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Review

# The role of cardiac fibroblasts in post-myocardial heart tissue repair

Dimitry A. Chistiakov [a], Alexander N. Orekhov [b,c,d], Yuri V. Bobryshev [b,e,f,*]

[a] Department of Molecular Genetic Diagnostics and Cell Biology, Institute of Pediatrics, Research Center for Children's Health, 119991 Moscow, Russia
[b] Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow 125315, Russia
[c] Institute for Atherosclerosis, Skolkovo Innovative Center, Moscow 143025, Russia
[d] Department of Biophysics, Biological Faculty, Moscow State University, Moscow 119991, Russia
[e] Faculty of Medicine, School of Medical Sciences, University of New South Wales, Kensington, Sydney, NSW 2052, Australia
[f] School of Medicine, University of Western Sydney, Campbelltown, NSW 2560, Australia

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ABSTRACT

The relative resistance of fibroblasts to hypoxia and their remarkable adaptive plasticity in response to rapid changes in local tissue microenvironment made interstitial cardiac fibroblasts to be a key player in post-myocardial infarction myocardial repair. Cardiac fibroblasts are abundantly presented in the interstitial and perivascular extracellular matrix. These cells can be rapidly mobilized in response to cardiac injury. Inflammatory activation of fibroblasts leads to the loss of their quiescent phenotype and inhibition of matrix-producing capacity. Acute inflammation that follows the infarct induces production of inflammatory mediators, matrix-degrading activity, proliferation, and migration of fibroblasts. Fibroblasts migrate to the injured myocardial site where undergo transdifferentiation to myofibroblasts in response to anti-inflammatory and mitogenic stimuli. They acquire capacity to synthesize matrix and contractile proteins. In the infarcted zone, fibroblasts/myofibroblasts actively proliferate, expand, and extensively produce and deposit collagen and other matrix proteins. The proliferative stage of heart healing transits to the scar maturation stage, in which collagen-based scar exhibits formation of intramolecular and extramolecular cross-links, deactivation and apoptosis of fibroblasts/myofibroblasts. Generally, cardiac reparation is strongly controlled. Inability to pass from one repair stage to another in a timely manner can induce detrimental events such as expansion of the infarct area due to advanced inflammation, cardiac fibrosis and adverse remodeling due to the excessive proliferative and profibrotic response, left ventricular hypertrophy, arrhythmogenicity, and heart failure.



**Contents**



* Corresponding author at: Faculty of Medicine, University of New South Wales, Sydney, NSW 2052, Australia.
*E-mail address:* y.bobryshev@unsw.edu.au (Y.V. Bobryshev).

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## 1. Introduction

Fibroblasts are broadly distributed in the connective tissue. Traditional view on the function of fibroblasts involves production of extracellular matrix (ECM) proteins, involvement in fibrosis, ECM remodeling, tissue repair, and scar formation. However, fibroblasts are not terminally differentiated cells with constitutive phenotype and function. They are phenotypically plastic and changes in the fibroblast phenotype and function are regulated by local tissue microenvironment. In addition to 'traditional' functions, fibroblasts are involved to inflammatory responses (Hartupee and Mann, 2016), vasculogenesis (Ito et al., 2007), and tumorigenesis (Bhowmick et al., 2004).

In the heart, fibroblasts are located in the interstitial and perivascular matrix (Souders et al., 2009). The adult human heart has low regenerative capacity. Myocardial repair depends on the removal of dead/damaged cardiomyocytes and scarring. Indeed, heart tissue healing includes a chain of events associated with clearance of the injured site from dead cells and cell debris followed by ECM deposition. Heart repair should be precisely controlled to avoid overactivity of cells that perform repair in order to prevent abnormal remodeling. After myocardial infarction (MI), fibroblasts undergo phenotypic changes to be involved in the post-MI inflammatory response and repair. In the review, we will characterize the role of fibroblasts in different stages of cardiac repair.

## 2. Fibroblasts in the normally functioning heart

In the heart, fibroblasts are thought very abundant (Nag, 1980). It was suggested that their number may exceed the number of cardiac muscle cells (Nag, 1980). However, a recent study of Pinto et al. (2016a) suggests that cardiac fibroblasts might be less abundant than previously thought. Nevertheless, the ratio between heart muscle and non-muscle cells can significantly vary depending on species, age, sex, technical features, *etc.* (Camelliti et al., 2004; Banerjee et al., 2007). In adult murine heart, fluorescence activated cell sorting (FACS) showed that cardiac muscle cells and fibroblasts account for 56% and 27% of a total cell content respectively (Banerjee et al., 2007). In cardiogenesis, fibroblasts activate proliferation of cardiac muscle cells through integrin-β1-mediated signaling (Ieda et al., 2009).

In the adult heart, function of fibroblasts is poorly understood. They are present in quiescent state. Cardiac fibroblasts are involved in maintaining and renewing content and structure of the interstitial matrix. Deletion of epicardin (a developmental transcription factor involved in the commitment of cardiac fibroblasts from pericardial precursors) in mice leads to the loss of cardiac fibroblasts and reduced production of collagens in the heart (Acharya et al., 2012). Indeed, fibroblasts play a central role in formation and maintaining cardiac interstitial matrix. These cells interact with cardiomyocytes and participate in transduction of electrical and mechanical signals thereby contributing to ventricular contraction (Dostal et al., 2015). Heart fibroblasts express connexins and form gap junctions coupling adjacent fibroblasts and cardiomyocytes to the functional network (McArthur et al., 2015). Recently, Mahoney et al. (2016) demonstrated that scar non-myocyte cells can be electrically coupled to myocytes in injured murine myocardium and this coupling depends on connexin-43 expression. In mice hearts double deficient for fibroblast-specific protein-1 and connexin-43, the coupling was significantly reduced. This observation suggests that fibroblasts can also sense and respond to changes in mechanical forces, and connexin-43 may be involved in electrical coupling conduction.

## 3. Stages of post-infarction healing

The role of fibroblasts has been intensely studied in both homeostatic heart and cardiac repair. Animal models of MI showed that cardiac ECM response to injury can be divided to three stages: acute early response, proliferation, and late maturation. In rodents, the duration of early response is up to 2 days; the proliferative stage lasts 2–5 days, and the maturation stage takes up 1 month. In large mammals, this time is prolonged for several days (early response), up to two weeks (proliferation), and 1–2 months and longer (Frangogiannis, 2008; Dobaczewski et al., 2010a). Each of these stages is distinct but overlapping. In each stage, cardiac fibroblasts have a distinct phenotype.

The inflammatory early post-MI response stage is characterized by acute reaction of innate immunity to massive death of heart muscle cells. In this phase, the injured myocardium recruits many mononuclear cells and neutrophils that migrate to the infarcted site and remove dead cells and debris (Frangogiannis, 2012a). When the clearance is completed, inflammation is then resolved by apoptotic death of neutrophils, which are engulfed by macrophages. Macrophages secrete anti-inflammatory cytokines such as interleukin 10 (IL-10) and transforming growth factor β (TGF-β) to inhibit inflammation. Macrophage also release specialized pro-resolving mediators (resolvins, lipoxins, protectins, maresins) needed to resolve inflammation and induce healing (Serhan, 2014). These mediators stimulate mesenchymal cells to initiate healing. On the proliferative stage, multiple fibroblasts and vascular cells migrate to the injured site to heal the damage. Activated fibroblasts transform to myofibroblasts that produce ECM proteins and generate the scar. Stimuli that inhibit profibrotic/angiogenic responses and mediate transition to the maturation stage are incompletely understood. The scar maturation is accompanied by apoptosis of cell elements with remaining cross-linked collagen matrix that constitute the mature scar (Chen and Frangogiannis, 2013).

During the post-MI repair, the left ventricle is subjected to unfavorable morphological and functional changes. After MI, ventricular remodeling leads to the hypertrophy of survived myocardium, dilation and increased volume of the chamber (Pfeffer and Braunwald, 1990). Geometrical alterations are associated with induction of arrhythmias and higher risk of heart failure and sudden death. The process of ventricular enlargement is mainly influenced by the infarct size. The large infarct typically leads to the abnormal remodeling. However, other factors also significantly contribute to adverse consequences of post-MI ventricular remodeling. For example, excessive matrix formation induces rigidity of ventricle and diastolic heart failure (Yu et al., 2007). Prolonged post-MI inflammatory response leads to higher matrix metalloprotease (MMP) activity, impaired ventricular remodeling, and worse cardiac dilation (Dobaczewski et al., 2010b). Cardiac fibroblasts play the most prominent role in the proliferative stage of heart repair but significantly contribute to each phase of healing process.

## 4. The role of fibroblasts in early inflammatory response stage

Compared to cardiomyocytes, cardiac fibroblasts are significantly less sensitive to acute hypoxic conditions induced by MI. Due to the abundant presence in the heart interstitium and tight contacts with muscle cells, fibroblasts are among the first cardiac cells who sense and respond to heart injury. In cell culture experiments, fibroblasts