In adult mammals, sudden death of myocardial cells overwhelms the negligible regenerative reserve of the myocardium; as a result, the infarcted heart heals through the formation of a collagen-based scar. Repair of the infarcted myocardium is dependent on timely activation and repression of an inflammatory reaction that serves to clear the infarct from dead cells and matrix debris. Inflammation after myocardial infarction is activated through the release of danger-associated molecular patterns from dying cells and degraded matrix. These danger signals have been reported to activate all cell types involved in cardiac injury and repair. Cardiac fibroblasts respond to danger-associated molecular patterns and can produce large amounts of chemokines and cytokines that may play an important role in the activation of the postinfarction inflammatory response. Moreover, it has been suggested that cardiac fibroblasts may modulate prosurvival signaling cascades in ischemic cardiomyocytes, affecting their susceptibility to apoptosis or necrosis. Unfortunately, these intriguing concepts on the role of fibroblasts in myocardial disease are currently supported almost exclusively by in vitro experiments and by associative evidence. Considering the wide range of cell types capable of responding to danger signals triggering the inflammatory reaction after myocardial infarction, the relative significance of fibroblasts remains unclear. Dissection and documentation of the role of fibroblasts as cellular effectors of myocardial inflammation have been hampered by the challenges in the development of fibroblast-specific targeting approaches in vivo.

In this issue of Circulation Research, Woodall et al provide the first direct in vivo evidence supporting a crucial role for cardiac fibroblasts in regulating cardiomyocyte survival and in triggering the inflammatory response after myocardial infarction. The authors generated mice with fibroblast-specific loss of G protein–coupled receptor kinase 2 (GRK2), a ubiquitous member of the GRK family with a central role in signal transduction. In a model of reperfused myocardial infarction, fibroblast-specific GRK2 loss reduced the size of the infarct, decreasing secretion of proinflammatory cytokines, such as tumor necrosis factor-\(\alpha\), and attenuating cardiomyocyte apoptosis. In vitro, GRK2 loss attenuated nuclear translocation of nuclear factor-\(\kappa\)B and subsequent tumor necrosis factor-\(\alpha\) synthesis in isolated fibroblasts. Moreover, conditioned media from fibroblasts lacking GRK2 potentiated Akt signaling in cardiomyocytes, suggesting the activation of a cytoprotective pathway. Although the study provides the first direct documentation of a crucial role for cardiac fibroblasts in regulating cardiomyocyte injury and inflammation in the early stages after myocardial ischemia, the molecular mechanisms responsible for the observed effects remain unclear.

Do Cardiac Fibroblasts in the Ischemic Myocardium Function as Inflammatory Cells? After myocardial infarction, release of danger-associated molecular patterns activates innate immune signaling pathways in several different cell types, triggering an intense inflammatory reaction. Endothelial cells, leukocytes, mast cells, and surviving cardiomyocytes have been suggested as likely cellular targets of danger-associated molecular patterns released by necrotic cells and may contribute to the activation of the postinfarction inflammatory response by secreting cytokines and chemokines. Cardiac fibroblasts are also capable of secreting large amounts of proinflammatory mediators on stimulation with danger signals. Interleukin-1 is rapidly released in the infarcted myocardium and promotes a proinflammatory and matrix-degrading fibroblast phenotype, while suppressing...
α-smooth muscle actin synthesis and inhibiting myofibroblast conversion.9 Thus, interleukin-1 stimulation may delay premature infiltration of the infarct with matrix-synthetic fibroblasts, until the wound is cleared from dead cells and matrix debris. Although the findings of this study are consistent with an important role of cardiac fibroblasts in promoting inflammation after myocardial infarction, the protective effects of GRK2 loss may not be caused by direct anti-inflammatory actions. Fibroblast-specific GRK2 loss decreased neutrophil infiltration in vivo and reduced tumor necrosis factor-α release in vitro. However, the in vivo attenuation of the inflammatory response may represent an epiphenomenon reflecting the significant reduction in infarct size, in the absence of a primary role of GRK2 in regulation of inflammation. The notion that GRK2 may be directly involved in the activation of a proinflammatory program is not supported by studies in immune cells. In vivo and in vitro investigations in T cells16 and in myeloid cells17 suggested that GRK2 not only does not stimulate inflammatory gene synthesis but may also be involved in negative regulation of inflammation.

**Fibroblasts May Regulate Cardiomyocyte Survival**

A growing body of evidence suggests that in injured and remodeling hearts, fibroblasts critically regulate cardiomyocyte responses. In the pressure-overloaded myocardium, activated fibroblasts transduce hypertrophic signals28 mediated at least in part, through secretion of miRNA-enriched exosomes.19 In myocardial ischemia, administration of the secretome of neonatal cardiac fibroblasts before reperfusion significantly reduced the size of the infarct.10 The current investigation suggests that endogenous fibroblast GRK2 signaling may extend ischemic injury, accentuating cardiomyocyte apoptosis. Several mechanisms may account for the proapoptotic effects of activated fibroblasts during the early postischemic phase (Figure). First, fibroblasts may secrete soluble proapoptotic mediators, such as proinflammatory cytokines, thus promoting cardiomyocyte death. Second, fibroblasts may indirectly reduce cardiomyocyte survival by modulating the composition of the extracellular matrix through the secretion of proteases. Protease-mediated degradation of the pericellular extracellular matrix may deprive ischemic cardiomyocytes from essential prosurvival signals. Third, ischemic fibroblasts may secrete exosomes that activate proapoptotic pathways in cardiomyocytes. Finally, activation of GRK2 in ischemic fibroblasts may inhibit a yet unidentified prosurvival mechanism that may involve fibroblast-derived secretion of soluble mediators or deposition of matricellular proteins. Unfortunately, this study did not systematically pursue the mechanisms responsible for these intriguing interactions between fibroblasts and cardiomyocytes.

**The Role of Activated Fibroblasts During the Proliferative Phase of Infarct Healing: Beyond Matrix Synthesis**

Clearance of the infarcted heart from dead cells and matrix debris is associated with the activation of anti-inflammatory pathways, leading to the suppression and resolution of the inflammatory response.20 Although cardiac fibroblasts are capable of producing large amounts of anti-inflammatory cytokines, such as interleukin-10 and transforming growth factor-β,21 whether they actively participate in negative regulation of the inflammatory response remains unknown. Growth factor-mediated conversion of fibroblasts into myofibroblasts is associated with the activation of a matrix-synthetic program and secretion of collagens. Deposition of structural matrix proteins is the best-documented function of myofibroblasts in healing infarcts.7 In addition to their role in scar formation, infarct myofibroblasts may also serve as an important source of growth factors and matricellular proteins, regulating the angiogenic response after myocardial infarction.22 Whether the diverse functions of infarct fibroblasts in inflammation and repair reflect the activation of specific subpopulations remains unknown. Although several different developmental sources of cardiac fibroblasts have been identified in normal and injured hearts,2 the functional properties of these cells have not been systematically investigated. The inducible collagen1C2-Cre driver used in this study should target all cardiac fibroblasts, thus precluding any conclusions on distinct effects of specific subsets.

**Targeting the Cardiac Fibroblast in the Infarcted and Remodeling Myocardium**

The consistent association between cardiac fibrosis and adverse outcome in a wide range of cardiac conditions has suggested that the fibroblast may be a promising therapeutic target in patients with myocardial infarction or heart failure. However, unlike primary fibrotic disorders in other systems (such as systemic sclerosis or idiopathic pulmonary fibrosis), in the myocardium, fibrotic remodeling often reflects...
a reparative process that is activated in response to cardiomyocyte injury. In conditions associated with replacement fibrosis, such as myocardial infarction, targeting the reparative functions of fibroblasts may have catastrophic consequences. Implementation of therapeutic strategies targeting fibroblasts is further complicated by the wide range of modulatory functions of fibroblasts on cardiomyocyte hypertrophy and survival, on inflammatory activation, and on angiogenesis. In vivo dissection of the diverse actions of cardiac fibroblasts after injury is crucial to design therapeutic strategies that target detrimental actions, without interfering with protective effects. Moreover, identification and characterization of fibroblast subsets with distinct phenotypic characteristics and functional profiles may explain the functional pluralism of fibroblasts in injured and remodeling tissues.

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None.

**References**

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