**REVIEW**

Molecular mechanisms underlying the divergent roles of SPARC in human carcinogenesis

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Communication between the cell and its surrounding environment, consisting of proteinaceous (non-living material) and extracellular matrix (ECM), is important for biophysiological and chemical signaling. This signaling results in a range of cellular activities, including cell division, adhesion, differentiation, invasion, migration and angiogenesis. The ECM non-structural secretory glycoprotein called secreted protein, acidic and rich in cysteine (SPARC), plays a significant role in altering cancer cell activity and the tumor’s microenvironment (TME). However, the role of SPARC in cancer research has been the subject of controversy. This review mainly focuses on recent advances in understanding the contradictory nature of SPARC in relation to ECM assembly, cancer cell proliferation, adhesion, migration, apoptosis and tumor growth.

Introduction

Matricellular proteins are non-structural and animatedly expressed proteins present in the extracellular matrix (ECM) (1). These proteins are transiently secreted to the ECM and do not become part of the ECM mesh. Acting at the interface between the cell surface and the ECM, matricellular proteins regulate cellular processes such as adhesion, migration, proliferation and differentiation (2,3). SPARC (secreted protein acidic and rich in cysteine), also known as basement membrane-40 (BM-40) tumor protein and/or osteonectin, is a 32–35 kDa multifunctional collagen or calcium-binding ECM glycoprotein belonging to a group of matricellular proteins (3). SPARC is located at 3q33.1 and consists of a single polypeptide (285 amino acids) comprising three biological structural domains, the acidic N-terminal (NT) domain, a follistatin-like domain and a Ca²⁺ binding extracellular domain (2,4). The NT domain has cell dispersion and chemosensitizing properties and induces apoptosis (5,6), the follistatin-like domain contains cysteine-rich residues and inhibits endothelial cell migration (7,8), whereas the C-terminal extracellular domain contains the ECM-Ca²⁺-binding segment (9) and may have antiangiogenic properties (5,8). A receptor for SPARC has not been known, and it is now reflect that SPARC may function as an competitor of other ligand–receptor interactions (10).

The expression of SPARC in cancer tissues and functional analyses of SPARC gene in tumor cell lines have been widely studied (Table I). The role of SPARC in tumorigenesis is controversial because of its complex pattern such as ‘downregulated pattern in a specific tumor cell types accompanied by upregulated pattern in adjacent stromal cells’ as described in ovarian, pancreatic and lung cancers (Fig. 1; 11–13). However, some investigations report a positive relationship between higher levels of SPARC and more aggressive cancer (14,15). Many studies, including our own discoveries, support the assessment that SPARC functions in part as a tumor suppressor in breast, colorectal, leukemia, lung, neuroblastoma, ovarian and pancreatic cancers (16–25). SPARC negatively regulates cell proliferation, angiogenesis and adhesion, but is increased in gliomas (grades II–IV) (26). These opposing actions of SPARC may be clarified by differences in the biological accomplishments of several proteolytic molecules including matrix metalloproteinases (MMPs), cathepsins, elastases and serine proteases (27). Therefore, variations in tissue-specific protease expression may explain the differences in the biological behavior of SPARC in different cancers and in carcinogenesis.

SPARC modulates ECM

SPARC is a non-collagenous ECM protein that functions as a regulator of matrix organization and a modulator of cell behavior (67). For example, SPARC induces focal adhesion disassembly and cell rounding when the purified protein is added to spread cells (68–70). In an orthotrophic model of pancreatic cancer, lack of SPARC in the host changes the tumor microenvironment (TME) and increases metastasis and invasion (71). Patient data suggest that higher expression of SPARC and FOXP3 are related with better disease outcome in stage II colorectal cancer (CRC) and may be predictive markers of this particular cancer survival (72). Higher levels of SPARC expression were found in the stromal cells adjacent to the gastric cancer cells, and its expression was statistically significantly different between gastric cancer and normal gastric tissue (P < 0.05) (73). Two sequences in SPARC (peptides derived from the C-terminal calcium-binding EF hand and from the cationic, cysteine-rich follistatin-like domain (peptide 2.1)) that are located in different regions can each stimulate focal adhesion reorganization. These results were confirmed by using antipeptide antibodies for each sequence, which fully blocked focal adhesion disassembly by the SPARC protein (68). Crystallographic data indicate that these two sites are in close proximity in the native protein and may form a binding pocket (2).

Several studies describe mechanisms by which SPARC regulates ECM assembly and the formation of MMPs and collagens (74). The development of mature ECM requires proper formation of an organized fibronectin matrix. SPARC is required for fibronectin-induced integrin-linked kinase (ILK) activation and intracellular signaling cascades that influence cellular contractile elements. Cells lacking SPARC exhibit diminished fibronectin-induced ILK activation and ILK-dependent cell contractile signaling (75). SPARC also plays a role in the assembly of fibrillar collagen in the ECM (76). A study by Nie et al. (77) demonstrated that SPARC induces the accumulation and activation of β-catenin in preadipocytes, leading to an enhanced association of β-catenin with T-cell factor/lymphoid enhancer factor and inhibition of adipogenesis. They also showed that ILK, but not Akt, is required for SPARC activation of β-catenin. Further, they suggested that SPARC regulates expression of α5- and α6-integrins through β-catenin. SPARC is known to accumulate in myofibroblasts in fibroblastic foci in idiopathic pulmonary fibrosis (78). A constitutive signaling cascade controlled by SPARC/β-catenin in idiopathic pulmonary fibrosis fibroblasts was revealed to increase the minimal expression of PAI-1, ensuing in opposition to plasminogen-stimulated apoptosis. This led to the destruction of epithelial restore and fibrosis in idiopathic pulmonary fibrosis (79).

Mice with a targeted interruption of SPARC have visible developmental abnormalities in the eye, adipose tissue and dermis (80,81) and show hastened closure of dermal wounds (10,82). These abnormalities have been elucidated, in part, by changed ECM assembly. Particularly, biopsies from SPARC-null (SP<sup>−/−</sup>) mice have less collagen than individuals from wild-type mice. The skin of SP<sup>−/−</sup> null mice has less hydroxyproline (less collagen) than that of SP<sup>+/−</sup> wild-type mice (83). Additionally, electron microscopy has revealed that the diameter
of collagen fibrils is significantly decreased in SP$^{+/−}$ compared with SP$^{+/+}$ dermis (80). The tumor burden was increased in SP$^{+/−}$ as compared with SP$^{+/+}$ mice after tumor cells were implanted subcutaneously, intraperitoneally or intravenously. A decreased quantity of collagen in the fibrils was also demonstrated around the tumors grown in SP$^{+/−}$ mice, and the collagen capsules that are contemporary had smaller cross-links and were of lesser diameter (33). The less restrictive ECM seen in SP$^{+/−}$ mice is permissive for enhanced pancreatic tumor growth (49). These observations highlight an important role for SPARC in the regulation of the fabrication and organization of the ECM in response to tumor development.

SPARC and cell adhesion

The process of cellular de-adhesion is potentially important for a cell’s ability to participate in morphogenesis and to respond to injurious stimuli. Anchorage-dependent cells require cell adhesion for survival (84–86). Dissimilarities in cell–matrix and cell–cell adhesion in tumors depend on the level of consistency and the nature of tumor expansion. Abrogation of regular cell adhesion function demonstrates a crucial role in the progression of cancer. This change in tumor cell adhesion is crucial because detachment of malignant tumor cells is an early step in the invasion of neighboring tissues and migration to distant sites. SPARC is considered ‘anti-adhesive’, because it does not directly support cell attachment (87). SPARC is expressed in response to injury and induces rapid transition to an intermediate state of adhesiveness characterized by loss of actin-containing stress fibers and restructuring of the focal adhesion plaque that includes loss of vinculin and α-actin (88). This intermediary state is suggested to facilitate expression of specific genes that are involved in repair and adaptation. SPARC binds to several integral components of the ECM and exhibits an antiadhesive function that includes abrogation of focal adhesions and disruption of cell spreading and motility (54,88). It has been shown that SPARC has counteradhesive activity in non-lens cells in vitro, for example, in endothelial cells (5,55), glioma cells (56), fibroblasts (89), smooth muscle cells and transfected F9 teratocarcinoma cells (90), in part by disruption of focal adhesion complexes and by prevention of cell spreading through unidentified mechanisms (88,90). SPARC was found to inhibit lens epithelial cell adhesion by several potentially related mechanisms that include diminishment of focal adhesions, inhibition of LN-1 deposition, downregulation of α6-integrin heterodimer formation and reduction of tyrosine-phosphorylated paxillin (54,55). Higher levels of

### Table I. Multifunctional SPARC in cancer (modified from our earlier publication GP Nagaraju and Sharma, 2011 (87))

<table>
<thead>
<tr>
<th>Types of cancer</th>
<th>Exogenous SPARC</th>
<th>Endogenous SPARC level</th>
<th>Knockdown of SPARC</th>
<th>Studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>Alters cell proliferation, induce differentiation, apoptosis and tumor growth</td>
<td>Low</td>
<td>Increases growth and reduces apoptosis</td>
<td>In vitro, in vivo</td>
<td>(21,28,29)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Inhibited proliferation and migration</td>
<td>Low</td>
<td>Increases invasion and metastatic behavior</td>
<td>In vitro, in vivo</td>
<td>(30–32)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Inhibits growth and angiogenesis, induces autophagy and apoptosis</td>
<td>Low</td>
<td></td>
<td>In vitro, in vivo</td>
<td>(23,33–36)</td>
</tr>
<tr>
<td>Lung</td>
<td>Inhibited cell growth</td>
<td>High</td>
<td>Inhibition of cell invasion</td>
<td>In vitro, in vivo</td>
<td>(37)</td>
</tr>
<tr>
<td>Breast</td>
<td>Inhibits cell proliferation and metastasis, stimulates cell migration, invasion and tumor growth</td>
<td>High</td>
<td></td>
<td>In vitro, in vivo</td>
<td>(38–43)</td>
</tr>
<tr>
<td>Bladder</td>
<td>Inhibits the growth of spheroids, induce invasion</td>
<td>High</td>
<td>Induce tumor growth</td>
<td>In vitro, in vivo</td>
<td>(44)</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td>Low or high level</td>
<td></td>
<td></td>
<td>(20,51–53)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Inhibits cell growth, migration and invasion</td>
<td>Low</td>
<td>Increases cell growth and reduces apoptosis</td>
<td>In vitro, in vivo</td>
<td>(13,48,49)</td>
</tr>
<tr>
<td>Leukemia cells, acute myeloid leukemia cell lines</td>
<td>Inhibits growth of cell lines and induces G$_2$/G$_1$ cell cycle arrest</td>
<td>Low</td>
<td></td>
<td>In vitro, in vivo</td>
<td>(50)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Inhibits cell growth and enhances apoptosis</td>
<td>Low or high level</td>
<td></td>
<td></td>
<td>(26,54–60)</td>
</tr>
<tr>
<td>Gliomas</td>
<td>Delay in tumor growth, inhibits cell proliferation, reduces apoptosis, increases migration, invasion and cell de-adhesion</td>
<td>High</td>
<td>Cell cycle succession</td>
<td>In vivo, in vitro</td>
<td>(23,25,34,61–63)</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Inhibits cell proliferation, stimulated G$_2$/M cell cycle arrest, autophagy and apoptosis, inhibits migration and invasion</td>
<td>Low</td>
<td></td>
<td></td>
<td>(23,64)</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Inhibits spreading, migration and proliferation, induces apoptosis</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stromal cells</td>
<td>Modulates proliferation</td>
<td>High</td>
<td>Inhibited proliferation, invasion and metastasis, induced apoptosis</td>
<td>In vivo, in vitro</td>
<td>(52,63)</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td>Suppressed invasion and significantly increased the apoptosis</td>
<td>In vivo, in vitro</td>
<td>(66)</td>
</tr>
</tbody>
</table>
SPARC induces cell de-adherence from matrix in gliomas (26). SPARC also changes glioma progression by altering the TME and by inhibiting vascular endothelial growth factor (VEGF) expression (26). These findings suggest a novel mechanism whereby SPARC blocks VEGF function by inhibiting the existing growth factor. SPARC inhibited VEGF- and integrin-mediated ID8 proliferation, showed adhesion to ECM proteins and peritoneal mesothelial cells in vitro and inhibited their tumorigenicity of ovarian cancer in vivo (91). This antiadhesive effect of SPARC was revealed to be mediated in part through considerable decrease of cell membrane expression and clustering of alpha(v)-integrin subunit, alpha(v)beta(5), alpha(v)beta(3)-heterodimers, and beta(1)-subunit, although less significantly in ovarian cancer cells (91).

SPARC and migration

It has been suggested that the intermediate state of adhesion favors cell motility (92,93). Matricellular proteins exhibit increased expression during development and in response to injury, suggesting that one of their functions may be the promotion of this intermediate adhesive state to facilitate cell migration. SPARC inhibits endothelial cell chemotaxis in response to fibroblast growth factor-2 (94). SPARC suppresses glioma growth, but promotes migration and invasion by mediating integrin and growth factor receptor-regulated kinases and their downstream effectors. AKT and SHC-RAF-ERK signaling pathways were shown to be involved in SPARC-induced invasiveness (95). SPARC inhibits the growth of pancreatic ductal adenocarcinoma cells; however, it also increases invasiveness (96). Overexpression of SPARC inhibited proliferation and migration of prostate cancer by interacting with integrin (30). Decreased SPARC secretion from stromal cells may involve prostate cancer development mediated through inhibiting AKT phosphorylation after interaction with integrin (1). Stable overexpression of SPARC in Daoy medulloblastoma cell lines significantly inhibited the activity of Rac, Rho and Cdc42, which all control the actin cytoskeleton. This inhibition was accompanied by an increase in the phosphorylation of Src at Tyr-416, which led to a loss of actin stress fibers and focal contacts, a decrease in the phosphorylation level of coflin and suppressed migration and invasion in vitro (61). This effect was reversed by the knockdown of SPARC and led to reversed Src-mediated disruption of the cytoskeleton organization as well as dephosphorylation of coflin and stimulation of Rho A (61). These results establish SPARC as an effector of Src-stimulated cytoskeleton disruption in medulloblastoma cells, which consequently leads to reduced migration and invasion. SPARC inhibits glioma growth but induces migration and invasion by mediating growth factor receptor-regulated kinases, integrin and their effectors. Coexpression of SPARC and PTEN inhibited glioma tumors with lesser invasive ability and longer animal survival (95). SPARC overexpression was associated with most aggressive human melanomas (14,97), and its expression was suggested to predict the clinical outcome of thin cutaneous melanoma (98). SPARC expression in melanoma cells has been also associated with the transition from epithelial to a more aggressive mesenchymal phenotype with decreased E-cadherin and increased N-cadherin expression levels as well as enhanced focal adhesion kinase activity (99). Integrin (4 controls SPARC protein to stimulate invasion in breast cancer (45). Treatment of prostate cancer cells with small interfering RNA-based knockdown of CXCL-1 or -2 and curcumin downregulates metastasis-promoting factors like SPARC, COX2, EFEMP, thereby inhibiting proliferation and inducing apoptosis (100). Recent studies suggest that inhibition of both HSP27 and pAKT may be a valuable therapeutic approach to inhibit SPARC-induced glioma cell survival and invasion in SPARC-positive/PTEN-null tumors and SPARC-positive/PTEN-wild-type (101). SPARC induces cathepsin B-mediated invasiveness through a collagen Iα1/α2β1 integrin pathway in melanoma (102). Expression of tumor protein 53-induced nuclear protein 1 (TP53INP1) and decreased cell migration by the transcriptional inhibition of SPARC. The effect of the novel TP53INP1 molecule on the regulation of SPARC levels could clarify in part its tumor suppressor role in pancreatic adenocarcinoma by changing cellular spreading through metastatic progression (103). Knockdown of SPARC in lung cancer cells (H322 and A549 cells) led to inhibition of cell invasion, comparable with that observed in Krüppel-like factor 4 (KLF4)-transfected cells. Overexpression of KLF4 suppresses lung cancer cell invasion by inhibiting SPARC levels (104). Expression of SPARC was increased.

Fig. 1. Schematic diagram showing the major signaling pathways that may account for the SPARC-mediated regulation of cellular processes involved in tumorigenesis.
in tumor tissue compared with non-tumor tissue in 89 non-small cell lung cancer patients, whereas KLF4 levels were decreased compared with that in the control tissue (105). SPARC expression may play a considerable role in the initiation and expansion of non-small cell lung cancer, whereas KLF4 inhibits metastases. These results suggest that SPARC and KLF4 proteins may be used as markers for assessing the biological distinctiveness and clinical stages of non-small cell lung cancer. SPARC expression was also significantly associated with poor survival of breast cancer patients (106), and inversely correlated with estrogen receptor content, indicating that SPARC expression is associated with less differentiated and more aggressive breast cancer tumors (38). However, this study did not investigate whether overexpression of SPARC in breast cancer cells yields tumors in vivo.

Cell survival and apoptosis

Disregulation of cellular activities disrupts the balance between cell survival and cell death. This abnormal activity can contribute to cancer initiation and advancement and can even impact tumor response to radiochemotherapy. We and others have previously revealed that overexpression of SPARC can impact cell growth and apoptosis (23,25). SPARC regulates a wide range of growth factors (2), which includes VEGF, platelet-derived growth factor and transforming growth factor (TGF), etc. SPARC inhibits VEGF- and fibroblast growth factor-2-stimulated proliferation of endothelial cells (Fig. 1). It can also suppress activity of platelet-derived growth factor in stromal cells (2). Previous studies have revealed that SPARC and TGF-β engage each other in a mutual relationship to regulate cellular activities. SPARC and TGF-β were revealed to be possible inhibitors of cell proliferation, cell cycle progression and in different types of cancer cells (10,94,107,108). SPARC stimulates TGF-β expression in mesangial cells and on the other hand, TGF-β induces SPARC expression in endothelial cells and keratinocytes (109–113). SPARC negatively controls epithelial cell proliferation by altering the TGF-β pathway, via pairing of the extracellular domain (114). Both TGF-β and SPARC are expressed in epithelial cells; however, the relationship between these two signaling molecules in directing epithelial cell activities remains to be studied.

SPARC has been shown to inhibit serum-stimulated growth of Lewis lung carcinoma cells in vitro (33). SPARC suppresses glioma cell proliferation in vitro (56,57) and delays tumor growth in rat brains in vivo (15). SPARC has been shown to act as a survival factor in stressed (initiated by serum withdrawal) glioma cells with increased AKT activation and decreased caspase 3/7 activity (115). Another study showed that SPARC mediates glioma tumor progression through the activation of two important cytoplasmic kinases, ILK and focal adhesion kinase (115).

SPARC inhibits breast cancer cell growth and cell division without enhancing metastasis (39). Haber et al. (63) reported that SPARC alters the proliferation of stromal cells, but not melanoma cells. They also confirmed that SPARC negatively controls endothelial cell proliferation and migration. Usually, low expression of integrins after introduction to SPARC considerably decreases cell proliferation and adhesion, in part by suppressing the triggering of MAPK 44/42, Akt, focal adhesion kinase and Src (91). In vitro treatment with exogenous SPARC considerably prevents the growth of several cancer cell lines including CRC, pancreatic cancer, neuroblastoma and leukemia cells (13,20,34,50). Depletion of SPARC in bladder cancer increased carcinogenesis and progression in mice (44). In human bladder cancer tissues, the incidence and level of SPARC expression were negatively correlated with disease-specific survival.

SPARC protects lens epithelial cells from stress-induced apoptosis in vitro via an interaction with integrin β1 heterodimers that enhances ILK activation and prosurvival activity (116). Knockdown of SPARC in glioma cell lines (U-87MG cells) suppressed p-c-Raf (Ser259) and increased p-GSK-3β (Ser9) and p-AKT (Ser473), which could have resulted in the cell cycle succession observed in cells treated with SPARC short hairpin RNA (58). Overexpression of SPARC rapidly increases AKT phosphorylation, an effect that is upturned by a compensating SPARC antibody. AKT phosphorylation is important for the antiapoptotic activities of SPARC, as the reduced apoptosis and caspase activity coupled with SPARC expression can be abolished with a dominant-negative AKT (Fig. 1; 59). These results conclude that SPARC functions, in part, to support tumor progression by facilitating tumor cells to live in stressful environments. Knockdown of SPARC decreased cervical cancer cell proliferation and metastasis (65). Overexpression of MMP-9 in the absence of SPARC has a protective effect in inducing tumor advancement (48). The investigations validate that mechanisms underlying the functions of SPARC in cancer growth are many-faceted and are swayed by cancer cell type and surrounding. SPARC initiates the triggering of the extrinsic pathway of apoptosis by coupling with caspase 8 (N-terminus) and caspase 7 (N-terminus), with subsequent contribution of the intrinsic cascade, via Bid, to stimulate apoptosis (117). In association with these explanations, Rahman et al. (6) revealed that the N-terminus domain of caspase 8 interacts instead with Bcl2 to decrease apoptosis. The inhibitory result on apoptosis is reversible in the presence of SPARC after endogenous overexpression. Further, these results were confirmed by utilizing stable cell lines overexpressing the synthetic 51-aa peptide spanning the NT-domain of SPARC and reflecting SPARC’s apoptotic activity (6). Knockdown of SPARC induced cervical cancer cell apoptosis (65). Conditioned medium from SPARC-overexpressed neuroblastoma cells suppressed cell proliferation, endothelial tube formation, stimulated programmed cell death in vitro and neovascularization in vivo (35). Bhoopathi et al. (23) found that SPARC induces autophagy in medulloblastoma cells. Knockdown of SPARC in glioma cell lines (U-87MG cells) was able to promote the cell cycle succession from the G1 to S phase (58). Overexpression of SPARC in SKOV3 (ovarian carcinoma) cell lines decreased the proliferation and induces differentiation (28). Knockdown of SPARC in human melanoma cells and xenografted A375 tumors elicit apoptotic cell death through the mitochondrial intrinsic pathway and by upregulation of caspase-3. This effect was dependent on p53 and stimulation of Bax (46).

SPARC and tumor growth

SPARC may promote tumor progression by modulating the activity of cytokines and stimulating secretion of tissue remodeling metalloproteases (27,118,119). Implanted cancer cells develop tumors more rapidly in mice without SPARC, indicating that SPARC is important for collagen deposition and fibrillogenesis (76). Knockdown of SPARC stimulated G1/M cell cycle arrest and tumor growth regression with activation of p53, p21 (Cip1/Waf1) and prevented mitotic progression in melanoma in vitro and in vivo. Further, abridged mesenchymal features and the invasive properties of SPARC-silenced cells were observed. SPARC controls, in a cell autonomous manner, cell proliferation and cell cycle progression through the p53/p21 pathway (46). Knockdown of SPARC inhibited cervical cancer cell proliferation, cell invasion and cell metastasis and induced cell apoptosis (65). Knockdown of SPARC in MGC803 and HGC 27 gastric cancer cells suppressed their invasion and significantly increased apoptosis. These results confirm that targeting of SPARC could be a useful therapeutic advance against gastric cancer (66). Knockdown of SPARC in human melanoma cell lines resulted in growth inhibition with G1 (1) cell cycle arrest accompanied by increase of p21, a cyclin-dependent kinase inhibitor, in vitro and delayed tumor growth in vivo (120). These observations suggest that SPARC contributes to cell proliferation and may possibly be a potential target molecule for melanoma therapy.

Overexpression of SPARC stimulated G1/M cell cycle arrest, which was mediated through suppression of the cyclin-B-regulated signaling cascade involving p21 and cdc2 in medulloblastoma in vitro and in vivo (25). Further, treatment of SPARC inhibited STAT3 phosphorylation at Tyr-705 and the tumor development and volume of preestablished orthotopic tumors in nude mice. These results suggest that STAT3 plays an essential role in SPARC-stimulated G1/M cell cycle arrest in
medulloblastoma cells. Tumors developed in SPARC-null mice exhibited changes in the fabrication and organization of ECM constituents and a decline in the infiltration of macrophages without any influence on tumor growth, indicating that host-derived SPARC is important for the organization of the ECM in reaction to implanted tumor cells and highlighting the significance of the ECM in regulating tumor development (33). Expression of SPARC in the stroma was suggested to facilitate the development of the thick collagenous stroma coupled with pancreatic ductal adenocarcinoma lesions. There was a decrease in fibrous tumor capsule when pancreatic adenocarcinoma cells were orthotopically implanted into SPARC-null mice. With this reduced mechanical control, tumors in the SPARC-null mice had faster growth and increased permeability and perfusion (121). Overexpression of SPARC in SKOV3 (ovarian carcinoma) cell lines suppressed the cell's ability to stimulate tumors in nude mice. These results support the postulation that SPARC has a role as a tumor suppressor (28).

SPARC might favor metastatic dissemination of malignant cells through the activation of matrix-degrading enzymes. It was shown that SPARC expression in human melanoma cells directly correlated with MMP-2 and MMP-9 levels and activity (14). Moreover, breast cancer cells responded to SPARC by showing increased activity of MMP-2 (16) and glioma cells had upregulated MT-MMP and MMP-2 in the presence of SPARC (122), indicating that SPARC might enhance the invasive capacity of tumor cells. Endogenous SPARC expression prevented MDA-MB-231 breast cancer cell metastasis to different organs including lung and bone by suppressing tumor cell–platelet aggregation, a potential mechanism by which tumor cells might disseminate (40).

Response to chemotherapy and radiation

There are preliminary data advising that SPARC in the TME may be helpful for targeting chemoradiotherapy. More recently, the response of head and neck cancers to a nab-paclitaxel (nanoparticle albumin-bound paclitaxel) was revealed to associate with SPARC expression in the TME (123). SPARC is well known to bind to albumin, and the interaction of SPARC with nab-paclitaxel may give attention to the drug in the tumor surrounding area and increase efficacy (124). Exogenous exposure in vivo promotes greater tumor regression in CRCs that had become refractory to conventional chemotherapies (20). Rahman et al. (6) demonstrated that tumor xenografts of cells overexpressing only the N-terminus domain of SPARC experienced the most dramatic tumor regression in response to chemotherapies. SPARC was revealed to enhance the apoptotic pathway, improving the outcome of cytotoxic agents used in cancer treatment. SPARC stimulates the activation of the extrinsic cascade of apoptosis by interacting with caspase 8 (N-terminus), with the subsequent contribution of the intrinsic cascade, via Bid, to increase apoptosis (117). Exposure to high levels of SPARC increases apoptosis and significantly decreases cell viability in CRC cells that have become resistant to chemotherapy (20,117). Overexpression of SPARC also induces neuronal differentiation of medulloblastoma cells via the Notch1/STAT3 pathway (125). This effect can sensitize medulloblastoma cells to treatment as differentiated cells are more susceptible to radiochemotherapy.

Treatment of mice carrying colorectal tumors with SPARC and CPT-11 leads to increased cellular senescence and tumor regression. These results indicate that the chemosensitizing outcome of SPARC in CRC is, thus, possibly mediated in part by triggering cellular senescence (126). Both SPARC and irradiation treatment resulted in greater cell death of medulloblastoma cell lines when compared with cells treated with either SPARC or irradiation treatment alone. Furthermore, our group also demonstrated that SPARC overexpression suppressed irradiation-stimulated SOX-4–mediated DNA repair (24). Recently, Sailaja et al. (127) demonstrated that overexpression of SPARC in combination with irradiation treatment led to the activation of caspase 3 and cleavage of poly (ADP ribose) polymerase and induced autophagy-mediated apoptosis in both SK-N-AS and NB-1691 neureoblastoma cell lines. Taken together, these results suggest combining SPARC with irradiation and/or chemotherapy as a new therapeutic approach for the treatment of neuro- and medulloblastoma.

Summary

Recent studies have begun to shed light on the mechanisms underlying SPARC-mediated effects on several aspects of cancer processes (Fig. 1). However, the role of SPARC is tumor specific, with the prospective to function as a tumor suppressor, as a factor or a proinvasive factor that may hamper or enhance the efficacy of chemotherapies and radiotherapy. These divergent roles make it difficult to define a clear direction for the development of SPARC as a potential target for cancer therapy. It may be most appropriate to consider the cell-dependent context, the background of each cell line tested and the influence of different dysregulated pathways in these cell lines, which will allow for targeting specific components in the development of SPARC-based treatment options.

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Divergent roles of SPARC

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