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Review article

Fibroblasts in myocardial infarction: A role in inflammation and repair

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ABSTRACT

Fibroblasts do not only serve as matrix-producing reparative cells, but exhibit a wide range of functions in inflammatory and immune responses, angiogenesis and neoplasia. The adult mammalian myocardium contains abundant fibroblasts enmeshed within the interstitial and perivascular extracellular matrix. The current review manuscript discusses the dynamic phenotypic and functional alterations of cardiac fibroblasts following myocardial infarction. Extensive necrosis of cardiomyocytes in the infarcted heart triggers an intense inflammatory reaction. In the early stages of infarct healing, fibroblasts become pro-inflammatory cells, activating the inflammasome and producing cytokines, chemokines and proteases. Pro-inflammatory cytokines (such as Interleukin-1) delay myofibroblast transformation, until the wound is cleared from dead cells and matrix debris. Resolution of the inflammatory infiltrate is associated with fibroblast migration, proliferation, matrix protein synthesis and myofibroblast conversion. Growth factors and matricellular proteins play an important role in myofibroblast activation during the proliferative phase of healing. Formation of a mature cross-linked scar is associated with clearance of fibroblasts, as poorly-understood inhibitory signals restrain the fibrotic response. However, in the non-infarcted remodeling myocardium, local fibroblasts may remain activated in response to volume and pressure overload and may promote interstitial fibrosis. Considering their abundance, their crucial role in cardiac inflammation and repair, and their involvement in myocardial dysfunction and arrhythmogenesis, cardiac fibroblasts may be key therapeutic targets in cardiac remodeling. This article is part of a Special Issue entitled Cardiac Fibroblast Review.

Contents

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1. Introduction

Fibroblasts are mesenchymal cells, abundantly distributed in connective tissues of most organs. Although traditionally viewed as matrix-producing cells that become activated following injury and participate in scar formation, fibroblasts have a diverse range of functions and exhibit remarkable plasticity, undergoing dynamic phenotypic alterations in response to changes in their microenvironment. Thus, the role of fibroblasts may extend beyond their contribution to scar formation and matrix remodeling. Experimental studies have suggested important fibroblast-mediated actions in regulating inflammation [1], in modulating oncogenic potential [2] and in stimulating angiogenesis [3]. Unfortunately, the lack of reliable tools for fibroblast-specific gene targeting has hampered efforts to understand the role of fibroblasts in tissue homeostasis and in various pathologic conditions.

The adult myocardium contains a large population of quiescent fibroblasts, enmeshed into the interstitial and perivascular matrix [4]. Due to their abundance, their strategic location and their potential for activation, cardiac fibroblasts may serve as sentinel cells that sense myocardial injury and trigger inflammatory and reparative responses. Because the adult mammalian heart has negligible regenerative capacity, cardiac repair following sudden loss of a large number of cardiomyocytes is dependent on the clearance of dead cells and on the formation of a collagen-based scar. Thus, repair of the infarcted heart requires timely activation of an inflammatory cascade to debride the wound from dead cells and matrix fragments, followed by induction of matrix-preserving signals that induce deposition of extracellular matrix. Tight temporal and spatial regulation of inflammatory and fibrogenic pathways is needed to prevent overactive responses that may accentuate injury and promote adverse remodeling and dysfunction. Fibroblasts undergo dynamic phenotypic changes following myocardial infarction and are capable of regulating the inflammatory and reparative cascade. Our review manuscript discusses the origin of fibroblasts in the healing infarct, the molecular signals responsible for fibroblast activation in the healing infarct and their involvement in repair and remodeling of the infarcted heart. Moreover, we identify potential therapeutic targets that may hold promise for treatment of patients with heart failure by interfering with fibroblast function.

2. Fibroblasts in cardiac homeostasis

Early experimental studies using scanning and transmission electron microscopy as well as gradient centrifugation have suggested that fibroblasts may outnumber cardiomyocytes in adult mammalian hearts [5,6]. However, it is now appreciated that the relative numbers of cardiomyocytes and non-cardiomyocytes in the myocardium are likely dependent on the species studied, on the age, gender and genetic background of the subjects, and on the technique and marker used for fibroblast identification [5–8]. Recent investigations using fluorescence activated cell sorting (FACS) analysis demonstrated that the adult murine heart consists of 56% myocytes and 27% fibroblasts [7]. Although fibroblasts are the predominant interstitial cells in normal mammalian myocardium, their function in cardiac homeostasis remains poorly understood. During cardiac development, embryonic fibroblasts may promote cardiomyocyte proliferation through interactions involving β1 integrin signaling [9]. In the absence of injury, cardiac fibroblasts remain quiescent, and are presumably shielded from mechanical stress by the stable interstitial extracellular matrix network. As matrix-producing cells, fibroblasts may be responsible for preservation of the normal interstitial matrix. Loss of the transcription factor TCf21 in mice results in failure to develop a cardiac fibroblast population and is associated with decreased myocardial expression of collagens, highlighting the important role of fibroblasts in generating and maintaining the structure of the cardiac interstitium [10]. Moreover, due to their close association with cardiomyocytes, fibroblasts may transduce survival signals, or may regulate the transmission of mechanical and electrical stimuli, thus contributing to normal systolic and diastolic function of the ventricle. Cardiac fibroblasts exhibit abundant expression of connexins in vivo and form highly coupled fibroblast:fibroblast and fibroblast:cardiomyocyte networks [11]. Moreover, as mechanosensitive cells, fibroblasts may function as independent sensors of alterations in the mechanical environment.

3. Repair and remodeling of the infarcted heart: temporal and spatial considerations

Because fibroblasts promptly respond to alterations in their microenvironment, understanding their phenotypic changes in the infarct requires knowledge of the pathology of cardiac repair. Healing of the infarcted heart can be divided in three distinct, but overlapping phases: the inflammatory phase, the proliferative phase and the maturation phase [12]; each phase is associated with distinct fibroblast phenotypes. Massive necrosis of cardiomyocytes in the infarcted heart triggers the inflammatory phase, which is characterized by activation of innate immune signals that induce cytokine and chemokine expression causing marked infiltration of the infarct with neutrophils and mononuclear cells. Infiltrating leukocytes clear the infarct from dead cells and matrix debris [13]. In the healing wound the inflammatory reaction is programmed to resolve: as neutrophils undergo apoptosis, they are phagocytosed by macrophages that secrete potent suppressors of inflammation, including transforming growth factor (TGF)-β, Interleukin (IL)-10 and proresolving lipid mediators (such as the lipoxins, resolvins, protectins and maresins) [14]. Repression of pro-inflammatory signals and induction of matrix-preserving mediators that activate mesenchymal cells mark the transition to the proliferative phase of infarct healing. At this stage the infarct is infiltrated with abundant fibroblasts and vascular cells; activated myofibroblasts secrete matrix proteins and form the scar (Fig. 1). Activation of poorly understood STOP signals inhibits the fibrotic and angiogenic response preventing expansion of fibrosis, and leads to the maturation phase of infarct healing, as the cellular elements undergo apoptosis, and a mature scar comprised of cross-linked collagen is formed.

As the infarct heals, the ventricle undergoes geometric and functional changes, collectively termed “post-infarction ventricular remodeling” [15]. Hypertrophy of the non-infarcted segments, and dilation and increased sphericity of the chamber are the major geometric alterations observed in the remodeling infarcted heart. In human patients, remodeling of the infarcted heart carries important prognostic information and is associated with increased mortality, a high incidence of arrhythmias and heart failure. Infarct size is a major determinant of adverse remodeling (as larger infarcts are generally associated with worse remodeling); however, the severity of post-infarction remodeling is also dependent on ventricular loading conditions and on the qualitative characteristics of the healing wound. For example, prolonged activation of post-infarction inflammation increases protease activity and is associated with enhanced dilative remodeling [16], whereas increased matrix deposition results in a stiffer ventricle and causes diastolic dysfunction [17]. Activation of cardiac fibroblasts in the infarct border

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