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RESEARCH ARTICLE

# SPARC: a matricellular regulator of tumorigenesis

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**Abstract** Although many clinical studies have found a correlation of SPARC expression with malignant progression and patient survival, the mechanisms for SPARC function in tumorigenesis and metastasis remain elusive. The activity of SPARC is context- and cell-type-dependent, which is highlighted by the fact that SPARC has shown seemingly contradictory effects on tumor progression in both clinical correlative studies and in animal models. The capacity of SPARC to dictate tumorigenic phenotype has been attributed to its effects on the bioavailability and signaling of integrins and growth factors/chemokines. These molecular pathways contribute to many physiological events affecting malignant progression, including extracellular matrix remodeling, angiogenesis, immune modulation and metastasis. Given that SPARC is credited with such varied activities, this review presents a comprehensive account of the divergent effects of SPARC in human cancers and mouse models, as well as a description of the potential mechanisms by which SPARC mediates these effects. We aim to provide insight into how a matricellular protein such as SPARC might generate paradoxical, yet relevant, tumor outcomes in order to unify an apparently incongruent collection of scientific literature.

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**Keywords** Angiogenesis · Extracellular matrix · Matricellular protein · Metastasis · Microenvironment · Osteonectin · SPARC · Tumor

**Abbreviations**

| | |
|---|---|
| bFGF | Basic fibroblast growth factor |
| ECM | Extracellular matrix |
| FAK | Focal adhesion kinase |
| ILK | Integrin-linked kinase |
| NSCLC | Non-small cell lung cancer |
| PDAC | Pancreatic ductal adenocarcinoma |
| PDGF | Platelet-derived growth factor |
| SCLC | Small cell lung cancer |
| siRNA | Small-interfering ribonucleic acid |
| SPARC | Secreted protein acidic and rich in cysteine |
| TGFβ | Transforming growth factor beta |
| VEGF | Vascular endothelial growth factor |

## Introduction

Historically, cancer research has focused on the molecular genetics and cell-autonomous behavior of malignant cells. However, understanding the interaction of cancer cells with their microenvironment has emerged as an essential step towards deciphering pathways that control transformation, primary tumor growth, metastasis, immune tolerance and therapeutic response (Desmouliere et al. 2004; Joyce and Pollard 2009; Kumar and Weaver 2009; Liotta and Kohn 2001; Lorusso and Ruegg 2008; Shan et al. 2009; Wernert 1997; Whiteside 2008; Zalatnai 2006). Cancer cells communicate with and elicit responses from the microenvironment at every stage of malignant progression. The tumor microenvironment is composed of tumor cells, extracellular

matrix (ECM), stromal cells, microvessels and immune cells (Farrow et al. 2008; Jung et al. 2002). The ECM is an extracellular protein scaffold that determines tissue architecture and provides the structural framework for cells (Bosman and Stamenkovic 2003). Furthermore, the ECM is a remodeling network that regulates cell differentiation, survival, proliferation and migration (Larsen et al. 2006).

Deposition and remodeling of the ECM is regulated by a functional family of extracellular proteins known as matricellular proteins. Although primarily non-structural, matricellular proteins define and contribute to the structural integrity and composition of the ECM (Bornstein and Sage 2002). The capacity to influence assembly and turn-over of the ECM is a governing attribute of matricellular proteins, which is emphasized by their enhanced expression at sites of tissue remodeling and during wound-healing (Bornstein 2001; Bornstein and Sage 2002). Matricellular proteins can also direct cell fate, survival, adhesion and motility by functioning as adaptors between the ECM and the cell surface (Bornstein 2001; Bornstein and Sage 2002; Brekken and Sage 2001).

SPARC (secreted protein acidic and rich in cysteine), also known as osteonectin and BM-40, is a multifunctional secreted glycoprotein that exemplifies the matricellular class of proteins (Framson and Sage 2004). Expression of SPARC during mammalian development and tissue differentiation is robust but declines in the majority of organs after maturation (Bradshaw and Sage 2001). Ultimately, the expression of SPARC is limited post-development to tissues with high ECM turnover, such as bone and gut epithelia (Bradshaw and Sage 2001). However, SPARC is induced during wound-healing, at sites of angiogenesis, and by the stroma during tumorigenesis (Bornstein 2002; Mendis et al. 1998; Pen et al. 2007; Podhajcer et al. 2008; Reed et al. 1993). These observations suggest that SPARC functions as a regulator of tissue remodeling. In fact, the phenotype of SPARC-deficient mice validates the findings that SPARC controls tissue remodeling and is required for proper collagen matrix assembly and maturation (Bradshaw et al. 2003b; Brekken et al. 2003; Gruber et al. 2005). Mice lacking SPARC exhibit early cataractogenesis, lax skin, progressive osteopenia and a characteristic curly tail reminiscent of ECM defects (Framson and Sage 2004). Furthermore, collagen deposition and fibrillogenesis are altered in the dermis and lens capsule of SPARC-deficient mice (Bradshaw et al. 2003b; Yan et al. 2002).

Consistent with its participation in ECM assembly and turn-over, SPARC directly binds ECM proteins such as collagen and influences the secretion and activation of matrix metalloproteinases (MMPs) (Fujita et al. 2002; Gilles et al. 1998; McClung et al. 2007; Sage et al. 1989; Sasaki et al. 1998, 1999; Shankavaram et al. 1997). Moreover, SPARC interacts with or indirectly regulates several growth factors involved in angiogenesis and tissue remodeling including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor β (TGFβ) (Francki et al. 2004; Hasselaar and Sage 1992; Kato et al. 1998; Kupprion et al. 1998; Motamed et al. 2003; Raines et al. 1992).

By directing ECM deposition, cell-ECM interactions, and growth factor signaling, SPARC is well placed to regulate multiple hallmarks of cancer including angiogenesis, migration, proliferation and survival. As it is suggested that the tumor microenvironment is reminiscent of a wound that never heals and because SPARC is a prominent participant in wound-healing, it is not surprising that many cancers exhibit altered expression of SPARC (Clark and Sage 2008; Dvorak 1986; Framson and Sage 2004; Podhajcer et al. 2008). However, published data on the function of SPARC during tumorigenesis are inconsistent and often contradictory, even among the same tumor types. Thus, it seems that the capacity of SPARC to promote or inhibit tumor progression is dependent on the initiating cell-type, the tumor stage, and the context of the tumor microenvironment.

This article provides a comprehensive review of the literature on SPARC in human cancers and mouse models. We explore the function of SPARC in extracellular matrix deposition and fibrillogenesis, as well as in integrin and growth factor signaling. In an attempt to unify a divergent field, we conclude by proposing a working model to rationalize how SPARC contributes to seemingly paradoxical tumor outcomes.

## Tumor promotion

SPARC displays oncogenic properties in many tumor types including gliomas, astrocytomas, melanomas, ductal carcinoma of the breast, colorectal carcinoma, clear-cell renal cell carcinoma, pancreatic ductal adenocarcinoma, and carcinoma of the prostate. Table 1 provides a list of those human correlative studies, along with associated mouse models and in vitro studies, which show evidence of SPARC as a tumor promoter.

Extensive data are available that show an increase in the expression of SPARC in glioblastomas, astrocytomas and meningiomas relative to that in normal brain, and reveal SPARC expression as a negative predictor of survival (Huang et al. 2000; Pen et al. 2007; Rempel et al. 1998; Rich et al. 2005). Furthermore, in vitro experiments demonstrate that endogenous and exogenous SPARC increase survival, adhesion, migration and invasion of glioblastoma cell lines (Golembieski et al. 1999, 2008; Kunigal et al. 2006; McClung et al. 2007; Rempel et al. 2001; Rich et al. 2003, 2005; Schultz et al. 2002; Seno et al. 2009; Shi et al. 2004,

**Table 1** SPARC as a tumor promoter

| Cancer | | Human biopsies | | | Mouse models or cell culture | |
|---|---|---|---|---|---|---|
| Site | Classification | Detection | Expression[a] | References | Description | References |
| Bladder | Carcinoma | RT-PCR; IHC | Increased stromal SPARC; Positive Correlation | (Nimphius et al. 2007; Yamanaka et al. 2001) | | |
| Blood | Leukemia | Microarray | Increased SPARC expression | (Hedvat et al. 2003; Martinez et al. 2003) | | |
| Bone | Osteosarcoma | Microarray; RT-PCR; IHC | Positive Correlation | (Dalla-Torre et al. 2006; Fanburg-Smith et al. 1999; Schulz et al. 1998) | | |
| Brain | Glioblastoma, Astrocytoma & Meningioma | Northern Blot; IHC; Microarray; RT-PCR | Positive Correlation; SPARC expression increased in invasive benign and malignant tumors | (Huang et al. 2000; Pen et al. 2007; Rempel et al. 1998, 1999; Rich et al. 2005) | SPARC increased invasion and survival; Endogenous SPARC increased adhesion and migration but decreased proliferation | (Golembieski et al. 1999, 2008; Kunigal et al. 2006; McClung et al. 2007; Rempel et al. 2001; Rich et al. 2003, 2005; Schultz et al. 2002; Seno et al. 2009; Shi et al. 2004, 2007) |
| Breast | Invasive Ductal Carcinoma | Microarray; IHC; RT-PCR; SAGE; ISH | High stromal SPARC; Positive Correlation | (Amatschek et al. 2004; Barth et al. 2005; Bellahcene and Castronovo 1995; Bergamaschi et al. 2008; Helleman et al. 2008; Iacobuzio-Donahue et al. 2002; Jones et al. 2004; Lien et al. 2007; Parker et al. 2004; Porter et al. 2003, 1995; Sarrio et al. 2008; Watkins et al. 2005; Woelfle et al. 2003) | Exogenous SPARC increased cancer cell invasion; Tumor growth reduced in SPARC deficient mice; SPARC expression increased in metastasis | (Briggs et al. 2002; Campo McKnight et al. 2006; Gilles et al. 1998; Jacob et al. 1999; Minn et al. 2005; Sangaletti et al. 2003, 2008; Zajchowski et al. 2001) |
| Colon | Colorectal Adenocarcinoma | Microarray; Western Blot; Northern Blot; ISH; IHC; RT-PCR | SPARC expression increased in tumor, tumor stroma and at metastatic sites | (Kaiser et al. 2007; Lussier et al. 2001; Madoz-Gurpide et al. 2006; Porte et al. 1995; Porter et al. 1995; St Croix et al. 2000; Wewer et al. 1988; Wiese et al. 2007) | Increased SPARC expression associated with increased invasive capacity; Reduced tumor development in SPARC deficient mice | (Sansom et al. 2007; Volmer et al. 2004) |
| Esophagus | Squamous Cell Carcinoma (ESCC) & Adenocarcinoma (EA) | Western Blot; Microarray; IHC; Northern Blot; RT-PCR | Positive Correlation | (Brabender et al. 2005; Che et al. 2006; Luo et al. 2004; Mitas et al. 2005; Porte et al. 1998; Wong et al. 2009; Xue et al. 2006; Yamashita et al. 2003) | | |
| Head & Neck | Squamous Cell Carcinoma (HNSCC) | IHC; Microarray | Positive Correlation | (Chin et al. 2005; Choi et al. 2008; Kato et al. 2005) | | |
| Kidney | Sarcomatoid & Clear-cell renal cell carcinoma | Microarray; IHC; Northern Blot | SPARC expression increased in tumors | (Amatschek et al. 2004; Gieseg et al. 2002; Sakai et al. 2001) | SPARC increased cancer cell invasion | (Kato et al. 1998) |
| Liver | Hepatocellular Carcinoma (HCC) | RT-PCR; IHC; ISH; Western Blot; Microarray | Positive Correlation | (Goldenberg et al. 2002; Lau et al. 2006; Le Bail et al. 1999) | | |
| Lung | NSCLC, Squamous Cell Carcinoma, | IHC; Microarray | High stromal SPARC; Positive Correlation | (Amatschek et al. 2004; Koukourakis et al. 2003; | SPARC expression increased during | (Fromigue et al. 2003; Siddiq et al. 2004) |

**Table 1** (continued)

| Cancer | | Human biopsies | | | Mouse models or cell culture | |
|---|---|---|---|---|---|---|
| Site | Classification | Detection | Expression[a] | References | Description | References |
| | Adenocarcinoma | | | Siddiq et al. 2004) | transformation and increased colony formation; Coculture of NSCLC lines & fibroblasts induced SPARC | |
| Ovary | Carcinoma | IHC; ISH | High stromal SPARC; Positive Correlation | (Brown et al. 1999; Paley et al. 2000; Porter et al. 1995) | | |
| Pancreas | Ampullary Carcinoma | Microarray; IHC | Positive Correlation | (Bloomston et al. 2007) | | |
| Pancreas | Ductal Adenocarcinoma (PDAC) | SAGE; Microarray; IHC; RT-PCR; ELISA | High stromal SPARC; Positive Correlation | (Guweidhi et al. 2005; Infante et al. 2007; Mantoni et al. 2008; Prenzel et al. 2006; Ryu et al. 2001; Sato et al. 2003) | Exogenous SPARC increased cancer cell invasion | (Guweidhi et al. 2005; Mantoni et al. 2008) |
| Prostate | Carcinoma | Microarray; IHC; ISH; RT-PCR | Increased SPARC expression at the metastatic site; Positive Correlation | (Best et al. 2005; Lapointe et al. 2004; Thomas et al. 2000) | Exogenous SPARC increased cancer cell invasion and bone metastasis | (Chen et al. 2007; De et al. 2003; Jacob et al. 1999) |
| Skin | Melanoma | IHC; Western Blot; ELISA | Positive Correlation; Serum SPARC levels useful as a diagnostic indicator | (Alonso et al. 2007; Ikuta et al. 2005; Ledda et al. 1997a; Massi et al. 1999) | SPARC knock-down inhibited tumor formation; Increased SPARC expression by metastatic cell lines; SPARC expression correlated with EMT | (Alvarez et al. 2005; Kato et al. 2000; Kuphal et al. 2005; Ledda et al. 1997b; Prada et al. 2007; Robert et al. 2006; Rumpler et al. 2003; Smit et al. 2007; Sosa et al. 2007; Sturm et al. 2002) |
| Skin | Squamous Cell Carcinoma | | | | SPARC deficient mice refractory to UV induced carcinogenesis | (Aycock et al. 2004) |
| Stomach | Gastric Cancer | Northern Blot; ISH; IHC; RT-PCR; Microarray | High stromal SPARC; Positive Correlation | (Inoue et al. 2002; Maeng et al. 2002b; Takeno et al. 2008; Wang et al. 2004; Wewer et al. 1988) | SPARC expression increased during transformation | (Maeng et al. 2002a) |
| Thyroid | Anaplastic Carcinoma | RT-PCR | High stromal SPARC expression in poorly differentiated tumors | (Takano et al. 2002) | | |
| Uterus | Cervical & Endometrial Carcinoma | RT-PCR; IHC; ISH; Western Blot | High stromal SPARC | (Chen et al. 2003; Rodriguez-Jimenez et al. 2007) | | |

[a] Positive Correlation refers to one of the following: 1) Tumors had increased SPARC expression compared to normal tissue 2) Increased SPARC expression correlated with increased tumor stage, grade or metastasis 3) Increased SPARC expression correlated with decreased survival or a negative prognosis 4) Decreased SPARC expression correlated with increased survival or a positive prognosis. This table combines, updates and expands the data presented in several previous reviews (Clark and Sage 2008; Framson and Sage 2004; Podhajcer et al. 2008)

2007). Forced expression of SPARC by non-invasive glioma cells induces an invasive phenotype in mouse models of glioblastoma (Rich et al. 2003; Schultz et al. 2002). On the other hand, down-regulation of SPARC by siRNA in invasive glioma cell lines abrogates dissemination into surrounding brain regions after intracerebral injection into mice (Seno et al. 2009).

In invasive ductal carcinoma of the breast, the expression of SPARC is enhanced in tumor tissue compared to normal controls and an increased level of SPARC is associated with higher histological grade and advanced pathological stage (Amatschek et al. 2004; Barth et al. 2005; Bellahcene and Castronovo 1995; Bergamaschi et al. 2008; Helleman et al. 2008; Iacobuzio-Donahue et al. 2002; Jones et al. 2004; Lien et al. 2007; Parker et al. 2004; Porter et al. 2003, 1995; Sarrio et al. 2008; Watkins et al. 2005; Woelfle et al. 2003). Both exogenous administration and endogenous upregulation of SPARC enhance in vitro breast cancer cell invasion (Briggs et al. 2002; Campo McKnight et al. 2006; Gilles et al. 1998; Jacob et al. 1999; Zajchowski et al. 2001). In orthotopic and intravenous lung metastasis mouse models of breast cancer, SPARC expression is increased at metastatic sites and confers enhanced metastatic potential (Minn et al. 2005). Moreover, orthotopic breast tumor growth and lung metastasis are impaired in SPARC-deficient mice (Sangaletti et al. 2003, 2008).

Non-small cell lung cancers (NSCLC), including squamous cell carcinoma and adenocarcinoma, display an increased expression of SPARC relative to that in normal lung (Amatschek et al. 2004; Siddiq et al. 2004). Elevated SPARC expression by tumor stroma is associated with a poor prognosis in NSCLC (Koukourakis et al. 2003). Coculture of NSCLC cell lines with normal fibroblasts stimulates expression of SPARC (Fromigue et al. 2003). Furthermore, SPARC is upregulated during carcinogen-induced transformation of bronchial epithelial cells and is associated with enhanced anchorage-independent colony formation (Siddiq et al. 2004).

SPARC is expressed highly in pancreatic ductal adenocarcinoma (PDAC) at both primary and metastatic sites (Guweidhi et al. 2005; Prenzel et al. 2006; Ryu et al. 2001). In addition, patients with PDAC, whose tumor-associated stroma express high levels of SPARC, have a worse prognosis compared to those with no stromal SPARC expression, which results in a relative hazard ratio of 1.89 (Infante et al. 2007; Mantoni et al. 2008). In vitro, exogenous SPARC enhances, while SPARC knock-down reduces, invasion of human pancreatic cancer cells (Guweidhi et al. 2005; Mantoni et al. 2008).

An elevated expression of SPARC is also found in primary and metastatic melanoma (Alonso et al. 2007; Ledda et al. 1997a). The expression of SPARC in cutaneous melanomas correlates significantly with an increase in disease progression and metastatic incidence, as well as with a decrease in survival (Alonso et al. 2007; Massi et al. 1999). Elevated SPARC levels are found in the serum of patients with malignant melanoma, a marker used to successfully identify 33% of melanoma patients including those with early stage disease (Ikuta et al. 2005). Human melanoma cell lines also express high levels of SPARC (Ledda et al. 1997a). Forced expression of SPARC induces motility of normal human melanocytes and enhances invasion of melanoma cells (Robert et al. 2006; Smit et al. 2007). Antisense suppression of SPARC reduces the in vitro adhesive and invasive capacity of melanoma cell lines, and abrogates in vivo tumor formation (Alvarez et al. 2005; Ledda et al. 1997b; Prada et al. 2007; Robert et al. 2006; Smit et al. 2007; Sosa et al. 2007). Lastly, metastatic variants of mouse melanoma cell lines show differential expression of SPARC; whereby, those with higher metastatic potential or those that demonstrate aggressive behavior express and/or secrete increased amounts of SPARC relative to low-metastatic variants (Kato et al. 2000; Rumpler et al. 2003).

## Tumor suppression

SPARC also shows characteristics of a tumor suppressor in many cancers including acute myeloid leukemia, neuroblastoma, carcinoma of the breast, colorectal adenocarcinoma, hepatocellular carcinoma, non-small cell and small cell lung cancer, carcinoma of the ovaries and pancreatic ductal adenocarcinoma. Table 2 presents a comprehensive list of human correlative studies, associated mouse models and in vitro studies that support the capacity of SPARC to impede tumor progression.

The promoter of the SPARC gene is hypermethylated in many epithelial cancers, effectively reducing SPARC production by tumor cells and supporting the idea that SPARC is tumor-suppressive in a variety of cancers (Table 2). SPARC promoter methylation is reported in colorectal, non-small cell and small cell lung, ovarian, pancreatic, prostate and uterine cancers (Brune et al. 2008; Cheetham et al. 2008; Hong et al. 2008; Rodriguez-Jimenez et al. 2007; Sato et al. 2003; Socha et al. 2009; Sova et al. 2006; Suzuki et al. 2005; Wang et al. 2005; Yang et al. 2007). In most cases, SPARC promoter methylation correlates with a poor prognosis and/or decreased survival.

The SPARC promoter is hypermethylated in 80–100% of colorectal adenocarcinomas and correlates with a worse prognosis (Cheetham et al. 2008; Yang et al. 2007). In addition, approximately 71% of human colorectal cancer cell lines are methylated within the SPARC locus (Cheetham et al. 2008; Yang et al. 2007). Further evidence comes from data showing chemoresistant human

colorectal cancer cells significantly downregulate SPARC production (Tai et al. 2005). More importantly, reexpression of SPARC or exogenous administration of SPARC restores chemosensitivity in resistant cell lines and leads to tumor regression in xenograft models when combined with chemotherapy (Cheetham et al. 2008; Taghizadeh et al. 2007; Tai et al. 2005).

SPARC gene methylation occurs in 71% of non-small cell lung cancers (NSCLC) and 33% of small cell lung cancers (SCLC) (Suzuki et al. 2005). The promoter methylation status of SPARC is an independent adverse prognostic factor with a relative risk of 4.65 in lung adenocarcinoma (Suzuki et al. 2005). Similar to human biopsies, 75% of NSCLC and 25% of SCLC cell lines show evidence of SPARC methylation (Suzuki et al. 2005). Furthermore, treatment of human lung cancer cells with the nonsteroidal anti-inflammatory drug NS398 reduces invasion by restoring SPARC expression through promoter demethylation, an effect that is blocked by an anti-SPARC antibody (Pan et al. 2008).

SPARC also functions as a tumor suppressor in ovarian carcinoma. Malignant epithelial cells in ovarian carcinoma tissue samples exhibit reduced SPARC immunoreactivity (Yiu et al. 2001). This reduction in SPARC expression in the tumor compartment is due to epigenetic silencing; whereby, 68% of ovarian carcinomas display aberrant methylation of the SPARC promoter (Socha et al. 2009). In fact, decreasing levels of SPARC protein in the malignant cells corresponds with disease progression (Socha et al. 2009). Ovarian cancer cell lines also show reduced expression and secretion of SPARC compared to normal ovarian epithelial cells, which express and secrete high levels of SPARC (Mok et al. 1996; Socha et al. 2009; Yiu et al. 2001). Moreover, forced expression or exogenous addition of SPARC attenuates in vitro proliferation and in vivo tumor growth of ovarian carcinoma cells (Mok et al. 1996; Socha et al. 2009; Yiu et al. 2001). In a mouse model of peritoneal ovarian carcinomatosis, *SPARC-null* mice experience diminished survival, enhanced peritoneal dissemination and increased accumulation of ascitic fluid compared to *wild-type* animals (Bull Phelps et al. 2009; Said and Motamed 2005; Said et al. 2007a, b).

In pancreatic ductal adenocarcinoma, malignant epithelial cells within the tumor often downregulate SPARC expression (Sato et al. 2003). SPARC methylation occurs in 91% of human infiltrating pancreatic adenocarcinoma, 88% of primary human pancreatic carcinoma xenografts and 94% of human pancreatic cancer cell lines (Brune et al. 2008; Hong et al. 2008; Sato et al. 2003). Gradual loss of SPARC expression and methylation in pancreatic ductal epithelial cells is also seen in the progression of intraductal papillary mucinous neoplasms, precursors to invasive adenocarcinoma (Hong et al. 2008). Treatment with exogenous SPARC reduces pancreatic cancer cell proliferation (Guweidhi et al. 2005; Sato et al. 2003). Additionally, subcutaneous and orthotopic tumor growth of murine pancreatic adenocarcinoma cells is enhanced in *SPARC-null* mice relative to *wild-type* counterparts (Arnold et al. 2008; Puolakkainen et al. 2004).

Lastly, SPARC expression is disregulated in uterine cancers. In human cervical carcinoma, SPARC is aberrantly methylated in 86% of cancer specimens and only in 5% of normal tissue (Sova et al. 2006). Furthermore, the frequency of SPARC hypermethylation is significantly increased in high-grade cervical lesions compared to low-grade neoplasias and normal cervical controls (Kahn et al. 2008; Sova et al. 2006). Endometrial cancers also display SPARC promoter methylation in 66% of human samples, as well as, a reduction in the expression of SPARC by the malignant epithelial cell compartment (Rodriguez-Jimenez et al. 2007).

## Compartmentalized expression

Several epithelial cancers present with contradictory compartmentalized SPARC expression; whereby, SPARC is upregulated by the intra- and peritumoral stroma but downregulated by the malignant cells. This paradoxical pattern of SPARC expression is observed in breast, colorectal, lung, ovarian, pancreatic and endometrial cancers (Barth et al. 2005; Iacobuzio-Donahue et al. 2002; Paley et al. 2000; Rodriguez-Jimenez et al. 2007; Sato et al. 2003; Suzuki et al. 2005; Yang et al. 2007; Yiu et al. 2001). Whereas SPARC is highly expressed by normal breast and colonic epithelium, invasive ductal breast and colorectal carcinoma show dramatically reduced expression by the malignant epithelial cells (Fig. 1). However, the tumor-reactive stroma displays intense SPARC immunoreactivity (Fig. 1) (Barth et al. 2005; Yang et al. 2007). Although the tumor compartment exhibits reduced SPARC production in lung and pancreatic cancers due to promoter hypermethylation, infiltrating stromal cells respond with a compensatory upregulation of SPARC (Sato et al. 2003; Suzuki et al. 2005). Overall SPARC levels are elevated in endometrial carcinoma, but this over-expression is limited to the stroma; whereas, the tumor cells themselves display attenuated SPARC expression (Rodriguez-Jimenez et al. 2007).

In regards to colorectal, lung, ovarian, pancreatic and endometrial cancers, the contradictory compartmentalized expression of SPARC is a result of the loss of SPARC expression by the malignant epithelial cells due to promoter hypermethylation, as discussed in the previous section (Barth et al. 2005; Paley et al. 2000; Rodriguez-Jimenez et al. 2007; Sato et al. 2003; Suzuki et al. 2005; Yang et al. 2007; Yiu et al. 2001). Furthermore, tumor cells may act in a paracrine

**Table 2** SPARC as a tumor suppressor

| Cancer | | Human biopsies | | | | Mouse models or cell culture | |
|---|---|---|---|---|---|---|---|
| Site | Classification | Detection | Expression[a] | References | Methylation | Description | References |
| Bladder | Carcinoma | Genetic mapping | Locus deletion associated with neoplasia | (Kram et al. 2001) | | | |
| Blood | Acute Myeloid Leukemia (AML) with MLL Translocation | Microarray; RT-PCR; Western Blot | SPARC expression decreased | (Bullinger et al. 2004; DiMartino et al. 2006; Ross et al. 2004) | | Exogenous SPARC inhibited proliferation; SPARC silencing associated with promoter methylation | (DiMartino et al. 2006) |
| Brain | Neuroblastoma | IHC | Inverse Correlation | (Chlenski et al. 2002) | | SPARC inhibited migration and angiogenesis but activated apoptosis | (Chlenski et al. 2002, 2004) |
| Breast | Carcinoma | Microarray | Inverse Correlation; Increased stromal SPARC | (Beck et al. 2008; Bergamaschi et al. 2008) | | SPARC overexpression inhibited proliferation; Endogenous SPARC expression reduced metastasis | (Dhanesuan et al. 2002; Koblinski et al. 2005) |
| Colon | Colorectal Adenocarcinoma | IHC; methylation specific PCR; Microarray; RT-PCR | Inverse Correlation | (Cheetham et al. 2008; Tai et al. 2005; Yang et al. 2007) | **80-100%** | SPARC expression decreased in chemoresistant cancer cells; SPARC treatment restored sensitivity to chemotherapy; SPARC methylated in **71%** cell lines | (Cheetham et al. 2008; Taghizadeh et al. 2007; Tai et al. 2005; Yang et al. 2007) |
| Kidney | Transformed Cells | | | | | Endogenous SPARC inhibited tumor growth | (Chlenski et al. 2006, 2007) |
| Liver | Hepatocellular Carcinoma (HCC) | | | | | SPARC overexpression reduced tumor growth and angiogenesis | (Lau et al. 2006) |
| Lung | NSCLC & SCLC | RT-PCR; IHC | Inverse Correlation | (Suzuki et al. 2005) | **69%** | SPARC methylated in **55%** cancer cell lines; SPARC promoter demethylation inhibited invasion; Increased tumor growth in SPARC deficient mice | (Brekken et al. 2003; Pan et al. 2008; Suzuki et al. 2005) |
| Nose & Pharynx | Nasopharyngeal Carcinoma | | | | | Endogenous SPARC inhibited proliferation | (Huang et al. 2008) |
| Ovary | Carcinoma | IHC; Western Blot; RT-PCR | Inverse Correlation | (Socha et al. 2009; Yiu et al. 2001) | **68%** | Reduced SPARC expression and secretion in cancer cells; SPARC inhibited tumor growth; Exogenous SPARC inhibited cancer cell proliferation, adhesion and invasion; enhanced apoptosis; Tumor growth and carcinomatosis augmented in SPARC deficient mice | (Bull Phelps et al. 2009; Mok et al. 1996; Said and Motamed 2005; Said et al. 2007a, b; Socha et al. 2009; Yiu et al. 2001) |

**Table 2** (continued)

| Cancer | | Human biopsies | | | | Mouse models or cell culture | |
|---|---|---|---|---|---|---|---|
| Site | Classification | Detection | Expression[a] | References | Methylation | Description | References |
| Pancreas | Ductal Adenocarcinoma (PDAC) | SAGE; Microarray; IHC; RT-PCR | SPARC methylation; Inverse Correlation | (Brune et al. 2008; Hong et al. 2008; Sato et al. 2003) | 88-92% | SPARC methylated in 94% cancer cell lines; SPARC inhibited cancer cell proliferation; Increased tumor growth in SPARC deficient mice | (Arnold et al. 2008; Guweidhi et al. 2005; Puolakkainen et al. 2004; Sato et al. 2003) |
| Prostate | Carcinoma | | | | | SPARC hypermethylated in cancer cell lines compared to normal cells | (Wang et al. 2005) |
| Skin | Melanoma | | | | | Endogenous SPARC inhibited migration and spheroid tumor cell growth; SPARC knock-down enhanced spheroid formation | (Prada et al. 2007) |
| Uterus | Cervical & Endometrial Carcinoma | Microarray; RT-PCR | Iinverse Correlation | (Kahn et al. 2008; Rodriguez-Jimenez et al. 2007; Sova et al. 2006) | 66-86% | | |

[a] Inverse Correlation refers to one of the following: 1) Tumors had decreased SPARC expression compared to normal tissue 2) Decreased SPARC expression correlated with increased tumor stage, grade or metastasis 3) Decreased SPARC expression correlated with decreased survival or a negative prognosis 4) Increased SPARC expression correlated with increased survival or a positive prognosis. This table combines, updates and expands the data presented in several previous reviews (Clark and Sage 2008; Framson and Sage 2004; Podhajcer et al. 2008)

fashion to induce SPARC expression by the surrounding stroma. Indeed, fibroblasts isolated from normal pancreas display augmented SPARC expression when cocultured with pancreatic cancer cells (Sato et al. 2003).

Therefore, the heterogeneity and compartmentalization of SPARC expression can explain contradictory results and correlations with SPARC among identical cancers and between differing tumor types. What the data suggest is that the effect of SPARC on tumor progression and patient outcome is both tumor-type and context dependent. In other words, the source and localization of SPARC in the tumor microenvironment contributes to the complexity of SPARC influence during tumorigenesis.

## Extracellular matrix

The primary function of the ECM is to maintain tissue shape and to provide the cellular compartment with structural support (Bosman and Stamenkovic 2003). However, the ECM is not just a passive bystander. It is a remodeling network that contributes substantially to tumor progression and metastasis by influencing cell adhesion, migration, differentiation, proliferation and survival (Engbring and Kleinman 2003; Ioachim et al. 2002; Streuli 2009; Streuli and Akhtar 2009; Timar et al. 2002). By binding to adhesion receptors such as integrins, the ECM can communicate directly with the cell and influence signaling responses (Berrier and Yamada 2007; Juliano 2002; Moser et al. 2009; Stupack 2007). The ECM can also regulate cell function by harboring matrikines and dictating bioavailability of cytokines (Schultz and Wysocki 2009). SPARC expression is increased concomitantly with activation of ECM deposition (Framson and Sage 2004). In addition, SPARC directly interacts with the ECM by binding basement membrane collagen IV and fibrillar collagens I, III and V (Sage et al. 1989; Sasaki et al. 1998; Sasaki et al. 1999).

There is ample evidence that SPARC is required for proper secretion, deposition and fibrillogenesis of collagen during development, wound-healing and tumor progression. SPARC-deficient mice exhibit a range of phenotypes as a result of disruption in ECM deposition and organization, including early cataract formation, accelerated dermal wound-healing, osteopenia and a curly tail (Bradshaw and Sage 2001). Premature cataractogenesis is observed in two independently generated *SPARC-null* mouse colonies, and is caused by disorganized deposition of collagen IV and laminin in the lens epithelial basement membrane (Gilmour et al. 1998; Norose et al. 1998; Yan et al. 2002, 2003). *SPARC-null* mice also show deficiencies in connective tissue, such as decreased levels of collagen I in skin, adipose, heart and bone (Bradshaw et al. 2003a, c; Delany et al. 2003). In addition to the reduction in collagen

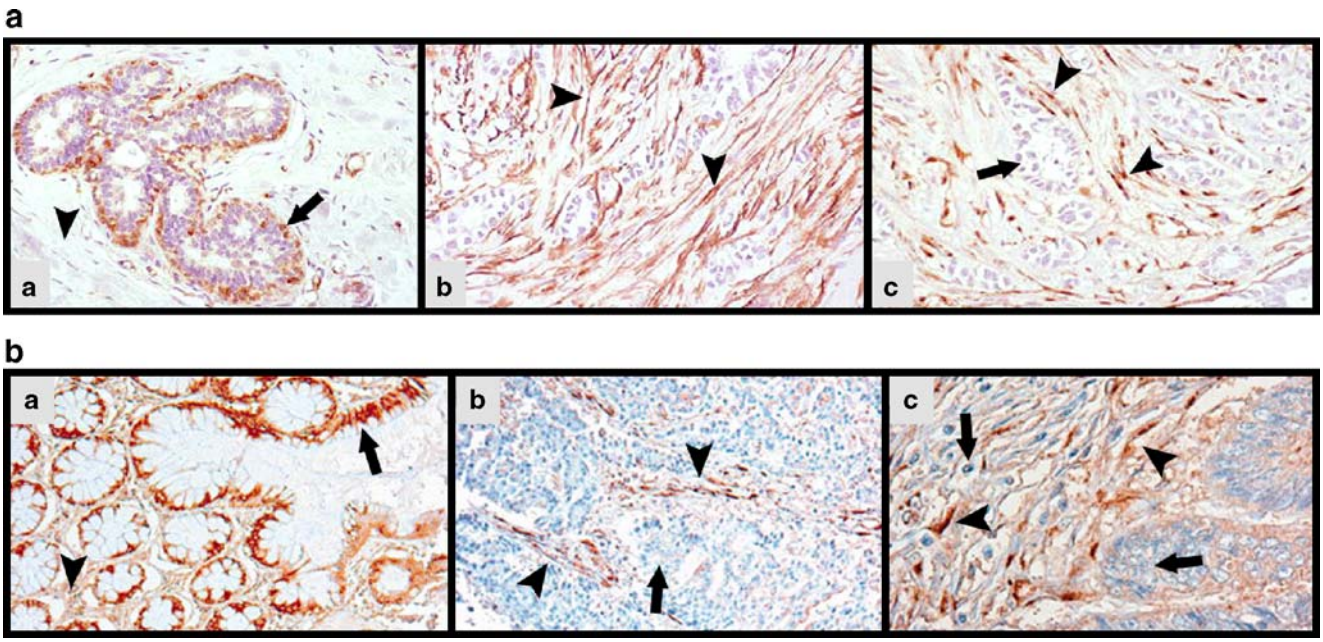


**Fig. 1** Compartmentalized SPARC expression in human cancer. **a** Immunohistochemical staining of human biopsies of normal breast and invasive ductal adenocarcinoma, adapted from Barth et al. (2005) Copyright © Springer. Reprinted with permission of Springer-Verlag Berlin Heidelberg New York, A member of BertelsmannSpringer Science + Business Media GmbH (*a*) SPARC is expressed in myoepithelial cells (*arrow*) and by a few stromal cells in the ducts of normal breast. However, much of the stroma lacks SPARC expression (*arrowhead*) (*b*) Staining for α-SMA in the tumor-associated stroma (*arrowheads*) reveals activated fibroblasts also positive for (*c*) SPARC immunoreactivity (*arrowheads*). The arrow points to malignant epithelial cells lacking SPARC expression. **b** Immunohistochemical analysis of SPARC expression in colonic mucosae and colorectal carcinomas, adapted from Yang et al. (2007) Copyright © 2005 Wiley-Liss, Inc. Reprinted with permission of Wiley-Liss, Inc., A Wiley Company. (*a*) Normal colonic epithelial cells (*arrow*) strongly express SPARC, while there is only minimal SPARC expression in the surrounding stroma (*arrowhead*). (*b*, *c*) SPARC expression by the carcinoma cells (*arrows*) is dramatically reduced or absent, while tumor stromal cells display strong expression of SPARC (*arrowheads*) (*c*) Higher magnification

deposition, collagen fibrils in the skin of SPARC-deficient mice are uniformly smaller in diameter compared to the heterogeneous fibrils found in wild-type dermis (Bradshaw et al. 2003b). Reduction in collagen deposition and fibrillogenesis in *SPARC-null* mice leads to accelerated dermal wound-healing, presumably due to increased contractility (Bradshaw et al. 2002, 2003c).

Not only do SPARC-deficient mice display alterations in the ECM during development and normal tissue turnover but, in the absence of SPARC, there is also a diminished foreign-body and tumor response in regard to encapsulation. Implantation of foreign material into mice elicits a stromal response that essentially encapsulates this material in a wall of ECM. However, the collagen capsule deposited in response to foreign-body implantation is markedly reduced in thickness in *SPARC-null* compared to *wild-type* mice (Puolakkainen et al. 2003). Furthermore, analogous to the alterations observed during development, the collagen fibrils bordering the implanted material are uniformly smaller in diameter and less mature in the absence of SPARC relative to fibers deposited in *wild-type* mice (Puolakkainen et al. 2003).

Similarly, many solid tumors show encapsulation demarcating the tumor from normal tissue. Subcutaneous tumor models of murine lung carcinoma, lymphoma and pancreatic adenocarcinoma present with enhanced growth in *SPARC-null* mice compared to *wild-type* controls (Brekken et al. 2003; Puolakkainen et al. 2004). Moreover, tumors grown in the absence of host SPARC exhibit deficits in collagen deposition and fibrillogenesis at the tumor capsule, as well as in intratumoral connective tissue highways (Brekken et al. 2003; Puolakkainen et al. 2004). There are also alterations in the composition of non-collagenous ECM proteins, such as laminin, in tumors grown in *SPARC-null* animals (Brekken et al. 2003). In addition, murine pancreatic cancer cells injected orthotopically into *SPARC-null* mice grow larger and metastasize more frequently than those in *wild-type* mice, thus highlighting the importance of SPARC function and ECM composition in tumor progression (Arnold et al. 2008). The fact that the tumor cells, but not the infiltrating stromal cells, express and secrete SPARC in the aforementioned studies also supports the observation that the effect of SPARC on tumorigenesis is context- and cell-type-dependent (Arnold et al. 2008; Brekken et al. 2003;

Puolakkainen et al. 2004). Thus, SPARC can influence tumor progression and metastasis by controlling deposition and composition of the ECM. Moreover, the diverse actions of SPARC in differing tumors may be a result of distinctive ECM profiles.

## Integrin signaling

The ECM directly interacts with cells through a family of cell-surface receptors known as integrins (Moser et al. 2009). Integrins anchor cells to the ECM, signal in response to ECM ligation ("outside-in" signaling) and regulate the interactions of the ECM in response to intracellular cues ('inside-out' signaling) (Moser et al. 2009). Integrin signaling pathways substantially interact with growth factor receptor pathways to dictate cellular events, such as survival, proliferation, adhesion and migration, all of which contribute to tumor growth and metastasis. Integrin complexes can also cluster directly with growth factor receptors. Furthermore, proper cytokine responses require intact integrin activation and signal propagation (Eliceiri 2001; Porter and Hogg 1998; Somanath et al. 2009; Streuli and Akhtar 2009).

Numerous studies suggest that SPARC regulates integrin signaling and the ability of integrins to interact with structural components of the ECM. SPARC induces cell rounding or an intermediate state of adhesion in several cell types, *in vitro*, including endothelial and mesenchymal cells (Bradshaw et al. 1999; Sage et al. 1989). This effect is due to disruption of focal adhesions (Bradshaw et al. 1999). In addition, many studies contribute to the emerging idea that SPARC influences downstream components of integrin signaling, specifically the activation of integrin linked kinase (ILK). Fibronectin-induced ILK activation and stress-fiber formation are reduced in primary lung fibroblasts isolated from SPARC-null mice and restored by forced SPARC expression (Barker et al. 2005). Furthermore, SPARC promotes cell survival of lens epithelial cells under serum-deprivation by enhancing ILK activation (Weaver et al. 2008). Moreover, recent publications report that SPARC binds integrin β1 with its copper-binding domain; thereby, directly affecting integrin/ILK signaling (Nie et al. 2008; Weaver et al. 2008).

The influence of SPARC on integrin/ILK responses is also observed in several cancer cell lines. SPARC increases survival and induces an invasive phenotype in human glioma cells (Schultz et al. 2002; Shi et al. 2004, 2007). However, targeting SPARC with short-hairpin RNA reduces cell survival and invasion, as well as attenuates the activity of ILK, focal adhesion kinase (FAK) and protein kinase B (Akt) (Shi et al. 2007). Moreover, SPARC-induced invasion and survival is abrogated by down-regulation of ILK and FAK (Shi et al. 2007). Total ILK expression is also found to be increased in glioma cells that are forced to express SPARC (Golembieski et al. 2008). In human ovarian cancer cells, SPARC inhibits adhesion, invasion and proliferation by reducing the surface localization and/or clustering of αv, β1, β3 and β5 integrins (Said et al. 2007a). SPARC attenuates integrin αv- and β1-induced proliferation in murine ovarian cancer cells. Furthermore, murine ovarian cancer cells adhere more readily to peritoneal explants and peritoneal mesothelial cells isolated from *SPARC-null* mice compared to *wild-type* counterparts (Said et al. 2007b). This effect is blocked by antibodies against αvβ3 and β1 integrins (Said et al. 2007b).

Together, these data reveal that SPARC influences integrin clustering and activation, as well as the ability of integrins to interact with structural components of the ECM. Moreover, SPARC potentially dictates if and how integrins converse with and reinforce other signaling cascades. Therefore, it is not surprising that SPARC elicits such diverse effects on tumorigenesis, given the fact that it possesses the ability to control the pleiotropic interactions and functions of integrins.

## Growth factor and cytokine signaling

Cross-talk between malignant cells and the surrounding stromal compartment induces ECM remodeling, angiogenesis, immune recruitment and metastasis (Davis and Senger 2005). Growth factors and their associated receptors are one way by which communication occurs between cellular compartments. It is established that SPARC modulates the activity of several growth factors including basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGFβ) (Francki et al. 2004; Hasselaar and Sage 1992; Kupprion et al. 1998; Raines et al. 1992). Although SPARC does not bind bFGF directly, it inhibits bFGF-induced migration of endothelial cells (Hasselaar and Sage 1992). SPARC binds PDGF and dose-dependently inhibits ligand binding and activation of PDGF receptors on human dermal fibroblasts (Raines et al. 1992). In addition, PDGF-stimulated proliferation of human arterial vascular smooth muscle cells is decreased in the presence of SPARC (Motamed et al. 2002).

Similar to PDGF, SPARC binds VEGF directly and prevents activation of VEGFR1 (Kupprion et al. 1998; Nozaki et al. 2006). This interaction attenuates VEGF-

induced proliferation of microvascular endothelial cells (Kupprion et al. 1998). On the other hand, VEGF induces the expression of SPARC in human vascular endothelial cells (Kato et al. 2001). Therefore, the induction of SPARC by VEGF stimulation might be a negative regulatory feedback mechanism. In support, VEGF production is enhanced in dermal fibroblasts and subcutaneous polyvinyl alcohol sponges from *SPARC-null* mice relative to *wild-type* controls, which results in a greater angiogenic response in the absence of SPARC (Bradshaw et al. 2001). When injected into the brain of nude rats, SPARC-expressing human glioblastoma cells reduce VEGF expression and angiogenesis related to tumor formation in comparison to SPARC-negative glioma cells (Yunker et al. 2008). In a mouse model of ovarian cancer, peritoneal dissemination and lethality is augmented in the absence of host-derived SPARC, which corresponds to VEGF accumulation in ascitic fluid (Said and Motamed 2005; Said et al. 2007b).

SPARC is also implicated in the regulation of TGFβ (Francki et al. 2004; Schiemann et al. 2003). TGFβ is a master regulator of wound-healing and fibrosis by inducing the synthesis of several ECM proteins including collagen and fibronectin (Verrecchia and Mauviel 2007). Ample data demonstrate that TGFβ induces SPARC expression (Ford et al. 1993; Pavasant et al. 2003; Reed et al. 1994; Wrana et al. 1991). However, there is also evidence that SPARC regulates the expression and activity of TGFβ, suggesting that there is a reciprocal regulatory feedback loop between SPARC and TGFβ. SPARC induces the expression and secretion of TGFβ1 in rat mesangial cells in vitro and in vivo (Bassuk et al. 2000). The synthesis of collagen I and TGFβ-1 is diminished in mesangial cells isolated from *SPARC-null* mice compared to those from *wild-type* mice, but is restored by the exogenous addition of SPARC (Francki et al. 1999). Moreover, SPARC enhances the stimulatory effects of TGFβ1 on mesangial cells by directly interacting with the TGFβ/TGFβRII complex (Francki et al. 2004). Likewise, SPARC augments the inhibitory functions of TGFβ1 in epithelial cells by stimulating smad2/3 phosphorylation (Schiemann et al. 2003).

Considering that growth factors such as bFGF, PDGF, VEGF and TGFβ are important contributors to tumor progression, angiogenesis and metastasis, it is clear that the interaction of SPARC with these signaling pathways influences its ability to dictate many aspects of tumorigenesis. In addition, SPARC interaction with growth factors, such as TGFβ, that have a dichotomous effect on the progression of solid tumors, explains the ability of SPARC to influence human cancers in such apparently paradoxical ways (Tian and Schiemann 2009).

## Conclusions

SPARC can modulate ECM assembly, integrin activity and growth factor signaling; thereby, controlling a range of cellular functions including adhesion, proliferation, survival and migration. Therefore, it is not surprising that the expression of SPARC is dysregulated in many human cancers and that this dysregulation contributes to patient outcome. Although there is no unifying mechanism, as yet, for the effects of SPARC in tumorigenesis, this protein clearly influences the microenvironment and signaling pathways involved in disease progression. The concept that SPARC regulates cell function through modulation of integrin binding and activation is provocative, since integrin receptors have also been implicated in each of the cellular processes influenced by SPARC. To date, no bona fide signaling receptor has been identified for SPARC. However, given that SPARC directly binds to the ECM, integrins and growth factor/receptor complexes, we propose that SPARC functions as an extracellular scaffolding protein; whereby, SPARC dictates the activating threshold at which integrin and growth factor-signaling processes propagate cellular events (Fig. 2). It is known that there is extensive cross-talk between integrin- and growth factor -signaling pathways, and that integrin signaling is required for proper cellular responses to cytokine stimulation (Eliceiri 2001; Porter and Hogg 1998; Somanath et al. 2009; Streuli and Akhtar 2009). In addition, integrins can associate directly with growth factor receptors (Eliceiri 2001; Porter and Hogg 1998; Somanath et al. 2009; Streuli and Akhtar 2009). By controlling the clustering and activation of integrins, as well as, the association and cross-talk with growth factor receptors, SPARC might function as a rheostat for cellular signaling and behavior. Thus, factors controlling the effects of SPARC on any particular cell would consist of the ECM composition, integrin profile, cytokine milieu, cell type (e.g. mesenchymal, endothelial or epithelial), and SPARC concentration/cell-surface localization. This concept provides a potential explanation for how SPARC modulates so many cellular events, and for why the considerable data collected in regard to SPARC during tumorigenesis have failed to elucidate any specific and consistent mechanism.

It is difficult to determine a mechanism when numerous confounding factors are involved, and when many groups publish seemingly contradictory data on the function of SPARC. However, we propose that this collection of incongruous data is a result of the dependence of SPARC function on multiple factors associated with its role as an extracellular scaffolding protein and signaling rheostat. Future experiments should aim to validate whether SPARC controls the formation of integrin- and growth factor-receptor complexes and, if so, to clarify how these

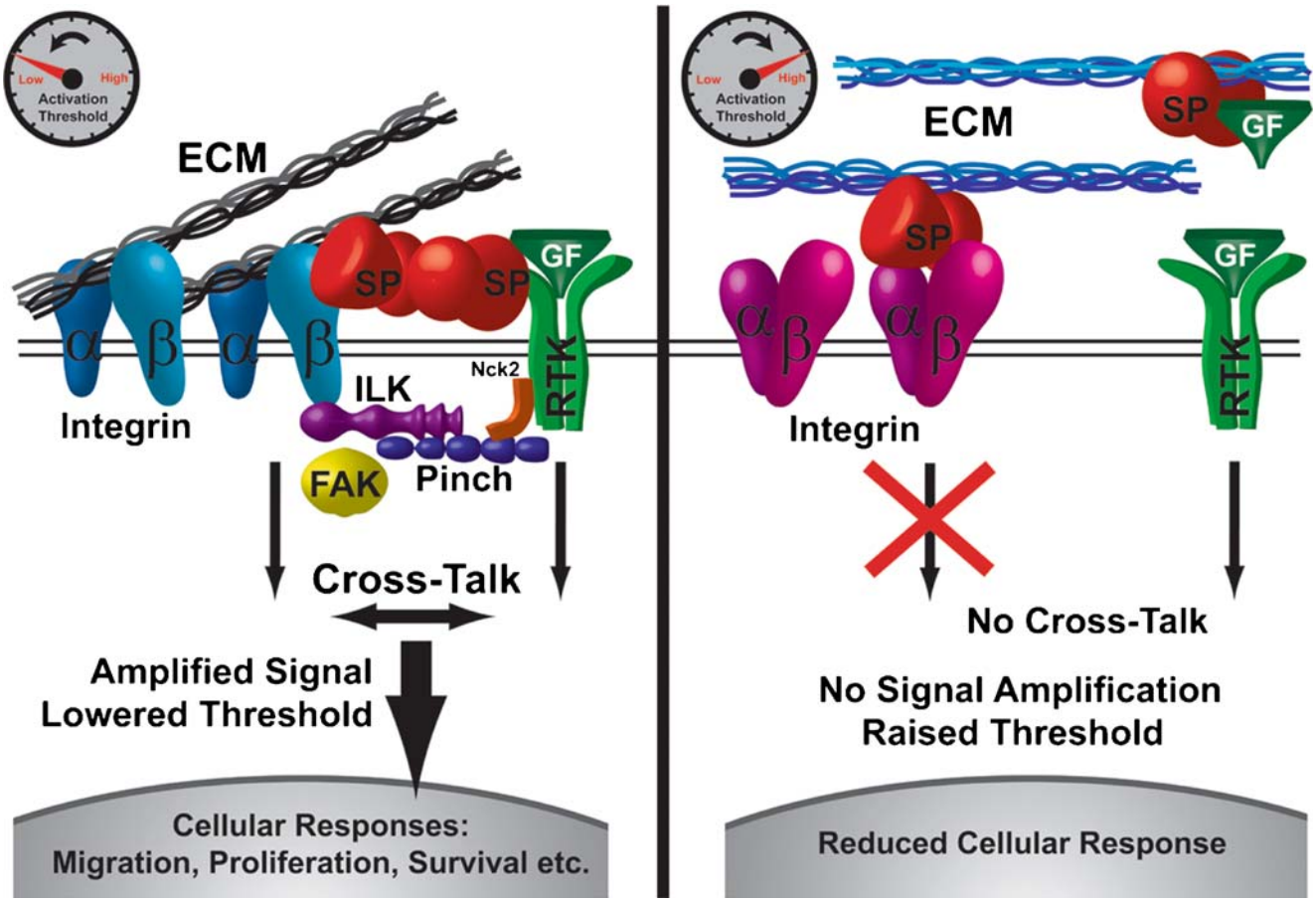


**Fig. 2** SPARC as an extracellular scaffolding protein and rheostat. We propose that SPARC (*SP*) acts as an extracellular scaffolding protein; whereby, SPARC controls the interactions and cross-talk between the extracellular matrix (*ECM*), integrins (α, β) and growth factor receptors (RTK). By controlling integrin clustering and activation, as well as, integrin communication with growth factor receptors, SPARC can function as a rheostat for signaling and cellular response. (*Left*) SPARC may decrease the activating threshold of certain growth factors (GF) by enhancing complex formation and cross-talk between integrins and growth factor receptors. Integrin-linked kinase (*ILK*), Pinch, and Nck2 link integrins and growth factor receptors, intracellularly, to form localized signaling cascades, while SPARC acts as an extracellular scaffold to reinforce this complex. Focal adhesion kinase (*FAK*) is just one example of a signaling molecule located downstream of both integrins and growth factor receptors whose activation is influenced by SPARC. Ultimately, integrin-growth factor receptor cross-talk leads to signal amplification and enhanced cellular responses. (*Right*) SPARC may also increase the activating threshold of integrins and growth factors by inhibiting the binding of certain integrins to the ECM, opposing integrin-growth factor receptor clustering, and/or sequestering growth factors in the extracellular milieu. All of these effects result in a loss of communication and signal amplification of integrins and growth factor receptors, which reduces cellular responses. ECM composition, integrin profile, cytokine profile, cell-type and SPARC concentration/cell-surface localization are all factors dictating this differential response to SPARC

associations control cellular responses to various cytokines. Additionally, it is pertinent to determine how SPARC dictates the activities of each cell type in the tumor microenvironment. Given that SPARC contributes to such a diverse and conflicting range of activities, targeting SPARC globally in human cancer has the potential to present with adverse off-target effects. Therefore, clarification of the molecular mechanisms that involve the role of SPARC during tumorigenesis is necessary in order to develop effective strategies that can target SPARC therapeutically and exploit the idea of manipulating the tumor microenvironment to control cancer growth and metastasis.

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**Competing Interests** The authors have no competing interests to declare.

**Author Contributions** SAA drafted the review, constructed the tables and conceptualized a working model. RAB edited and revised the review for intellectual content and continuity, as well as contributed to the development of a working model.



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