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Revealing the Hidden Danger: Insights into Subclinical Myocardial Dysfunction in Contemporary Cardiology.

Jacob Muller *

Division of Cardiovascular Medicine, Brigham and Women's Hospital, USA

***Correspondence to:** Peter Libby, Division of Cardiovascular Medicine, Brigham and Women's Hospital, USA. Email: Peter23@edu.in

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Introduction

Cardiac extracellular matrix (ECM) remodeling is a dynamic and multifactorial process that plays a central role in both physiological adaptation and pathological transformation of the heart. The ECM in cardiac tissue is not merely a passive structural framework; it is a highly active and interactive environment that communicates with cardiac cells to regulate function, survival, and repair. Composed primarily of fibrous proteins like collagens, elastin, fibronectin, laminin, proteoglycans, and glycoproteins, the cardiac ECM maintains the structural integrity of the myocardium, facilitates mechanotransduction, and modulates cellular behavior. However, in the setting of injury, stress, or chronic disease, the ECM undergoes significant remodeling that can lead to fibrosis, impaired cardiac function, and ultimately heart failure.

During normal cardiac development and function, the ECM undergoes tightly regulated synthesis and degradation processes. Enzymes such as matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) are critically involved in maintaining this balance. Disruption in this equilibrium is a hallmark of many cardiac pathologies. In response to acute myocardial infarction (MI), for example, ECM remodeling begins with a phase of proteolytic degradation of damaged matrix components, followed by the infiltration of inflammatory cells, activation of fibroblasts, and excessive deposition of newly synthesized ECM, primarily type I and III collagen. This leads to scar formation, which, although necessary for structural containment, can result in a stiff, non-contractile myocardial segment contributing to adverse left ventricular (LV) remodeling.

Chronic pressure overload, such as that seen in hypertension or aortic stenosis, similarly triggers ECM remodeling but through more gradual mechanisms. Mechanotransduction pathways involving integrins and focal adhesion kinases stimulate fibroblast proliferation and transformation into myofibroblasts, which secrete large amounts of collagen and fibronectin. The ensuing interstitial fibrosis reduces myocardial compliance and contributes to diastolic dysfunction. Likewise, volume overload conditions, including valvular regurgitation or dilated cardiomyopathy, initiate a unique ECM response characterized by changes in collagen cross-linking and the deposition of matrix fragments that can alter the mechanical and electrical properties of the heart.

The role of cardiac fibroblasts in ECM remodeling is critical. These cells, once considered merely supportive in nature, are now recognized as central players in myocardial remodeling. Upon activation by transforming growth factor-beta (TGF-β), angiotensin II, or other cytokines, fibroblasts differentiate into myofibroblasts, acquiring contractile properties and enhanced ECM synthetic capacity. Myofibroblasts secrete ECM proteins and modulate their turnover via MMPs and TIMPs. They also contribute to the pro-fibrotic milieu by secreting growth factors and signaling molecules that promote inflammation and further matrix deposition. Persistent myofibroblast activation is a key feature of pathological fibrosis, contributing to myocardial stiffening, impaired oxygen diffusion, and arrhythmogenic substrate development. Recent advances in omics technologies, including transcriptomics, proteomics, and single-cell RNA sequencing, have unveiled the heterogeneity of cardiac fibroblasts and their diverse roles in ECM regulation. This has opened new avenues for

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targeted therapies that modulate specific fibroblast subsets or signaling cascades without disrupting necessary repair mechanisms. Furthermore, the advent of high-resolution imaging techniques, such as cardiac magnetic resonance imaging (MRI) with T1 mapping and positron emission tomography (PET), has allowed for non-invasive assessment of myocardial fibrosis, providing valuable prognostic information and guiding therapeutic decisions.

At the molecular level, several signaling pathways regulate ECM remodeling. TGF-β/Smad signaling is perhaps the most well-characterized, playing a central role in fibrogenesis. Other important pathways include the renin-angiotensin-aldosterone system (RAAS), the endothelin pathway, and inflammatory cascades involving interleukins and tumor necrosis factor-alpha (TNF-α). The cross-talk between cardiomyocytes, endothelial cells, immune cells, and fibroblasts orchestrates a complex response that is context-dependent, varying according to the nature, duration, and intensity of the injury or stress. For instance, in heart failure with preserved ejection fraction (HFpEF), ECM remodeling contributes to increased myocardial stiffness and impaired diastolic function, while in heart failure with reduced ejection fraction (HFrEF), it is associated more with ventricular dilation and systolic impairment.

Conclusion

cardiac extracellular matrix remodeling is a central process in the pathogenesis and progression of various cardiovascular diseases. It reflects a complex interplay between structural components, signaling molecules, cellular responses, and mechanical forces. While it is essential for repair following injury, unchecked or maladaptive remodeling can lead to fibrosis, stiffness, and heart failure. Advances in our understanding of ECM biology have opened new opportunities for diagnosis, prognosis, and treatment

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