Defining the Developmental Signals of the Cardiac Fibroblast

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http://hdl.handle.net/2152.5/1213
Date Available: 12/20/2014

Keywords: cardiac fibroblast, epicardium, Tcf21, Nfl, epithelial to mesenchymal transmission

Cardiac fibroblasts play a central role as a mediator of inflammatory and fibrotic response and also secrete extracellular matrix components that provide structural support for regeneration and remodeling of the wound. Despite the importance of the cardiac fibroblast in heart disease, very little is known about factors that are essential for differentiation along the cardiac fibroblast lineage. Using a combination of gene knockout and cardiac fibroblast-detecting methods, we have identified genes that are involved in the formation of cardiac fibroblasts. Our results demonstrate that in the absence of Tcf21, a basic helix-loop-helix transcription factor, cardiac fibroblast progenitors fail to migrate into the myocardium resulting in a specific loss of the cardiac fibroblast population. Loss of the receptor tyrosine kinase Pdgfr? also results in loss of the cardiac fibroblast population. Interestingly, Tcf21 and Pdgfra are involved in the epithelial to mesenchymal transition (EMT) of epicardial cells.

The epicardium (outer surface of the heart) functions as a pool of progenitor cells for the coronary vasculature and interstitial connective tissue during embryonic development. Although several signaling pathways have been identified that disrupt EMT, no component has been reported that negatively regulates EMT, which may also involved in the cardiac fibroblast development. Using a conditional knockout of neurofibromin 1 (Nf1) in the epicardium, we identified Nf1 as a key mediator of epicardial EMT. We found that the process of EMT occurred earlier in Nf1 mutant hearts, with an increase in epicardial cells entering the compact myocardium. Moreover, loss of Nf1 caused increased epicardial-derived cell proliferation and resulted in the expansion of cardiac fibroblasts and coronary vascular smooth muscle cells. In addition to revealing the function of Nf1, Tcf21 and Pdgfra in epicardial EMT and cardiac fibroblast development, we generated and established mouse models to study the role of cardiac fibroblasts and the function of these genes during heart pathogenesis. Because developmental processes are often recapitulated in normal and pathological conditions, a better understanding of the epicardium and cardiac fibroblast development may help identify targets for therapeutics to treat heart disease.