© Med Sci Monit, 2007; 13(2): RA25-30
PMID: 17261993

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Review Article

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Received: 2006.12.01
Accepted: 2006.12.15
Published: 2007.01.30

Role of SPARC – matricellular protein in pathophysiology and tissue injury healing. Implications for gastritis and gastric ulcers

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Source of support: Supported by the VA Merit Review (to AST) and the AHA grant-in-aid Program to A.S.T.

Summary

In this paper we reviewed roles of SPARC in cell functions with a focus on tissue injury healing. SPARC (Secreted Protein, Acidic and Rich in Cysteine) is a matrix-associated glycoprotein that influences a variety of cellular activities *in vitro* and *in vivo*. SPARC and its related peptides bind to several proteins of the extracellular matrix (ECM), affect ECM protein expression, alter cell shape, reduce cellular adhesion, influence migration, and modulate growth factor-induced cell proliferation and angiogenesis. SPARC influences cell interactions with the extracellular milieu during embryonic development and in response to tissue injury. This paper reviews the roles of SPARC in the cellular and molecular events taking place during healing of tissue injury. We also present preliminary data on increased SPARC expression in gastritis and in granulation tissue of human gastric ulcer.

key words: **SPARC • osteonectin • tissue healing • ECM • angiogenesis • gastric ulcer**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/473774

Word count: 2548
Tables: 1
Figures: 2
References: 48

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BACKGROUND

SPARC (**S**ecreted **P**rotein, **A**cidic and **R**ich in **C**ysteine), also known as osteonectin, is a member of the matricellular protein family. Matricellular proteins interact with cell-surface receptors, extracellular matrix (ECM), growth factors and proteases, but they do not contribute to the structural properties of ECM [1].

SPARC was first described as a major constituent of bovine and human bone [2]. However, it is also expressed in a variety of tissues during embryogenesis and repair [3]. It is found only in specific organs of mouse embryo, whereas in adult mouse, SPARC is limited to tissues undergoing remodeling such as the gut, bone, and injured tissues [4]. SPARC is present at a moderate level in human steroidogenic cells, chrondrocytes, placental trophoblast, vascular smooth muscle, and endothelial cells [5]. It is strongly expressed in fibroblast, endothelial cells, epithelial cells, and macrophages in injured tissues [5–8]. Furthermore, the increased level of SPARC is also associated with increased capacity for invasion *in vitro* in prostate cancer [9], breast cancer [10], gastric cancer [11], glioblastoma [12], and malignant melanoma [13].

SPARC and its related peptides derived from SPARC proteolysis promote changes in cell shape [3,14], disrupt cell adhesion [15,16], inhibit cell cycle [17], regulate extracellular matrix [18,19] and modulate cell proliferation [17,20] and migration [21,22]. They also influence cellular response through interaction with growth factors, such as platelet-derived growth factor (PDGF) [23], vascular endothelial growth factor (VEGF) [20], basic fibroblast growth factor (bFGF) [15], and transforming growth factor (TGF) [24].

ROLE OF SPARC IN TISSUE INJURY/WOUND HEALING

The main activities of SPARC include modulating cell-ECM interactions, delaying cell-cycle progression, inhibiting proliferation and angiogenesis, and regulating the expression of a number of growth factor and ECM proteins. These functions underlie the process of wound repair, which consists of inflammation, cell migration, proliferation and angiogenesis [25].

Immunohistochemistry and *in situ* hybridization demonstrated a spatial and temporal distribution of SPARC in injured tissues implicating its significant role in repairing dermal wounds [7], intestinal anastomosis and short bowel syndrome [6], wounded cornea [8] and ischemic myocardium [5,22]. The importance of SPARC in wound healing is further substantiated by that fact that in absence of SPARC, the healing process is modified. For example, there are two contradictory reports of wound healing response in mice: Basu et al. [26] reported that in SPARC-null mice there is a delayed healing following the creation 25 mm, but not 6 mm, wound. In contrast, Bradshaw et al. [27] demonstrated an enhanced healing of 5 mm wound in SPARC-null mice.

This article presents an update on the role of SPARC in processes associated with wound healing.

MOLECULAR STRUCTURE

SPARC is a product of a single gene localized in chromosome 5q321-33 in human and is conserved in a variety of species [3]. The SPARC gene encodes a protein of 298-304 amino acids. Prior to its secretion, the initial 17 amino acids signal sequence is removed [28]. The secreted form of SPARC is 43 kD [28].

SPARC consists of three distinct modules (Figure 1). Importantly, *in vitro* studies showed that SPARC can be proteolytically cleaved into peptides that can function differently than the native SPARC.

Module I (amino acid 1-52) is the NH_2-terminal acidic domain that binds calcium ions with low affinity and mediates the interaction with hydroxyapatite [28]. It contains the major immunological epitope of SPARC [28]. A sequence of this module termed peptide 1.1 causes cell rounding and de-adhesion [29], inhibits migration [21], and influences expression of ECM protein [30].

Module II (amino acid 52-137), a cysteine-rich follistatin-like (FS) domain, is an elongated nonglobular structure that consists of two weakly interacting modules stabilized by internal disulfide bonds [28]. The NH2-terminal module of the FS domain is a beta-hairpin structure. It contains a sequence designated as peptide 2.1 that delays endothelial cell cycle [17,31], causes de-adhesion [32], inhibits endothelial proliferation and angiogenesis [31], and exerts both negative and positive effect on proliferation of fibroblast [31]. The COOH-terminal module of the FS domain consists of a pair of antiparallel alpha-helices [28]. Its peptide 2.3 and the (K)GHK sequence increase the expression of metalloproteinases [18], enhance proliferation of endothelial cells and fibroblasts and angiogenesis [31,33].

Module III (amino acid 138-286) constitutes a C-terminal extracellular (EC) module that consists of two EF-hand motifs [28]. It contains a sequence known as peptide 4.2, which inhibits proliferation [20,34] and migration [21] of endothelial cells, affects expression of ECM protein [18,30], causes cell rounding [29] and abrogates cell adhesion [32].

The different and sometimes opposing effects conferred by the native SPARC and its proteolytic peptides suggest regulatory role of SPARC. The biphasic modulation of certain cellular activities may serve to regulate and restore the cell/tissue homeostasis once the remodeling and development of the cell is completed.

SPARC AND ECM

Many cellular activities are regulated in part by interaction with the extracellular matrix (ECM). ECM is secreted locally by fibroblasts, epithelial, smooth muscle and endothelial cells and assembles into a network in the extracellular space. SPARC is not detected in an established ECM of normal cells, but it is predominantly expressed at sites of ECM turnover.

An important aspect of wound healing process involves the degradation and remodeling of the basement membrane. Tremble et al. [18] showed that native SPARC and its peptides 2.3 and 4.2 enhanced the expression of collagenase, stromyelysin, and 92-kD gelatinase in cultured rabbit synovial fibroblasts. These proteins are capable of degrading both basement membranes and interstitial connective tissue ma-

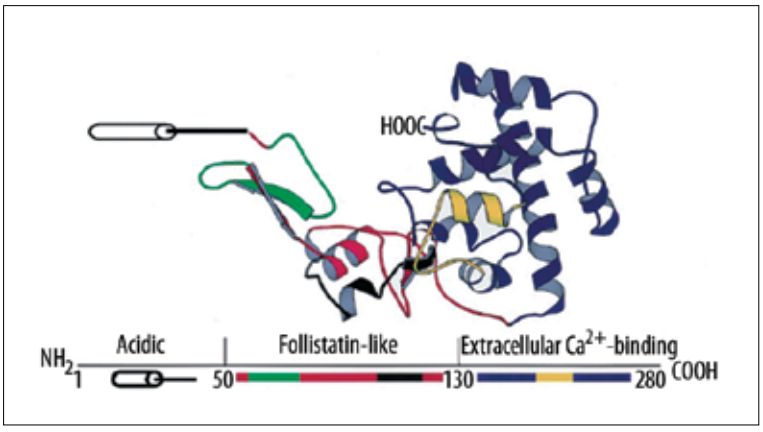

Figure 1. Modular structure of human SPARC. The ribbon diagram derived from crystallographic data indicates three structural modules. The follistatin-like domain, aa 53-137, is shown in red except for peptide 2.1, aa 55-74, and the (K) GHK angiogenic peptide, aa 114-130, which are shown in green and black, respectively. The EC-module aa 138-286 is shown in blue except for peptide 4.2, aa 255-274, which is shown in yellow. (aa: amino acid). (Reprinted from reference 3, with permission from authors and from Elsevier).

trices during the process of tissue remodeling. SPARC and its peptide 4.2 also induced the expression of plasminogen activator inhibitor (PAI) in bovine aortic endothelial cells [30,35]. PAI regulates plasminogen that plays a key role in the process of proteolytic degradation of ECM [35].

SPARC's activity in the organization of ECM during development and in response to injury also involves fibronectin, an essential component for the stabilization of mature ECM [19]. Barker et al. [19] showed that SPARC, via integrin linked kinase, enhanced the fibronectin-induced assembly of ECM. SPARC also interacts with other extracellular matrix proteins, including binding to collagen Type I, II and III and IV [3]. These interactions can contribute to the remodeling of ECM.

Possibly, the expression of SPARC in response to injury or tissue remodeling is activated to facilitate the production of an ECM that is permissive for cell migration, proliferation, and angiogenesis.

SPARC and Cell Shape and De-adhesion

One important property of SPARC is that it regulates cell shape and adhesion, which in turn can influence cell proliferation, migration and angiogenesis. For example, injecting SPARC into developing *Xenopus* embryos causes the rounding of migrating mesodermal cells and severe developmental abnormalities [36]. In SPARC-null mice, severe cataracts developed at an early age and this was partly due to abnormalities in cell shape [37]. This effect on cell rounding is specific to cell types; exogenous SPARC induces cell rounding of endothelial cell, fibroblasts, and smooth muscle, but not in other cells like F9, PYS-2, and 3T3 cells [38].

Two separate regions of SPARC, peptide 1.1 and peptide 4.2, have been implicated in causing cell rounding [29]. Several mechanisms have been elucidated for SPARC's induction of cell rounding. Goldblum et al. [14] demonstrated that exogenous SPARC induced cellular rounded morphology and intercellular gap in bovine pulmonary artery endothelial cells. This effect was proposed to be mediated via F-actin because prior stabilization of F-actin protected against these effects induced by SPARC. Interaction of SPARC with specific matrix proteins including type III collagen, type V collagen, and thrombospondin has also been suggested to play a role in cell rounding [38].

SPARC also influences cellular activity via its de-adhesive property. De-adhesion is defined as a process involving the transition of the cell from a strong adherent state to a state of intermediate adherence [39]. De-adhesion involves loosening of structural links between the cytoskeleton and the extracellular matrix and is more conducive for processes such as mitogenesis and motility [39].

SPARC and peptide 1.1 decrease cell adhesion by inducing cell rounding and inhibiting cell spreading. However, SPARC peptides 2.1 and 4.2 reduce the number of focal adhesions in BAE cells by inducing a loss of vinculin and redistribution of F-actin fibers [32]. In addition, SPARC's de-adhesive effects may be due to its competition with adhesive ECM proteins, such as collagens and vitronectin, for their receptors, and this interference results in focal adhesion disassembly [16].

SPARC and Cell Migration

Cell migration is dependent on cytoskeletal rearrangement. During wound repair, cell migration is essential for the recruitment of cells to the damaged area. This process is also modulated by SPARC via interaction with cytokines and growth factors. Wu et al. [22] showed that SPARC was significantly increased in the necrotic region of myocardial infarction in mice and promoted migration of fibroblasts via an integrin-dependent mechanism. This elevation of SPARC probably served to loosen the connections between surviving cells and connective tissue, thus allowing migration of fibroblasts and other cells to the injured area [22]. Also, dermal wound healing in SPARC-null mice is compromised due to impaired fibroblast migration resulting in delayed granulation tissue formation [26]. These findings highlight the critical role of SPARC in cell migration in the context of wound healing.

The role of SPARC in cell migration may be cell type specific. SPARC is required for the migration of fibroblasts into the wound site, but it is not essential for the motility of keratinocytes [22]. On the other hand, absence of SPARC enhances migration of leukocytes [40].

SPARC alone does not serve as a stimulus for the cell migration but exerts its effect via interaction with growth factors and cytokines. Hasselaar et al. [21] demonstrated that exogenous SPARC and synthetic peptides 1.1 and 4.2 inhibit-

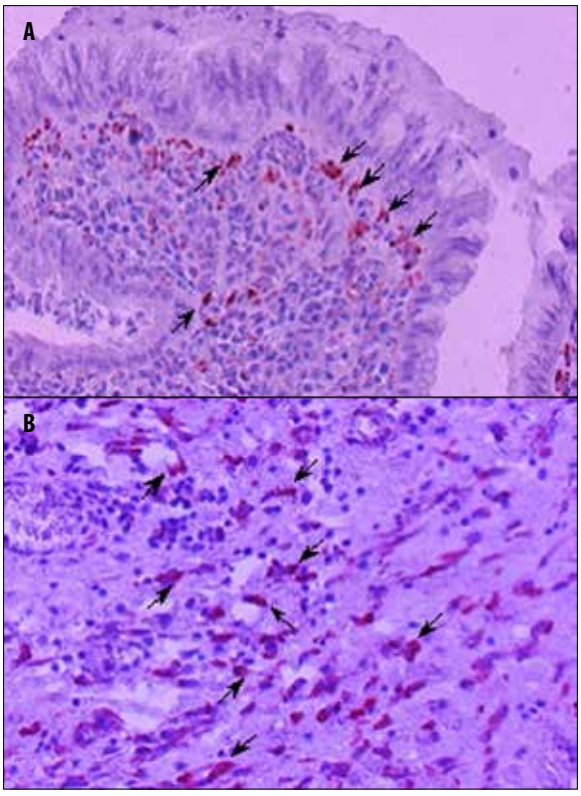

Figure 2. Expression of SPARC in human gastric tissue. (**A**) In gastritis in some of the inflammatory cells and (arrows) (**B**) In granulation tissue of gastric ulcer undergoing remodeling SPARC expression (dark-brown staining arrows) is strong in fibroblasts, myofibroblasts and endothelial cells of microvessels undergoing angiogenesis.

ed the migration of bovine aortic endothelial cells (BAEC) induced by bFGF in experimental wounds. In the absence of bFGF, SPARC and its peptides did not influence the migration of BAEC [21]. Similarly, SPARC influences the migration of fibroblasts in the presence of fibronectin (FN) [22]. Interestingly, SPARC acts as a biphasic modulator of fibroblast migration. Wu et al. [22] showed that in combination with FN, low concentration of SPARC promoted migration while high concentration resulted in impairment of FN-stimulated migration. The dual effect of SPARC on cellular migration was also observed in glioma cell line [41]. These data suggest that it is not the level of SPARC but rather the balance between SPARC and its binding partner that influences the process of cellular migration.

SPARC and Cell Proliferation

The role of SPARC in wound healing is not limited to modification of the ECM and cell migration, but it also involves modulation of cell proliferation. SPARC and its peptide 2.1 and 4.2 arrest cell cycle and delay entry into S phase; they inhibit the uptake of [3H]-thymidine in BAEC, transformed fetal bovine arterial endothelial cell, bovine capillary endothelial cell and human umbilical vein endothelial cell [17,34]. Interestingly, a synthetic peptide from another cationic region of SPARC (peptide 2.3) increases [3H]-thymidine incorporation into BAEC cells and fibroblasts in a dose-dependent manner [31]. In contrast, SPARC and peptide 2.1 have an opposing effect on the proliferation of fibroblasts. Human foreskin fibroblasts and fetal bovine ligament fibroblasts exhibit an increase in the incorporation of [3H]-thymidine in the presence of low concentration of SPARC. However, at higher concentration, inhibition is observed [31].

The antiproliferative effect of SPARC is achieved by the modulation of the activity of growth factors. SPARC peptides from domain IV and domain II inhibit the mitogenic effects of VEGF in human microvascular endothelial cell (HMVEC) by reducing VEGF's stimulation of tyrosine phosphorylation and protein kinase Erk1 and Erk2 [20]. They also inhibit the mitogenic activity of VEGF via direct binding to VEGF and reducing binding of VEGF to its cell surface receptor [20].

SPARC also interacts with platelet-derived growth factor (PDGF). The expression of SPARC and PDGF is minimal in most normal adult tissues but is increased after injury [23]. The activities conferred by PDGF depend on the presence of different dimers and their receptor subunits [42]. Raines et al. [23] showed that SPARC inhibited the binding of PDGF-BB and PDGF-AB, but not PDGF-AA to receptors on human dermal fibroblasts. These specific interactions inhibit the mitogenic effect of PDGF [23].

Schiemann et al. [24] showed that SPARC also inhibited epithelial cell proliferation in part through its stimulation of the transforming growth factor (TGF-β) signaling system. TGF-β is a potent tumor suppressor which inhibits the proliferation of epithelial, endothelial, and hematopoietic cells [43,44]. In Mv1Lu cell, SPARC and SPARC-EC domain exert their effect by activating TGF-receptors and their downstream targets Smads 2 and 3 [24]. The stimulation of TGF-β signaling by SPARC also occurs in endothelial cells [24].

SPARC also inhibits the biological effects of fibroblast growth factor 2 (FGF-2), a potent stimulator of growth and differentiation in cells [45]. SPARC and peptide 4.2 suppress ligand-induced auto-phosphorylation of the FGF receptor 1 and inhibit DNA synthesis in HMVEC [46].

SPARC and Angiogenesis

Angiogenesis is defined as the development of new vessels from preexisting vasculature. It plays an essential role in repairing injured tissue. SPARC modulates this process at several levels including interaction with vascular ECM, endothelial migration and proliferation as discussed above. SPARC expression correlates temporally and spatially with the formation of new vessels in a variety of tissues such as in dermal wounds, atherosclerotic aortic valves, and chorioallantoic membrane [7,47,48]. Addition of SPARC to cultured endothelial cell undergoing angiogenesis *in vitro* resulted in increased number of capillary-like structures [47,48].

Similar to its role in migration and proliferation SPARC and its proteolytic peptides may exert different actions on angiogenesis. Intact SPARC protein inhibits cellular proliferation, and has an anti-angiogenic activity *in vitro*. However, fragments of SPARC with the KGHK motif of module II are strong inducers of angiogenic activity both *in vitro* and *in vivo* [33,49].

Iruela-Arispe et al. [48] showed that incubation of SPARC with chorioallantoic membrane from different developmen-

Table 1. Effect of SPARC and its related peptide on cell functions during remodeling.

	ECM	Migration	Proliferation	Angiogenesis
Native SPARC	• Regulates secretion of ECM proteins. • Induces cell rounding in endothelial cells, fibroblasts, and smooth muscle cells. • Induces de-adhesion* in endothelial cells, fibroblasts.	• Impact on cell migration is cell/tissue specific.	• Inhibits proliferation of endothelial cells. • Arrests cell cycle of endothelial cells. • Exerts opposing effect on proliferation of fibroblasts.	• Inhibits
Peptide 1.1	• Induces cell rounding in endothelial cells, fibroblasts, smooth muscle. • Induces de-adhesion* in endothelial cells, fibroblasts. • Regulates secretion of ECM protein in angiogenesis.	• Inhibits migration in endothelial cells.	• None	• Regulates secretion of ECM protein in angiogenesis.
Peptide 2.1	• Induces de-adhesion* in endothelial cell and fibroblasts.	• None.	• Inhibits proliferation of endothelial cells. • Arrests cell cycle of endothelial cells. • Exerts opposing effect on proliferation fibroblast	• Inhibits
Peptide 2.3	• Regulates secretion of ECM proteins.	• None	• Stimulates proliferation of endothelial cells and fibroblasts.	• Stimulates
Peptide 4.2	• Regulates secretion of ECM proteins • Induces cell rounding in endothelial cells, fibroblasts, smooth muscle. • Induces de-adhesion* in endothelial cells, fibroblasts.	• Inhibits migration in endothelial cells.	• Inhibits proliferation of endothelial cells and epithelial cells.	• Inhibits

* De-adhesion is defined as a process involving the transition of the cell from a strong adherent state to a state of intermediate adherence [39].

tal ages causes extracellular proteolysis of SPARC that was consistent with proteolytic pattern produced by plasmin. The dual role of SPARC and its fragments implicates an regulatory function in angiogenesis, proliferation and migration. A combination of these opposing effects of SPARC on cellular activities can be due to availability of proteases that is necessary for the type of tissue activity.

Relevance to and Implications for Gastric Ulcer

Expression of SPARC in gastritis or in gastric ulcer has not been yet examined. However, our preliminary data demonstrated a strong expression of SPARC in human gastric mucosa in chronic gastritis; in some of the inflammatory cells and macrophages (Figure 2A) and in granulation tissue of human gastric (Figure 2B) in fibroblasts, myofibroblasts and endothelial cells of microvessels undergoing angiogenesis. Further explanation of the role of SPARC in gastrointestinal ulcer healing will provide a new mechanistic insight.

Conclusions

Although much is known about SPARC and its role in processes involved in wound healing, further investigation is necessary to elucidate the specific regulatory mechanisms of the native protein and its fragments. In Table 1 are summarized SPARC's actions on various cellular activities. As demonstrated in several studies *in vitro* and *in vivo*, SPARC, through its interaction with cytokines and growth factors, is an important contributor to wound healing. The general principles and the cellular and molecular events during healing of tissue injury are similar regardless of the tissue, and they involve cell migration, proliferation, angiogenesis, matrix degradation and matrix deposition [49].

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