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The Role and Mechanism of Various Cell Types in Myocardial Fibrosis

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Abstract: ***Myocardial fibrosis is linked to the repair of myocardial injury and pathological ventricular remodeling. Various cell types, including fibroblasts, endothelial cells, cardiomyocytes, and immune cells, participate in the process of myocardial fibrosis through various mechanisms. However, there is a lack of effective targets for myocardial fibrosis. Thus, this review focuses on the effector cells for myocardial fibrosis and their potential mechanisms, which enhances the understanding of myocardial fibrosis and provides a theoretical foundation for its diagnosis and treatment.***

Keywords: Myocardial fibrosis, Cardiomyocyte, Fibroblast, Myofibroblasts, Endothelial cell**.**

1. Introduction

The regenerative capacity of adult mammalian cardiomyocytes is limited. Fibrotic responses can repair damaged cardiomyocytes, which is crucial for maintaining the structural and functional integrity of the heart. However, persistent and excessive activation of the fibrotic program leads to myocardial fibrosis, decreased cardiac function, and the occurrence of arrhythmias. Myocardial fibrosis, characterized by abnormal proliferation of fibroblasts and excessive deposition of collagen in the cardiac extracellular matrix (ECM), results in decreased cardiac function and arrhythmias, severely affecting the prognosis of cardiovascular diseases. Studies have shown that myocardial fibrosis is a dynamic process involving multiple cell types, and the roles of various cell types in the fibrotic response depend on the type of myocardial injury. Activated fibroblasts and myofibroblasts are the main effector cells of myocardial fibrosis, and cardiomyocytes, endothelial cells, pericytes, and immune cells are also involved. However, current targeted therapies for myocardial fibrosis are not satisfactory. Therefore, understanding the effector cells of myocardial fibrosis and their mechanisms of action, and timely and precise regulation of the fibrotic process, are crucial for the prevention and treatment of fibrosis. This review will focus on the effector cells of myocardial fibrosis and their related molecular mechanisms.

2. Fibroblasts and Myofibroblasts

Fibroblasts are the most abundant mesenchymal cells in connective tissue, possessing stem cell characteristics and the ability to produce a rich extracellular matrix (ECM) to maintain the basic structure and function of tissues and organs [1]. Cardiac fibroblasts exhibit heterogeneity and can originate from the epicardium or endocardium through epithelial-mesenchymal transition (EMT) or endothelial-to-mesenchymal transition (EndMT) [2]. Activated fibroblasts and myofibroblasts are the core effector cells of fibrosis, secreting large amounts of ECM [3]. Resident cardiac fibroblasts are the main source of myofibroblasts; however, bone marrow-derived hematopoietic cells, endothelial cells, pericytes, and macrophages can also be converted into myofibroblasts to exert their effects [4].

During the acute phase of injury, fibroblasts are activated, proliferate, and transform into myofibroblasts that express α-smooth muscle actin (α-SMA) and periostin (POSTN) and have strong secretory functions; one week after injury, the activation and proliferation of fibroblasts reach a peak and then begin to decline [5]. In the inflammatory repair phase, myofibroblasts start to secrete collagen and other ECM proteins at high levels and produce proteases, such as matrix metalloproteinases (MMPs), and their inhibitors to regulate matrix remodeling [6], increasing the tensile strength of collagen at the injury site to maintain the structural integrity of the heart and the mechanical function of the ventricles [7]. In the scar maturation phase, most activated fibroblasts undergo apoptosis; if fibroblasts are continuously activated, myocardial fibrosis will form [8]. The characteristics of myocardial fibrosis are excessive proliferation of fibroblasts and excessive deposition of ECM proteins, leading to increased ventricular stiffness and dysfunction of cardiac contraction and relaxation [9]. In addition, excessive ECM and fibroblasts can impair the electromechanical coupling of cardiomyocytes, thereby reducing cardiac contraction and increasing the risk of arrhythmias and death. Myofibroblasts can also induce cardiomyocyte hypertrophy through paracrine mechanisms, leading to impaired cardiac function. Angiotensin II (AngII) and aldosterone, which are profibrotic neurohumoral signals, and pro-inflammatory cytokines (such as IL-1 and TNF-α), can induce the transcription of IL-10, PDGFs, or members of the TGF-β superfamily, causing fibroblasts or myofibroblasts to exhibit a macrophage-like phenotype to phagocytose dead cells, promoting inflammation resolution and tissue repair after myocardial infarction [10]. The activation of fibroblasts and their conversion to the myofibroblast lineage are regulated by a variety of cytokines, with the PDGF pathway, TGF-b superfamily pathway, canonical WNT pathway, as well as mechanotransduction and DAMP playing major roles [11].

3. Cardiomyocytes

Cardiomyocytes play a significant role in the process of myocardial fibrosis, influencing the fibrotic process through direct or indirect cytokine pathways. Under pathological conditions of the heart, such as myocardial infarction (MI) or chronic pressure overload, cardiomyocytes may release a variety of signaling molecules, including inflammatory

cytokines (such as CCL2, IL-1, IL-6, and TNF-α), reactive oxygen species (ROS), and soluble growth factors. These molecules recruit inflammatory cells and promote inflammatory responses. Additionally, they can directly induce cardiomyocyte hypertrophy and the transformation of fibroblasts into myofibroblasts [12].

Following myocardial infarction, necrotic cardiomyocytes trigger early fibrotic reactions through damage-associated molecular patterns (DAMPs), which include RNA, DNA, histones, heat shock proteins, and fragments of extracellular matrix (ECM) molecules [13]. Ischemic cardiomyocytes release extracellular vesicles that activate a pro-inflammatory phenotype in macrophages via the p38-MAPK pathway [16], thereby exacerbating the fibrotic response. Moreover, cardiomyocytes induce the release of MERTK from macrophages to inhibit the phagocytosis of necrotic cardiomyocytes by macrophages, thus promoting inflammation [14].

In pressure overload injury, cardiomyocytes can promote the development of cardiac fibrosis through TGF-β receptor II signaling [15]. In the aging heart, the insulin-like growth factor 1 (IGF-1) signaling pathway in cardiomyocytes is also involved in the development of interstitial fibrosis [16]. Additionally, cardiomyocytes express plasminogen activator inhibitors-1 (PAI-1), which protect the myocardium from fibrotic remodeling by reducing the synthesis of transforming growth factor-β (TGF-β) [17].

4. Macrophages

Normal adult mammalian hearts contain a small number of resident cardiac macrophages (RCMs), which originate from yolk sac-derived primitive macrophages that migrate to the heart during early embryonic development and develop there. These macrophages can survive into adulthood through local self-renewal [18]. RCMs maintain myocardial homeostasis by participating in coronary vessel maturation, engulfing exosomes containing damaged organelles, promoting atrioventricular conduction, forming electrotonic coupling with cardiomyocytes, and defending against pathogens [19]. With increasing age or in response to injury, monocyte-derived macrophages infiltrate the cardiac tissue and gradually replace the embryonic-origin macrophages [20]. Activated macrophages exhibit high heterogeneity, with diverse functions and phenotypes, and are widely involved in the regulation of inflammation, fibrosis, matrix remodeling, angiogenesis, and regeneration during the progression of fibrosis [21].

Macrophages are categorized into two states based on their activation forms: M1 and M2. M1 macrophages can be induced by IFN-γ, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF), expressing pro-inflammatory cytokines and activating ROS-dependent signaling cascades. In contrast, M2 macrophages are induced by interleukin IL-4 or IL-13, expressing large amounts of IL-10 and participating in the resolution of inflammation, angiogenesis, and tissue repair [22]. Within a few hours after myocardial infarction, necrotic cells release DAMPs, which activate Toll-like receptors (TLR) in macrophages and recruit monocytes and neutrophils to the infarct site, leading to fibroblast activation and an inflammatory response [23]. Macrophage recruitment typically peaks around three days after myocardial infarction. By approximately ten days post-infarction, anti-inflammatory or reparative macrophages proliferate rapidly, leading to inflammation resolution and entry into the reparative tissue remodeling phase of myocardial infarction. The recruited monocyte-macrophage population usually returns to baseline levels around 14 days after myocardial infarction but can persist in areas distant from the infarct for several months [24]. During the inflammatory phase, macrophages that engulf apoptotic cells in the infarct area can induce the resolution of tissue inflammation and transition to the proliferative phase of myocardial infarction healing [25], which is crucial for preventing arrhythmias and secondary necrosis [26]. However, after engulfing apoptotic cells, nucleic acid sensing within macrophages activates the interferon regulatory factor 3 (IRF3) pathway and induces type I interferon (IFN-I), promoting myocardial inflammatory responses [27]. Dying cardiomyocytes overexpress CD47 on their surface, which can bind to signal regulatory protein alpha (SIRPα) on cardiac macrophages, impeding the clearance of apoptotic cells in the infarct area by macrophages [28]. Additionally, amphiregulin released by cardiac macrophages regulates the phosphorylation and translocation of connexin 43 (Cx43) in cardiomyocytes, inhibiting arrhythmogenesis [29]. Macrophages with high expression of matrix metalloproteinases (MMPs) can degrade the ECM, thereby improving fibrosis [30]. Moreover, macrophages can release cytokines and growth factors, regulating fibrosis through the secretion of matrix remodeling proteases [31]. In summary, macrophages are essential effector cells in the fibrotic response to myocardial infarction and cardiac pressure overload [32].

5. Cardiac Endothelial Cells

Endothelial cells are the most abundant non-myocytes in the hearts of adult mammals [33], accounting for one-third of all cardiac cells and serving as direct targets for all cardiovascular risk factors [34]. These cells not only act as a barrier between the blood and myocardial tissue but also participate in immune responses and communicate with adjacent cells by releasing peptides, proteins, extracellular vesicles, and microRNAs [35].

Endothelial dysfunction has been recognized as a primary pathological alteration in the development of heart failure, particularly in heart failure with preserved ejection fraction (HFpEF), where it induces cardiomyocyte hypertrophy and stiffness, triggers fibrosis, and promotes immune cell infiltration [36]. In the myocardium of acute myocardial infarction, endothelial cells interact with leukocytes by secreting cytokines and chemokines, thereby promoting leukocyte migration to the infarct site, a process that requires endothelial cell activation [37]. Initially, dying cells release inflammatory cytokines (such as IL-1 and TNF) and auto-inflammatory factors (such as histamine), which stimulate endothelial cells in the infarct area and upregulate the expression of endothelial adhesion molecules, such as intercellular cell adhesion molecule-1 (ICAM-1), thereby triggering adhesion to activated leukocytes [38]. Subsequently, histamine binds to the H1 receptor and rapidly

mobilizes preformed P-selectin from Weibel-Palade bodies to the endothelial cell surface [39]. E-selectin is also upregulated in endothelial cells within the infarct area in response to a cytokine-rich environment. After expression on the endothelial cell (EC) surface, selectins engage in weak transient interactions with their leukocyte ligands, capturing leukocytes and mediating their rolling along the endothelium [40]. Thereafter, leukocytes expressing specific chemokine and cytokine receptors interact with ligands bound to glycosaminoglycans on the EC surface, inducing conformational changes in leukocyte integrins (such as LFA-1, Mac-1, and VLA-4), which strengthen the adhesion interactions [41], causing leukocytes to remain on the endothelial surface and adhere firmly. Integrin-mediated adhesion interactions involve binding to ICAM-1 or vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, the latter of which is upregulated on the endothelial cell surface in response to cytokine stimulation. Subsequently, leukocytes actively migrate to the sites of endothelial cell activation, which serve as exit points for extravasating cells in the endothelial and pericyte layers [42]. Following myocardial infarction, endothelial-specific activation of the transcription factor FoxO4 has been shown to promote neutrophil infiltration in the infarcted heart [43]. Endothelial cells are also important sources of profibrotic mediators, such as TGF-β1, FGFs, or endothelin-1 (ET-1). In models of angiotensin II-induced cardiomyopathy and diabetes [44], endothelial cell-derived ET-1 has been implicated in the development of myocardial fibrosis. In addition to their profibrotic role, endothelial cells can act as negative regulators of fibrosis by secreting mediators that inactivate cardiac fibroblasts. Studies have shown that endothelial cell hypoxia-inducible factor-1 (HIF-1) can participate in pressure overload-induced antifibrotic effects in the myocardium by inhibiting TGF-β signaling [45]. Moreover, CXCL10 released by endothelial cells is a mediator that inhibits fibroblast migration and exerts antifibrotic effects in myocardial infarction [46]. Endothelial cells produce nitric oxide (NO), which, by activating soluble guanylate cyclase (sGC), promotes the generation of cGMP, leading to vasodilation [47]. Conversely, decreased NO production and bioavailability result in reduced cGMP levels, causing vasoconstriction of smooth muscle cells and increased stiffness of cardiomyocytes [48].

6. Summary and Outlook

The pathophysiological heterogeneity of myocardial fibrosis and the complexity of effector cells involved in myocardial fibrosis have made the development of antifibrotic strategies for cardiomyopathies extremely complex. Current therapeutic agents for fibrotic responses mainly include RAAS (renin-angiotensin-aldosterone system) inhibitors, β-blockers, endothelin antagonists, and cytokine inhibitors such as pirfenidone, as well as colchicine, which inhibits cell proliferation. However, these pharmacological interventions are still far from satisfactory. Other antifibrotic approaches, such as cell recruitment, scar mechanics, cardiomyocyte-fibroblast coupling, or targeting miRNA, periostin, or caveolin signaling, have not been clinically applied due to concerns over their efficacy and safety. Inducing cardiomyocyte regeneration, biomaterial-assisted therapies, and stem cell treatments are increasingly attracting attention, but their therapeutic effects remain to be evaluated. The current challenge in fibrosis treatment is still how to identify targets for antifibrotic therapy. Considering the heterogeneity of effector cells during the fibrotic process, it is crucial to determine the characteristics of effector cell subpopulations in health and disease, as well as the relationships between different transcriptomic or proteomic profiles and functional properties. Subpopulations of effector cells in fibrotic hearts may serve as potential targets for antifibrotic therapies. This review has summarized the roles and mechanisms of different effector cells in myocardial fibrosis, especially the functional regulation of inflammatory cells such as macrophages and mast cells, which may provide a new theoretical basis for antifibrotic treatments in myocardial fibrosis.

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