Intramyocardial Fibroblast–Myocyte Communication

Rahul Kakkar, Richard T. Lee

Abstract: Cardiac fibroblasts are emerging as key components of normal cardiac function, as well as the response to stressors and injury. These most numerous cells of the heart interact with myocytes via paracrine mechanisms, alterations in extracellular matrix homeostasis, and direct cell–cell interactions. It is possible that they are a contributor to the inability of adult myocytes to proliferate and may influence cardiac progenitor biology. Furthering our understanding of how cardiac fibroblasts and myocytes interact may provide an avenue to novel treatments for heart failure prevention. This review discusses the most recent concepts in cardiac fibroblast–myocyte communication and areas of potential future research. (Circ Res. 2010;106:47-57.)

Key Words: cardiac failure ■ fibroblasts ■ cardiac differentiation ■ cytokines ■ growth factors

Cardiac fibroblasts have received relatively little attention compared to their more famous neighbors, the cardiomyocytes. Cardiac fibroblasts are often regarded as the “spotters,” nonchalantly watching the cardiomyocytes do the real weight-lifting and waiting for a catastrophe that requires their actions. However, emerging data now reveal the fibroblast as not only a critical player in the response to injury but also as an active participant in normal cardiac function.

Interest in cardiac fibroblasts has grown with the recognition that cardiac fibrosis is a prominent contributor to diverse forms of myocardial disease.1–5 In the early 1990s, identification of angiotensin receptors on the surface of cardiac fibroblasts linked the renin–angiotensin–aldosterone system directly with pathological myocardial and matrix extracellular remodeling.6,7 Fibroblasts were also revealed as a major source of not only extracellular matrix but also the proteases that regulate and organize matrix. New research has uncovered paracrine and well as direct cell-to-cell interactions between fibroblasts and their cardiomyocyte neighbors, and cardiac fibroblasts appear to be dynamic participants in ventricular physiology and pathophysiology.

This review focuses on several aspects of fibroblast–cardiomyocyte communication, including mechanisms of paracrine communication. Because it is now clear that fibroblasts can directly affect several important physiological properties of myocardium, this topic is particularly timely given the broad interest in cardiac regeneration, including cell therapy. Ongoing efforts at regeneration of cardiac tissue focus primarily on increasing the number of cardiomyocytes in damaged myocardium. Although getting cardiomyocytes into myocardium is an important goal, understanding intercellular paracrine communication between different cell types, including endothelial cells but also fibroblasts, may prove crucial to regenerating stable myocardium that responds to physiological conditions appropriately.

Fibroblast–Cardiomyocyte Interactions During Development and Repair
Cardiac fibroblasts may communicate with cardiomyocytes early in development, but surprisingly few investigations have addressed this question in vivo. This may be attribut-
able, in part, to the lack of a single definition of a fibroblast, as well as the lack of specific cardiac fibroblast molecular markers and enhancers. Ieda et al demonstrated a unique effect of embryonic cardiac fibroblasts on developing cardiac myocytes. Embryonic cardiac fibroblasts reside within the developing compact myocardium and increase in number over the course of development. They express many components of the extracellular matrix, including fibronectin, collagen, peristin, hyaluronan, and proteoglycan link protein 1. Embryonic cardiomyocytes grown on plates enriched with fibronectin, collagen type III, peristin, or laminin showed an increase in proliferation. This effect involves \( \beta_2 \)-integrin signaling and HB-EGF (heparin-binding epidermal growth factor–like growth factor), with induction of downstream extracellular signal-regulated kinase and p38 mitogen-activated protein kinase signaling. Interestingly, when embryonic mouse cardiac myocytes were cocultured with adult cardiac fibroblasts, a hypertrophic rather than a proliferative phenotype was seen, with increased sarcomeric organization and cell size. This suggests that paracrine factors derived from cardiac fibroblasts may influence the phenotype of cardiomyocytes during development in a manner distinct from effects in the adult (Figure 1).

Several molecules known to be produced by cardiac fibroblasts have been implicated in cardiac myocyte development, including fibroblast growth factors (FGFs). FGF2 and FGF4 induce expression of early cardiac transcription factors, as well as ventricular (but not atrial) specific markers,
in the developing chick embryo. The loss of FGF1 arrests multipotent precursor cells in their development toward a cardiac myocyte lineage. Other FGFs have been implicated in Wnt/β-catenin signaling and anterior heart field formation, suggesting that specific FGF family members may influence cardiac morphogenesis in a regional manner. Gp130, a transmembrane protein subunit that serves as a signaling relay for members of the interleukin (IL)-6 family, also plays a prominent role in cardiac development. The Gp130 knockout mouse fails to develop compact myocardium and dies in mid to late gestation (reviewed elsewhere). Interestingly, members of the IL-6 family that are known to be produced by cardiac fibroblasts, such as cardiotrophin (CT)-1 and leukemia inhibitory factor (LIF), are not required for cardiac development, and deletion of multiple members of the IL-6 family does not result in cardiac lethality in utero, suggesting functional redundancy in this developmentally critical signaling pathway.

The role of cardiac fibroblasts in cardiomyocyte regeneration in the adult heart is also unclear, although there is support for the concept that fibroblast activity impairs regeneration. Most tissues that regenerate in mammals can heal without extensive fibrosis. For example, the epidermis undergoes healing with minimal scar formation. Critical differences between scar formation in epidermal tissue and in cardiac tissue include myofibroblast apoptosis during epidermal wound evolution in comparison with persistence of cardiac tissue include myofibroblast apoptosis during epidermal wound evolution in comparison with persistence of activated fibroblasts within injured myocardium. Non-mammalian species with robust regenerative capacity, such as zebrafish and Urodele amphibians, repair wounds with minimal scar formation. Whether regeneration occurs via lineage commitment of a progenitor cell such as in zebrafish myocardial repair or dedifferentiation and replication of terminally differentiated resident cells within the heart as in Urodèles, there appears to be a balance between functional regenerative capacity and fibrotic scar formation. It is unclear whether the tendency for fibrosis in the mammalian heart after injury is the result of an inherent inability of adult cardiomyocytes to divide, necessitating an exuberant fibrotic response, or whether the fibrosis itself prevents cardiomyocytes from adopting a replicative phenotype.

Fibroblasts are bone marrow–derived cells that circulate in the blood, express hematopoietic cell surface markers, and can produce extracellular matrix proteins. Fibrocyte cells can differentiate down multiple mesenchymal lineages depending on their molecular microenvironment and may participate in pathological end-stage organ fibrosis. They may even be coaxed to manifest properties of mature cardiomyocytes themselves. It has been shown in the context of myocardial infarction that bone marrow–derived cells can invade the myocardium and differentiate into cells with surface markers consistent with a fibroblast phenotype. Möllmann and colleagues used sublethally irradiated mice with subsequent reconstitution of bone marrow with hematopoietic cells expressing green fluorescent protein (GFP). After experimental myocardial infarction via epicardial coronary artery occlusion, the number of GFP+ cardiomyocytes was negligible in relation to the numerous GFP+ fibroblasts and myofibroblasts, as identified by cell surface markers. This process of myofibroblast commitment may be mediated by transforming growth factor (TGF)β1 signaling. Although these data suggest that circulating progenitors play a role in the cardiac response to injury, the relative contribution of bone marrow-derived fibroblast cells versus resident fibroblasts remains unclear.

During early endocardial cushion development, migrating cells of endothelial origin lineage switch to form mesenchyme (reviewed elsewhere). Recent data suggest that this endothelial-to-mesenchymal transition may contribute to the cardiac fibroblast pool in the adult mouse. Zeisberg et al have demonstrated that cells of endothelial origin, during biomechanical overload, and under direction of TGFβ signaling, lose endothelial-specific and gain fibroblast-specific markers, and produce proteins such as vimentin, procollagen, and α-smooth muscle actin that are typically associated with fibroblasts. How such endothelium-derived cardiac fibroblasts may regulate potential cardiac repair and the biology of cardiac progenitor cells remains to be explored.

**Fibroblast–Cardiomyocyte Paracrine Communication**

Cardiac fibroblasts may regulate cardiomyocyte phenotype through paracrine hormonal pathways, and it is also likely the cardiomyocytes regulate fibroblast phenotype. There are numerous lines of evidence indicating that cardiac fibroblasts and myocytes release into their local microenvironment proteins that regulate neighboring cells. Although multiple factors have been implicated in this intercellular crosstalk, the following discussion will focus on the best studied of these factors for which the strongest data have been published, including TGFβ1, FGF2, members of the IL-6 family of proteins, and the recently discovered cytokine IL-33.

**Transforming Growth Factor β**

TGFβ regulates the ventricular response to pressure overload as well as injury, including fibrosis and cellular hypertrophy. TGFβ exists in 3 forms: TGFβ1, TGFβ2, and TGFβ3, each encoded by a distinct gene; these forms are intracellular, as well as extracellular, residing within the interstitium in an inactive state bound to LTBP (latent TGFβ-binding protein). When activated by proteolytic cleavage, TGFβ can bind to cell surface transmembrane receptors to activate Smad-mediated transcriptional events. Ablation of any TGFβ gene results in distinct phenotypic derangements, highlighting the separate roles of the TGFβs in mammalian physiology.

Not only is TGFβ expressed by cardiomyocytes and interstitial cells of both the adult and fetal heart, it is actively released from myocytes and cardiac fibroblasts. TGFβ1 is induced and released from cardiomyocytes in response to mechanical stretch, and its expression is upregulated in the context of pressure overload and myocardial infarction. The receptors for TGFβ are found on both ventricular myocytes and fibroblasts. TGFβ1 can elicit myofibroblast transformation, as well as a marked increase in extracellular protein production. Through the angiotensin type 1 receptor, angiotensin II stimulation of fibroblasts induces TGFβ1, may alter TGFβ1 receptor
In addition to its effects on fibrosis and hypertrophy, TGFβ has also been shown to coax pluripotent cells toward a cardiomyocyte transcriptional and morphological phenotype.57–70 Behfar et al first showed that TGFβ upregulates cardiac transcription factors Nkx2.5 and MEF2C in mouse embryonic stem cells and enhanced the formation of rhythmically contractile embryoid bodies. Stem cells expressing a dominant negative TGFβ failed to differentiate.67 These observations raise the question of whether fibroblast–myocyte communication may be taking place not only at the level of terminally differentiated cardiomyocytes but on a cardiomyogenic progenitor cell pool as well.

**Fibroblast Growth Factor-2**

FGF2 is an intracellular and extracellular protein synthesized by both myocytes and nonmyocytes. On release into the interstitial space, FGF2 binds to heparin sulfate proteoglycans and components of the basement membrane (reviewed elsewhere71). FGF2 exists in 2 forms of different molecular weights (reviewed elsewhere72). In cardiomyocytes, FGF2 is induced by adrenergic stimulation and, in a positive feedback loop, by products of its own synthesis.73,74 FGF2 is also upregulated by angiotensin II stimulation and ischemia or hypoxia (Figure 2).75,76 FGF2 lacks a canonical aminoterminal secretory sequence, and the mechanisms by which it is released from myocytes and cardiac fibroblasts are incompletely defined. There is evidence that FGF2 is released from cells during periods of a loss in cell membrane integrity. This may occur in the setting of toxic or hypoxic cellular injury, programmed cell death, during vesicular “shedding” or during transient, reversible disruptions in the context of cellular contraction.77–79 Interestingly, embryonic and adult cardiac fibroblasts predominantly express the higher-molecular-weight form of FGF2, which is further upregulated and released on angiotensin II exposure. High-molecular-weight FGF2 induces a fetal gene program and promotes hypertrophy of cardiomyocytes (see Jiang et al80 and reviewed previously81).

Germline genetic ablation of FGF2 results in a marked diminution of myocardial hypertrophy in the face of experimental pressure overload.82 Pellieux et al have documented that FGF2-null cardiac myocytes respond normally to both angiotensin II and FGF2. However, FGF2 deficient fibroblasts are not only deficient in FGF2 release, but also lack the ability to produce other (unidentified) trophic factors released by wild-type cardiac fibroblasts.83 These data indicate that FGF2 is secreted primarily by cardiac fibroblasts, mediating a paracrine, prohypertrophic response in neighboring cardiomyocytes. FGF2 acts not only on receptors on the surface of target myocytes; in autocrine fashion, it also activates fibroblasts themselves to release other prohypertrophic factors into the interstitium.

Low-molecular-weight FGF2 may mediate a variety of physiological effects, including the ability to induce stem cell factor (the ligand for the c-kit receptor) and to concentrate c-kit+ cells within the site of experimental infarction.71 FGF2 may promote differentiation of embryonic stem cells,84 as well as putative resident stem cells within the myocardium toward a cardiomyocyte phenotype.85 It may also promote

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**Figure 2.** Paracrine bidirectional cardiac fibroblast–myocyte crosstalk during biomechanical strain. Under biomechanical overload, cardiac fibroblasts and myocytes respond to an altered environment via multiple mechanisms including integrin–extracellular matrix interactions and renin–angiotensin–aldosterone axis activation. Cardiac fibroblasts increase synthesis of matrix proteins and secrete a variety of paracrine factors that can stimulate myocyte hypertrophy. Cardiac myocytes similarly respond by secreting a conglomerate of factors. Hormones such as TGFβ1, FGF2, and the IL-6 family members LIF and CT-1 have all been implicated in this bidirectional fibroblast–myocyte hormonal crosstalk.

expression,54 and increases matrix protein synthesis.55–57 Importantly, this accumulation of fibroblast-derived extracellular collagen occurs only when fibroblasts are cocultured with cardiomyocytes.58–61 Zeisberg et al have documented that in the context of pressure overload, cardiac fibroblasts may arise from endothelial cells in a manner dependent on TGFβ1 and downstream Smad signaling.29 TGFβ1 has clearly been implicated in cardiomyocyte hypertrophy62 and may participate in the pathogenesis of human hypertrophic cardiomyopathy.63–65 TGFβ1 is likely a key mediator of myocyte growth in response to angiotensin II but in a manner that may require cardiac fibroblasts. Gray et al demonstrated that angiotensin II induces myocyte hypertrophy in coculture with fibroblasts but not in monoculture preparations; a similar effect was seen with fibroblast-conditioned medium. Of note, the preponderance of angiotensin receptor expression was seen in fibroblasts rather than myocytes.66 This suggests that the primary target of angiotensin is the cardiac fibroblast, with its ultimate effect on cardiomyocytes occurring in a paracrine fashion via TGFβ (Figure 2). This paracrine effect may not be homogenous throughout the heart. Transgenic expression of constitutively active TGFβ1 in cardiac myocytes results in atrial but not ventricular fibrosis, as well as increased ventricular fibroblast apoptosis.66
retention of exogenously delivered cardiospheres in regions of infarct. These data suggest that FGF2 may be part of a conglomerate of fibroblast-derived signals for the homing and differentiation of circulating precursors and/or commitment of resident stem cells toward a myocyte fate.

The IL-6 Family: Leukemia Inhibitor Factor and CT-1

The IL-6 family of peptides can regulate myocyte hypertrophy, and several may be secreted by cardiac fibroblasts. A diverse set of polypeptides with minimal sequence homology, members of the IL-6 family signal through the transmembrane gp130 protein subunit. Both LIF and CT-1 are members of the IL-6 family that are synthesized by cardiac myocytes and fibroblasts and may act as mediators of fibroblast-myocyte crosstalk. LIF induces cardiac myocyte and fibroblast hypertrophy but inhibits the myofibroblast transition and collagen deposition. CT-1 also promotes myocyte hypertrophy but promotes fibroblast proliferation. There is evidence that LIF and CT-1 derived from cardiac fibroblasts mediates the prohypertrophic effects of angiotensin II (Figure 2). Sano et al investigated the expression of the IL-6 family in cultured cardiac fibroblasts after exposure to angiotensin II. LIF and CT-1 were significantly upregulated in contrast to other family molecules. Conditioned medium from angiotensin-stimulated cardiac fibroblasts resulted in phosphorylation of gp130 and STAT3, as well as increased cardiomyocyte cell size. These effects were partially blocked by antisense nucleotides to LIF and CT-1, suggesting that these members of the IL-6 family are part of, but do not comprise in totality, a fibroblast secretory cascade produced on angiotensin II stimulation which can affect myocyte hypertrophy.

Interleukin-33

IL-33 (or IL-1F11) is a newly discovered member of the IL-1 family that represents a novel paracrine signaling system between fibroblast and myocyte. IL-33 was discovered in 2005 by Schmitz et al by mining the public genomic database for a protein structure common to IL-1 and FGF, and the protein identified represented the end of a search for the ligand for the ST2 receptor that lasted 2 decades. Work by Sanada et al suggests that IL-33 is produced primarily by cardiac fibroblasts, with expression markedly upregulated by cyclic strain. Although initial speculation suggested that IL-33 resembled IL-1 in its requirement for processing by caspase-1, IL-33 appears to be secreted or released in its active state and is instead inactivated via proteolytic cleavage by caspases. In the extracellular space, IL-33 binds to 1 of 2 differentially transcribed forms of its receptor, ST2. A transmembrane form of ST2 (ST2L) transduces signals that in part converge on NF-κB. A truncated, “soluble” form of ST2 (sST2) is produced by many cell types and appears to act as a “decoy receptor” to sequester IL-33 away from the biologically available pool, or it may bind a transmembrane form, ST2L, on the surface of cardiac myocytes. In the face of prohypertrophic stimuli in vitro or pressure overload in vivo, IL-33 appears to confer antihypertrophic and antifibrotic properties to the myocardium.

Extracellular Matrix–Based Fibroblast–Cardiomyocyte Interactions

Fibroblasts have long been recognized as a major source of nonbasement membrane collagen and other proteins of the extracellular space. Extracellular matrix proteins, including collagens and fibronectin, signal through cell surface heterodimeric integrin receptors and, therefore, can act as communicative intermediaries in the dialogue between cardiac fibroblast and myocytes. As in mammalian tissues, fibrillar collagen is the primary extracellular matrix protein of...
the normal myocardium. Of the various forms, the cardiac interstitium contains mostly types I and type III collagen, with a greater proportion of type I than III noted in most studies (see elsewhere101,102 and reviewed previously103). In the context of altered loading conditions, the normal balance of collagen subtypes is altered.104–106 In both end-stage cardiomyopathy, as well as in response to cyclic strain in vitro, cardiac fibroblasts not only increase total collagen content of the ventricle but also increase the ratio of collagen type I to type III.107–110

Rat neonatal cardiomyocytes cultured on collagen types I and III display enhanced physical association between cytoskeletal components (specifically filamentous actin), cellular adhesion points (such as vinculin), and the matrix β1-integrin receptors when compared with cultures on a laminin sublayer.111 Electron microscopy studies of striated muscle grown on various matrices reveal that the composition of those matrices regulates patterns and distributions of both striated myofibrils and focal adhesions. Differences in matrix components can also regulate the physical colocalization of signaling molecules that associate with intracellular membrane-associated proteins.112 Interestingly, direct inhibition of collagen synthesis disrupts in vitro embryonic cardiac myocyte differentiation, an indication that fibroblast-mediated regulation of matrix could affect cardiomyocyte development and regeneration.113

Fibroblast-induced changes in collagen composition represent only one of the matrix proteins that can pass signals to myocytes. Fibronecin is produced by cardiac fibroblasts and is induced by angiotensin II in an epidermal growth factor dependent manner.113 Fibronecin interacts with myocyte surface integrins to mediate cellular hypertrophy (see elsewhere115 and reviewed previously116,117). Moreover, fibronec tin acts coordinately with secreted extracellular collagens to promote embryonic myocyte proliferation via β1-integrin signaling in a manner that is independent of its effects on cellular adhesion.8

Remodeling and maintenance of the extracellular space requires not only synthesis but also coordinated degradation of matrix proteins. The matrix metalloproteinases (MMP) and their tissue inhibitors (TIMPs) are classic participants in matrix homeostasis, and these proteins are produced and secreted by both cardiac myocytes and fibroblasts (reviewed elsewhere118,119). In humans, dilated cardiomyopathy as well as left ventricular remodeling after myocardial infarction are accompanied by an increase in MMP activity, and the postinjury maladaptive ventricular phenotype can be abrogated by MMP inhibition in some animal models (see elsewhere120–125 and reviewed previously126–130). Collagen fragments produced by the action of MMP-1 on collagen promote fibroblast activation and transition to a myofibroblast phenotype.131 Creemers et al noted that TIMP-1 null mice, which have an obligate increase in MMP activity, have an exaggerated hypertrophic and dilated ventricular phenotype after myocardial infarction, with hypertrophy of surviving cardiomyocytes and a pronounced loss of fibrillar collagen.132 Thus, there is an ongoing interplay of matrix synthesis and degradation by both myocytes and fibroblasts both in physiological and pathophysiologic environments with feed-back to both cell types that regulates myocardial physiology and response to injury.

**Direct (Cell–Cell) Fibroblast–Cardiomyocyte Communication and Electric Coupling**

In addition to interactions between cardiomyocytes and fibroblasts that are mediated by extracellular matrix components and secreted proteins, there is fascinating evidence for important direct cell-to-cell interaction between the 2 cell types. Chemielectric communication between fibroblast and myocytes may occur in a manner similar to the known gap junction-based connections among cardiac myocytes that allow the myocardium to act as a syncytium.

Direct cardiomyocyte cell–cell interactions use connexin 43 as the major protein component of gap junctions.132–134 Cardiac fibroblasts express connexin 43 within gap junctions and appear to use connexin 45 when in close proximity to cardiomyocytes, in contrast to connexin 40 when adjacent to other fibroblasts.135–137 Electric conductance between fibroblasts and myocytes displays properties of a hemichannel, likely reflecting a mixed pool of gap junctions.138 Cardiac fibroblasts demonstrate connexin plasticity; under conditions of myocardial injury, fibroblast gap junctions show an alteration in connexin subtype.139 These data suggest the presence of functional cell–cell interactions between cardiac myocytes and fibroblasts that mediate intercellular communication. In support of this, movement of membrane-impermeant dyes and calcium fluxes has been documented between myocytes and neighboring fibroblasts.140 Fibroblasts may also facilitate myocyte electric communication at a distance in a connexin-dependent manner.141 On a functional level, cardiac fibroblasts in culture acquire the rhythmic depolarization of neighboring cardiomyocytes, mediate myocyte electric synchrony142–144 and appear to contribute to myocyte automaticity by altering the depolarization characteristics of the myocyte.145 Additionally, fibroblasts display changes in ion conductance and cation flux in response to mechanical stretch.146–149 The combination of myocyte-fibroblast electric coupling and the fibroblast response to mechanical stimuli may be particularly active in the cardiac atrium at the level of the sinoatrial node, where cardiac fibroblasts are most abundant (Figure 4).136,150–152 Taken together, these data suggest that there is direct cell-to-cell connections between fibroblasts and myocytes that allow a dynamic and environmentally responsive transfer of molecular and ionic signals between these cell types.

Direct myocyte–fibroblast cell–cell interactions may also contribute to the entry of myocytes into a chronic “hibernating” state. Myocardial hibernation is a phenotype characterized by sarcomere depletion and loss of cytoplasmic structure, specifically the sarcoplasmic reticulum and T-tubules, glycogen accumulation, a preservation of cellular volume, nuclear heterochromatin redistribution, and mitochondrial redistribution. Hibernating mitochondria are functional, with a switch from fatty acid to glucose substrate utilization for ATP production.153 It has been suggested that the changes of hibernation mimic a more embryonic cellular phenotype and, hence, a form of myocyte “dedifferentiation”; these changes can be seen in the context of myocardial ischemia, pressure...
overload, and atrial fibrillation.\textsuperscript{153,154} In an in vitro model, a dedifferentiated phenotype was induced in cardiomyocytes cocultured with cardiac fibroblasts but not in monoculture or in the presence of fibroblast conditioned medium.\textsuperscript{155,156} This influence of fibroblasts on neighboring myocytes may involve activation of the transcription factor GATA4.\textsuperscript{157}

**Cardiac Fibroblast–Myocyte Interactions in Tissue Engineering**

An area of active research in cardiovascular therapeutics is the attempt to engineer, ex vivo, functional myocardial tissue that may be engrafted onto areas of injured ventricle. Recent data suggest that the inclusion of cardiac fibroblasts in 3D cultures greatly enhances the stability and growth of the nascent myocardium. Cardiac fibroblasts when included in polymer scaffolds seeded with myocytes and endothelial cells have the ability to promote and stabilize vascular structures.\textsuperscript{158,159} Naito et al constructed 3D cultures of neonatal rat cell isolates on collagen type I and Matrigel (a basement membrane protein mixture), and isolates of a mixed cell population versus a myocyte-enriched population were compared. The mixed population cultures, which contained a higher fraction of cardiac fibroblasts than the myocyte-enriched cultures, displayed improved contractile force generation and greater inotropic response despite an equivalent overall cell number. Greater vascularity was also seen in the mixed-pool cultures.\textsuperscript{160} Building on this, Nichol et al demonstrated that in a self-assembling nanopeptide scaffold, embedded rat neonatal cardiomyocytes exhibit greater cellular alignment and reduced apoptosis when cardiac fibroblasts were included in the initial culture.\textsuperscript{161} A similar result was noted when polymer scaffolds were pretreated with cardiac fibroblasts before myocyte seeding, suggesting a persistent paracrine effect.\textsuperscript{162} These data reinforce the concept that engineering functional myocardium, either in situ or ex vivo, will require attention to the nature of cell–cell interactions, including fibroblasts.

**Conclusion and Future Directions**

To date, a broad initial sketch of cardiac fibroblast–myocyte interactions has been drawn. Future studies in this field will better describe these interactions. How do multiple paracrine factors interact to produce a cohesive and coordinated communication scheme? What are the changes in coordinated bidirectional signaling that during development promotes myocyte progenitor proliferation but have different roles in the adult? Might fibroblasts actually be required for improved cardiac repair and regeneration?

Recent studies have begun to apply genetic and cellular fate-mapping techniques to document the origins of cardiac fibroblasts, the dynamic nature of their population, and how that population may be in flux during time of injury or pressure overload. It is crucial to define on a more specific molecular basis the origins and fates of cardiac fibroblasts. Do fibroblasts that have been resident within the ventricle since development fundamentally differ from those that arise from endothelial transition or that infiltrate from the bone marrow during adulthood? Do fibroblasts from these different origins behave differently or take on different roles in the face of ventricular strain or injury?

Our understanding of the nature of the cardiac fibroblast is evolving from the concept of the fibroblast as a bystander that causes unwanted fibrosis to the picture of a more complex role of fibroblasts in the healthy as well as diseased heart. The pathways used by cardiac fibroblasts to communicate with their neighboring myocytes are only partially described, but the data to date indicate that these pathways will be important for cardiac repair and regeneration.

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**Disclosures**

Brigham and Women’s Hospital has filed for patents on IL-33 and ST2, with R.T.L. listed as an inventor.

**References**


68. Tyagi SC, Kumar SG, Alla SR, Reddy HK, Voller DJ, Janicki JS. Extracellular matrix metalloproteinases and tissue inhibitors of metalloproteinases (TIMPs) and their inhibitors (TIMP5) in the myocardium of patients with deteriorating heart failure requiring left ventricular assist device support. J Heart Lung Transplant. 2006;25:1413–1419.


74. Tyagi SC, Kumar SG, Alla SR, Reddy HK, Voller DJ, Janicki JS. Extracellular matrix metalloproteinase and tissue inhibitors of metalloproteinases (TIMPs) and their inhibitors (TIMP5) in the myocardium of patients with deteriorating heart failure requiring left ventricular assist device support. J Heart Lung Transplant. 2006;25:1413–1419.


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