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SPARC: A Potential Prognostic and Therapeutic Target in Pancreatic Cancer

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Abstract: Pancreatic cancer is a complex and heterogeneous disease that often lacks disease-specific symptoms in early stages. The malignancy is currently the fourth leading cause of cancer-related death in Western countries. In advanced stages, the overall 5-year survival is less than 1% to 2%. Most available treatments lack convincing cost-efficiency determinations and are generally not associated with relevant success rates. Targeting stromal components and stromal depletion is currently becoming an area of extensive research in pancreatic cancer. In this context, a glycoprotein, SPARC (secreted protein acidic and rich in cysteine) appears to play a central role. Still, the role of SPARC in carcinogenesis is controversial because conflicting results have been reported, and the pathways involved in SPARC signaling are not well established. Nonetheless, SPARC is highly expressed in the tumor stroma, principally in peritumoral fibroblasts, and the overexpression of SPARC in this compartment is associated with poorer prognosis. Interestingly, it has been suggested that SPARC present in the tumor stroma could sequester albumin-bound paclitaxel, enhancing the delivery of paclitaxel into the tumor microenvironment. In the present review, we summarize the known associations between SPARC and pancreatic cancer. Moreover, present and future therapies comprising SPARC-targeting are discussed.

Key Words: albumin-bound paclitaxel, pancreatic cancer, pathophysiological mechanisms, SPARC, stromal depletion

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Pancreatic cancer is a devastating disease. Worldwide, more than 200,000 people are diagnosed every year, and rising incidence numbers have been reported.[1,2] The malignancy is currently the fourth leading cause of cancer-related death in Western countries, but it may become the second leading cause of cancer-related death in the United States within this decade if no substantial breakthroughs are made in the management of this disease.[3]

Pancreatic ductal adenocarcinoma (PDAC) is by far the most common form of pancreatic cancer. Pancreatic ductal adenocarcinoma is a complex and heterogeneous disease that often lacks disease-specific symptoms in early stages. Several novel biomarkers have been proposed, but none of them meets the requirements needed for clinical use. Raised concentrations of the serum carbohydrate antigen 19-9 (CA 19-9) are reported in about 80% of patients. However, CA 19-9 is not a primary screening test because of its poor specificity in early disease.[4] Consequently, PDAC is habitually diagnosed in late stages. Once detected, the disease is almost unavoidably lethal within 5 to 6 months. In advanced stages, the overall 5-year survival is less than 1% to 2%.[5] Furthermore, resectable tumors are present in only 10% to 15% of patients. Unfortunately, long-term complete remission is unusual, and the median survival observed after surgery and concomitant adjuvant chemotherapy is about 20 months.[6]

Palliative chemotherapy is thus the only treatment justifiable in most cases. Unfortunately, the existing treatments have had minimal impact on the natural course of PDAC. Gemcitabine increases the quality of life, but only prolongs the mean survival by 30 days.[7] FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) further prolongs the mean survival by 4 months compared with gemcitabine monotherapy. Yet, FOLFIRINOX is suitable only for patients with a good performance status.[8] Thus, gemcitabine still represents the criterion standard for most patients. As the drug is well tolerated and inexpensive compared with alternative treatments, most research has focused on finding ideal "drug chaperons" that facilitate and/or potentiate the effect of gemcitabine. Several cytotoxic agents have been tried in combination with gemcitabine. For instance, the combination gemcitabine and erlotinib (Tarceva) has been approved in metastatic PDAC.[9] In recent years, several agents targeting both tumor cells and the tumor stroma have been developed. Indeed, SHH (sonic hedgehog) inhibitors, CD40 agonists, platelet-derived growth factor receptor inhibitors, and hyaluronidase have been proposed as novel potential treatments in PDAC.[10] Therefore, targeting stromal components and stromal depletion is currently becoming an area of extensive research in PDAC. In this context, a glycoprotein, SPARC (secreted protein acidic and rich in cysteine), appears to play a central role.[11,12] In addition, the role of SPARC in PDAC may not be limited to its linkage to the tumor stroma, as SPARC is related to several pathophysiological mechanisms in numerous cancer forms.[13]

We aim to summarize known and hypothetical associations between SPARC and PDAC. In addition, present and future therapeutic strategies comprising SPARC are reviewed.

TUMOR STROMA AND SPARC

The causes of PDAC are mainly unknown. Pancreatic intraepithelial neoplasia (PanIN) is considered the primordial precursor of PDAC.[14] Several mutations have been reported, but the activation of the *KRAS2* oncogene together with *CDKN2A/p16* loss and the inactivation of *TP53* and *SMAD4/DPC4* seem to be characteristic in PDAC. For instance, aberrantly activated *KRAS2* and inactivated *CDKN2A* genes are found in 90% and 95% of PDAC tumors, respectively.[15]

Another hallmark of PDAC is its tumor stroma, which comprises 80% to 90% of the tumor volume. The stroma contains dense fibrotic tissue composed of extracellular matrix (ECM) proteins, pancreatic stellate cells (PSCs), immune-inflammatory cells, adipocytes, and blood and lymphatic vessels.[16] The resulting microenvironment supports tumor initiation, progression, invasion, and metastasis. Moreover, stromal cells express multiple proteins and growth factors associated with treatment resistance, restrained

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antitumor immunity, and poor prognosis.[15] Pancreatic stellate cells are activated myofibroblasts responsible for stromal development and turnover. These cells contribute to the poor vascularization that is characteristic of PDAC.[17] Moreover, PSCs produce soluble factors that stimulate signaling pathways related to proliferation and survival of PDAC cell lines.[18] Cells of the innate and the adaptive immune system, such as T cells and macrophages, are able to create an immunosuppressive tumor microenvironment in PDAC.[19]

SPARC, also known as osteonectin and/or BM-40 (basement membrane 40), is a 32- to 35-kd multifunctional calcium-binding glycoprotein belonging to a group of matricellular proteins. SPARC is transiently secreted to the ECM and does not become a part of the ECM mesh.[20] The *SPARC* gene is located on human chromosome *5q31.3-q32*, and the transcription consists of a single polypeptide (285 amino acids) that can be divided into 3 different structural domains. The N-terminal is highly acidic, binds calcium ions with low affinity, and interacts with hydroxyapatite. The follastatin-like domain is a cysteine-rich structure. Finally, the C-terminal constitutes the extracellular calcium ion–binding domain.[13]

SPARC is involved in many biologic processes, including development, wound repair, tissue remodeling, angiogenesis, matrix cell adhesion, cell differentiation, proliferation, and migration.[21–24] The functions of SPARC might be in part mediated by interactions with matrix metalloproteinases (MMPs) and several growth factors, such as transforming growth factor β (TGF-β) and fibroblast growth factor.[22] Interestingly, there are no known SPARC receptors, and the protein part is rapidly the subject of proteolysis by several proteases.[21] In the adult, the expression of SPARC is restricted to tissues with high ECM turnover, such as bone and the gut epithelium.[25]

SPARC expression and secretion in tumor tissue emerge as an important clinical factor in several malignancies (briefly reviewed in Table 1). SPARC is involved in numerous mechanisms in cancer, comprising proliferation, cell cycle progression, angiogenesis, apoptosis, cell adhesion, migration, and metastasis (shown in Fig. 1).[13] Still, the role of SPARC in carcinogenesis is controversial because conflicting results have been reported, and the pathways involved in SPARC signaling are not well established. Nevertheless, the overexpression of SPARC in stromal cells in

TABLE 1. The Role of SPARC in Human Cancer

Tumor Type	Endogenous SPARC: mRNA Expression and/or Protein Level	Prognosis	Reference
Ampulla of Vater	High/low SCs	Poorer: high SPARC in SCs	26
Bladder	High/low (TT)	Poorer: high SPARC in TT	27
Breast	High/low (CCs)	Poorer: high SPARC in CCs	28
	High (SCs)	Better: high SPARC in SCs	29
Colon	Low (CCs)	Poorer: low SPARC in SCs	30
	High (SCs)		
DLBCL	High/low (CCs)	Better: high SPARC in CCs/SCs	31
	High/low (SCs)		
Endometrial	Low (TT)	Unknown	32
Gastric	Low (CCs)	Poorer: high SPARC in SCs	33
	High (SCs)		
Glioma	High (CCs)	Poorer: high SPARC in VT	34
	High (VT)		
Head and neck	Low (CCs)	Poorer: high SPARC in SCs	35
	High (SCs)		
Leukemia	Low (CCs)	Poorer: high SPARC	36
Hepatocellular	Low (CCs)	Poorer: high SPARC in SCs	37
	High (SCs)		
Lung	Low (CCs)	Poorer: high SPARC in CCs	38
	High (SCs)	Poorer: high SPARC in SCs	39
Melanoma	High/low (CCs)	Poorer: high SPARC in CCs	40
Neuroblastoma	Low (CCs)	Unknown	41
	High (SSCs)		
Esophagus	High (CCs)	Poorer: high SPARC in CCs	42
	High/low (SCs)		
Osteosarcoma	High/low (TT)	Poorer: high SPARC in TT	43
Ovarian	Low (CCs)	Unknown	44
	High (SCs)		45
Pancreatic	Low (CCs)	Poorer: high SPARC in SCs	46–48
	High (SCs)		
Prostate	Low (CCs)	Poorer: high SPARC in CCs	49,50
Thyroid	High/low (CCs)	Unknown	51
	High (SCs)		

CCs indicates cancer cells; DLBCL, diffuse large B-cell lymphoma; SCs, stromal cells; SSCs, stromal Schwann cells; TT, tumor tissue; VT, vascular tissue.

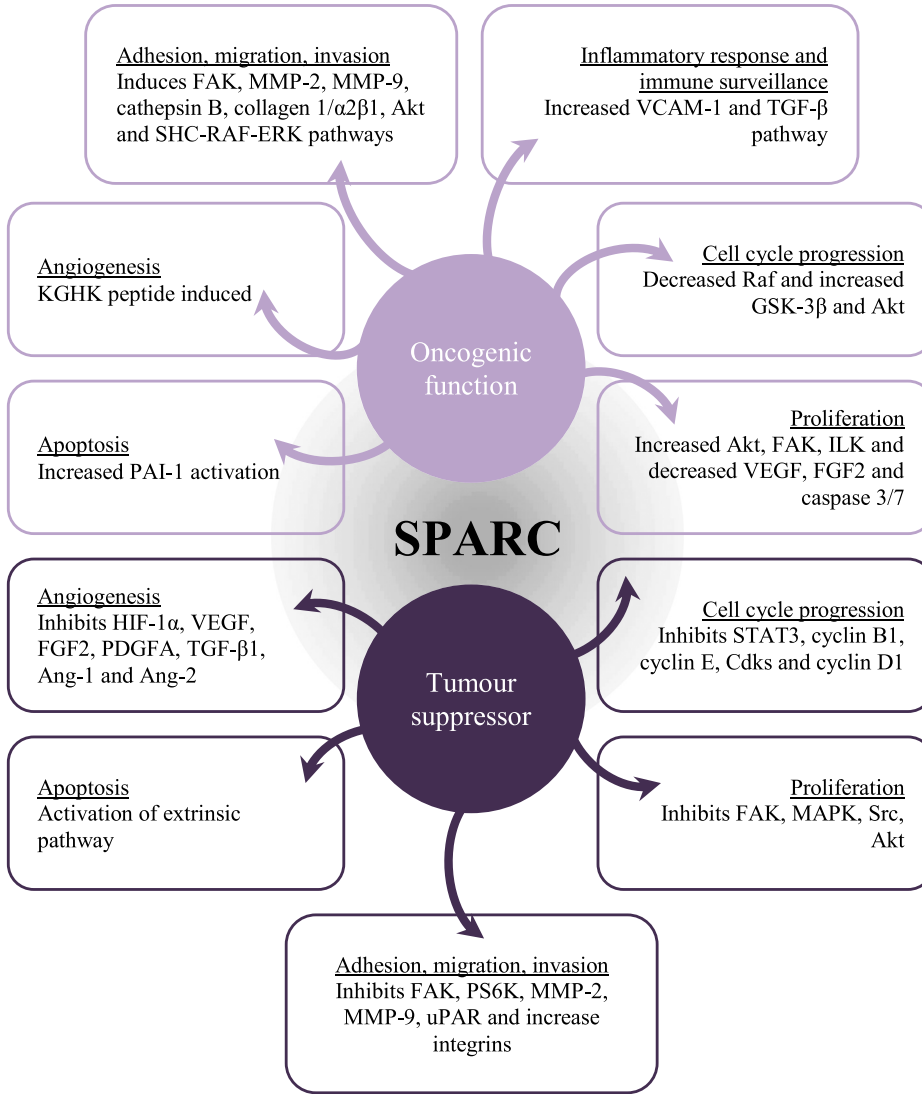

FIGURE 1. The diverging role of SPARC in carcinogenesis. A brief selection of the reported associations is shown.[13,52,53]

cancer seems to be strongly related to increased invasive capacity and poorer prognosis.[12]

SPARC GENE SILENCING IN PDAC

Epigenetic alterations are identified to contribute to the development of PDAC. Histone modifications, microRNAs, and DNA methylation are well-known epigenetic mechanisms. Hence, the intervention of these mechanisms has been subject of intense research in PDAC.[54] It has been shown that DNA methylation is associated with the inactivation of tumor suppressor genes in cancer.[55]

SPARC gene expression is present in normal pancreatic duct epithelial cells and in immortalized nonneoplastic pancreatic epithelial cells (HPDE).[56] Intriguingly, the abnormal methylation of the *SPARC* gene *CpG* islands is found in 28% of resected PanIN tissue.[57] Early recognition of PanINs would dramatically change the prognosis of PDAC because most patients could be cured through a surgical resection before they develop metastatic disease. Unfortunately, PanINs are microscopic lesions that are usually less than 5 mm and undetectable for available imaging methods as of today.[58] In contrast to PanINs, intraductal papillary mucinous neoplasms (IPMNs) are precursors of PDAC that can be detected by imaging.[59] In IPMNs, the expression of SPARC is lost in 50% of low-grade and moderate dysplasia. In high-grade dysplasia, the expression of SPARC is lost in 80% of the IPMNs.[60] Thus, augmenting SPARC loss in IPMNs appears to be related to tumor development. Intraductal papillary mucinous neoplasms and PDACs have similar pathophysiological genomic alterations, but significant molecular dissimilarities between PDA and IPMNs have been reported.[61] Besides, the differentiation between IPMNs and other pancreatic cysts and neoplasms is often challenging. These results are still promising and suggest that loss of SPARC expression is a characteristic feature of premalignant pancreatic lesions. Possibly, the implementation of methylation panels including SPARC and other common hypermethylated genes (such as *Reprimo*) could be used for early detection of PanINs and IPMNs by the analysis of pancreatic juice and/or cystic fluid.[62,63] It has recently been reported that the SPARC *CpG* islands are hypermethylated in 58% of fine-needle aspirates from PDAC patients (sensibility 68%, specificity 100%).[64]

SPARC gene *CpG* islands are also aberrantly methylated in PDAC cell lines and tumor xenografts. While all *CpG* sites were completely unmethylated in HPDE and primary fibroblasts from PDAC, most cell lines were completely or partially methylated. Altogether, the *SPARC* gene was aberrantly methylated in 94% (16/17) of the examined PDAC cell lines and in 88% (21/24) of the tumor xenografts established from primary PDAC. Importantly, this methylation pattern was absent in normal epithelium samples. Predictably, the hypermethylation of SPARC resulted in loss of mRNA expression of SPARC in 94% of PDAC cell lines. The administration of a demethylating agent (5Aza-2′-deoxycytidine) reestablished the mRNA expression of SPARC in 88% of the challenged cells.[56]

The methylation of the *SPARC* gene transcriptional regulation region is more prominent in *CpG* region 1 (*CpG* sites 1-7) and *CpG* region 2 (*CpG* sites 8-12) in PDAC. Importantly, the methylation at both regions is also present in pancreatic tissue, chronic pancreatitis (CP), and nonneoplastic tissue adjacent to the tumors. The frequency of methylated regions increases gradually from normal tissue to pathological tissue. *CpG* region 2 methylation was more sensitive in pancreatic carcinogenesis. Moreover, the percentage of methylation at the *CpG* region 2 was associated with larger tumor size and exposure to tobacco smoke and alcohol consumption. Besides, increased tumor size, tobacco smoking, and alcohol consumption were independent contributors to the percentage of *CpG* region 2 methylation.[65] The authors concluded that the aberrant methylation of *CpG* region 2 could be useful as a marker for early PDAC diagnosis, but their results need to be verified in larger studies, because the conclusions were based on 40 PDAC cases alone.

Nevertheless, the correlation between SPARC methylation and tobacco smoke is of particular concern because the latter is a major risk factor for PDAC. At least 20% of the tumors have been reportedly caused by cigarette smoking.[5] Tobacco smoke can induce *KRAS* gene mutation in PDAC, and the associations between tobacco smoke and the hypermethylation of tumor suppressor genes are currently being elucidated.[66,67] Heavy alcohol intake can lead to CP and liver cirrhosis, which have been related to an increased risk of PDAC.[68] A family history is also a well-defined risk factor for PDAC, present in 5% to 10% of cases.[5] SPARC is hypermethylated in ≈92% of familiar PDAC, which indicates that both sporadic and familiar PDACs share pathophysiological mechanisms that involve SPARC.[69]

In a dose-depended manner, gemcitabine altered the SPARC expression in a PDAC cell line.[70] The mechanisms behind this effect are mainly unknown, but it has been reported that gemcitabine can

TABLE 2. *SPARC* Gene Silencing and mRNA Expression in PDAC Cell Lines

Cell Line	Derivation	Metastasis	Differentiation	Silenced *SPARC* Gene	SPARC mRNA Expression	Reference
A818-4	Pancreas	No	Moderate to poor	Undetermined	Absent	75
As (R)	Ascites	Yes	Moderate	Undetermined	Present	75
AsML (R)	Pancreas	Yes	Moderate to poor	Undetermined	Present	75
AsPC-1*	Ascites	Yes	Poor	Hypermethylation	Mostly absent	56,75–77
BxPC-3*	Pancreas	No	Moderate to poor	Mostly hypermethylated	Absent	56,75–77
Capan-1*	Liver	Yes	Well	Hypermethylation	Mostly absent	56,75–77
Capan-2*	Pancreas	No	Well	Hypermethylation	Absent	56
CFPAC-1*	Liver	Yes	Well	Hypermethylation	Absent/present	56,75
Colo357	Lymph node	Yes	Moderate	Hypermethylation	Absent/moderate to low	56,75,76
DAN-G	Pancreas	No	Moderate	Undetermined	High	75
HPAC*	Pancreas	No	Moderate	Undetermined	Present	78
HPAF-II*	Ascites	Yes	Well	Undetermined	Low	78
Hs766T*	Lymph node	Yes	Not described	Hypermethylation	Absent	56
MiaPaCa-2*	Pancreas	Yes	Poor	Hypermethylation	Absent/moderate to low	56,75–77
Panc-1*	Pancreas	Yes	Poor	Partially hypermethylated	High	56,75–77
Pan02 (M)	Pancreas	Yes	Poor	Undetermined	Present	79
Patu 390	Pancreas	No	Moderate	Undetermined	Absent	75
Patu 8988	Pancreas	No	Moderate to poor	Hypermethylated	Undetermined	65
PK8	Liver	Yes	Moderate	Undetermined	Present	80
PK45H	Pancreas	No	Moderate	Undetermined	Present	80
PK59	Pancreas	No	Moderate	Undetermined	Present	80
PL-1, 3, 6, 10-13	Pancreas	No	Moderate	Hypermethylated	Absent	56
PL-9	Pancreas	No	Moderate	Mostly hypermethylated	Present	56
PL45	Pancreas	Yes	Poor	Undetermined	Low	78
PSN-1	Pancreas	Yes	Poor	Undetermined	Absent	46
Suit2-007	Liver	Yes	Moderate to poor	Undetermined	Present	75
Suit2-013	Liver	Yes	Moderate to poor	Undetermined	Absent	75
SU.86.86*	Liver	Yes	Moderate to poor	Undetermined	High	76
T3M4	Lymph node	Yes	Poor	Undetermined	Absent/moderate to low	75–77
YPK-1	Ascites	Yes	Moderate to poor	Undetermined	Absent	70

*Most referred PDAC cell lines in the literature.[81]

(M) indicates murine PDAC cell line; (R), rat PDAC cell line.

function as a DNA methyltransferase inhibitor in other solid tumors.[71] Moreover, SPARC overexpression seems to enhance the chemosensitive of PDAC cells to gemcitabine.[72] Likewise, curcumin analogs seem to be DNA-methylating agents that increase SPARC expression in PDAC cell lines and in tumor xenografts.[73]

In summary, the hypermethylation of *SPARC* gene CpG islands in premalignant lesions and PDAC cell lines and tissue strongly indicates that the protein is involved in the development and progression of PDAC. Similar associations have been reported in other gastrointestinal malignancies.[52] Other mechanisms responsible for *SPARC* gene silencing in PDAC could be loss of heterozygosity. Loss of heterozygosity at 5q is found in up to 20% of PDAC tumors.[74]

SPARC EXPRESSION AND EFFECT IN PDAC

Conflicting results have been reported concerning the mRNA expression of SPARC in PDAC cell lines. As described above, almost all cells (94%) showing aberrant methylation patterns lack SPARC expression, and conditioned media from several cell lines show undetectable SPARC levels.[56] However, several PDAC cell lines appear to express SPARC, and even cell lines initially reported as lacking SPARC expression in PDAC have shown conflicting results.[75] The different PDAC cell lines, their reported methylation pattern, and supposed mRNA expression of SPARC are presented in Table 2. Here, we found that the mRNA expression of SPARC is absent or low in about 64% of the 11 most referred cell lines in PDAC.[81] Panc-1 and MiaPaCa-2 are important exceptions showing high to moderate SPARC expression.[75,76] Possibly, the patients' ethnicity, the derivation tissue, or the grades of differentiation of the cells cause the differing expression of SPARC among these cell lines. Importantly, SPARC is expressed in murine and rat PDAC cell lines.

In vitro experiments have shown that the inhibition of endogenous SPARC enhances cell growth in PDAC.[77] Moreover, treatment with exogenous SPARC significantly suppressed the growth

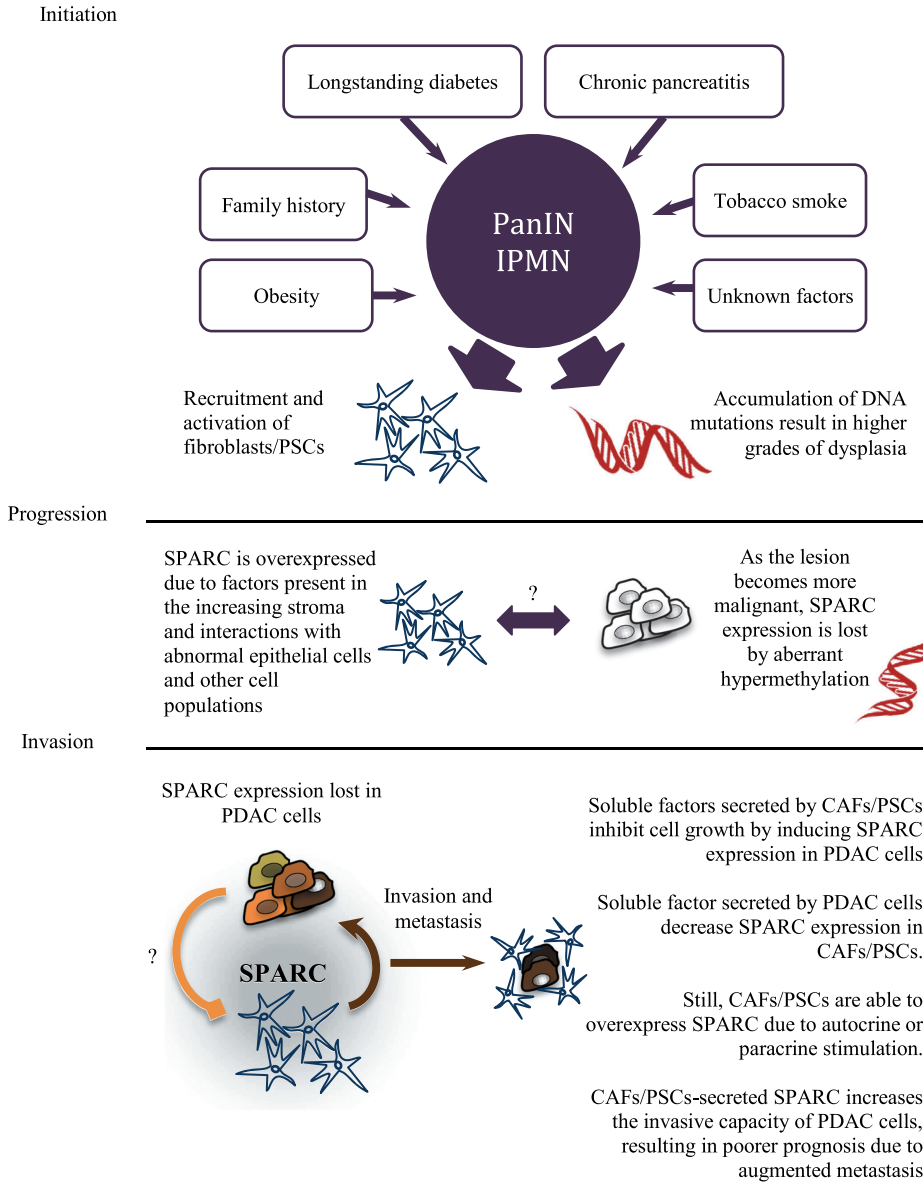

FIGURE 2. The role of SPARC in the pathophysiology of PDAC. A suggested model.

of PDAC cell lines, independently of their endogenous expression and without inducing apoptosis.[56,75,76] Furthermore, exogenous SPARC caused transient *G1/S* phase accumulation in Colo357 and MiaPaCa-2 cells (moderate to low endogenous SPARC levels).[76,82] SPARC increased the invasive capacity of Colo357 cells. In addition, down-regulation of vascular endothelial growth factor (VEGF) and increased expression of MM2 and *p21* were observed. Inversely, SPARC down-regulation in Panc-1 (high endogenous SPARC levels) led to increased cell growth and VEGF expression, decreased MMP-2 and *p21* expression, and reduced the invasive capacity of the.[76,82] Furthermore, the down-regulation of SPARC in MiaPaCa-2 cells decreases their invasive capacity.[83]

Matrix metalloproteinases and their blockage have been subject of intensive research. The overexpression of MMP-2 is associated with tumor progression, invasion, and metastasis in PDAC.[84,85] Interestingly, SPARC expression in PDAC cell lines was positively associated with MMP-2 expression.[75] SPARC seems to stimulate MMP-2 expression in cancer cells, augmenting their metastatic potential. Moreover, SPARC undergoes proteolysis via MMPs, and the degradation products may have different biological activities.[86,87] A peptide of SPARC seems to modulate and enhance apoptosis in MiaPaCa-2 cells.[88]

The cyclin-dependent kinase inhibitor *p21* promotes cell cycle arrest in response to several stimuli.[89] Pancreatic ductal adenocarcinoma cells challenged with the controversial drug Ukrain (also called celandine) showed up-regulation of SPARC expression. In addition, the drug inhibited cell proliferation and cell cycle *G2/M* arrest.[78] Thus, cell cycle modulation may be 1 of the mechanisms behind the antiproliferative properties of SPARC in PDAC. Supposedly, *p21* up-regulation could be a key factor in this context. However, *p21* has also shown a tumor-promoting function because it is also an inhibitor of apoptosis in cancer.[89] Moreover, it has recently been suggested that SPARC induces *G1/S* cell cycle arrest by the up-regulation of $p53$, $p27^{Kip1}$ and down-regulation of phosphorylation *pRB*.[82]

SPARC may act as an angiogenesis inhibitor by regulating the activity of VEGF and platelet-derived growth factor.[90] The SPARC-dependent down-regulation of VEGF in PDAC cells is a puzzling phenomenon also seen in colon cancer.[30] Hypothetically, SPARC may in part be responsible for the deregulation of angiogenesis in PDAC, resulting in decreased tumor growth (due to hypoxia), poor vascularization, and changes in the deposition and organization of the tumor microenvironment.

The overexpression of TGF-β1 has been associated with pancreatic cancer.[91] Transforming growth factor β1 signaling is important in pancreatic carcinogenesis and can be either tumor suppressive or tumor promoting.[92] Moreover, high levels of TGF-β are correlated with metastasis, angiogenesis, and a poor prognosis in cancer.[91] Exogenous SPARC stimulates the expression of TGF-β1 in PDAC cells, whereas TGF-β1 expression decreases the expression of SPARC in tumor cells.[76] The consequences of this observed feedback loop in PDAC carcinogenesis are unknown.

As shown previously, cancer-associated fibroblasts (CAFs) isolated from PDAC tissue lack the abnormal pattern of methylation found in several cancer cell lines.[56] Consequently, SPARC is highly expressed in these cells, including PSCs.[46,56,77] Interestingly, fibroblasts derived from CP or noncancerous tissue from a PDAC patient show a weaker SPARC expression as compared with CAFs.[56] When cocultured, cancer cells significantly increase the expression of SPARC in fibroblasts from noncancerous tissue.[56] Unexpectedly, conditioned medium from cancer cells reduced the endogenous expression of SPARC in PSCs. Furthermore, conditioned medium from PSCs has no effect on the endogenous expression of SPARC in cancer cells.[77] Altogether, it seems that PDAC cells modulate the expression of SPARC in stromal fibroblasts. It is unclear why PDAC cells have opposite effects in naive fibroblasts and PSCs. Remarkably, in vitro experiments exploring the associations between SPARC and PSCs/CAFs in PDAC are very limited. Still, CAFs/PSCs are main protagonists in PDAC tissue, as described above. Based on reported data from PDAC and other malignancies, we propose a model for the role of SPARC in PDAC cells (Fig. 2). This suggestion should be interpreted with caution, because the associations between SPARC and fibroblasts in PDAC are largely unknown.

In PDAC tissue samples, SPARC expression is found both in tumor and stromal cells.[46–48,56,76,82,93] In normal pancreas, SPARC is weakly expressed. In normal ductal cells, SPARC is reported as mainly absent or weakly expressed.[56,76] Compared with normal pancreas, a 31-fold increase in SPARC expression in PDAC has been reported. Likewise, a 16-fold increase was observed in CP when compared with normal.[76] These results correlate well with *SPARC* gene methylation patterns found in other experiments.[56] However, the grade of SPARC overexpression in the different PDAC compartments is debated, as immunohistochemical methods have shown conflicting results (reviewed in Fig. 3). SPARC levels in serum do not appear to be suitable for general screening.[56,76] Nonetheless, SPARC is highly expressed in the tumor stroma, principally in peritumoral fibroblasts, and the overexpression of SPARC in this compartment is associated with a less favorable prognosis (results presented in Table 3).[46–48,82,94]

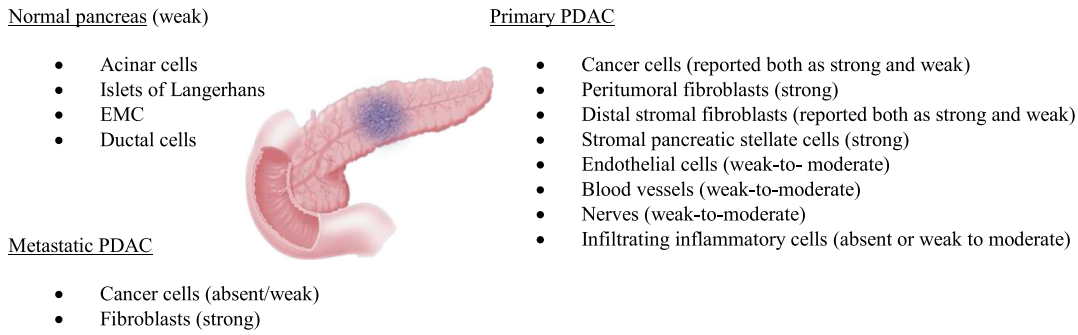

FIGURE 3. Immunohistochemical staining of SPARC in normal pancreas and PDAC. SPARC is found in most tissue samples from PDAC patients. SPARC is highly expressed in stromal fibroblasts. The anatomical image adapted from Don Bliss. The original image was released into the public domain by its author, who has granted anyone the right to use this work for any purpose, without any conditions, unless law requires such conditions. The original image is work of the National Cancer Institute, www.cancer.gov. As a work of the U.S. Federal Government, the image is in the public domain. August 2014.

TABLE 3. SPARC as a Prognostic Factor in PDAC

Samples	Survival	SPARC Expression	Survival High/Positive SPARC	Survival Low/Negative SPARC	Prognostic Factor	Reference
29	5 y: 20%	Negative: 68.7% Positive: 31.3%	5 y: 31.7%	20%	SPARC-negative cases had significantly poorer prognosis than SPARC-positive cases	82
299	MOS: 17 mo	Expression most clearly seen in peritumoral fibroblasts	MOS: 15 mo	MOS: 30 mo	UA: stromal SPARC expression in peritumoral fibroblast was correlated with poor prognosis. HR, 2.36 (95% CI, 1.67–3.34)	47
	5 y: 20%	Tumor negative/stroma negative: 17% Tumor positive/stroma negative: 17% Tumor negative/stroma positive: 52% Tumor positive/stroma positive: 15%			SPARC expression in PDAC cells was not associated with prognosis MA: SPARC expression in peritumoral fibroblast was associated with worse prognosis. HR, 1.89 (95% CI, 1.31–2.74)	
49	MOS: 10 mo	Expressed predominantly in the peritumoral and distal stroma	MOS: 7.6 mo 10-mo survival: 29% 15-mo survival: 12%	MOS: 10.2 mo 10-mo survival: 52% 15-mo survival: 35%	High SPARC expression in peritumoral stroma was not a prognostic factor MA: high SPARC expression in distal stroma was a strong prognostic factor for survival in patients treated with CRT. HR, 2.23 (95% CI, 1.31–2.74)	46
31	MOS: 14 mo (Range, 2–60)	Low: 64.5% High: 35.5%	10 mo (95% CI, 6–14 mo)	27 mo (95% CI, 7-47 mo)	No statistical significance reached	93
104	1 y: 64.9% 2 y: 40.8% 5 y: 20.24%	Low: 90.4% High: 9.6%	5 y: 0.0%	5 y: 22.48%	UA: high SPARC expression was positively correlated with poor prognosis MA: high SPARC expression was an independent prognostic factor for poor survival. HR, 2.92 (95% CI, 1.63–5.50)	94
160	MDFS: 11.2 mo (Range, 9.2–13.3) MOS: 21.5 (Range, 17.6–25.4)	Low stromal: 41.9% High stromal: 58.1% Low cytoplasmic: 40.6% High cytoplasmic: 59.4%	MDFS Stromal: 9.0 mo (95% CI, 5.4–12.5 mo) Cytoplasmic: 10.7 mo (95% CI, 7.6–14 mo) Stromal: 19.5 mo (95% CI, 14–25.7 mo) Cytoplasmic: 20.4 mo (95% CI, 16.5–24.3 mo)	MDFS Stromal: 12.6 mo (95% CI, 9–16 mo) Cytoplasmic: 11.8 mo (95% CI, 9.1–14.5 mo) MOS Stromal: 26.6 mo (95% CI, 17.2–36.1 mo) Cytoplasmic: 26.2 mo (95% CI, 18.6–34.7 mo)	Strong stromal SPARC expression was associated with worse MDFS and MOS in gemcitabine-treated patients. The same association was found for high cytoplasmic SPARC expression MA: SPARC expression was independently predictive of patient outcome. HR, 1.47 (95% CI, 1.02–2.14)	48

CI indicates confidence interval; CRT, chemoradiation; HR, hazard ratio; MA, multivariate analysis; MDFS, median disease-free survival; MOS, median OS; UA, univariate analysis.

SPARC in Murine PDAC

Pan02 is a murine PDAC cell line with the capacity to cause aggressive tumors in orthotopic models.[95] This cell line has been used in several important experiments. In murine PDAC, SPARC is involved in several mechanisms comprising tumor growth, apoptosis, invasive capacity, angiogenesis, ECM composition, and immune response.[39,79,96–100] Interestingly, Pan02 is capable of producing SPARC both in vitro and in vivo, a finding that strongly differs from data reported in human PDAC cell lines.[56,79] Apparently, SPARC has mainly tumor suppressor functions in murine disease. Nevertheless, murine PDAC models have resulted in invaluable data for the elucidation of the role of SPARC in human PDAC. The associations found in murine PDAC are summarized in Table 4.

In essence, in vitro studies indicate that SPARC has both oncogenic and tumor suppressor properties. Seemingly paradoxical, the influence of SPARC in PDAC may be explained by pole-opposite effects that the protein has in different cell populations in the tumor microenvironment. Interestingly, SPARC is found not only in primary tumors, but also in metastases. This indicates that SPARC is associated with PDAC, independently of differentiation grade or site of metastasis. As in murine disease, SPARC seems to be a tumor suppressor in PDAC cells, but as SPARC overexpression is related to a poor prognosis, it can be assumed that the oncogenic functions in stromal cells are prevailing in PDAC. However, SPARC seems to interact with albumin-bound paclitaxel (nab-paclitaxel, Abraxane, ABI-007), opening a new window of opportunity in PDAC.

TABLE 4. The Role of SPARC in Murine PDAC

Reported Association	Reference
SPARC is expressed in Pan02 cells and in tumors	79
SPARC is produced by Pan02 cells in vitro and in vivo	79
SPARC enhances the migration potential in Pan02 cells	98
Exogenous SPARC does not affect the proliferation rate in Pan02 cells	79
Increase in pericyte recruitment by diminishing TGF-β1 activity	100
Lack of host endogenous SPARC causes	
Enhanced tumor growth	79,96,97
Reduced apoptosis in tumor cells	79
Alteration in the disposition of ECM constituents within the tumor	79
Decrease in collagen fibrillogenesis at the tumor borders	99
Increased macrophage recruitment/activation	99
Polarization of the macrophages within tumor toward an M2 phenotype	99
Altered distribution of macrophages within the tumor	79
Increased recruitment and mobilization of regulatory T cells	98
Decreased microvessel density	99
Increased perfusion and vascular permeability	99
Reduced density of the vascular basement membrane	99
Discontinuous endothelial cell layer	99
Decreased hypoxia in tumors	99
Reduced pericyte recruitment	99
A decrease in the percentage of blood vessels that maintain pericyte support	79
Increased invasion and metastasis	97–99
Less differentiated tumors	96
Reduced survival	96,99
Increased TGF-β1 activity	98

TARGETING SPARC IN PDAC

Paclitaxel is a microtubule-stabilizing agent that inhibits the depolymerization of microtubules, inducing mitotic arrest in *G2* and *M* phases of the cell cycle, resulting in cell death.[101–103] Consequently, paclitaxel shows selectivity for proliferating cells over quiescent cells. Paclitaxel is considered a cornerstone of therapy in breast, ovarian, and non–small cell lung cancer.[104] Solvent-based (sb-) paclitaxel and docetaxel (a semisynthetic analog) have shown encouraging results in several clinical trials and are approved treatment components in different cancer types.[105] However, these compounds are associated with less predictable pharmacologic profiles, hypersensitivity reaction, and toxicity.[106] Thus, the promising effect of paclitaxel was self-limited by the occurrence of serious adverse events (AEs), and novel formulations were highly demanded.

Albumin is the most abundant protein in blood plasma, constituting more than 50% of total proteins. Albumin, noncovalently and reversibly, binds molecules in the bloodstream. Moreover, the protein has a long lifetime (about 21 days) and does not elicit an immune response. These characteristics make albumin an attractive candidate for selective drug delivery.[107,108] Nab-paclitaxel is formulated with human serum albumin with a concentration similar to the concentration of albumin seen under physiological conditions.[109] The drug is obtained by high-pressure homogenization in which particles measuring 130 nm in diameter are created. Importantly, albumin and paclitaxel are not covalently bound after the process, but rather linked through hydrophobic interactions.[110] Upon injection, the particles dissolve into soluble albumin-paclitaxel complexes measuring 10 nm. Because of its combination with albumin, nab-paclitaxel can be reconstituted with simple saline solution.[106] Thus, nab-paclitaxel can be administered without solvent-related risks and steroid or antihistamine prophylaxis. Moreover, nab-paclitaxel can be administered at higher doses when compared with sb-paclitaxel and docetaxel, and it has a more predictable pharmacokinetic profile.[106,111]

The mechanisms of delivery of nab-paclitaxel are closely associated with the biological properties of albumin. Two major mechanisms have been described: transcytosis and the enhanced permeability and retention effect. Both mechanisms have recently been summarized by others and are described in Figure 4.[104,106] Importantly, it has been shown that injected albumin-conjugated molecules accumulate in proximity of tumors.[112,113] SPARC has high affinity for albumin.[86] It has been suggested that SPARC present in the tumor stroma could sequester nab-paclitaxel, enhancing the delivery of paclitaxel into the tumor microenvironment. The resulting "stromal collapse" effect is defined as stromal depletion that brings tumor cells closer to each other and to blood vessels.[114] Still, it has been debated if SPARC is related to nab-paclitaxel efficacy, because SPARC deficiency did not affect the intratumoral paclitaxel concentration, stromal deposition, and the immediate therapeutic response in genetically engineered mice.[115] Results from murine models suggest that nab-paclitaxel reduces the levels of cytidine deaminase, an enzyme responsible for the primary metabolism of gemcitabine.[116]

Several clinical trials evaluating the effect of nab-paclitaxel in metastatic PDAC have been completed with encouraging results (Table 5). In a phase I/II clinical trial, the nab-paclitaxel maximum tolerated dose (MTD) has been established at 125 mg/m^2 on days 1, 8, and 15 every 28 days in combination with fixed doses of gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 28 days).[118]

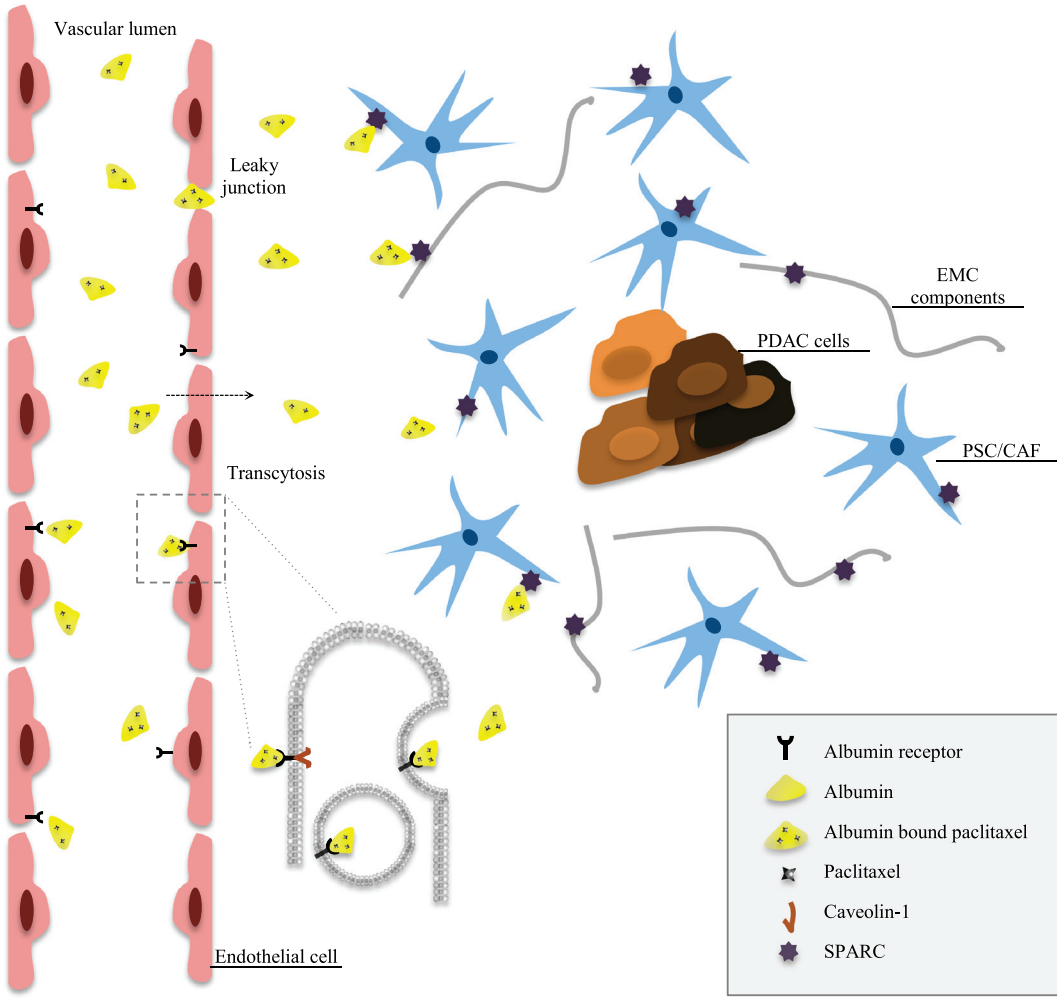

FIGURE 4. Mechanisms of delivery and accumulation of nab-paclitaxel in PDAC. Transcytosis: albumin binds to albumin-specific membrane receptors (such as gp60) in endothelial cells. Upon the activation of the cytoplasmic protein caveolin-1, nab-paclitaxel is transported in vesicles (caveolae) across the cytoplasm of the endothelial cell before fusing with the membrane of the other side of the cell. Nab-paclitaxel is then released in the interstitial space. This active transport found in tissues with high perfusion and metabolic rate. EPR: The vasculature around the tumor is leaky, allowing nab-paclitaxel transport through gaps between endothelial cells. As the lymphatic drainage is compromised in the tumor microenvironment, the drug is accumulated around the tumor. As SPARC has high affinity for albumin, nab-paclitaxel is accumulated in the tumor stroma, eventually causing "stromal collapse".[53,104,106] EPR indicates enhanced permeability and retention effect.

Dose-limiting toxicities (DLTs) were neutropenia and sepsis. At the MTD, a median overall survival (OS) of 12.2 months was registered. The response rate was 48%. The OS was correlated with stromal SPARC, decreased CA 19-9 levels, and complete metabolic response analyzed by ^{18}F-fluorodeoxyglucose positron emission tomography. Interestingly, patients with complete metabolic response had significantly longer survival (20.1 months) than those without complete response (10.3 months). The expression of SPARC was evaluated in 36 patients. Those with high SPARC expression had a significant increase in OS compared with patients with low SPARC expression (17.8 vs 8.1 months). Concordantly with previous results (Table 3), stromal SPARC levels (but not SPARC in tumor cells) were a significant predictor for OS in multivariate analysis. Thus, nab-paclitaxel appears to interact with stromal SPARC. Interestingly, stromal SPARC, a confirmed factor for poorer prognosis in PDAC, has become good news upon nab-paclitaxel treatment, as SPARC overexpression seems to be associated with better treatment response rates and increased OS. Preclinical studies coupled to this study showed that in mice with human PDAC xenografts nab-paclitaxel, alone or combined with gemcitabine, caused stromal depletion. Tumor regression was observed in 64% of the animals. Likewise, nab-paclitaxel treatment increased 2.8-fold the intratumoral concentration of gemcitabine when compared with gemcitabine monotherapy. Altogether, these results support previous theories about the association between SPARC, nab-paclitaxel, and stromal depletion.

In another phase I/II trial, the combination of nab-paclitaxel and gemcitabine was evaluated in Chinese patients.[119] Nab-paclitaxel at 120 mg/m^2 on days 1 and 8 every 21 days in combination with fixed doses of gemcitabine (1000 mg/m^2 on days 1 and 8 every 28 days) was administered. The regimen was well tolerated. Moreover, the MTD was not met, but similar results concerning DLTs and median OS were observed. Interestingly, this regimen resulted in lower response rates and progression-free survival (PFS) as compared with previous results. This may in part be caused by the lower dose of nab-paclitaxel administered.

TABLE 5. Clinical Trials Evaluating the Effect of Nab-Paclitaxel (Abraxane) in PDAC

Phase	Tumor Stage	Combination	No. of Patients	Arms/Groups	Efficacy Results	Safety Results	Reference
I	Metastatic	Gemcitabine (750 or 1000 mg/m^2 on day 4 every 14 d) Capecitabine (750 mg/m^2 BID days 1–7 every 14 d)	15	Abraxane 100 mg/m^2 + gemcitabine 750 mg/m^2 on day 4 + capecitabine 750 mg/m^2 BID days 1–7 (dose level 0) Abraxane 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 4 + capecitabine 750 mg/m^2 BID days 1–7 (dose level 1)	MTD: dose level 0 Median PFS (n = 14): 4.5 mo Median OS (n = 14): 7.5 mo 1-y Survival = 28.6% Partial response, dose level 0: 14.3%	DLTs: anemia, neutropenia and nausea/vomiting Treatment-related AEs (most common): anemia (80%), fatigue (80%), maculopapular rash (66.7%), alopecia (60%), anorexia/weight loss (60%), nausea/vomiting (53%), pruritus (53%), and hand-foot syndrome (46.7%) Most common grade ≥3 AEs: elevated LFTs (13.3%), nausea/vomiting (13.3%), anemia (6.7%), and neutropenia (6.7%). Ten patients (66.7%) experienced at least 1 grade 3–4 AE	117
I/II	Metastatic	Gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 28 d)	67	Abraxane 100 mg/m^2 + gemcitabine (dose level 1) Abraxane 125 mg/m^2 + gemcitabine (dose level 2) Abraxane 150 mg/m^2 + gemcitabine (dose level 3)	MTD: dose level 2 (n = 44) Median PFS: 7.9 mo (95% CI, 5.8–11.0 mo) Median OS: 12.2 mo (95% CI, 8.9–17.9 mo) 1-y Survival: 48% For all 67 patients: Median PFS: 7.1 mo (95% CI, 5.7–8.0 mo) Median OS: 10.3 mo (95% CI, 8.4–13.6 mo) ORR dose level 2: 48% ODCR dose level 2: 68%	DLTs: sepsis and neutropenia Treatment-related AEs: anemia (98%), leukopenia (91%), neutropenia (89%), thrombocytopenia (83%), fatigue (76%), alopecia (76%), sensory neuropathy (63%), and nausea (48%) Most common grade ≥3 AEs: neutropenia (67%), leukopenia (44%), thrombocytopenia (23%), fatigue (21%), and sensory neuropathy (15%)	118
I/II	Metastatic	Gemcitabine (1000 mg/m^2 on days 1 and 8 every 21 d)	21	Abraxane 80 mg/m^2 + gemcitabine (dose level 1) Abraxane100 mg/m^2 + gemcitabine (dose level 2) Abraxane 120 mg/m^2 + gemcitabine (dose level 3)	MTD: was not met; dose level 3: Median PFS: 5.23 mo (95% CI, 3.42–7.04 mo) Median OS: 12.17 mo (95% CI, 4.09–20.14 mo) For all 21 patients: Median PFS: 4.43 mo (95% CI, 4.01–4.83 mo) Median OS: 12.17 mo (95% CI, 9.49–14.84 mo) ORR dose level 3: 41.67% ODCR dose level 3: 83.33%	DLTs: elevated ALT and febrile neutropenia Treatment-related AEs: nausea vomiting (61.90%), neutropenia (57.14%), alopecia (42.86%), anemia (33.33%), fatigue (38.10%), thrombocytopenia (19.05%), sensory neuropathy (9.52%), elevated ALT/AST (9.52%), diarrhea (4.76%), and rash (4.76%) Most common grade ≥3 AEs: neutropenia (9.52%), febrile neutropenia (4.76%), thrombocytopenia (4.76%), and sensory neuropathy (4.76%)	119

(Continued on next page)

TABLE 5. *(Continued)*

Phase	Tumor Stage	Combination	No. of Patients	Arms/Groups	Efficacy Results	Safety Results	Reference
II	Advanced	None	19	Abraxane 100 mg/m^2 on days 1, 8, and 15 every 28 d	Median PFS: 1.7 mo (95% CI, 1.5–3.5 mo) Median OS: 7.3 mo (95% CI, 2.8–15.8 mo) 6-mo OS: 58% (95% CI, 33%–76%) 1 Patient had confirmed partial response 6 Patients (32%) had stable disease as their best response	Treatment-related AEs (most common): nausea (63%), anorexia (47%), hypocalcaemia (37%), and vomiting (26%) Most common grade ≥3 AEs: neutropenia (32%), febrile neutropenia (11%), and anemia (11%)	96
III	Metastatic	Gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 28 d)	861	Albumin-bound paclitaxel 125 mg/m^2 + gemcitabine (N + G) Gemcitabine 1000 mg/m^2 weekly for 7 of 8 wk (cycle 1) and then on days 1, 8, and 15 every 28 d (cycle 2 and subsequent cycles) (G)	Median PFS (N + G): 5.5 mo (95% CI, 4.5–5.9 mo); median PFS (G): 3.7 mo (95% CI, 3.6–4.0 mo); HR, 0.69 (95% CI, 0.58–0.82) Median OS (N + G): 8.5 mo (95% CI, 7.9–9.5 mo); median OS (G): 6.7 mo (95% CI, 6.0–7.2 mo); HR, 0.72 (95% CI, 0.62–0.83) 1-y Survival (N + G): 35% (95% CI, 30%–39%); 1-y survival (G): 22% (95% CI, 18%–27%) 2-y Survival (N + G): 9% (95% CI, 6%–13%); 2-y survival (G): 4% (95% CI, 2%–7%) ORR (N + G): 23% (95% CI, 19%–27%); ORR (G): 7% (95% I, 5%–10%)	Treatment-related AEs (N + B): fatigue (54%), alopecia (50%), and nausea (49%) Most common grade ≥3 AEs (N + B vs B): neutropenia (38% vs 27%), leukopenia (31% vs 16%), fatigue (17% vs 7%), peripheral neuropathy (17% vs 1%), thrombocytopenia (13% vs 9%), and anemia (13% vs 12%) AE leading to death was the same in N + B and B (4%)	12

ALT indicates alanine transaminase; AST, aspartate aminotransferase; HR, hazard ratio; LTFs, liver function tests; ODCR, overall disease control rate; ORR, overall response ratio.

As nab-paclitaxel alone results in stromal depletion and tumor regression in tumor xenografts,[118] a small phase II trial with the drug as monotherapy was carried out in patients with advanced disease as second-line therapy following gemcitabine-based therapy.[120] At 100 mg/m^2 on days 1, 8, and 15 every 28 days, nab-paclitaxel administration resulted in a median PFS of 1.7 months, an OS of 7.3 months, and a 6-month survival of 58%. Unexpectedly, only 2 of 15 patients had positive SPARC expression in examined tissues, and these patients did not respond to treatment. Even if this report supports results from experiment in mice that dismiss the role of SPARC in the nab-paclitaxel effect, it should be noted that the origin of the biopsies in this clinical trial was not specified.[115] This is of significance because the pattern of SPARC expression may differ between primary tumors and metastases.[76]

Other drugs have been tested in combination with nab-paclitaxel. For instance, nab-paclitaxel combined with gemcitabine and increasing doses of vandetanib (Caprelsa) was tried in a phase I study in different solid tumors, including metastatic PDAC.[117] Vandetanib is a kinase inhibitor commonly used in medullary thyroid cancer.[121] The combination showed acceptable tolerance levels and a partial response rate of 14.3%. However, AEs of grade 3 or greater were experienced by more than 66% of patients. Nab-paclitaxel, combined with 5-fluorouracil, leucovorin, oxaliplatin, and bevacizumab, has shown a surprisingly high response rate (50%) in a phase II trial.[122] According to clinicaltrials.gov, there are 39 clinical trials registered (4 active–not recruiting and 35 recruiting) for the evaluation of nab-paclitaxel, alone or in combination with other agents, in different PDAC stages (search results for "nab-paclitaxel" AND "pancreatic cancer," "Abraxane" AND "pancreatic cancer"; accessed August 2014).

The promising results of phase I/II trials led to a very important phase III clinical trial comprising 861 PDAC patients (MPACT: Metastatic Pancreatic Adenocarcinoma Clinical Trial).[12] The previous regimen of nab-paclitaxel at 125 mg/m^2 on days 1, 8, and 15 every 28 days in combination with fixed doses of gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 28 days) was compared with gemcitabine monotherapy (1000 mg/m^2 weekly for 7 of 8 weeks and then on days 1, 8, and 15 every 28 days). The results are summarized in Table 5. Briefly, the combination increased the PFS (5.5 vs 3.7 months) and the median OS (8.5 vs 6.7 months). Importantly, nab-paclitaxel combined with gemcitabine showed superior response rates (23% vs 7%), 1-year survival (35% vs 22%), and 2-year survival (9% vs 4%), as compared with gemcitabine alone. Even if grade 3 or higher AEs were observed (especially sensory neuropathy), these were reversible and disappeared or improved to grade 1 in less than 30 days. Based on these solid data, the Us Food and Drug Administration approved nab-paclitaxel combined with gemcitabine for first-line treatment in metastatic PDAC in September 2013.

Like FOLFIRINOX, nab-paclitaxel combined with gemcitabine has become a new option among therapeutic agents used against PDAC. The next quest is to find combinations that take advantage of the stromal depletion induced by nab-paclitaxel. Similarly to FOLFIRINOX, the implementation of the new regimen may not be limited to metastatic disease and could be implemented as neoadjuvant therapy in less malignant PDAC stages.[123] Retrospective studies have shown promising results in resectable, locally advanced, and borderline/unresectable PDAC.[124–126] Interestingly, sequential neoadjuvant administration of nab-paclitaxel plus gemcitabine and FOLFIRINOX seems to induce complete remission in locally advanced and unresectable PDAC.[127] Thus, nab-paclitaxel has emerged as a central therapeutic agent in PDAC, and it may become part of novel therapeutic regimens in the future.

CONCLUSIONS

Despite conflicting results, most data indicate that SPARC plays an important role in the pathophysiology of PDAC. The fact that the *SPARC* gene is already hypermethylated in premalignant lesions indicates that the protein is important in tumor initiation and progression. Even if SPARC acts as a tumor suppressor in PDAC tumor cells, the overexpression of SPARC in peritumoral fibroblast has devastating effects leading to an even worse prognosis. Apparently, PDAC cells and components of the tumor microenvironment induce SPARC overexpression in stromal cells. However, the mechanisms behind this effect are completely unknown. While serum SPARC levels do not seem to be useful as a tumor marker, increased SPARC levels in serum, pancreatic juice, or ascites could be used in the prediction of response rates to nab-paclitaxel–containing regimens. Likewise, methylation panels comprising SPARC may be suitable for early detection.

The associations between nab-paclitaxel and SPARC are controversial. Preclinical results suggest that stromal depletion achieved upon nab-paclitaxel treatment is associated with SPARC. However, murine studies suggest the opposite. The combination of nab-paclitaxel and gemcitabine has shown promising results, but it should be remembered that the median survival is prolonged only by 1.8 months when compared with gemcitabine alone. Thus, despite the improvements accomplished during the past years, PDAC still has a dismal prognosis. Perhaps, more efforts should be put on the development of novel compounds that takes advantage of the high affinity of SPARC for albumin. Nab technology could be combined with other chemotherapeutic agents.[128] The use of nanoparticles for drug delivery in cancer is a reality, and it is only a matter of time before novel and more effective compounds targeting SPARC in PDAC are discovered.[129] To reach this goal, further research and elucidation of involved mechanisms between SPARC and PDAC are warranted.

REFERENCES

References are available online at: http://links.lww.com/MPA/A450.