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Anticancer role of SPARC, an inhibitor of adipogenesis

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Abstract

SPARC (a secreted protein acidic and rich in cysteine) has a reputation for being potent anti-cancer and anti-obesity molecule. It is one of the first known matricellular protein that modulates interactions between cells and extracellular matrix (ECM) and is associated with the 'balance' of white adipose tissue (WAT) as well as lipogenesis and lipolysis during adipogenesis. Adipogenesis is an indication for the development of obesity and has been related to a wide variety of cancers including breast cancer, endometrial cancer, esophageal cancer, etc. Adipogenesis mainly involves ECM remodeling, changes in cell-ECM interactions, and cytoskeletal rearrangement. SPARC can also prevent hypertrophy of adipocytes and hyperplasia of adipocyte progenitors. In addition to SPARC's inhibitory role in adipogenesis, it has also been known to be involved in cell cycle, cell proliferation, cell invasion, adhesion, migration, angiogenesis and apoptosis. Molecular cancer biology and clinical biochemistry have significantly enhanced our understanding of the mechanisms that motivate the anti-cancer and anti-obesity action of SPARC. Recent studies elucidating the signaling pathways that are activated by SPARC can help develop the beneficial aspects of SPARC for cancer therapy and obesity prevention. This review focuses on the anti-cancer role of SPARC as it pertains to obesity.

Keywords

SPARC; cancer; adipogenesis

Introduction

Recent contribution of research in the areas of physiology, biochemistry, molecular biology, endocrinology, nutrition, pathology and molecular genetics has resulted in new scientific advances that have enhanced the efficacy of cancer therapy. Despite multimodal treatment regimens including surgery, radiation, and chemotherapy, tumor recurrence is frequent, and most of these patients eventually die from progressive tumorigenesis.[1] Many of these treatments are also toxic and can lead to long-term disabilities.[2, 3] Consequently, finding novel ways to suppress tumor growth using low-toxicity therapies is a major goal of various

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cancer research laboratories. Many groups have demonstrated tumor growth inhibition by targeting potent intra- or extra-cellular molecules.[4, 5] SPARC (Secreted protein, acidic and rich in cysteine), a well-known matricellular molecule is known to be involved in multiple processes in various cancers (Table. 1).[6]

SPARC is also known as osteonectin and basement-membrane protein and is secreted by endothelial cells.[7–9] Initially discovered as a component of bone, SPARC is also expressed in epithelia showing high rates of turnover.[10, 11] Immunocytochemical analysis of embryonic chicken cells *in vitro* and *in vivo* show the presence of SPARC in the nucleus. In addition, elution of soluble proteins and DNA from these cells show that SPARC may be a constituent of the nuclear matrix.[12] These evidences suggest that SPARC mediates interactions between cells and components of the extracellular matrix. SPARC binds rapidly to precise components of the extracellular matrix (ECM) and modulates the interaction of cells.[8] The ECM is a storehouse for a number of growth regulatory factors.[13] Further, matrix proteins modulate cell proliferation and migration.[14, 15] The stimulation of growth *in vitro* by ECM components has been attributed to morphological changes that result from interactions between cells and their supportive matrices.[16] Nevertheless, many matrix-associated proteins also possess potential growth stimulatory activities that are autonomous of their adhesive properties. SPARC is expressed in many cell types and its expression increases during embryogenesis, adult bone tissues, wound healing, and tissue remodeling.

Even though earlier studies linked SPARC overexpression with bone mineralization, current studies have shown that SPARC has pleiotropic effects on biological functions. Phenotypically, SPARC-null mice develop age-related abnormalities due to unusual differentiation of lenticular epithelial cells and partial fiber cell differentiation.[17] SPARC over-expression has been observed in human colorectal cancers (CRCs) that are sensitive to chemotherapy, in contrast to therapy-refractory tumors.[18] *In vitro* experiments have shown the influence of SPARC on several cellular processes (Table. 1). SPARC has been shown to inhibit cell adhesion to the extracellular matrix and modify cell shape.[19] SPARC inhibits cell cycle progression. SPARC also binds to collagens and other extracellular matrix proteins and possibly plays a role in the organization of these components.[20, 21] SPARC has been shown to bind several growth factors including platelet-derived growth factor and vascular endothelial growth factor and alter their biological activity.[22, 23] SPARC indirectly influences the effects of basic fibroblast growth factor, and transforming growth factor-β.[24, 25] SPARC functions as a chemotherapy sensitizer by stimulating tumor deterioration in response to radiation and chemotherapy in tumor xenograft models of chemotherapy-resistant tumors.[26] Following topics will be considered in this review.

1. Structure of SPARC

SPARC is an extracellular matrix-associated glycoprotein and product of a single-copy gene mapped to mouse chromosome 11 and to the long arm of human chromosome 9. Sequence analysis of SPARC gene in bovine, mouse, and human has revealed a high degree of sequence similarity and an absence of canonical CAAT and TATA box sequences. Vertebrate SPARC cDNAs encode proteins of 298–303 amino acids that are post-translationally modified by N-linked glycosylation.[27] The open reading frame (ORF) of SPARC gene is conceptually translated into a putative protein consisting of a typical hydrophobic signal peptide with 17 amino acids followed by mature protein (Fig.1).[28] The signal peptide is removed during processing. The mature peptide of SPARC consists of three individual structural domains (Fig. 1) based on the predicted secondary structure and thought to mediate precise biological activities.[29] 1. An N-terminal highly acidic calcium-binding domain (low affinity) of 52 amino acids (Ala1-Glu52) that inhibits cell spreading, prevents chemotaxis, enhances plasminogen activator inhibitor-1(PAI-1) and decreases

fibronectin (FN) and thrombospondin-1 (TSP-1).[30] 2. A cysteine-rich (contains 10 cysteine residues) FS-like domain is located between the N-terminus domain sequence and EC binding domain. This FS-like domain is 85 amino acids (Asn53-Pro137) long and consists of several internal disulfide bonds that stabilize two weakly interacting molecules. This domain abrogates focal adhesions, promotes angiogenesis and proliferation. 3. EC-binding domain (extracellular calcium-binding domain); high affinity, which is 149 amino acid residues (Cys138-Ile286) at the C-terminus, Val -Ile where the Valine residue serves as an amidation site, followed by a stop codon. This domain has two EF-hand motifs that bind to calcium with high affinity, and comprise almost entirely of α-helices. This region induces MMPs, interactions between cells and matrix, inhibits cell spreading, proliferation and adhesion.[9, 31, 32] Follistatin-like domain of SPARC has been shown to control the proliferation of endothelial cells *in vitro*.[33] Amino acids 54-73 (Cationic region 1) have been shown to inhibit the proliferation of sub-confluent endothelial cells, while amino acids 113-130 (cationic region 2) stimulates DNA synthesis (Fig.1). The role of phosphorylation in the function of SPARC is unclear. The posttranslational phosphorylation modification has been reported in bone osteonectin and in SPARC from PYS-2 cells, it was not found in SPARC produced by endothelial cells.[9, 34, 35]

2. Truncation of SPARC protein

Matrix metalloproteinases (MMP-2, -3, -7 and -13, plasmin and trypsin, have been shown to cleave SPARC *in vitro*, producing KGHK-containing fragment.[7, 36] The presence of truncated form of SPARC protein has been recently reported in hepatocellular carcinoma (HCC) samples and esophageal carcinoma.[37, 38] Immunoblotting studies show higher levels of truncated SPARC (24-27kDa) in tissues in comparison to intact SPARC (37-43 kDa).[37] Interestingly, cell lysates do not show truncated SPARC indicating that the presence of truncated SPARC in tissues may possibly be associated with the existence of certain proteinases in the surrounding environment. Cleavage of SPARC by MMP3 produces peptides containing the KGHK sequence that can stimulate angiogenesis.[36] Alpers et al.[39] have suggested that AON-5031(anti-SPARC) recognizes the *N*-terminal part (amino acids 5–23) of the mature SPARC protein. So, the truncated protein should have the *N*-terminal half of intact SPARC, which contains the KGHK sequence located at amino acids 119–122 from the *N*-terminus (Genebank AN: BC072457). Truncated SPARC in the tumor sinusoidal area has been correlated to the tumor microvessel density (MVD), suggesting that truncated SPARC may play a significant pro-angiogenic role in HCC.[37] Over-expression of SPARC leads to a decrease in MVD, at least in part, resulting in delayed tumor formation and reduction of tumor size. The decrease in MVD–CD34 observed in nude mice xenografts has been attributed to the high expression of anti-angiogenic intact-SPARC. In clinical samples, the positive relationship between SPARC protein expression and MVD has been probably due to the low expression of anti-angiogenic intact-SPARC and high expression of pro-angiogenic truncated-SPARC. Likewise, high expression of truncated-SPARC protein in tumor sinusoidal areas has been associated with increased tumor MVD while over-expression of full-length SPARC correlates with a decrease in tumor MVD, accompanied by a delay in tumor formation and a decrease in tumor size. Importance of exact sequence and the angiogenic properties of truncated- and intact-SPARC proteins observed in human liver cancer will be the subject of many future studies.

3. Receptors and modulators for SPARC

Even though receptors have been discovered for some of the matricellular molecules, it remains uncertain how SPARC cooperates with the cell surface to stimulate its effects. Recent research has suggested that stabilin-1 and integrins α5 and β3 may mediate some of the effects of SPARC.[40, 41] Byzova and group [40] have shown that tumor cell migration

attributed to SPARC is mediated by α5 β3 integrins and is controlled by an autocrine loop in which VEGF engages VEGFR-2. Kzhyshkowska and group,[41] using a phage display, have proposed stabilin-1 as a cellular receptor for SPARC. Stabilin-1 interrelates with SPARC through the extracellular epidermal growth factor (EGF)-like domain containing the sequence FHGTAC. SiRNA knockdown of Stabilin-1 reduces SPARC expression, while elevated SPARC level is observed in Stabilin-1 over-expressing cells.[42] Stabilin-1 mediates the internalization and delivery of SPARC to the endocytic pathway in stably transfected CHO cells. These observations show that stabilin-1 acts as a specific and efficient receptor in macrophages that mediates internalization of extracellular SPARC and its targeting to lysosomes. ShRNA of SOX-5 in nasopharyngeal carcinoma (NPC) cells causes a significant increase in SPARC. SOX-5 can bind directly to the SPARC promoter in a chromatin immunoprecipitation assay signifying that SOX-5 acts as a vital transcriptional repressor of SPARC.[43] Exogenous TGF-β induces over-expression of both collagen and SPARC, while this response is significantly attenuated in fibroblasts, pre-transfected with SPARC small interfering RNA.[44]

4. DNA methylation

SPARC expression gets altered in both normal and tumor cells depending upon the tumor type and culture conditions. Higher levels of SPARC expression have been observed in some types of solid tumors, such as melanoma,[45] glioblastomas,[46] breast,[47] and prostate[48] while some others, such as endometrium, colorectal, and leukemia showed lower or undetectable levels of SPARC due to SPARC promoter hypermethylation (Table. 1).[49–53] These studies imply that carcinogenic effect of SPARC is cell type specific and may depend on the tumor microenvironment. In general, alteration in DNA methylation involves DNA methyltransferases (1, 3a and 3b) leading to inactivation of many tumor suppressor genes during tumor growth.[54, 55] DNA methylation is also involved in maintaining a normal balance between cell proliferation and apoptosis in some cancer cell lines.[56, 57] Several studies have shown that changes in the methylation levels of SPARC promoter may lead to SPARC silencing leading to tumor growth. For example, low SPARC expression in lung cancer cell lines is due to DNA hypermethylation of the gene promoter. Consequently, treatment with 5-Aza-2'-deoxycytidine leads to higher expression of SPARC in lung cancer cells.[58] Similar studies also demonstrated in colorectal cancer[52] and pancreatic cancer cells.[51] 5-Aza-2'-deoxycytidine is a demethylating agent and inhibits DNA methyltransferase activity to upregulate SPARC expression. This mechanism leads to decreased cell viability and improved response of cancer cells to chemotherapy.[52]

5. SPARC in adipogenesis

Obesity is a disorder that results from excess white adipose tissue (WAT) and has been known as a risk factor for a wide variety of cancers including breast cancer, endometrial cancer, esophageal cancer, colon cancer, rectal cancer, pancreatic cancer, kidney cancer, ovarian cancer, cervical cancer and liver cancer.[59, 60] Understanding the associations between obesity, overweight and different types of cancers, as well as the underlying biological mechanisms, remain a budding and presently very fascinating area of research. WAT is an endocrine organ that plays a central role in the regulation of energy metabolism mediating its biological effects by secreting a variety of peptide and protein hormones (adipokines; such as leptin, adiponectin, visfatin, retinol-binding protein-4, tumor necrosis factor and interleukin-6).[60, 61] These adipokines target the central nervous system and peripheral tissues (WAT, liver and muscle) to modulate energy metabolism.[62–64]

Adipogenesis or adipocyte differentiation is a greatly controlled process that has been extensively studied for the last 35 years. Nutritional and hormonal signaling affects

adipogenesis in a positive or negative manner, and factors involved in cell-matrix or cell-cell interactions are also crucial in regulating the preadipocyte differentiation process. Multiple signaling pathways regulate preadipocyte differentiation, including transforming growth factor-β (TGF-β), tumor necrosis factor-α, Wnt, insulin/ insulin-like growth factor-1, and other growth factors. The first characteristic feature of the adipogenesis process is the remarkable change in cell shape as the cells switch from fibroblastic to spherical shape. These morphological alterations are paralleled by changes in the level and kind of cytoskeletal components and the level of extracellular matrix (ECM) components.[62] Adipogenesis is characterized by cell-associated ECM switches from a Fibronectin (FN)-enriched matrix into Laminin (LN)-rich basement membrane (BM); correspondingly, integrin expression changes from α5 (FN) to α6 (LN).[65] SPARC is the first known matricellular protein associated to the 'balance' of WAT; during adipogenesis. SPARC increases the deposition of FN and the expression of its receptor, α5 integrin.[65] SPARC also inhibits the deposition of LN during adipogenesis as well as expression of the α1 chain and its receptor, α6.[65] Further, SPARC also down-regulates the secretion and deposition of LN in lens cells.[66] LN and type IV collagen increase adipogenesis, in two-dimensional cell culture.[67] In addition, SPARC interacts with types 1 and IV collagen for stability of basal lamina.[29, 68] So, it is possible that SPARC inhibits adipogenesis in part by interference with the formation of basement membrane. SPARC is enriched in both mesenteric and subcutaneous WATs showing elevated levels of SPARC transcript.[69] In humans, the plasma concentration of SPARC was correlated positively with body mass index.[70] The excess of WAT is associated with increased TGF-β,[71] which leads fibrosis and might enhance the expression of SPARC. But, other adipokines may override the effects of TGF-β, SPARC, and collagen.

SPARC-null mice show increased accumulation of WAT along with an increase in both adipocyte size and number as compared to wild type (WT) mice.[72] SPARC-null mice might be highly susceptible to protease degradation and remodeling functions allowing adipocytes to develop a larger size, hence, contribute to hyperplastic WAT. The ECM remodeling associated with adipogenesis requires SPARC, to stabilize the tissue and maintain the balance of lipogenesis and lipolysis. SPARC, to some extent, can prevent hypertrophy of adipocytes and hyperplasia of adipocyte progenitors. Further SPARC-null mice contain higher levels of soluble type VI collagen in their skin,[72] and it may influence the expression, folding, post-translational modification, and secretion of type VI collagen in WAT. Consequently, SPARC could control adipogenesis through type VI collagen. SPARC also interact with integrin α5β1 and this complex inhibits preadipocyte adhesion, focal adhesion kinase (FAK), integrin-linked kinase (ILK) activity and it leads to cell migration. SPARC also stimulates the phosphorylation and activation of FAK in glioma cells.[73] Likewise SPARC can also inhibit the formation of adipocytes but enhances that of osteoblastocytes by its enrichment of the accumulation of β-catenin in both cytosol and the nucleus.[66, 74] Both endogenous and exogenous SPARC enhance the accumulation of β-catenin. Wnt/Beta-catenin represses the expression of C/EBPα and PPARγ at early stages of adipocyte differentiation.[75] Further, SPARC also inhibits the expression of C/EBPα and PPARγ at later stages of adipocyte differentiation. These evidence shows that SPARC suppresses the central transcriptional cascades of adipogenesis through the Wnt/Beta-catenin pathway. Further research is required to decipher the mechanisms underlying the inhibitory consequences of SPARC on adipogenesis *in vivo*.

6. Role of SPARC in cell cycle and proliferation

Generally, 'vital functions' of the cells are gauged by assaying for one of these parameters: cell viability, cell proliferation and cell growth. These 'vital functions' of the cells are mainly modulated by the signaling molecules or growth factors that convey information to

cells during cellular differentiation or growth. Recent studies have shown that SPARC and TGF-β employ each other in a mutual relationship to modulate these cellular functions. SPARC and TGF-β acts as inhibitors of cell cycle progression and proliferation in several types of cells.[31, 32, 76, 77] SPARC stimulates TGF-β expression in mesangial cells and, on the other hand, TGF-β stimulates SPARC expression in a number of cell types, including endothelial cells, fibroblasts, keratinocytes, and smooth muscle cells.[20, 78-81] SPARC inhibits epithelial cell proliferation by commandeering the TGF-β signaling system, via coupling of C-terminal extracellular calcium (EC)-domain (i.e., SPARC-EC) to a TGF-β receptor/Smad2/3-dependent pathway.[82] SPARC and TGF-β are both expressed in epithelial cells; however, the association between these signaling molecules in regulating epithelial cell behaviors remains to be addressed. SPARC negatively regulates breast cancer cell proliferation without stimulating metastasis.[83] Elevated levels of SPARC increases cell de-adhesion from matrix in gliomas.[84] SPARC also alters glioma growth by changing the tumor microenvironment and by repressing tumor vascularity through inhibition of VEGF expression.[84] These results present a novel mechanism, whereby SPARC controls VEGF function by preventing the available growth factor. Haber et al.[85] show that SPARC alters the proliferation of stromal but not melanoma cells. They also show that SPARC inhibits endothelial cell proliferation, spreading, and migration. In fact, low expression of integrins following exposure to SPARC considerably reduces cell proliferation and adhesion, in part by down-regulating the activation of Akt, FAK, MAPK 44/42 and Src.[86] Treatment with exogenous SPARC significantly inhibits the growth of pancreatic cancer, colorectal cancers, neuroblastomas, and leukemia cells.[18, 87]

SPARC and its peptide 2.1 and 4.2 (from a disulfide-bonded domain of SPARC) inhibit DNA synthesis in BAEC, as determined by (^{3}H) thymidine incorporation and delay the entry of cells into S phase.[88] An inhibitory effect of SPARC on cell-cycle progression might facilitate the short-term withdrawal from the cell cycle that frequently happens after cellular responses to developmental or injury signals. Over-expression of SPARC protein and mRNA is frequently observed in non-proliferating, but actively secreting, Leydig, Sertoli cells and migrating cells [89, 90] showing that SPARC might direct a metabolic pathway in addition to cell cycle. SPARC is stimulated after cells have primarily proliferated and may function to withdraw cells temporarily from the cell cycle in preparation for migration.[90] The recognition of SPARC as an anti-spreading factor for specific cells, together with its capability to direct noticeable changes in cell shape, suggests that the evident proliferation in the presence of SPARC may result from alteration in cell shape.[90] Nevertheless, potential actions of SPARC on mitosis and cellular migration, need disconnection from ECM, have not been studied very well.

In contrast, SPARC expression increases cell survival under stress commenced by serum removal through a decrease in apoptosis.[91] Administration of SPARC quickly stimulates AKT phosphorylation, an effect that is blocked by a neutralizing SPARC antibody. AKT activation is crucial for the anti-apoptotic effects of SPARC as the reduced apoptosis and caspase activity linked with SPARC expression can be blocked with a specific AKT inhibitor or dominant-negative AKT.[91] As tumor cells experience stressful microenvironments predominantly during the metastatic process, these results propose that SPARC functions, in part, to help tumor progression by facilitating tumor cells to survive under stressful environment. Greater MMP9 expression in the absence of SPARC has an additive effect in stimulating tumor development.[92] The mechanisms of SPARC functions in cancer development remain multifaceted and depend on tumor cell type and the microenvironment.

7. Role of SPARC in cell invasion, adhesion and migration

Understanding the molecular mechanisms controlling invasion, adhesion and migration of tumor cells is essential for improvement of novel therapies to cancer. Invasion and metastasis are constituted of several steps, which are not well distinguished at the cellular and molecular levels. The early steps in invasion and metastasis by a tumor cell consist of the breakdown of cell-cell connections, disconnection of tumor cells, proteolysis of the ECM, and distribution throughout neovascularization. SPARC inhibits cellular adhesion. Several *in vitro* studies have shown that secretion of SPARC influences cell morphology by reducing the number of focal acquaintances and blocking the adhesion of cells to their substratum or to adjacent cells.[93, 94] SPARC regulates cell-ECM communications that manipulate cell adhesion and migration. *In vitro*, pancreatic cancer cells over-expressing MMP9 show higher cell invasion and migration, which can be efficiently inhibited by the addition of SPARC.[92] Over-expression of SPARC in gliomas induces brain tumor invasion and migration *in vitro* and *in vivo*,[95] whereas administration of SPARC siRNA into glioma cells results in down-regulation of SPARC expression, and considerable suppression in glioma cell migration *in vitro*[96] and lower tumor cell survival and invasion.[73] The level of SPARC correlates with total and phosphorylated HSP27. SPARC and HSP27 co-localize to invading cells *in vivo*. Inhibition of HSP27, mRNA reverse SPARC–stimulated changes in morphology, migration and invasion *in vitro*.[95] These experiments indicate that HSP27-mediated actin polymerization, cell migration and contraction are novel downstream effectors of SPARC functions on cell morphology and migration. Variations in cell-cell and cell-matrix adhesion in tumors depend on the degree of cohesiveness and the mode of tumor growth. Abrogation of general cell adhesion function plays a vital role in the development of cancer. This change in tumor cell adhesion is essential because detachment of tumor cells is an initial step in the invasion of adjacent tissues and metastasis to distant sites. *In vitro* experiments have revealed that addition of exogenous SPARC to cultured cells inhibits cell distribution and stimulates cellular rounding. This effect leads to the detachment of cells.[19] SPARC and TSP inhibit cell attachment and spreading and cause partial detachment and rounding of cells *in vitro*.[9] Over-expression of SPARC in stably transfected F9 embryonal carcinoma cell lines results in rounding and aggregation.[97] SPARC may change these cell-cell or cell-matrix connections by breaking cell-substrate bonds and stimulating the reorganization of actin cytoskeletal elements.[19] SPARC plays a role in melanoma progression, because lower levels of SPARC limits the invasive and adhesive capabilities of melanoma cells *in vitro*, where as *in vivo*, down-regulation of SPARC in melanoma cells inhibits tumor development in nude mice, but also show an increase in polymorphonuclear leukocytes (PMNs) recruitment to this peri-tumoral region,[98] because lower levels of SPARC stimulated greater migration of PMNs to the site of the tumor.[99] High levels of SPARC in normal human melanocytes inhibits expression of E-cadherin and P-cadherin and stimulates a fibroblast-like morphology.[100] However, this study does not explore whether melanocytes over-expressing SPARC produce tumors *in vivo*. Further notably, is it the secretion of SPARC by melanocytes or by adjacent myofibroblasts that is essential for tumorigenesis in this microenvironment?

8. Role of SPARC in angiogenesis

Angiogenesis, the process of new blood vessel formation from pre-existing ones, plays a vital role in various pathological and physiological circumstances, including embryonic development, wound repair, tumor growth and inflammation.[101] From a pathological point of view, angiogenesis is a major limiting step in tumor progression and is necessary for tumor development at metastatic sites. Angiogenesis consists of a sequence of phases that includes suspension of basement membrane, migration, and proliferation of endothelial cells, formation of vascular loop and formation of new basement membrane. These multiple

steps are regulated by different factors such as growth factors, proteases, oxygen levels and extracellular matrix components, during which the endothelium gives rise to new vessels. Over the past two decades, matricellular proteins have expanded more attention in their role in regulating cellular functions and angiogenesis. SPARC has nominal effects on angiogenesis *in vivo*. Nevertheless, SPARC has some angiogenic properties.[102] Microarray studies showed that SPARC and SPARC-like 1 are over-expressed in HCC and clustered with CD34 (a well-known angiogenic marker compared with non-tumorous liver cells, and both genes may play a role in HCC angiogenesis.[103]

SPARC modulates cell adhesion and proliferation and is thought to function in tissue remodeling and angiogenesis. SPARC binds to VEGF, thus inhibiting VFGF interaction with EC surface, ERK 1/2 activation and VEGF stimulated DNA synthesis.[23] SPARC also binds to PDGF-AB and -BB, but not -AA, and inhibits the interaction of these growth factors with TK receptors.[22] SPARC can also inhibit angiogenesis indirectly by regulating the expression of MMPs and TGF-β1 *in vivo*.[25, 37, 92, 104, 105] SPARC, in combination with other known angiogenic factors, may act pleiotropically during angiogenesis. Angiostatin, a cleavage product of plasminogen, most probably acts through inhibition of angiogenesis. Over-expression of SPARC is correlated with a good prognosis in neuroblastoma, probably due to reduced angiogenesis.[87] SPARC mediated inhibition of angiogenesis is indicated in SPARC-null mice that shows increased angiogenic activity in sponge cell invasion assays.[106] The angiogenic activity of SPARC is complex, as different proteolytic fragments show contrasting effects. An EGF-like part of the follistatin-like domain in SPARC has been shown to be angiosuppressive.[104] Whereas another fragment of this domain in SPARC consists of a KGHK amino acid sequence that is pro-angiogenic.[20, 107] However, it is feasible that secreted modular calcium-binding protein (SMOC-2) apply its effects via the follistatin-like domain, which has been shown to have growth factor binding potential. *In vivo*, SPARC is also capable of suppression of VEGF-stimulated integrin activation and down-regulation of MMP-2 and -9.[87, 92, 108] Recent research is paying attention on the angiostatin and angiogenic and antiangiogenic properties of SPARC. This research will offer a better understanding of how these key factors regulate angiogenesis.

9. Role of SPARC in apoptosis

Programmed cell death, apoptosis is vital for normal development and tissue homeostasis. Nevertheless uncontrolled apoptosis may occur after treatment with cytostatic chemicals. It is a patho-physiological process and is connected with the various human diseases.[109] In general, there are two different pathways that initiate apoptosis: one is extrinsic pathway mediated by death receptors on the cell surface and the other is intrinsic pathway mediated by mitochondria.[109, 110] In both extrinsic and intrinsic pathways, cysteine aspartyl-specific proteases (caspases) are stimulated that cleave cellular substrates, leading to the morphological and biochemical changes that feature apoptosis. Evidence that SPARC may promote apoptosis in cancer cells is presented by Yiu and colleagues, who show that exogenous treatment of various ovarian cancer cell lines with SPARC induces apoptosis.[111] In support of this observation SPARC exposure increases cleaved caspase 3 in human ovarian carcinoma cells.[108] SPARC induces apoptosis of endothelial cells in a dose-dependent manner, accomplishing maximal effect with 20μg/ml of SPARC.[87] In colorectal cancer cell lines, over-expression of SPARC reduces cell viability and enhances apoptosis in cells exposed to various chemotherapeutic agents.[18] This SPARC-mediated apoptosis occurs by activating the extrinsic pathway while enhancing the intrinsic pathway of apoptosis.[112] The ability of SPARC to enhance apoptosis appears to involve its physical interaction with the N-terminus of caspase 8, which enhances the chemosensitivity of colorectal cancer cells through the apoptotic cascades.[112] Apoptosis of colorectal cancer cells overexpressing SPARC can be further augmented following concomitant exposure to vitamin D and

chemotherapy, by reducing phosphorylation of Akt and subsequent inactivation of the pro-survival pathway.[26]

Conclusion

Recent studies have putforth many promising molecules that are integral for metastatic progression of cancer cells including many proteases, angiogenic factors, and adhesive or deadhesive molecules. Depending on the type of SPARC is either associated with aggressive tumor phenotype (gliomas, melanoma, gastric cancers) or exhibits anti-tumor activity (ovarian, colorectal, neuroblastoma).[113] The present review provides an overview of SPARC's role as an anti-cancer molecule and its role in obesity.

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List of Abbreviations

CRCs	Colorectal cancers
3-D	3-dimensional
EGF	Epidermal growth factor
EC	Extracellular calcium
ECM	Extracellular matrix
FN	Fibronectin
FAK	Focal adhesion kinase
HSP	Heat shock protein
HCC	Hepatocellular carcinoma
ILK	Integrin-linked kinase
LN	Laminin
MMP	Matrix metalloproteinases
MVD	Microvessel density
NPC	Nasopharyngeal carcinoma
NMR	Nuclear magnetic resonance
ORF	Open reading frame
PAI-1	Plasminogen activator inhibitor-1
PDGF	Platelet-derived growth factor
PMNs	Polymorphonuclear leukocytes
SMOC-2	Secreted modular calcium-binding protein
SPARC	Secreted protein acidic and rich in cysteine
TSP-1	Thrombospondin-1
TGF-β	Transforming growth factor

VEGF	Vascular endothelial growth factor
WAT	White adipose tissue
WT	Wild type

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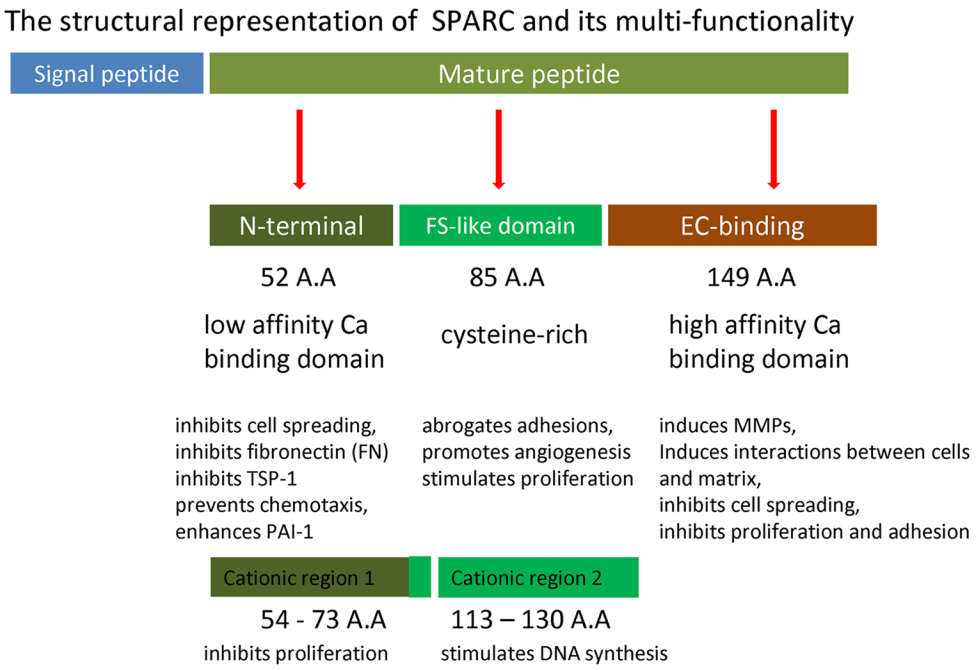

Figure 1.

Table 1

Multifunctional SPARC in cancer

	Exogenous SPARC	Endogenous SPARC level	Down regulation of SPARC	DNA hypermethylation	Studies	References
Ovarian cancer	Alters cell proliferation, apoptosis and tumor growth	Low level	Increases growth and reduces apoptosis		*In vitro, in vivo*	[108, 111]
Prostate cancer		Low level	Enhances aggressive and metastatic behavior	Yes	*In vitro* *In vivo*	[49, 114]
Neuroblastoma	Inhibits growth and angiogenesis Enhances autophagy and apoptosis	Low level			*In vitro* *In vivo*	[87, 115]
Lung cancer				yes		[58]
Breast cancer	Inhibits cell proliferation and metastasis Stimulates cell migration and invasion	High level			*In vitro* *In vivo*	[83, 116–118]
Melanoma	Inhibits the growth of spheroids	High level	Inhibits invasion, adhesion and tumor growth		*In vitro* *In vivo*	[98, 119]
Pancreatic	Inhibits cell migration and invasion	Low level	Increases growth and reduces apoptosis	yes	*In vitro* *In vivo*	[51, 92]
Leukemia cells AML cell lines	Inhibits growth of cell lines, and induces cell cycle arrest	Low level		yes		[53]
Colorectal	Inhibits cell growth and enhances apoptosis	Low or High level		yes		[56, 57, 60, 112, 120]
Colon adenocarcinoma		Low			*In vivo*	[121]
Gliomas	Delay in tumor growth Reduces apoptosis and increases invasion	High level			*In vivo* *in vitro*	[91, 122–123]
Medulloblastoma	Inhibits cell proliferation Induces autophagy, apoptosis				*In vivo* *in vitro*	[115]
Endothelial cells	Inhibits spreading, migration and proliferation. Induces apoptosis				*In vivo* *in vitro*	[115, 124–125]
Stromal cells	Modulates proliferation	High levels		yes	*In vivo* *in vitro*	[51, 85]