The term “fibroblast” designates a highly heterogeneous group of cells that exhibit distinct differentiated phenotypes in different organs. The study of fibroblast and myofibroblast biology in specific organs is an important but relatively understudied area, especially in the heart. Recent novel data indicate that ventricular fibroblast activation and cardiac fibrosis are primary events in ventricular remodeling rather than secondary to cardiomyocyte injury.

In larger mammalian species, including humans, cardiac fibroblasts represent the most numerous nonmyocytes in the myocardium. These cells function to synthesize and organize collagens, fibronectins, and other interstitial components and, thus, maintain the integrity of the cardiac extracellular matrix (matrix). Matrix remodeling can manifest as interstitial fibrosis of an otherwise normal myocardium. This remodeling may occur with the onset of hypertension or as the progressive evolution of the structure of the infarct scar. Remodeling of the matrix occurs later in the noninfarcted myocardium, in the etiology of heart failure after myocardial infarction. The dogma that cardiac fibrosis is merely a secondary disease modifier after cardiomyocyte damage is losing ground to the idea that fibrosis is a primary disease process. Therefore, the need to identify and characterize the specific signals that might trigger the phenocconversion of relatively quiescent fibroblasts to myofibroblasts takes on new importance.

In normal heart tissue, matrix protein secretion and deposition are carried out exclusively by cardiac fibroblasts with relatively low turnover of proteins. Conversely, contractile and hypersynthetic myofibroblasts are the relevant phenotypic variants in wound healing or in hypertrophied and failing hearts. Specific factors that signal for fibroblast-to-myofibroblast phenoconversion are now known and include mechanical loading or transforming growth factor-β1 stimulation. An increase in α-smooth muscle actin expression in these cells is synonymous with increased contractile force generation.

α-Smooth muscle actin expression is also increased in myofibroblasts in fibrotic hearts subjected to pressure or volume overload or in the infarct scar of postmyocardial infarction hearts. Causal factors in this conversion are compressibility of the substrate when ventricular fibroblasts are plated in vitro and overexpression of R-Smad. Enhanced contractility that attends α-smooth muscle actin expression is believed to be important in allowing these cells to contract while bound to matrix collagens and other proteins, thereby allowing for physical remodeling of the matrix itself. Thus, myofibroblasts are the primary mediators of wound healing in the damaged ventricle, and we have demonstrated previously that they are the dominant cell type in the infarct scar.

Investigation of these cells in hypertrophied hearts is clinically relevant, because they contribute to wound healing, matrix remodeling, and eventual cardiac fibrosis through the elevated production of fibrillar and nonfibrillar collagens. Much of the current literature that addresses cardiac fibroblast or myofibroblast function deals with the effects of a limited number of profibrotic factors and infrequently addresses the interplay of these stimuli. Although interstitial fibrosis is a component of cardiac hypertrophy and contributes to the development of heart failure, the precise signaling of tryptase and protease-activated receptor 2 (PAR-2) in the regulation of cardiac myofibroblast activation by this ligand is not well understood.

Unlike primary heart cells cultured at the bench top, cells in vivo rarely, if ever, operate in isolation, and cardiac fibroblasts are no exception. Recently, Levick et al provided compelling evidence that cardiac mast cells are key players in the development of cardiac fibrosis in the hypertensive rat heart, and these cells are associated with the release of tryptase by an unidentified mechanism. How then is this accomplished? The new data published by the McLarty et al in this issue of Hypertension shed considerable light on this heretofore undiscovered mechanism and at the same time contribute to our understanding of tryptase as a stimulus for fibroblast-myofibroblast phenoconversion. At the core of their new finding is the tryptase/PAR-2 pathway. Recent literature has pointed to a role for tryptase/PAR-2 in activation of collagen synthesis in various primary cell types. Masamune et al reported previously that PAR-2 agonists increased collagen synthesis in rat pancreatic stellate cells (themselves an important player in the pathogenesis of pancreatic inflammation and fibrosis) via activation of c-Jun N-terminal kinase. In addition, Gaca et al demonstrated that PAR-2 receptors activated by either thrombin or tryptase may support
sustained liver fibrosis by promoting proliferation and collagen synthesis by stellate cells. Nonetheless, the current report is the first of its kind to show the linkage and dependence of mast cell-derived tryptase/PAR-2 activation and increased collagen synthesis in cardiac fibroblasts. This finding is interesting for a number of reasons. The connection between mast cell signals and activation is of importance probably not just in hypertensive heart but also in the initial stages of postmyocardial infarction wound healing after the early tissue granulation that occurs within days after acute myocardial infarction. Equally interesting to the writer is the trend toward elevated expression of α-smooth muscle actin in cardiac fibroblasts treated with tryptase. Although α-smooth muscle actin is commonly held as the gold standard as a marker for cardiac myofibroblastic phenotype, an equally useful (and perhaps more sensitive) marker is extra domain-A (ED-A) fibronectin. Its marked upregulation after exposure to tryptase is significant, because these cells may be actual myofibroblasts, which are now widely regarded to be important in remodeling of the matrix in various cardiac disease pathologies (Figure). The possibility that tryptase/PAR-2 contributes to the phenoconversion of cardiac fibroblasts to myofibroblasts and the elevation of collagen synthesis is intriguing. One is then led to wonder whether the conversion from fibroblast to myofibroblast becomes the rate-limiting step in hypertensive rat heart, that is, a chicken-and-egg question. If these findings represent what occurs in human hypertension, the putative manipulation of the tryptase/PAR-2 pathway is associated with phenoconversion of quiescent fibroblasts to hypersecretory myofibroblasts, and is usually attended by the onset of fibrosis in hypertensive heart.

Further research of this novel tryptase/PAR-2 pathway for activation of cardiac fibroblasts is warranted and, in particular, whether this mechanism operates in atrial and/or ventricular human cardiac fibroblasts. Perhaps the first experiments to tease out this possibility may be carried out in vitro using a standard human cell culture approach in combination with viral target gene knock-in and ablation techniques. Nonetheless, the current experiments provide further information in teasing out the precise signals that eventually lead to activation of normally quiescent cardiac fibroblasts in hypertension and provide a significant step forward in understanding PAR-2 function in the regulation of cardiac matrix in this disease.

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None.

References


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