

Research progress and prospect on the mechanism of extracellular matrix remodeling based on myocardial cells

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Abstract: Cardiovascular disease is the most lethal disease in all kinds of diseases in the world, and it has important global public health significance for its prevention and treatment. Myocardial fibrosis is one of the typical pathological manifestations of cardiovascular disease, which seriously affects the diastolic and systolic function of the ventricle and ultimately leads to heart failure. The matrix of cells surrounding cardiomyocytes has an important role in controlling cell proliferation, differentiating, and preserving the structural and functional integrity of the heart. The predominant factor contributing to myocardial fibrosis is the dysregulation of collagen homeostasis within the cardiomyocyte extracellular matrix. Therefore, preventing and reversing myocardial extracellular matrix remodeling has become an important goal for improving cardiac dysfunction and treating cardiovascular diseases. Modern studies have found that its reconstruction is often related to the expression of multiple pathways and the regulation of related factors. Based on this, together with the advancements in traditional Chinese and Western medical treatment, new concepts for enhancing cardiac function and patient quality of life are predicted to emerge.

Keywords: Cardiomyocyte extracellular matrix; Myocardial fibrosis; Cardiovascular disease; Integration of traditional Chinese medicine and Western medicine

1. Introduction

Cardiovascular disease (CVD) is a leading worldwide cause of mortality and has a substantial economic influence. Approximately two out of every five deaths are attributable to CVD, surpassing cancer and other diseases in terms of mortality rates [1]. As populations age and modern lifestyles undergo changes, both the incidence and mortality rates of cardiovascular-related conditions exhibit an increasing trend. Therefore, prevention and treatment of CVD carry paramount importance. Cardiovascular diseases encompass various conditions, including primary hypertension (such as hypertension renal disease and hypertensive heart disease) and ischemic heart disease (including angina and sudden myocardial infarction, and other forms of ischemic heart disease), acute and chronic rheumatic heart disease, pulmonary embolism, arrhythmias, and heart failure. The development of cardiovascular disease occurs as a continuous and progressive dynamic process. Risk factors like hypertension, hyperlipidemia, and hyperglycemia contribute to the development of atherosclerosis and left ventricular hypertrophy, leading to coronary artery atherosclerotic heart disease. Subsequent progression of coronary artery disease causes myocardial ischemia, and thrombosis formation within atherosclerotic plaques leads to coronary artery occlusion and myocardial infarction. Finally, ventricular remodeling leads to ventricular dilation and eventual development of heart failure.

Myocardial fibrosis (MF) is a prevalent pathological occurrence of CVD in its end-stage. It is the microscopic pathological basis that leads to structural damage, decreased cardiac function, arrhythmias, and even heart failure. Studies have found that the changes of myocardial extracellular matrix (ECM) has a significant role in the onset and progression of cardiovascular diseases, with excessive deposition of myocardial ECM being the main cause of MF. Therefore, the alteration of the cardiac ECM is crucial in the progression and advancement of cardiovascular disease. In-depth research on the mechanisms and interventions targeting myocardial ECM is of crucial importance in reducing the incidence of complications and mortality rates in cardiovascular disease patients and improving their

prognosis.

2. Role of myocardial extracellular matrix in cardiovascular diseases

ECM of cardiac myocytes is an intricate and ever-changing network made up of various components, including collagen proteins, fibronectin, elastin, and proteoglycans. It not only provides vital support for maintaining cardiac structural integrity but also influences the growth, proliferation, and differentiation of cardiac myocytes while maintaining a state of equilibrium between the processes of synthesis and degradation. Within the components of ECM, collagen is the major component, with collagen fibers of types I, II, and III accounting for over 90% of the myocardial interstitium. Type I collagen, comprising 80% of the collagen content, exhibits thicker fibers with greater stiffness and tensile strength, playing a role in maintaining ventricular wall strength. Type III collagen accounts for 11% and possesses thinner fibers with good elasticity and extensibility [2]. The ratio between type I and type III collagens is essential for preserving the normal structure of myocardial tissue and integrity of cardiac function. Collagen is primarily produced and secreted by cardiac fibroblasts, which are responsible for maintaining a dynamic balance between synthesis and degradation under normal conditions. However, myocardial injury triggers the activation of various neuroendocrine hormones and cytokines, disrupting the dynamic balance between ECM degradation and synthesis, leading to the occurrence of ECM remodeling.

The restructuring of ECM in the cardiac interstitium is associated with detrimental effects on both systolic and diastolic ventricular functions. More specifically, the abrupt accumulation of cross-linked collagen proteins within the cardiac interstitium can significantly increase myocardial stiffness, thereby impairing diastolic relaxation and contributing to diastolic dysfunction. ECM deposition can disrupt the coordinated excitation-contraction coupling of the myocardium, resulting in systolic dysfunction. ECM remodeling can also compromise myocardial perfusion [3]. Imbalances in the equilibrium between proteases and antiproteases within the cardiac interstitium can disrupt the degradation of fibrous collagen proteins. This leads to a disruption of ECM-dependent mechanisms that control the contraction of cardiac cells, resulting in systolic dysfunction [4]. The activation of pro-inflammatory factors by ECM fragments and subsequent recruitment of immune cells to the cardiac interstitium contribute to myocardial cell dysfunction and death. Concurrently, increased ECM synthesis within the cardiac interstitium results in excessive collagen protein accumulation, initiating a cascade leading to myocardial fibrosis, hypertrophy, ventricular stiffening, and deteriorating diastolic function. Conversely, excessive ECM degradation leads to elastin degradation, decreased ventricular compliance, impaired cardiac contraction, accelerated cardiac dilation, and progression of cardiac dysfunction, potentially compromising cardiac integrity. Hence, manipulating the makeup and arrangement of the cardiac ECM presents itself as a hopeful strategy for averting and managing cardiovascular ailments.

3. The most classic mechanism pathway and expression of ECM

Remodeling of ECM in cardiac myocytes is a multifaceted process that encompasses several variables, including cell apoptosis, immune-inflammatory injury, oxidative stress, stimulation of the renin-angiotensin-aldosterone system, and cellular signaling pathways. Although these factors play important roles in ECM remodeling, the specific mechanisms and signaling pathways involved remain incompletely understood and require further investigation. Current research indicates that the NF- κ B/TGF- β 1/Smad3 signaling pathway activation is essential for MF development, making it a potential target for inhibiting ECM remodeling [5]. Additionally, the delicate balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) is of utmost importance in maintaining extracellular matrix (ECM) stability and serves as a significant indicator for assessing MF [6].

3.1 Expression of the mechanism of action of MMPS / TIMPs

MMPs have a crucial function in the breakdown of the ECM. They possess the capacity to break down almost all protein constituents of ECM, with collagen breakdown mostly controlled by MMPs. In normal myocardium, MMPs exist mainly in an inactive state, and TIMPs are the main factors responsible for the inactivation of MMPs [7]. TIMPs can bind to MMPs in a 1:1 ratio, inhibiting their activity and inactivating already activated MMPs, rendering them inactive [8]. The balance between MMPs and TIMPs is an essential factor in maintaining ECM stability [9]. When MMPs expression is

enhanced, ECM matrix proteins can be directly degraded, and the degradation products can serve as stimulators for collagen synthesis, leading to an increase in immature fibrous tissue in the myocardium and consequently increasing collagen content in cardiac tissue, triggering cardiac ECM remodeling [10].

The ECM remodeling in cardiac myocytes is important in the course of heart disease. MMPs are endogenous proteolytic enzymes that include Ca^{2+} and Zn^{2+} ions. They consist of MMP-1 interstitial collagenase, MMP-2 and MMP-9 gelatinases, and other components. MMP-2 and MMP-9 are involved in cellular apoptosis and ventricular remodeling, and they serve as good markers for assessing cardiac function [11]. It has been shown that rosuvastatin can effectively alleviate ECM deposition and fibrosis, and its mechanism is associated with the suppression of MMP-2 and MMP-9 gene expression in the myocardium [12]. Enhanced MMP activity leads to ECM degradation and the breakdown of collagen that maintains myocardial function, weakening the constraint on excessive elongation of cardiomyocytes, and triggering ventricular wall thinning and left ventricular enlargement. TIMPs are endogenous low-molecular-weight protein inhibitors of MMPs, and elevated TIMP levels can reflect left ventricular hypertrophy. Modulating the levels and function of MMPs and TIMPs offers a potential strategy for restoring the dynamic balance of collagen synthesis and degradation, thereby correcting myocardial ECM remodeling, controlling ventricular remodeling, and improving cardiac function. These findings provide new directions for the treatment of heart diseases.

3.2 The mechanism of NF- κ B / TGF- β 1 / Smad3 signaling pathway

Nuclear factor kappa-B (NF- κ B) has a crucial role in the orchestration of inflammatory reactions, consisting of two subunits, p50 and p65. In the cytoplasm, NF- κ B p65/p50 forms a complex with inhibitory protein I κ B, maintaining a resting state and inhibiting its activation. However, when exposed to continuous stimuli such as oxidative damage or inflammation, the I κ B kinase complex is activated, promoting the dissociation of NF- κ B from I κ B, further activating it, and regulating downstream inflammatory factors [13]. The expression of these inflammatory factors initiates a series of inflammatory reactions, which in turn become stimulating factors for NF- κ B activation, exacerbating inflammation and promoting cardiac extracellular matrix fibrosis, significantly influencing the development of cardiac fibrosis [14]. The TGF- β 1/Smad3 signaling pathway is a crucial pathway in cardiac fibrosis and a typical signaling pathway that directly induces the expression of ECM-related genes. This signaling pathway is crucial in processes such as fibroblast transformation into myofibroblasts (MFBs), ECM secretion, cell migration, and proliferation, making it one of the most extensively studied pro-fibrotic pathways currently.

The TGF- β family is a crucial group of regulatory factors involved in embryonic development, vascular angiogenesis, and immune modulation, playing an important part in cardiac repair regulation, remodeling, and fibrosis [15]. Among them, TGF- β 1 (transforming growth factor beta 1) is the main growth factor that regulates ECM metabolism and functions as a classical initiating factor in fibrosis formation. TGF- β 1 suppresses inflammation, upregulates collagen synthesis, downregulates ECM degradation, promotes ECM deposition, and control the growth, change, movement, and death of fibroblasts. The synthesis of ECM components, mainly collagen, is particularly important [16]. Additionally, TGF- β 1 can trigger the conversion of cardiac fibroblasts (CFBs) into cardiac myofibroblasts (CMFs) with increased tissue contractile performance. [17]. However, excessive activation of CMFs can lead to excessive collagen deposition and cardiac interstitial proliferation, which increases cardiac workload, induces cardiac fibrosis and functional abnormalities, and accelerates the progression of cardiac diseases. The role of TGF- β 1 is of paramount importance in myocardial fibrosis and cardiac repair and remodeling.

The Smad protein family is a highly conserved group of proteins that play a central role as downstream signaling molecules of TGF- β 1 in the process of signal transduction from the cell membrane receptor to the nucleus. As the exclusive substrates of the TGF- β receptor kinases, Smad proteins act as intermediate molecules in transcriptional regulation, enabling the transcriptional control and TGF- β 1 signaling mediation. TGF- β 1 has the ability to increase the expression of α -smooth muscle actin (α -SMA), which promotes the transformation of CFBs into MFBs, by regulating the activation of Smads [18, 19]. Among the Smad protein family, Smad2 and Smad3 are important signal transduction mediators [20]. Smad3, the preeminent constituent of the Smad family, is engaged in stimulating ECM synthesis and the promotion of CFB activation, in addition to upregulating the expression of TIMPs.

4. Mechanism of myocardial fibrosis in ECM remodeling of cardiomyocytes and current status of western medicine treatment

The activation of The RAAS (renin-angiotensin-aldosterone) system and the resulting increase in angiotensin II (Ang II) levels are important variables that contribute to the development of cardiac fibrosis during ECM remodeling. In addition, various factors such as endothelin-1 (ET-1), TGF- β 1, tumor necrosis factor- α (TNF- α), NF- κ B, interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), C-C chemokine ligand 2 (CCL2), connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF) have been identified as contributors to the stimulation of collagen secretion by cardiac fibroblasts. [21, 22]. On the contrary, bradykinin (BK), MMPs, nitric oxide (NO), adrenomedullin (AM), N-terminal pro B-type natriuretic peptide (NT-proBNP), and peroxisome proliferators-activated receptors (PPARs) can inhibit and degrade myocardial fibrosis. At present, Western medicine does not provide any targeted therapy options for myocardial fibrosis. While angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs), beta-blockers, antiplatelet drugs, statins, as well as medications for controlling blood pressure and blood glucose have shown limited efficacy in improving fibrosis-related cardiac function indicators. In addition to their low efficiency, the long-term use of these drugs is also limited by their side effects in fibrosis treatment [23]. Surgical interventions, such as coronary stenting (PCI), coronary angiography (CAV), and coronary artery bypass grafting (CABG), have a substantial impact on reducing death rates and enhancing ventricular remodeling and prognosis. However, these procedures inevitably lead to myocardial ischemia reperfusion injury (MIRI) during clinical application. Given the complexity of the pathogenesis of MF, it often involves the regulation of multiple pathways and related factors. Long-term combined drug therapy for CVD has unstable efficacy, poor medication compliance, and a high risk of recurrence. The risks and harmful effects on the body associated with surgical treatment should not be overlooked. Therefore, there is a pressing necessity to discover safer and more efficacious alternative treatment methods, which have become important directions in CVD research.

5. The advantages of ECM remodeling in TCM treatment

Traditional Chinese medicine (TCM), with its rich historical foundation, holds promising potential and offers unique advantages in the realm of preventing and treating CVD. During the course of clinical practice, TCM can be used in combination therapy or multi-target treatment through multiple levels and pathways. It ensures long-term medication for patients with minimal side effects and low cost. TCM formulations often consist of multiple herbal ingredients, which possess various pharmacological active components. They are characterized by TCM theories and individualized treatment strategies and exhibit comprehensive regulation of body functions. TCM has significant advantages and prospects in research and treatment of upstream pathways in cardiovascular diseases. TCM has become a viable method for preventing and treating complex chronic illnesses, particularly CVD. TCM offers distinct advantages that contribute to its potential effectiveness in managing these conditions. [24]. With the continuous improvement of modern extraction techniques and equipment for Chinese herbal medicine, significant progress has been made in the study of effective components and mechanisms of TCM in protecting against myocardial ischemia. Research has shown that the active components of TCM have multiple effects, including regulating oxidative stress, inhibiting inflammatory factors, suppressing cell apoptosis, inhibiting calcium overload, improving lipid metabolism, and dilating coronary arteries. The protective mechanisms of TCM mainly include [25]: 1) reducing myocardial oxygen consumption; 2) scavenging free radicals and exerting antioxidant effects; 3) inhibiting the response of inflammatory factors; 4) improving endothelial cells and regulating vascular active factors; 5) increasing adenosine triphosphate (ATP) content to improve energy metabolism; 6) exerting calcium antagonistic effects and inhibiting calcium influx; 7) inhibiting cell apoptosis; 8) promoting vascular regeneration. TCM has achieved significant results in the treatment and research of MF. However, due to technical and methodological limitations, most of the research is still in the basic research stage, mainly focusing on pharmacological studies. The regulatory mechanism of ECM expression in MF remains an unresolved clinical challenge, especially with limited research on ECM. Further related research is needed in this area.

6. Conclusion

Myocardial fibrosis serves as a prominent pathological manifestation in numerous cardiovascular diseases and is closely associated with the remodeling processes occurring within the ECM of the heart.

This imbalance results in increased stiffness and reduced compliance of the ventricles, ultimately impairing their contractile and diastolic functions. These changes serve as the microscopic pathological basis for the development of heart structural damage, decreased cardiac function, myocardial infarction, and heart failure. Currently, interventions in modern medicine mainly target downstream disease processes, while the triggers of myocardial ECM remodeling are diverse. However, experimental research suggests that interventions targeting only a single pathway and its related factors may not achieve satisfactory results. Therefore, it is necessary to integrate and analyze relevant research findings and explore the upstream pathways as the next step in research. Customized therapeutic approaches rooted in TCM have garnered substantial momentum in the prevention and management of CVD. TCM has clear benefits and has great potential in studying the first routes of cardiovascular illnesses. Therefore, the progress in integration of traditional Chinese medicine and Western medicine for the treatment of myocardial fibrosis and other cardiovascular illnesses shows potential and requires more extensive research and widespread implementation.

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