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The role of secreted protein acidic and rich in cysteine (SPARC) in cardiac repair and fibrosis: Does expression of SPARC by macrophages influence outcomes?

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ABSTRACT

Secreted protein acidic and rich in cysteine (SPARC) is a matricellular, collagen-binding protein. Matricellular proteins are described as extracellular matrix-associated proteins that do not serve classical structural roles in the matrix such as those ascribed to laminins and collagens. The family of matricellular proteins modulates cell:extracellular matrix interactions and is actively expressed during tissue remodeling. Functional activities attributed to SPARC in cultured cells include regulation of cell adhesion, cytoskeletal rearrangement, proliferation, and matrix assembly. The primary phenotype characteristic of SPARC-null mice is a deficit in amounts of fibrillar collagen and fibril morphology. Strikingly, SPARC-null mice demonstrate a blunted fibrotic response in a number of different tissue settings. The role of monocyte/macrophages as an important component of tissue fibrosis is becoming increasingly appreciated. Expression of SPARC by bone marrow derived inflammatory cells raises the interesting proposition that SPARC produced by infiltrating leukocytes might contribute to the course of inflammation and tissue fibrosis in the heart. This review will summarize results from studies defining the function of SPARC in myocardial repair and fibrosis and results from other non-cardiac tissues that shed light onto possible consequences of SPARC expression by monocyte/macrophages in the setting of heart disease.

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1. Introduction

Matricellular proteins influence a variety of cardiac responses to injury and inflammation (Papageorgiou and Rienks JMCC 2016; Kirk and Cingolani JMCC 2016). The matricellular protein SPARC is a secreted, collagen-binding protein that has been established as an essential mediator of fibrosis [1]. Studies in skin, liver, lung, intestines, and heart have shown that the absence of global SPARC expression in mice results in significant attenuation of fibrosis [1]. In addition, the expression of SPARC closely mirrors that of collagen expression and deposition in human fibrotic diseases such as scleroderma, liver fibrosis, and glaucoma [1]. Hence, although there are likely tissue-specific processes that contribute to fibrosis indicative to each organ, given the range of tissues

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that are resistant to fibrosis in the absence of SPARC expression, SPARC appears to provide a critical, fundamental function for fibrotic deposition of collagen. SPARC is expressed by multiple cell types including fibroblasts — the primary cell type responsible for fibrillar collagen production in healthy and diseased tissues [2]. Recently, expression of SPARC by inflammatory cells, notably macrophages, has come to light [3,4]. Given that increases in inflammation and macrophage infiltration have been associated with various types of fibrotic diseases, an interesting possibility is that expression of SPARC by recruited inflammatory cells might contribute to increases in collagen deposition and accumulation in tissues. This review will summarize current results outlining the contribution of SPARC to extracellular matrix (ECM) remodeling and fibrosis in the heart and a potential role of SPARC in inflammatory-mediated collagen deposition.

2. Cardiac pressure overload

Although expression of SPARC in adult hearts is relatively low, SPARC-null mice exhibit reduced amounts of cardiac fibrillar collagen in normal, healthy hearts [5]. Pressure-overload (PO) hypertrophy induced by transverse aortic constriction (TAC) in mice leads to increased collagen accumulation, increased SPARC, and increased myocardial stiffness. In response to TAC, SPARC-null mice have less collagen and significantly reduced levels of stiffness in comparison to WT mice [5]. Collagen fibers generated in the absence of SPARC in PO myocardium appear thinner than WT as visualized by picrosirius red staining under polarized light. Thus robust collagen accumulation and increases in myocardial stiffness in PO myocardium are dependent upon SPARC expression. Increases in insoluble collagen are accompanied by decreases in soluble collagen in WT mice. In the absence of SPARC, levels of soluble collagen increase versus WT mice however levels of insoluble collagen are significantly reduced [5]. The increase in soluble collagen suggested that SPARC acts in the extracellular space to facilitate collagen deposition and, in the absence of SPARC, the collagen that is produced is not efficiently incorporated into ECM.

In fact, procollagen production by cardiac fibroblasts demonstrated that whereas levels of procollagen production were not significantly different in SPARC-null versus WT cells, differences in procollagen processing to collagen (procollagen: C and N propeptides retained, collagen: C and N terminal propeptides removed) were observed [6]. Greater amounts of processed collagen I were found associated with SPARC-null cell surfaces. Addition of exogenous SPARC slowed procollagen processing and resulted in less collagen I on cell surfaces [6]. Analyses of procollagen production and processing by cardiac fibroblasts supported the concept that SPARC is an important mediator of procollagen processing and deposition and that SPARC acts primarily in the extracellular space. Hence, expression and secretion of SPARC by non-collagen producing cells, i.e. other than fibroblasts, might influence procollagen processing and deposition in the myocardium.

In response to pressure-overload in mice, increases in monocyte/macrophage recruitment have been detected. Weisheit et al. found increases in macrophages populations at days 3, 6 and 21 after induction of PO with peak increases noted at day 6. Macrophages represented the dominant immune cell population in the myocardium with approximately half (53.55%) of the immune cells attributed to macrophages. $Ly6C^{low}$ or alternatively activated (M2) macrophages were detected at greater levels in PO hearts versus $Ly6C^{hi}$ classically activated (M1) macrophages [7]. The over-simplification of macrophages into M1 and M2 classes, particularly in regard to tissue macrophages, is noted but serves to facilitate comparisons of results from separate studies ([8] and in this issue reviewed by Hulsmans et al., JMCC, 2016). Generally, M1 or classically activated macrophages are associated with tissue remodeling and ECM degradation and have been designated as pro-inflammatory [9]. M2 or alternatively activated macrophages are found in higher amounts in areas of ECM deposition and tissue repair and thus the designation of anti-inflammatory [9]. Whether SPARC-expressing monocyte/macrophage populations increase after PO and/or whether SPARC production is preferentially associated with classical versus alternatively activated macrophages is currently unknown.

3. Cardiac aging

Aged mice (>18 months) exhibit increased levels of collagen versus young (3–4 months) and middle-aged mice (8–12 months) [10]. The age-dependent increase in collagen is associated with increased levels of SPARC. Levels of cardiac collagen in aged SPARC-null mice increased from that of young SPARC-null mice but not nearly to the same degree as that of aged WT mice. In fact, levels of collagen in aged myocardium of SPARC-null mice approximated that of young WT mice whereas aged WT myocardium showed a greater than 2 fold increase over that of young WT [10,11]. Interestingly, although macrophage numbers were increased in aged WT myocardium in comparison to younger ages, no increase in macrophage numbers was detected in aged SPARC-null mice [11].

An association with elevated levels of SPARC and increases in macrophage numbers in aged myocardium presented at least three possible scenarios, 1) SPARC acts directly to recruit or retain monocyte/macrophages in cardiac tissue, 2) the ECM assembled in the absence of SPARC limits monocyte/macrophage recruitment and/or retention, and 3) the monocyte/macrophage population might be a significant source of SPARC in aged myocardium and in the absence of SPARC produced by monocyte/macrophages, collagen accumulation was attenuated.

4. Myocardial infarction

Relatively more is known in regard to the role of monocyte/macrophages in cardiac ECM remodeling after myocardial infarction (MI) than in aged or PO myocardium (see Review by Nahrendorf et al. [12]). Briefly, early remodeling phases following permanent coronary ligation, a murine model of MI, are characterized by increases in classically activated, M1, macrophages. M1 macrophages are considered pro-inflammatory and are often tied to ECM digestion and turnover. Later stages after MI show an increase in alternatively activated macrophages, M2, which are associated with tissue repair and ECM deposition [13].

In response to MI levels of myocardial SPARC increased markedly [14]. Notably, a significant portion of SPARC expressing cells at day 3 following MI was found to be CD45+ suggesting infiltrating, bone marrow derived cells contributed to increased levels of myocardial SPARC in the infarct zone. A higher incidence of lethality was recorded in SPARC-null mice, particularly in males (41% of male SPARC-null mice did not survive versus 9% of WT males) attributed to rupture of the myocardium. Notably, infarct size was not significantly different between genotypes [14]. Collagen organization in the scar of SPARC-null mice was loosely organized with thinner collagen fibers than that of the densely packed, thick collagen fibers in WT scars. SPARC-null collagen fibrils, visualized by electron microscopy, were smaller in diameter than those of WT [14]. The smaller collagen fibril diameter morphology was also indicative of SPARC-null fibrils in dermis [15]. At day 14 following MI, a significant decrease in levels of infiltrating leukocytes was noted in SPARC-null versus WT hearts although no differences were observed at day 7. Distinctions in leukocyte populations, e.g. monocyte/macrophages, in WT versus SPARC-null mice were not addressed in this study [14].

In a separate study, a closer examination of early time points following MI in SPARC-null mice was performed [16]. Overall, McCurdy et al. found that ventricular dilation and decreases in ejection fraction characteristic of WT mice at day 3 following MI were mitigated in the absence of SPARC. Differential expression of specific mRNA species by microarray analysis in WT versus SPARC-null fibroblasts isolated from mice at day 3 following MI was noted. Whereas fibronectin and collagen IV expression increased in WT MI fibroblasts, these increases were not detected in SPARC-null cells. Notably, protein expression in cardiac MI

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