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Cardiac Fibrosis: Only from Resident Cardiac Fibroblasts?

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The European Society of Cardiology defines heart failure as a complex clinical syndrome characterized by symptoms such as shortness of breath, persistent coughing or wheezing, ankle swelling, and fatigue, that may be accompanied by increased jugular venous pressure, pulmonary crackles, increased heart rate, and peripheral edema[1]. About half of the people who developed heart failure die within five years and heart-failure related medication, hospitalization, and medical costs consume almost 10% of total health expenditure in the USA, suggesting that heart failure is a substantial public health burden[2,3]. Based on the ejection fraction, this condition is classified into heart failure with preserved, mid-range, and reduced ejection fraction. Heart failure with preserved ejection fraction, previously named diastolic dysfunction, is more prevalent in older individuals, with accompanied risk factors such as obesity, diabetes, hypertension, or coronary artery diseases[4]. The pathologic basis of heart failure with preserved ejection fraction is left ventricular remodeling, especially abnormal left ventricular relaxation and an increased left ventricular myocardial stiffness. Regrettably, the treatment options for heart failure with preserved ejection fraction are limited today[5].

Usually, cardiac fibroblasts are responsible for the production of the extracellular matrix. The extracellular matrix forms the structural scaffold for cardiomyocytes, distributes mechanical forces throughout cardiac tissue, and mediates electronic conduction. The creation of the extracellular matrix is a continuous process of remodeling where older collagen is broken down, and new collagen is deposited[6,7]. However, as a reaction to injuries (e.g., ischemia, hypertension, degeneration, etc.), fibroblasts undergo a phenotypic transition to myofibroblasts. Activated myofibroblasts can redundantly express extracellular matrix-related genes to synthesize several types of collagens, including collagen I and III. An altered ratio of collagen type I to collagen type III is attributed to cardiac fibrosis[8]. Fibrotic scars of the cardiac muscle most commonly occur after myocardial infarction, but the excessive deposition of extracellular matrix culminates in several pathologies, such as reduced cardiac contractility, diastolic dysfunction, impaired coronary blood flow, and malignant arrhythmias. Altogether, these processes lead to a decrease in tissue compliance and impaired cardiac function, ultimately accelerating the progression of heart failure. As cardiac resident fibroblasts deposit extracellular matrix from the organogenesis, the gene expression profile and functions differ from the other fibroblasts. Recent publication

using genome-wide RNA sequencing and ribosome profiling analysis revealed that widespread transcriptional changes occur during the TGFβ-1 mediated myofibroblast activation[9]. However, the myofibroblasts in cardiac tissue display a substantial heterogeneity that can partially be explained by the different origins of the myofibroblasts[10]. In addition to fibroblasts of cardiac origin, bone marrow-derived, circulating monocyte-derived, and endothelium-derived myofibroblasts have been identified[11-14]. These results indicate the importance of further studies of the origin, activation, molecular pathway of the activated myofibroblasts. The findings will allow us to disentangle the molecular mechanism of cardiac fibrosis, which may further lead to the discovery of the druggable targets.

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