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Secreted Protein Acidic and Rich in Cysteine (SPARC) in Cancer

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Abstract

The local tissue microenvironment "niche" is composed of cellular and non-cellular components and plays an important role in regulating cell behaviour, during embryogenesis, and in physiologic and pathologic contexts including cancer. The cellular component is formed of specialized cell types endowed for the biological functions of the organ and tissues. The non-cellular component of the niche comprises the extracellular matrix (ECM) which functions not only as a scaffold for the cellular component maintaining tissue morphology, but dynamically influences fundamental aspects of cell behaviour. Matricellular proteins are a group of extracellular matrix (ECM) molecules that are not components of the structural scaffold of the ECM but serve as cell regulators and modulators of cellular behaviour and signaling. Secreted Protein Acidic and Rich in Cysteine (SPARC) is one of the matricellular proteins and is implicated in myriad physiological and pathological conditions characterized by extensive remodelling and plasticity. The role of SPARC in cancer is being increasingly recognized as it plays multi-faceted contextual roles depending on the cancer type, cell of origin and the surrounding milieu. The role of SPARC in the multistep cascades of carcinogenesis, cancer progression and metastasis has been studied retrospectively in human tumors, preclinical models using cell lines and models of oncogene-driven and carcinogen-induced cancers. Below we review several of these tumor types where SPARC biology has been evaluated.

Keywords: Niche; Extracellular matrix; SPARC; Matricellular proteins

Introduction

Matricellular proteins are a group of Extracellular Matrix (ECM) molecules that are not components of the structural scaffold of the ECM but serve as cell regulators and modulators of cellular behaviour and signaling during embryonic development, cell differentiation myriad physiological and pathological contexts[1-5] (Figure 1). The diverse group of matricellular proteins includes the glycoproteins secreted protein acidic and rich in cysteine (SPARC/osteonectin/BM40), thrombospondin (TSP), tenascin C (TNC), osteopontin (OPN) and periostin (POSTN) [2]. In this review, we will focus on SPARC. Initially discovered as a bone matrix and a basement membrane protein, the role of SPARC in tissue development and homeostasis was rapidly noted (reviewed in [1,4]). *In vivo,* SPARC has been shown to regulate collagen deposition, fibrillogenesis and assembly and hence it has been implicated in myriad physiological and pathological conditions characterized by extensive remodelling and plasticity where it functions to maintain tissue homeostasis (summarized in [3,4,6-11]). The role of SPARC in tissue homeostasis is exemplified by the phenotypes of SPARC-deficient mice as cataract formation and osteopenia, decreased size and tensile strength of dermal collagen fibers, and increased deposition of adipose tissue [12,13]. Other phenotypes, evolved when these mice were challenged as accelerated wound healing, angiogenesis, increased cardiac rupture, dysfunction and mortality in response to myocardial infarction, increased lung fibrosis and glomerulosclerosis. Reported phenotypes were related to defects of fibroblast differentiation and plasticity and increased leukocyte recruitment [3-5,7-11,14-17].

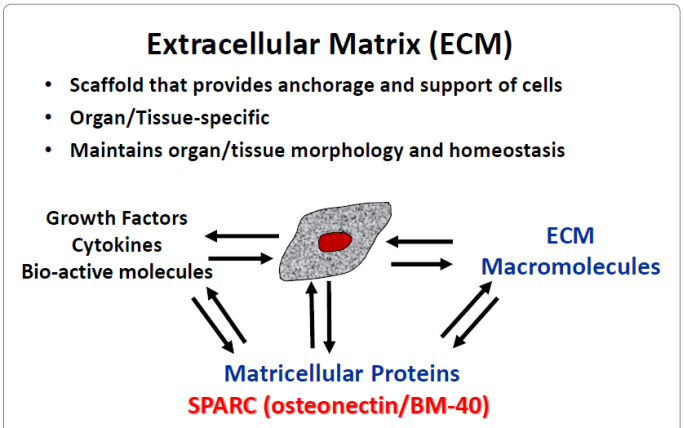

Figure 1: Extracellular matrix and matricellular proteins as modulators of cell interactions with its environment.

The role of SPARC in cancer is being increasingly recognized. SPARC plays multi-faceted contextual roles depending on the cancer type and whether it is produced by cancer cells or surrounding stromal cells in a given milieu (summarized in [5,14,15,18-20]). In many cases, cancer cells down-modulate SPARC whereas disease progression is associated with high level of stromal SPARC (summarized in [19]). The role of SPARC in the multistep cascades of carcinogenesis, cancer progression and metastasis has been studied retrospectively in human tumors, preclinical models using cell lines and models of oncogene-

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driven and carcinogen-induced cancers. Below we review several of these tumor types where SPARC biology has been evaluated.

Prostate Cancer

Two studies were reported on the role of SPARC on autochthonous oncogene-driven prostate cancer in *SP*-/- mice crossed with Transgenic Adenocarcinoma Of The Mouse Prostate (TRAMP) [20,21]. Crossing TRAMP mice with SPARC-null mice and generation of $T^+/SP^{+/+}$ and $T^+/SP^{-/-}$ mice allowed the study of the effect of SPARC on early phases of transformation and carcinogenesis [20]. When $T^+/SP^{-/-}$ mice with a C57Bl/6 genetic background were compared to their $T^+/SP^{+/+}$ controls, loss of SPARC was associated with accelerated cancer development, progression, and metastasis [20]. On the other hand, when $T^+/SP^{-/-}$ mice in a mixed C57Bl/6/129 genetic background were compared to $T^+/SP^{+/-}$ (haploid insufficient) mice, no significant difference in tumor incidence, take and metastasis albeit a greater proportion of $T^+/SP^{-/-}$ mice developed a more severe grade of prostate cancer [21]. The effects of SPARC liming prostate cancer progression was mediated through multiple effects on cancer cells and the surrounding stroma [20]. On cancer cells, SPARC inhibited cell proliferation and induced cell cycle arrest at G1-S phase. Using murine TRAMP cell lines to form SC tumor implants in $SP^{+/+}$ and $SP^{-/-}$ mice, and examining prostate tumors form $T^+/SP^{+/+}$ and $T^+/SP^{-/-}$ [20], we found that host SPARC restrains tumor growth, and this is associated with enhanced maturity of fibrillar collagen at the tumor periphery, decreased angiogenesis and proteolytic activity. The suppressive effects of SPARC on prostate cancer reported herein may, in part, be attributed to its negative effect on the constituents of the tumor microenvironment. Moreover, we observed enhanced proteolytic activity in the $T^+/SP^{-/-}$ prostate tumors suggesting a role in increased tumor angiogenesis by increasing the bioavailability of angiogenic growth factors and pro-angiogenic inflammatory cytokines such as VEGF (and bFGF), IL-6, and MCP-1, as well as making the ECM more permissive for neo-vascular growth and inflammatory cell influx [20]. The anti-proliferative effect of SPARC on human and murine prostate cancer cells *in vitro* mirrored it's *in vivo* effects [20]. Interestingly, exogenous and/or overexpression of SPARC inhibited prostate cancer cell invasiveness. Paradoxically, when used as a chemo-attractant, SPARC enhanced the invasive properties of many prostate carcinoma cell lines, and induced matrix metalloproteinase activity *in vitro* [20,22,23].

The effect of prostate stromal SPARC was recently studied using human prostate cancer tissue microarrays. Shin and colleague [24] reported higher expression of SPARC protein in normal human prostate tissue compared with cancerous tissues with higher expression in the stromal compartment compared to the cancerous compartment. They also reported higher secretion of SPARC protein from normal Prostate-Derived Stromal Cell (PrSC) compared to PCa-derived Stromal Cell (PCaSC) and prostate cancer cells. Mechanistically, using co-cultures of established human prostate cancer cell lines with normal and cancer associated stromal cells Shin and colleagues revealed that SPARC produced by normal prostate stromal cells exerted inhibitory effect on prostate cancer cell proliferation and AKT phosphorylation more than that of PCaSC. Immunoprecipitation studies revealed interaction of SPARC and integrin β1 in PCa cells which was further shown to be essential for the inhibitory effect of SPARC on prostate cancer cell proliferation and migration.

Because the TRAMP and other murine models do not produce bone metastasis, they were not useful for testing the impact of SPARC on prostate cancer skeletal metastases. *In vitro* models has been developed using SPARC protein, bones and/or bone extracts from $SP^{-/-}$ and $SP^{+/+}$ mice with human cell lines *in vitro* to mechanistically decipher the role of SPARC in the propensity of prostate cancer to metastasize to bones. The increased migration of prostate cancer cells was attributed to bone-SPARC activating tumor $\alpha_v\beta_3$ and $\alpha_v\beta_5$-VEGF axis [25]. In addition, metastatic prostate cancer cells expressed a secreted isoform of ErbB3 (p45-sErbB3), and induced SPARC expression and secretion by bone marrow osteoblastic lineage with subsequent increase in cancer cell invasiveness, that was blocked by neutralizing antibodies to SPARC [23]. Finally, immunohistochemistry of human and murine tumors demonstrated that both normal prostate epithelial cells and primary prostate carcinomas express low to moderate levels of SPARC, however, its expression is increased in metastatic foci [20,26-28].

A growing body of evidence suggests that SPARC exerts differential roles on prostate cancer cells in the bone microenvironment [20,23,25-27].The effect of bone matrix-SPARC was further investigated using $SP^{-/-}$ and $SP^{+/+}$ murine osteoblasts *in vitro* to represent the complex, crosslinked, and mineralized bone matrix [29] and was found to attenuate the growth of bone metastatic prostate cancer PC-3 cells, and increased their sensitivity to ionizing radiation [29]. The dynamic changes in the morphology and growth of PC-3 cells on $SP^{-/-}$ and $SP^{+/+}$ bone matrices suggests a complex series of changes in collagen topography preceding the observed differences [29]. In support of this is the enhanced osteolysis and enhanced growth of murine prostate cancer cells injected intra-osseously [30] suggesting that the proteolysis of SPARC could result in a more favorable microenvironment for metastatic cells. Consistently, cleavage of SPARC by metalloproteinases and cathepsin K [31,32] has been shown to release proteolytic fragments exerting distinct biological properties from those of the intact protein [33]. Metastatic prostate cancer cells have been shown to compete with hematopoietic stem cells for interaction with the skeletal niche, suggesting that bone matrix-SPARC could influence this interaction by affecting remodeling of the niche as well as the differentiation, fate commitment, and survival of niche cells [29,30,34-37].

Indeed the differential roles of SPARC in human prostate cancer progression and metastasis are still complex and controversial. The complexity is exemplified by the fact that gene expression profiling data may not reflect the exact pathological changes in prostate cancer due to technical variations in obtaining, transport and processing the samples for analysis. Most importantly, tumor heterogeneity adds an additional layer of complexity to interpretation of microarray analysis (summarized in [38]). These were reflected in results from a study by Gregg et al. [39] showing that the gene profiles from micro-dissected tumor epithelial cells and surrounding stroma where SPARC expression was significantly up-regulated in the juxta-tumoral stromal compartment compared to adjacent prostate cancerous tissues. In contrast, the transcriptome of laser capture-micro-dissected prostate tumor cells with poorly differentiated (PD) and with well differentiated (WD) phenotype were analyzed for gene expression and biochemical pathway alterations [40] and a significant association between SPARC expression (transcript and protein) and aggressive prostate cancer was reported. Therefore, Derosa and colleagues suggested SPARC as a potential early marker of less favorable outcome. The discordant reports on SPARC expression in clinical samples and reported functions in preclinical model systems beget more comprehensive clinical study designs, data mining and development of preclinical model systems that could really mimic *in vivo* scenarios of the human disease reflecting tumor heterogeneity, different stages and grades.

Urothelial Cancer of the Urinary Bladder

We have recently reported a comprehensive study to distinguish the role of tumor- versus host-SPARC during the evolution of bladder cancer [19]. SPARC protein expression was shown to have differential compartmentalization in human and murine bladder cancers with a decrease in the cancerous compartment as a function of disease progression while being concomitantly expressed in the tumor associated stroma [19].

To study the differential roles of SPARC in the early phases of urothelial transformation that are difficult to assess in humans, we introduced a chemical carcinogen, BBN in drinking water to $SP^{-/-}$ and $SP^{+/+}$ mice (Figure 2). This model recapitulates human bladder cancer and the induced rodent tumors exhibit similarity of gene expression to the human disease [19]. The ensuing urothelial pathology was associated with progressive generation of ROS and markers of DNA, protein and lipid oxidative damage; a scenario that was accelerated in $SP^{-/-}$ mice [19].

The expression of markers of oxidative damage as nicotinamide *N*-methyltransferase (NNMT) and sulfiredoxin; was augmented in $SP_{-/-}$ bladder along with increased activation of signaling cascades that converge in the activation of AP-1 and NFκB, the major orchestrators of inflammation, carcinogenesis, invasiveness and metastasis [41-43].

In an attempt to unravel the role of stromal- SPARC in the evolution of carcinogen-induced urothelial cancer, we first demonstrated the kinetics of SPARC protein expression during differentiation of primary fibroblasts and macrophages. We found that SPARC expression increased during early differentiation, then decreased to basal levels in macrophages but remained steady in differentiated fibroblasts. Heterotypic co-cultures of normal and cancerous urothelial cells with normal and tumor associated stromal cells indicated that SPARC inhibited the acquisition inflammatory secretory phenotype of Tumor Associated Macrophages (TAMs) and Cancer Associated Fibroblasts (CAFs) through inhibition of the activation of NFκB and AP-1 with subsequent decrease in their secreted cytokines and cancer cell invasiveness. The panel of secreted factors from CAF-cancer cell co-cultures revealed that TGF-β and SDF1 were exclusively produced by CAFs and were significantly downregulated by SPARC. These findings suggested that SPARC inhibited the inflammatory feed-forward loop in cancer cells, TAMs, and CAFs through secreted inflammasomes.

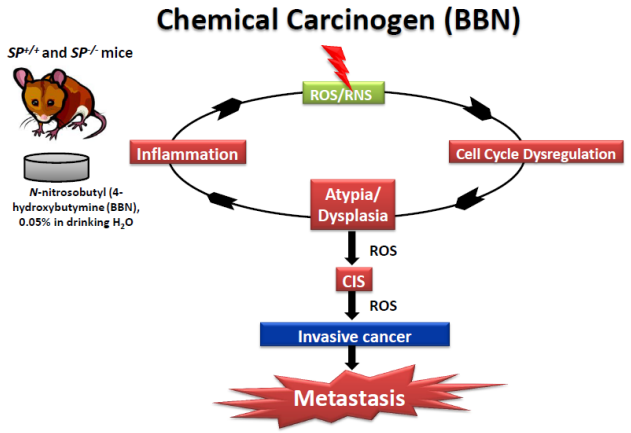

Figure 2: Chemical carcinogenesis model of bladder cancer.

On the one hand, inflammasomes sustain cancer cell proliferation, invasiveness, angiogenesis, and metastasis while on the other hand they play a critical role in recruitment and differentiation of stromal cells. The kinetics of SPARC expression in cancerous and stromal cells implicated SPARC in the intricate tightly-regulated programs of cellular recruitment, proliferation, differentiation and de-differentiation. These observations are supported by earlier studies that associated SPARC with differentiation of bone marrow mesenchymal stem/progenitor cells as osteoblasts, adipocytes, fibroblasts, myeloid cells and neuronal progenitors [4,12,13,44,45].

Gastrointestinal Cancers

Intestinal adenomas

The involvement of SPARC in oncogene-driven intestinal adenomas was studied by crossing *SP-/-* with $Apc^{Min/+}$ mice generating cohorts of $Apc^{Min/+}SP^{+/+}$ and $Apc^{Min/+}SP^{-/-}$ mice [46] and comparing the ensuing adenomas of these crosses. SPARC exhibited a 2-3 upregulation in adenomas at both the transcript and protein levels compared to the normal epithelium. SPARC deficiency resulted in decreased number of adenomas in both the small and large intestines with no difference in their size, distribution, malignant transformation to adenocarcinomas or extra-intestinal malignancies. The phenotype observed was attributed to the effect of SPARC on enterocyte migration along the crypt–villus axis.

Colorectal cancer (CRC)

SPARC is been considered a tumor suppressor in CRC according to the evidence from experimental cell models, $SP^{-/-}$ mice and clinical cohort studies [47]. In addition, exogenous SPARC, in combination with chemotherapy, was highly efficacious in achieving tumor regression in animal xenografts [47]. Genome-wide analysis revealed *Sparc* promoter hypermethylation in advanced therapy resistant CRC cells and tumors, and identified specific methylated CpG islands in the promoter. SPARC expression was restored by demethylating agent 5-Aza-dideoxycytidine, leading to improved sensitivity to chemotherapy [48-50]. Recently, SPARC expression was assessed in approximately 1120 normal and paired CRCs stages I-IV in tissue microarrays along with FOXP3. SPARC expression was significantly greater in CRC than normal colon with high SPARC expression correlated with good disease outcome and less adjuvant chemotherapy [51].

In a chemical carcinogenesis model of colorectal cancer using *SP-/-* mice and their $SP^{+/+}$ counterparts [52], Aoi *et al* reported the protective function of exercise-induced SPARC released from muscle tissue into the circulation significantly reducing the number of aberrant crypt foci (ACF) and crypts (AC) in the colons of $SP^{+/+}$ mice, but not in $SP^{-/-}$ mice. The injection of low- or high-dose recombinant SPARC also prevented the formation of chemically induced ACF and AC in the colons of $SP^{+/+}$ mice. Mechanistic studies indicated that both transcriptional and translational mechanisms potentiate the production and secretion of SPARC protein. This study suggested that SPARC can directly induce the apoptosis of colon cancer cells and inhibit their proliferation, and may indirectly prevent tumorigenesis by regulating the microenvironment in the colonic tissue; however such possibilities were not investigated [52,53].

Pancreatic cancer

In pancreatic cancer aberrant methylation of *Sparc* promoter has been reported in tumor tissues from patients with pancreatic cancer.

Gene expression profiling and confirmatory RT-PCR demonstrated that SPARC mRNA was expressed in non-neoplastic pancreatic ductal epithelial cells, but was not expressed in a majority of pancreatic cancer cell lines. SPARC protein was overexpressed in the stromal fibroblasts immediately adjacent to the neoplastic epithelium in primary pancreatic cancers, but rarely expressed in the cancers themselves [54]. Methylation of the *Sparc* CpG region 2 was linked to increased tumor size and tobacco smoke and alcohol exposure, whereas methylation of CpG Region 2 was more encountered in early pancreatic carcinogenesis [43]. *Saprc* methylation has been recently detected, with high sensitivity and accuracy, though with less frequency in retrospective analysis of fine percutaneous fine needle pancreatic biopsies [55]. The silencing of SPARC gene expression could be reversed by 5-Aza-2′deoxycytidine in pancreatic cancer [43,54,56]. A recent study reported that treatment of pancreatic cancer cell lines with novel curcumin analogues EF31 and UBS109 as demethylating agents resulted in significantly higher inhibition of proliferation and cytosine methylation and was associated with re-expression of silenced SPARC, along with p16, and E-cadherin. Mechanistically, the demethylating effect of EF31 and UBS109 was mediated through inhibition of HSP-90 and NF-κB-DNA methyltransferase-1 (DNMT-1) axis [57]. Primary fibroblasts derived from pancreatic cancer strongly expressed SPARC mRNA and secreted SPARC protein into the conditioned media, and treatment of pancreatic cancer cells with exogenous SPARC resulted in growth suppression. SPARC expression in fibroblasts from noncancerous pancreatic tissue was augmented by co-culture with pancreatic cancer cells [43,54,56,58]. However, SPARC expression in peritumoral stromal fibroblasts was increased and correlated with poor patient survival. SPARC expressed by human pancreatic stellate cells (hPSCs) exerted a paracrine effect increasing invasion of pancreatic cancer cells [59]. In contrast, another study [60] reported that knockdown of SPARC expression in pancreatic cancer cells inhibited *in vitro* and *in vivo* growth and metastases. Experimental mouse models indicate host SPARC is an inhibitor of tumor growth and metastasis. Murine pancreatic adenocarcinoma cells injected subcutaneously grew significantly faster and attained larger sizes in *SP-/-* mice [61]. Lack of endogenous (host) SPARC resulted in decreased collagen deposition, alterations in the distribution of tumor-infiltrating macrophages, and decreased tumor cell apoptosis. Although there was no difference in microvessel density of tumors from $SP^{-/-}$ or $SP^{+/+}$ mice, tumors grown in $SP^{-/-}$ had a lower percentage of mature blood vessels expressing the pericyte marker α-smooth muscle actin. Consistently, orthotopic pancreatic tumors produced more metastasis in $SP^{-/-}$ mice [62] that was mediated in part through MMP-9 impacting ECM deposition and angiogenesis in the tumor microenvironment. Another explanation is that the absence of stromal-derived SPARC, aberrant TGFβ levels and bioavailability accelerated tumor growth and metastasis in $SP^{-/-}$ mice with increased vascular endothelial cell permeability, inflammation and fibrosis [6,63,64].

Esophageal cancer

Alteration in SPARC expression has been observed in esophageal squamous cell carcinoma and adenocarcinoma [65-68]. Progressive increase in SPARC expression from normal and premalignant to malignant lesions in esophageal cancer was demonstrated [65,67,68] suggesting the utility of SPARC screening for diagnosis of occult malignancies in patients with Barrets esophagus. Several investigators have shown that SPARC levels may have prognostic significance in esophageal cancer [65,66] using genome-wide gene expression profiling of resected esophageal cancers, indicating that patients with low SPARC had a significant improvement in outcome. Another study revealed that SPARC was not detected in normal esophageal mucosa, but was expressed in stromal fibroblasts in 84.6% of esophageal SCC cases and in cancer cells in 7.8% of esophageal SCC cases [69]. While the expression of SPARC alone was not significantly correlated with survival patients with elevated levels of laminin-5γ2 chain and SPARC expressions had a poorer prognosis [69].

Gastric cancer

Human gastric cancer cell lines expressed variable levels of SPARC. Down-regulation of SPARC in high expressing cell lines inhibited their invasion and growth [70]. The expression of SPARC protein was mainly in the stromal cells surrounding the gastric cancer tissues, and was significantly negatively correlated with the expression of VEGF, vascular density and in tumor cell proliferation [71,72]. Conversely, SPARC transcript and protein levels were found to be up-regulated in tissues of diffuse-type gastric cancer and intestinal-type gastric cancer patients and were correlated with invasiveness and poor prognosis [73,74]. cDNA microarray identified SPARC as being up-regulated in primary gastric carcinoma tissue and the corresponding lymph node metastasis compared with the non-neoplastic mucosa. However, immunostaining of SPARC in these tumors revealed increased frequency and intensity of SPARC expression in fibroblasts rather than in tumor cells. Recently, the associations between SNPs in the SPARC 3'-untranslated region (UTR) and time to gastric cancer recurrence findings revealed that patients carrying at least one G allele of the SPARC rs1059829 polymorphism (GG, AG) showed a longer median time to tumor recurrence (TTR) of 3.7 years compared with 2.1 years TTR for patients with AA; whereas, patients harboring the G-A-A haplotype had the highest risk of tumor recurrence [75].

Hepatocellular carcinoma

The methylation status of *Sparc* was analyzed in one HCC cell line (SMMC-7721) and 60 pairs of HCC and corresponding non-tumorous tissues [76].In the SMMC-7721 cell line, the loss of SPARC expression was correlated with the aberrant methylation that was reversed by the demethylating agent 5-aza-2'-deoxycytidine. Methylation frequency of *Sparc* in HCC tissues was significantly higher than corresponding non-tumorous tissues and was correlated with down-regulation of SPARC mRNA expression, pathological classification and poorer overall survival [76].

Gynecologic Cancers

Ovarian cancer

Although SPARC was found abundantly expressed by stroma cells in advanced phases of human ovarian cancer, evidence points to SPARC as a protein that tries to normalize the microenvironment to counter tumor growth [14]. Particularly, SPARC normalizes ovarian cancer cell microenvironment by reducing inflammation [77,78] as evidenced by molecular analysis of the ascitic fluid from $SP^{-/-}$ mice implanted with ovarian cancer cells, containing less IL-6, MCP-1, VEGF and MMPs than $SP^{+/+}$ counterparts. *In vitro* and *in vivo* studies have identified SPARC as a novel ovarian cancer suppressor (Figure 3) that functions primarily by virtue of its de-adhesive ability [18], anti-proliferative and pro-apoptotic effects [14,18,78,79]. These effects have attributed to the effects of SPARC inhibiting integrin-mediated and growth factor-mediated survival signaling pathways [14,78,79]. In addition, SPARC inhibited ovarian cancer cell adhesion to various ECM proteins enriched in the peritoneal microenvironment as collagen I,collagen IV, fibronectin, laminin and vitronectin as well as peritoneal mesothelial cells through an axis that involved β1 and β3 integrins-MMPs-VEGF-

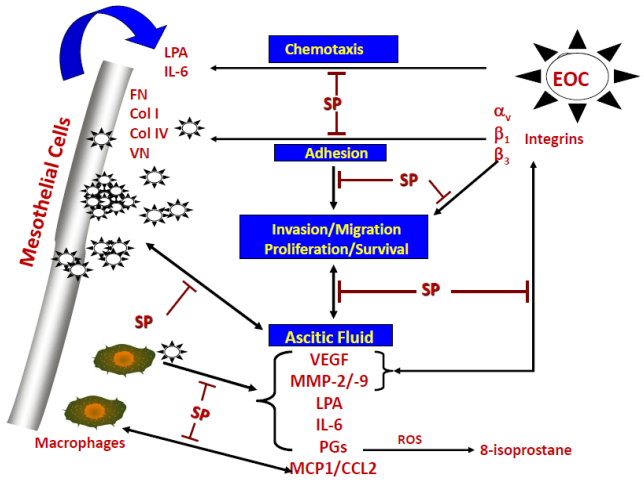

Figure 3: Mechanism of SPARC involvement in ovarian cancer.

VEGFR2 [14,18,79]. SPARC also inhibited ovarian cancer cell matrix and transmesothelial invasiveness through inhibition of LPA-induced and cytokine-mediated inflammation and survival signaling [14,77-79]. Earlier reports demonstrated that SPARC expression in ovarian cancer cells is inversely correlated with the degree of malignancy [80-83]. In agreement with these findings, the decreased expression of SPARC in ovarian tumors is attributed to the aberrant hypermethylation of the *Sparc* promoter [84]. We have also reported the ability of SPARC to modulate ovarian cancer cell interaction with the ECM components, the production and the activity of specific growth factors, cytokines, proteases, and bioactive lipids [14, 77-79]. Moreover, we found that in the immunocompetent *SP*$^{-/-}$ mice, the enhanced peritoneal ovarian carcinomatosis was concomitant with recruitment of macrophages and was positively correlated with the augmented levels and biological activity of ascitic fluid and its constituents, namely, VEGF, MMPs, MCP-1, IL-6, prostanoids, and bioactive lipids [14,77-79]. The effect of tumor-SPARC in modulating the ovarian cancer micro-environment, was studied using *in vitro* systems to dissect the molecular mechanisms of the interactions between human ovarian cancer cells, mesothelial cells, and macrophages [77,78]. Restoration of SPARC expression in ovarian cancer cells disrupted the interplay between these key players, resulting in attenuated macrophage recruitment and expression of known markers of inflammation [14,77-79]. Forced expression of SPARC decreased growth of platinum-resistant ovarian cancer cell lines *in vitro* and increased their sensitivity to chemotherapy *in vitro* and *in vivo* [85].

Cervical cancer

A genome-wide screening study for identification of hypermethylated genes in Squamous Intraepithelial Lesions (SIL) and Invasive Cervical Cancer (ICC) revealed that SPARC exhibited highest frequency of aberrant methylation in ICC specimens [86]. Consistently, another study performed in normal cervix, low-grade (L)SIL, high-grade (H)SIL, adenocarcinomas and squamous cell cervical cancers, and in corresponding cervical scrapings revealed that the methylation frequency of SPARC increased with severity of the underlying cervical lesion. Methylation ratios in scrapings reflected methylation status of the underlying lesions [87,88]. Another study using a different technology confirmed methylation of *Sparc* CpG islands that was highly correlated with the incidence of invasive cervical cancer [89]. Whereas in a recent study using isolated and established high and low invasive subclones from human cervical cancer cell lines HeLa and SiHa [90], SPARC was over-expressed in the highly invasive subclones [90]. Knockdown of SPARC inhibited cell proliferation, and induced cell cycle arrest at the G1/G0 phase through the p53/p21 pathway, caused cell apoptosis and inhibited cell invasion and metastasis [90].

Endometrial cancer

A significant down-regulation of SPARC mRNA and protein expression was observed in endometrial tumor tissues, and was attributed to aberrant hypermethylation of its CpG-rich region. The down-regulation of the SPARC gene in endometrial tumors, formed by at least 80% of epithelial tumor cells, contrasted with a frequent overexpression of SPARC protein, with strong immunoreactivity in the surrounding stromal tissues [91].

Breast Cancer

The role of SPARC in breast cancer initiation, progression and metastasis is another example of its context dependent expression and function that was made challenging confounded by the multiple subtypes of breast cancer. The role of SPARC in oncogene-driven breast cancer was investigated by Wong et al. [21] using murine mammary tumor virus-polyoma middle T (MMTV-PyMT) crossed with *SP*$^{-/-}$ mice. Examining in tumor development in SPARC null and heterozygous mice revealed that loss of SPARC had no significant effects on tumor initiation, progression, angiogenesis ECM or metastasis. Similar to the observation by the same group in oncogene-driven prostate cancer model [21], the insignificant difference may be attributed to SPARC gene dosage. In contrast, increased expression of SPARC is found in malignant breast tumors and is considered as a marker of poor prognosis and recurrence [92-97]. Studies utilizing human breast cancer cell line models *in vitro* or injected in nude mice appear to be conflicting due to variations in the models used. For example, forced expression of SPARC by adenoviral vector [98] or inducible Tet-On system [99] did not affect MDA-231 cell proliferation, apoptosis, migration, cell aggregation, or protease cleavage of collagen IV but inhibited *in vitro* matrix invasion and *in vivo* metastasis that was attributed to reduced tumor cell-platelet aggregation and suggesting that the acquired resistance to the SPARC inhibitory effects in SPARC-expressing MDA-231, has been acquired as a selective pressure, as it occurs for TGF-β.

Models utilizing murine 4T1 breast cancer cell line in *SP*$^{-/-}$ mice backcrossed onto a BALB/c genetic background, reported smaller mammary tumors in *SP*$^{-/-}$ mice, accompanied by an enhanced infiltration of inflammatory leukocytes further highlighting the role of host-derived SPARC influencing the growth of these tumors. The differential effects are likely due to the immediate tumor environment, and not to the tumor cells themselves [16, 100,101]. Up-modulating SPARC expression in 4T1 cells using a retroviral vector reduced tumor growth and reduced metastasis, a phenotype that was related to the SPARC anti-proliferative effect rather than to migration induced by SPARC from the stroma as demonstrated by bone marrow transplantation performed to dissect the role of tumor- and stroma-derived SPARC [4].

Skin Cancer and Melanoma

The effect of SPARC on spontaneous development of skin cancer was investigated by crossing *SP*$^{-/-}$ mice with SKH-1 hairless mice to generate hairless *SP*$^{-/-}$ mice and exposed them UV-irradiation [102]. Following 23 weeks of exposure to UVB, tumor development in the

wild-type mice developed severe extensive squamous cell carcinomas whereas *SP*$^{-/-}$ mice were strikingly tumor-resistant, developing less than one small non-cancerous papilloma per mouse. SPARC was undetectable immunohistochemically in skin from the non-irradiated control group yet was present in relatively high quantities in the basal and superficial areas of the tumor mass.

In melanoma, SPARC expression has been reported to increase with tumor progression, and its expression was shown to be a marker for poor prognosis [103]. SPARC knockdown in melanoma cells led to the complete loss of their *in vivo* tumorigenic growth in nude mice [104,105] through a mechanism involving the activation of polymorphonuclear cell–anti-tumor activity. Importantly, SPARC expression in melanoma cells has been associated with the acquisition of mesenchymal characteristics with reduced E-cadherin expression. However the *in vivo* tumorigenicity and invasiveness were of melanoma cells injected in nude mice were dependent on tumor cell SPARC and metalloproteinase activity not fibroblast SPARC [103,106-112].

Lung Cancer

The expression of SPARC in human Non-Small Cell Lung Cancer (NSCLC) tissues was significantly lost in the cancerous compartment, whereas substantial production of SPARC by stromal fibroblasts was noted [113]. Stromal SPARC correlated with tumor necrosis, nodal metastasis, markers of and poor prognosis [113]. Loss of SPARC expression was reported in 60% of lung cancer cell lines and primary tumors due to promote rmethylation [114], while nonmalignant lung tissues had very low rates of *Sparc* promoter methylation. In lung adenocarcinomas, *Sparc* promoter methylation correlated with poor prognosis [114]. SPARC protein expression was lost in the cancerous compartment, week in bronchial epithelium and strong in juxtatumoral stromal tissues [114]. Interestingly, *Sparc* promoter has been found to be methylated in lung cancer cell lines and tissue by a mechanism that involved activation of DNMT1 by Cox2 [115].

Neurologic Malignancies

Meningiomas

The expression of SPARC in benign, noninvasive primary meningiomas was compared with its expression in invasive, aggressive, primary and recurrent meningiomas. SPARC was not expressed in benign, noninvasive tumors, but was highly expressed in invasive tumors, regardless of the grade suggesting that SPARC is a potential diagnostic and predictive marker of invasive meningiomas [116]. The relationship of basement membrane intactness and SPARC protein expression at the meningioma-brain border was examined in brain-invasive meningiomas (meningothelial meningiomas grade I, atypical grade II, and anaplastic grade III tumors) and non-invasive grade I meningothelial meningiomas [117]. SPARC was expressed at the tumor-brain interface of invasive meningiomas, in spindle-shaped tumor cells; with no significant difference across tumor grades. In this study, SPARC+ spindle cells inversely correlated with basement membrane proteins as epithelial membrane antigen (EMA), collagen IV and glial fibrillary acidic protein (GFAP). However, the destruction of the basement membrane and appearance of SPARC+ spindle cells were not coincident during the course of brain invasion by meningiomas. Consistently, SPARC expression was more frequent in atypical and in anaplastic than in benign meningiomas and was significantly associated with tumor recurrence [118]. The high SPARC expression scores (both frequency and intensity) were predominantly identified in meningothelial, fibrous and chordoid meningiomas; whereas low SPARC expression scores were spotted in secretory and psammomatous meningiomas. High SPARC expression was significantly associated with poor patient survival [118]. In agreement of the pro-invasive effect of SPARC on meningiomas, SPARC has been found to be negatively regulated by meningioma tumor suppressor CD13/aminopeptidase N (APN) whose expression and enzymatic function is reduced in aggressive meningiomas [119].

Glioma

SPARC expression is increased in infiltrating gliomas at the brain-tumor interface, suggesting that SPARC may be involved in tumor infiltration and aggressive behavior [120-122]. Comprehensive gene expression profiling data analysis of advanced glioma, Glioblastoma Multiforme (GBM) patient samples [123] identified the prognostic and predictive utility of SPARC along with doublecortex (DCX), and Semaphorin3B. The concordance of higher values of these three genes together seems to associate with poorer survival; however none of them serves as a useful predictive marker alone. The expression levels of individual genes were not highly correlated with one another [123]. In contrast, co-expression of doublecortex (DCX) and SPARC in glioma cell lines by adenovirus transduction counteracted the invasion-promoting effects of SPARC, and collaboratively diminished radioresistance of glioma cells, interfered with cell cycle turnover and increased irradiation-induced apoptosis [124]. Studies by Rempel and colleagues showed that higher SPARC expression in glioma cell lines delayed tumor growth *in vitro* and inversely correlated with tumor volume in vivo [125-128]. However, higher-SPARC expressing cells also gave rise to more invasive tumors [128] through mechanisms that involve modulation of cell proliferation, matrix adhesion and upregulation of MMPs and uPA [126,127]. SPARC-expression in glioma cell lines as well as exogenous SPARC exhibited survival advantage and increased invasiveness through upregulating PI3K-Akt activity, Focal Adhesion Kinase (FAK) and Integrin-Linked Kinase (ILK) [129,130]. In addition, upregulation of urokinase-type plasminogen activator (uPa) may also be involved in SPARC-mediated Akt activation [131,132]. The tumor suppressor PTEN inhibits SPARC-induced migration through suppression and differential regulation of pAkt and the p38 MAPK-MAPKAPK2-HSP27 signaling pathway [131].

A study by Capper et al. [133] reported that SPARC was highly expressed in astrocytomas and decreased with tumor progression and grade. Increased SPARC expression was associated with decreased proliferation. While there is no association between the level of SPARC in the tumor cells and patient survival, increased tumor vascular SPARC expression is associated with decreased patient survival [133].

Medulloblastoma

SPARC expression exerts a tumor suppressor effect on medulloblastoma and induces neuronal differentiation through multiple pathways [44,134-137]. SPARC was identified as an effector of Src-induced cytoskeleton disruption in medulloblastoma cells, which led to decreased migration and invasion [135]. Overexpression of SPARC inhibited *in vivo* angiogenesis through inhibition of MMP-9-VEGF axis [134]. In addition, the anti-proliferative and cell cycle inhibitory effects of SPARC on medulloblastoma were dependent on IL6-STAT3-Notch axis which induced neuronal differentiation and render these tumors to be more susceptible to chemo- and radiotherapy [44,136]. In addition, SPARC treatment exerted a synergistic effect with irradiation increasing medulloblastoma cell death in vitro and in vivo. SPARC expression prior to irradiation suppressed checkpoints-1,-2

and p53 phosphorylation and DNA repair gene XRCC1 as well as irradiation induced SOX-4 mediated DNA repair [137].

Neuroblastoma

SPARC has been reported as a tumor suppressor in neuroblastoma through inhibition of cell proliferation, invasiveness, and angiogenesis in vitro and vivo [15,138-140]. The anti-proliferative effect of SPARC was attributed to suppression of AKT activity accompanied by an increase in the tumor suppressor protein PTEN both in vitro and in vivo models [141]. The anti-angiogenic effect of SPARC was mediated by its follistatin-like (FS) domain [15]. In addition, consistent with the effect on SPARC on medulloblastoma, overexpression of SPARC in neuroblastoma cells sensitized cells to radiation therapy *in vitro* and *in vivo* [141].

Conclusions

The role of SPARC in different cancers is still controversial due to the lack of preclinical models that recapitulate pre-neoplastic and neoplastic evolution of a given cancer and the dynamic interactions of tumor and stromal compartments. A point that requires further investigation in a given cancer is whether stromal SPARC is a reaction to restrain or foster tumor growth. The translational significance of the inhibitory effect of tumor cell and host SPARC on carcinogenesis, progression, and metastasis makes SPARC a viable candidate in the adjuvant and/or neoadjuvant settings as a single agent or in combination with standard of care radiation or chemotherapies. Restoration of SPARC expression can be achieved by demethylating agents, administration of synthetic full length protein or tumor suppressor domains. The inverse relationship between SPARC tumor expression and the increased activation of NFκB and AP-1 target molecules represents an additional viable therapeutic target by small molecule inhibitors and/or neutralizing antibodies to retard metastatic disease. In addition, in cancers with high stromal SPARC, SPARC can be exploited as biomarker for targeted stromal therapy and delivery of chemo- or immunotherapeutics.

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