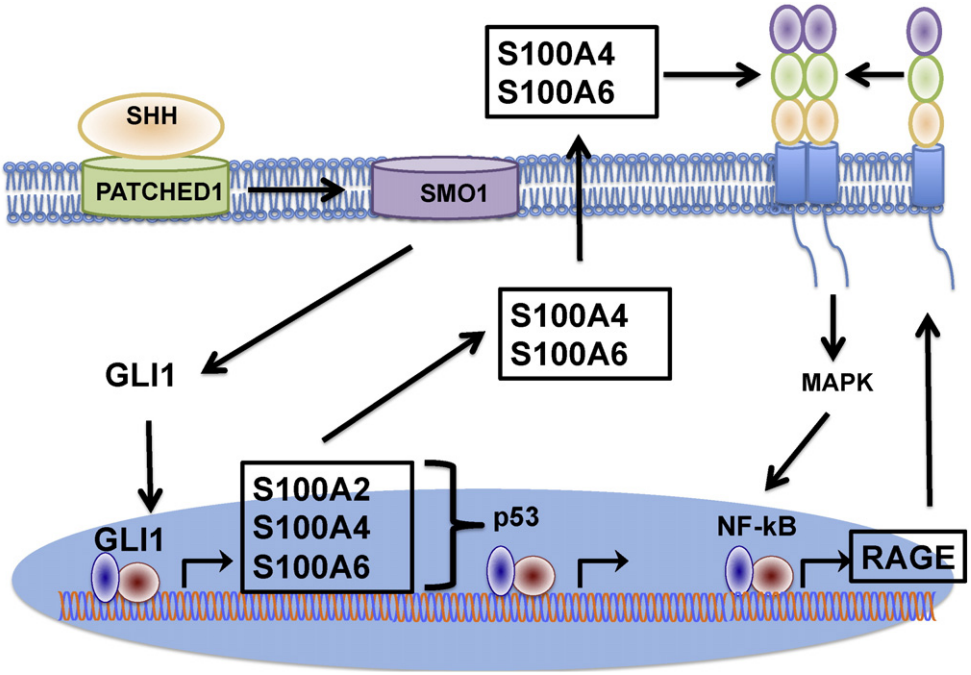

Fig. 3. Signaling of S100A2, S100A4 and S100A6 in pancreatic-cancer cells.

RAGE. For example, the activation of RAGE by S100A8/A9 has been shown to promote tumorigenesis in a colitis-induced colon-cancer mouse model as well as to increase the proliferation of colon- and breast-cancer cells [3,11,12,38]. In the lungs, S100A8 has been shown to favor the homing of metastatic cells by locally enhancing vascular permeability [39].

S100A8 and S100A9 were shown to contribute to pancreatic-cancer progression. In one study, higher levels of S100A8 were found in pancreatic ductal adenocarcinoma compared to normal and pancreatitis tissues. A subsequent proteomic study revealed that, in pancreatic tumors, the level of both S100A8 and S100A9 varied according to the expression level of the tumor-suppressor Smad4 protein [40]. In another study, a detailed analysis of the signaling pathways regulated by S100A8 and S100A9 in pancreatic tumors showed different modes of NF-κB and AKT regulation, depending on the expression of Smad4 [41]. Smad4 is a key transcription factor in the TGF-β signaling pathways, 1 of 12 core pathways that is deregulated in pancreatic adenocarcinomas [42]. Using pancreatic-cancer cells (Panc-1) in a culture, Ang et al. showed that, when stimulating the cells with recombinant S100A8, S100A9 resulted in increased cell migration [43] and that the increased migration by S100A8 could be reverted when Smad4 was knocked down by siRNA [43]. In a different study, it was shown that deleting Smad4 in pancreatic-cancer cells resulted in a higher expression of S100A8/A9, leading to increased levels of myeloid-derived suppressor cells (MDSCs) and advanced stages of PDAC [44]. In addition, in prostate cancer, S100A9 was shown to promote tumor growth through the activation of TLR4 [45]. Signaling crosstalks among the RAGE, TLR4, TGF-β and Smad4 pathways could, thus, take place in pancreatic-cancer cells (Fig. 2B) [46]. S100A8 and S100A9 measured in the pancreatic main-duct fluid were suggested to serve as prognostic biomarkers [47].

3.6. S100A11

S100A11 is another member of the S100 protein family that is present in a large number of tissues but is more abundantly expressed in smooth muscle. S100A11 was studied, in detail, in chondrocytes where it acted as a catabolic cytokine. Like S100A2, S100A11 was shown to play the role of a tumor suppressor, such as in bladder or renal carcinoma, or as a tumor promoter, such as in pancreatic cancer [3,11,12]. It was shown that the levels of S100A11 increased during the early stages of pancreatic cancer but decreased during the advanced stages of pancreatic cancer [48]. Interestingly, it was also reported that high expression levels of S100A11 in pancreatic ductal adenocarcinoma are associated with an unfavorable prognosis for patients who had undergone surgical resection [49]. Several target proteins were described for S100A11: the tumor-suppressor p53 protein; members of the annexin family (annexin 1 and 2); the DNA repair protein, RAD54B; and RAGE [3,11,12]. Although S100A11 was associated with RAGE signaling in chondrocytes, a direct interaction between RAGE and S100A11 as well as a role for S100A11/RAGE signaling in PDAC have yet to be demonstrated.

4. Conclusion and therapeutic approaches

Recently, RAGE has emerged as a new therapeutic target. Several small molecular inhibitors, such as TTP488, have been developed [50]. In pancreatic cancer, current efforts aim at specifically targeting the RAGE/S100P interaction. The small molecule cromolyn and its derivatives have shown encouraging results in mouse models of the disease [7,36]. A S100P-derived peptide has also shown efficacy in mice [30,34]. Another therapeutic approach consists of targeting S100 proteins with monoclonal antibodies. Recent studies have shown that treatment with anti-S100P or anti-S100A4 antibodies could effectively reduce the tumor's growth and the formation of metastases in mouse models of pancreatic cancer [37]. In conclusion, blocking the RAGE/S100 ligand axis appears to be a promising, new therapeutic approach to treat pancreatic ductal adenocarcinoma.

In pancreatic cancer, the expression of S100A2, S100A4 and S100A6 has been shown to be regulated by the transcription factor, GLi1, an important downstream element of the sonic hedgehog pathway that has been implicated in pancreatic ductal adenocarcinoma. The sonic hedgehog homolog (SHH) protein binds to its receptor, Patched (PTCH1), which leads to the release of inhibition of the receptor smothered (SMO) and the translocation to the nucleus of the glioma-associated oncogene homolog 1 (GLI1) transcription factor. GLI1 controls the expression of S100A2, S100A4 and S100A6. These S100 proteins can interact with p53 and can also modulate its transcriptional activity. Alternatively, S100 proteins can be released in the extracellular media and interact with RAGE at the cell surface. RAGE engagement by the S100 proteins can lead to the activation of several MAP kinases, resulting in the transcription of NF-κB regulated genes, including RAGE.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

This work was supported, in part, by a Pilot Project Award to EL at the Center for Protease Research (NIH-COBRE grant # 5P30GM103332) and by the College of Health Professions at North Dakota State University.

References

[1] E. Fokas, E. O'Neill, A. Gordon-Weeks, S. Mukherjee, W.G. McKenna, R.J. Muschel, Pancreatic ductal adenocarcinoma: from genetics to biology to radiobiology to oncoimmunology and all the way back to the clinic, Biochim. Biophys. Acta 1855 (2015) 61–82.
[2] J. DiNorcia, M.K. Lee, D.N. Moroziewicz, M. Winner, P. Suman, F. Bao, H.E. Remotti, Y.S. Zou, S.F. Yan, W. Qiu, G.H. Su, A.M. Schmidt, J.D. Allendorf, RAGE gene deletion inhibits the development and progression of ductal neoplasia and prolongs survival in a murine model of pancreatic cancer, J. Gastrointest. Surg. 16 (2012) 104–112.
[3] R. Donato, B.R. Cannon, G. Sorci, F. Riuzzi, K. Hsu, D.J. Weber, C.L. Geczy, Functions of S100 proteins, Curr. Mol. Med. 13 (2013) 24–57.
[4] A. Riehl, J. Nemeth, P. Angel, J. Hess, The receptor RAGE: bridging inflammation and cancer, Cell Commun. Signal 7 (2009) 12.
[5] G. Fritz, RAGE: a single receptor fits multiple ligands, Trends Biochem. Sci. 36 (2011) 625–632.
[6] B.I. Hudson, A.M. Carter, E. Harja, A.Z. Kalea, M. Arriero, H. Yang, P.J. Grant, A.M. Schmidt, Identification, classification, and expression of RAGE gene splice variants, FASEB J. 22 (2008) 1572–1580.
[7] T. Arumugam, V. Ramachandran, D. Sun, Z. Peng, A. Pal, D.S. Maxwell, W.G. Bornmann, C.D. Logsdon, Designing and developing S100P inhibitor 5-methyl cromolyn for pancreatic cancer therapy, Mol. Cancer Ther. 12 (2013) 654–662.
[8] R. Kang, D. Tang, N.E. Schapiro, T. Loux, K.M. Livesey, T.R. Billiar, H. Wang, B. Van Houten, M.T. Lotze, H.J. Zeh, The HMGB1/RAGE inflammatory pathway promotes pancreatic tumor growth by regulating mitochondrial bioenergetics, Oncogene 33 (2014) 567–577.
[9] K. Kondratska, A. Kondratskyi, M. Yassine, L. Lemonnier, G. Lepage, A. Morabito, R. Skryma, N. Prevarskaya, Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma, Biochim. Biophys. Acta 1843 (2014) 2263–2269.
[10] G. Fritz, C.W. Heizmann, 3D structures of the calcium and zinc binding s100 proteins, in: J.W. Sons (Ed.), Encyclopedia of Inorganic and Bioinorganic Chemistry, Wiley Online Library, 2011.
[11] A.R. Bresnick, D.J. Weber, D.B. Zimmer, S100 proteins in cancer, Nat. Rev. Cancer 15 (2015) 96–109.
[12] S.R. Gross, C.G. Sin, R. Barraclough, P.S. Rudland, Joining S100 proteins and migration: for better or for worse, in sickness and in health, Cell. Mol. Life Sci. 71 (2014) 1551–1579.
[13] J.B. Bachet, R. Marechal, P. Demetter, F. Bonnetain, J. Cros, M. Svrcek, A. Bardier-Dupas, P. Hammel, A. Sauvanet, C. Louvet, F. Paye, J.C. Vaillant, T. Andre, J. Closset, I. Salmon, J.F. Emile, J.L. Van Laethem, S100A2 is a predictive biomarker of adjuvant therapy benefit in pancreatic adenocarcinoma, Eur. J. Cancer 49 (2013) 2643–2653.
[14] N.B. Jamieson, S.M. Denley, J. Logue, D.J. MacKenzie, A.K. Foulis, E.J. Dickson, C.W. Imrie, R. Carter, C.J. McKay, D.C. McMillan, A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma, Ann. Surg. Oncol. 18 (2011) 2318–2328.
[15] E. Leclerc, G. Fritz, S.W. Vetter, C.W. Heizmann, Binding of S100 proteins to RAGE: an update, Biochim. Biophys. Acta 1793 (2009) 993–1007.

[16] F. Nutter, I. Holen, H.K. Brown, S.S. Cross, C.A. Evans, M. Walker, R.E. Coleman, J.A. Westbrook, P.J. Selby, J.E. Brown, P.D. Ottewell, Different molecular profiles are associated with breast cancer cell homing compared with colonisation of bone: evidence using a novel bone-seeking cell line, Endocr. Relat. Cancer 21 (2014) 327–341.
[17] H. Sekine, N. Chen, K. Sato, Y. Saiki, Y. Yoshino, Y. Umetsu, G. Jin, H. Nagase, Z. Gu, S. Fukushige, M. Sunamura, A. Horii, S100A4, frequently overexpressed in various human cancers, accelerates cell motility in pancreatic cancer cells, Biochem. Biophys. Res. Commun. 429 (2012) 214–219.
[18] S. Kozono, K. Ohuchida, T. Ohtsuka, L. Cui, D. Eguchi, K. Fujiwara, M. Zhao, K. Mizumoto, M. Tanaka, S100A4 mRNA expression level is a predictor of radioresistance of pancreatic cancer cells, Oncol. Rep. 30 (2013) 1601–1608.
[19] N. Tsukamoto, S. Egawa, M. Akada, K. Abe, Y. Saiki, N. Kaneko, S. Yokoyama, K. Shima, A. Yamamura, F. Motoi, H. Abe, H. Hayashi, K. Ishida, T. Moriya, T. Tabata, E. Kondo, N. Kanai, Z. Gu, M. Sunamura, M. Unno, A. Horii, The expression of S100A4 in human pancreatic cancer is associated with invasion, Pancreas 42 (2013) 1027–1033.
[20] S.H. Lee, H. Kim, J.H. Hwang, E. Shin, H.S. Lee, D.W. Hwang, J.Y. Cho, Y.S. Yoon, H.S. Han, B.H. Cha, CD24 and S100A4 expression in resectable pancreatic cancers with earlier disease recurrence and poor survival, Pancreas 43 (2014) 380–388.
[21] M. Dahlmann, A. Okhrimenko, P. Marcinkowski, M. Osterland, P. Herrmann, J. Smith, C.W. Heizmann, P.M. Schlag, U. Stein, RAGE mediates S100A4-induced cell motility via MAPK/ERK and hypoxia signaling and is a prognostic biomarker for human colorectal cancer metastasis, Oncotarget 5 (2014) 3220–3233.
[22] H.R. Siddique, V.M. Adhami, A. Parray, J.J. Johnson, I.A. Siddiqui, M.T. Shekhani, I. Murtaza, N. Ambartsumian, B.R. Konety, H. Mukhtar, M. Saleem, The S100A4 oncoprotein promotes prostate tumorigenesis in a transgenic mouse model: regulating NFkappaB through the RAGE receptor, Genes Cancer 4 (2013) 224–234.
[23] C. Haase-Kohn, S. Wolf, N. Herwig, B. Mosch, J. Pietzsch, Metastatic potential of B16-F10 melanoma cells is enhanced by extracellular S100A4 derived from RAW264.7 macrophages, Biochem. Biophys. Res. Commun. 446 (2014) 143–148.
[24] X. Xu, B. Su, C. Xie, S. Wei, Y. Zhou, H. Liu, W. Dai, P. Cheng, F. Wang, X. Xu, C. Guo, Sonic hedgehog–Gli1 signaling pathway regulates the epithelial mesenchymal transition (EMT) by mediating a new target gene, S100A4, in pancreatic cancer cells, PLoS One 9 (2014), e96441.
[25] P. Che, Y. Yang, X. Han, M. Hu, J.C. Sellers, A.I. Londono-Joshi, G.Q. Cai, D.J. Buchsbaum, J.D. Christein, Q. Tang, D. Chen, Q. Li, W.E. Grizzle, Y.Y. Lu, Q. Ding, S100A4 promotes pancreatic cancer progression through a dual signaling pathway mediated by Src and focal adhesion kinase, Sci. Rep. 5 (2015) 8453–8463.
[26] G. Zihao, Z. Jie, L. Yan, Z. Jing, C. Jing, L. Xue, Z. Jing, L.W. Heng, G. Ru, H. Jianyu, Analyzing S100A6 expression in endoscopic ultrasonography-guided fine-needle aspiration specimens: a promising diagnostic method of pancreatic cancer, J. Clin. Gastroenterol. 47 (2013) 69–75.
[27] X. Chen, X. Liu, H. Lang, S. Zhang, Y. Luo, J. Zhang, S100 Calcium-binding protein A6 promotes epithelial–mesenchymal transition through beta-catenin in pancreatic cancer cell line, PLoS One 10 (2015), e0121319.
[28] S.K. Mohan, A.A. Gupta, C. Yu, Interaction of the S100A6 mutant (C3S) with the V domain of the receptor for advanced glycation end products (RAGE), Biochem. Biophys. Res. Commun. 434 (2013) 328–333.
[29] E. Jurewicz, A. Goral, A. Filipek, S100A6 is secreted from Wharton's jelly mesenchymal stem cells and interacts with integrin beta1, Int. J. Biochem. Cell Biol. 55 (2014) 298–303.
[30] T. Arumugam, C.D. Logsdon, S100P: a novel therapeutic target for cancer, Amino Acids 41 (2011) 893–899.
[31] A. Ali, V. Brown, S. Denley, N.B. Jamieson, J.P. Morton, C. Nixon, J.S. Graham, O.J. Sansom, C.R. Carter, C.J. McKay, F.R. Duthie, K.A. Oien, Expression of KOC, S100P, mesothelin and MUC1 in pancreatico-biliary adenocarcinomas: development and utility of a potential diagnostic immunohistochemistry panel, BMC Clin. Pathol. 14 (2014) 35.
[32] H. Hu, Q. Zhang, C. Huang, Y. Shen, X. Chen, X. Shi, W. Tang, Diagnostic value of S100P for pancreatic cancer: a meta-analysis, Tumour Biol. 35 (2014) 9479–9485.
[33] S.R. Penumutchu, R.H. Chou, C. Yu, Structural insights into calcium-bound S100P and the V domain of the RAGE complex, PLoS One 9 (2014), e103947.
[34] T. Arumugam, V. Ramachandran, S.B. Gomez, A.M. Schmidt, C.D. Logsdon, S100P-derived RAGE antagonistic peptide reduces tumor growth and metastasis, Clin. Cancer Res. 18 (2012) 4356–4364.
[35] S.R. Penumutchu, R.H. Chou, C. Yu, Interaction between S100P and the anti-allergy drug cromolyn, Biochem. Biophys. Res. Commun. 454 (2014) 404–409.
[36] C.E. Kim, S.K. Lim, J.S. Kim, In vivo antitumor effect of cromolyn in PEGylated liposomes for pancreatic cancer, J. Control. Release 157 (2012) 190–195.
[37] S. Dakhel, L. Padilla, J. Adan, M. Masa, J.M. Martinez, L. Roque, T. Coll, R. Hervas, C. Calvis, R. Messeguer, F. Mitjans, J.L. Hernandez, S100P antibody-mediated therapy as a new promising strategy for the treatment of pancreatic cancer, Oncogenesis 3 (2014), e92.
[38] C. Yin, H. Li, B. Zhang, Y. Liu, G. Lu, S. Lu, L. Sun, Y. Qi, X. Li, W. Chen, RAGE-binding S100A8/A9 promotes the migration and invasion of human breast cancer cells through actin polymerization and epithelial–mesenchymal transition, Breast Cancer Res. Treat. 142 (2013) 297–309.
[39] S. Hiratsuka, S. Ishibashi, T. Tomita, A. Watanabe, S. Akashi-Takamura, M. Murakami, H. Kijima, K. Miyake, H. Aburatani, Y. Maru, Primary tumours modulate innate immune signalling to create pre-metastatic vascular hyperpermeability foci, Nat. Commun. 4 (2013) 1853.
[40] A.A. Sheikh, D. Vimalachandran, C.C. Thompson, R.E. Jenkins, T. Nedjadi, A. Shekouh, F. Campbell, A. Dodson, W. Prime, T. Crnogorac-Jurcevic, N.R. Lemoine, E. Costello, The expression of S100A8 in pancreatic cancer-associated monocytes is associated with the Smad4 status of pancreatic cancer cells, Proteomics 7 (2007) 1929–1940.
[41] D. Basso, E. Greco, A. Padoan, P. Fogar, M. Scorzeto, E. Fadi, D. Bozzato, S. Moz, F. Navaglia, C.F. Zambon, R. Seraglia, E. De Carlo, A. Valerio, C. Reggiani, S. Pedrazzoli, M. Plebani, Altered intracellular calcium fluxes in pancreatic cancer induced diabetes mellitus: relevance of the S100A8 N-terminal peptide (NT-S100A8), J. Cell. Physiol. 226 (2011) 456–468.
[42] S. Jones, X. Zhang, D.W. Parsons, J.C. Lin, R.J. Leary, P. Angenendt, P. Mankoo, H. Carter, H. Kamiyama, A. Jimeno, S.M. Hong, B. Fu, M.T. Lin, E.S. Calhoun, M. Kamiyama, K. Walter, T. Nikolskaya, Y. Nikolsky, J. Hartigan, D.R. Smith, M. Hidalgo, S.D. Leach, A.P. Klein, E.M. Jaffee, M. Goggins, A. Maitra, C. Iacobuzio-Donahue, J.R. Eshleman, S.E. Kern, R.H. Hruban, R. Karchin, N. Papadopoulos, G. Parmigiani, B. Vogelstein, V.E. Velculescu, K.W. Kinzler, Core signaling pathways in human pancreatic cancers revealed by global genomic analyses, Science 321 (2008) 1801–1806.
[43] C.W. Ang, T. Nedjadi, A.A. Sheikh, E.M. Tweedle, S. Tonack, S. Honap, R.E. Jenkins, B.K. Park, I. Schwarte-Waldhoff, I. Khattak, B. Azadeh, A. Dodson, H. Kalirai, J.P. Neoptolemos, P.S. Rooney, E. Costello, Smad4 loss is associated with fewer S100A8-positive monocytes in colorectal tumors and attenuated response to S100A8 in colorectal and pancreatic cancer cells, Carcinogenesis 31 (2010) 1541–1551.
[44] D. Basso, P. Fogar, M. Plebani, The S100A8/A9 complex reduces CTLA4 expression by immature myeloid cells: implications for pancreatic cancer-driven immunosuppression, Oncoimmunology 2 (2013), e24441.
[45] E. Kallberg, T. Vogl, D. Liberg, A. Olsson, P. Bjork, P. Wikstrom, A. Bergh, J. Roth, F. Ivars, T. Leanderson, S100A9 interaction with TLR4 promotes tumor growth, PLoS One 7 (2012), e34207.
[46] D. Basso, D. Bozzato, A. Padoan, S. Moz, C.F. Zambon, P. Fogar, E. Greco, M. Scorzeto, F. Simonato, F. Navaglia, M. Fassan, M. Pelloso, S. Dupont, S. Pedrazzoli, A. Fassina, M. Plebani, Inflammation and pancreatic cancer: molecular and functional interactions between S100A8, S100A9, NT-S100A8 and TGFbeta1, Cell Commun. Signal, 12 (2014) 20.
[47] K.T. Chen, P.D. Kim, K.A. Jones, K. Devarajan, B.B. Patel, J.P. Hoffman, H. Ehya, M. Huang, J.C. Watson, J.L. Tokar, A.T. Yeung, Potential prognostic biomarkers of pancreatic cancer, Pancreas 43 (2014) 22–27.
[48] K. Ohuchida, K. Mizumoto, S. Ohhashi, H. Yamaguchi, H. Konomi, E. Nagai, K. Yamaguchi, M. Tsuneyoshi, M. Tanaka, S100A11, a putative tumor suppressor gene, is overexpressed in pancreatic carcinogenesis, Clin. Cancer Res. 12 (2006) 5417–5422.
[49] M.B. Xiao, F. Jiang, W.K. Ni, B.Y. Chen, C.H. Lu, X.Y. Li, R.Z. Ni, High expression of S100A11 in pancreatic adenocarcinoma is an unfavorable prognostic marker, Med. Oncol. 29 (2012) 1886–1891.
[50] A.H. Burstein, I. Grimes, D.R. Galasko, P.S. Aisen, M. Sabbagh, A.M. Mjalli, Effect of TTP488 in patients with mild to moderate Alzheimer's disease, BMC Neurol. 14 (2014) 12.