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The Mechanisms and Therapies Aiming to TGF-β Signaling Pathway on Cardiac Fibrosis after Myocardial Infarction

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Abstract

After myocardial infarction, cardiac fibrosis develops and is crucial to the long-term prognosis of cardiac. The most significant pathway on cardiac fibrosis following myocardial infarction is TGF-β signaling, but no one has systematically elaborated the twofold effects and therapies target to TGF-β signaling. The effects of TGF-β on the cardiac are dual: the protective effect was mostly seen in reducing inflammation and promoting remodeling, while the negative effect was seen in fibrogenesis. Therefore, therapies that target the TGF-β signaling pathway have emerged as a research hotspot in recent years. These therapies include gene therapy, pharmacological therapy, metabolic process regulation, herbal medicine, and more. However, the subsequent problems, such as causing or accelerating the processes of other diseases, must be carefully addressed. In this review, we highlighted the effects, therapies, and issues aiming to the TGF-β signaling pathway on cardiac fibrosis following myocardial infarction.

Keywords: cardiac fibrosis; TGF-β signaling pathway; myocardial infarction; therapies; effects.

1. Introduction

Ischemia and hypoxia of cardiac cells cause myocardial infarctions (MI), and the death of related cells changes the structure and function of the heart[1]. Reactive fibrosis and replacement fibrosis are both types of cardiac fibrosis[2]. In replacement fibrosis, normal cardiomyocytes are replaced by scar tissue, while in reactive fibrosis, stiffness and compliance are altered after MI [3, 4]. When the production and degradation of extracellular matrix(ECM) is imbalanced, cardiac fibrosis develops[5,6], followed by the accumulation of scar tissue, which leads to the occurrence of major adverse cardiac events (MACEs) including heart failure(HF), arrhythmia, cardiogenic shock and even cardiac rupture[7-10].

TGF-β superfamily includes 33 members at least and the TGF-β(TGF-β1, TGF-β2, TGF-β3) subfamily plays a greater role in cardiac fibrosis after MI. The receptors of TGF-β are type I receptor (TβRI) and type II receptor(TβRII), on the targeted cell surface, TGF-β ligands bind to TβRII which recruits and phosphorylates TβRI, and rephosphorylates receptor regulated SMAD proteins (R-SMAD) binding to coSMAD. As a transcription factor in the nucleus, R-SMAD/coSMAD participates in the regulation of target gene expression, cell growth, differentiation, apoptosis, and homeostasis and other cellular functions[11-16]. In addition to the TGF-β Signaling Pathway, the angiotensin pathway, mitogen-activated protein kinase(MAPK) pathway, Notch pathway and Wnt/β-Catenin pathway also participate in fibrosis after MI[17, 18]. A major focus of this review is on the effects, therapies and problems relating to the TGF-β signaling pathway on cardiac fibrosis after MI.

2. Effects

2.1 Cardiac fibrosis after myocardial infarction

As MI progresses, there are three stages: the inflammation stage, the reparative stage, and the maturation stage[11]. When cardiac cells underwent ischemia, hypoxia, and necrosis, the complement cascade and toll-like receptor (TLR) are activated, resulting in the expression of adhesion molecules, the generation of free radicals, and the release of chemokine, cytokines andtumor necrosis factor-α(TNF-α). This leads to the migration of inflammatory cells (neutrophils, mononuclear cells, macrophages) to the area of infarction for the clearing of necrotic cardiomyocytes, and ultimately the transformation of macrophages into fibroblasts[12-14]. In the reparative stage, the activation of TGF-β induces the conversion of fibroblasts to myofibroblasts and suppresses inflammation, cytokines, and chemokines[11,12,15]. The myofibroblasts promote the synthesis of ECM proteins and the expression of alpha-smooth muscle actin (α-SMA), resulting in the formation of fibrosis and scar tissue in cardiac[16, 17].

2.2 TGF-β Signaling Pathway on Cardiac Fibrosis

The expression of TGF-β increases in several kinds of cardiovascular diseases: dilated cardiomyopathy, idiopathic hypertrophic cardiomyopathy, atrial fibrillation, myocardial infarction, heart failure and even in hypertension[18-23]. The increasing levels of TGF-β1 serve as warning signs of cardiac fibrosis[24, 25]. In mice injected with TGF-β ,the level of collagen and granulation tissue increased[26], which means TGF-β exacerbates fibrosis. When rats received TGF-β1 gene transformation, the lung fibrosis characterized by the deposition of ECM proteins became more severe[27]. However, when we selectively deleted the receptor of TGF-β,the fibrosis of kidney alleviated[28].

TGF-β plays a great role in cardiac fibrosis, but its mechanism needs to be clarified. TGF-β inhibits the production of cytokines and chemokines, suppresses inflammation, promotes angiogenesis, and alleviates the remodeling of left ventricle[29-34]. On the other sides, TGF-β stimulates the production of myofibroblasts, which secrete ECM proteins and induce the synthesis of protease inhibitors to inhibit the degradation of the ECM proteins[35-39], following with the cross-link of tropocollagen [40, 41]. Dual effects of TGF-β on cardiac is showed in Figure 1.

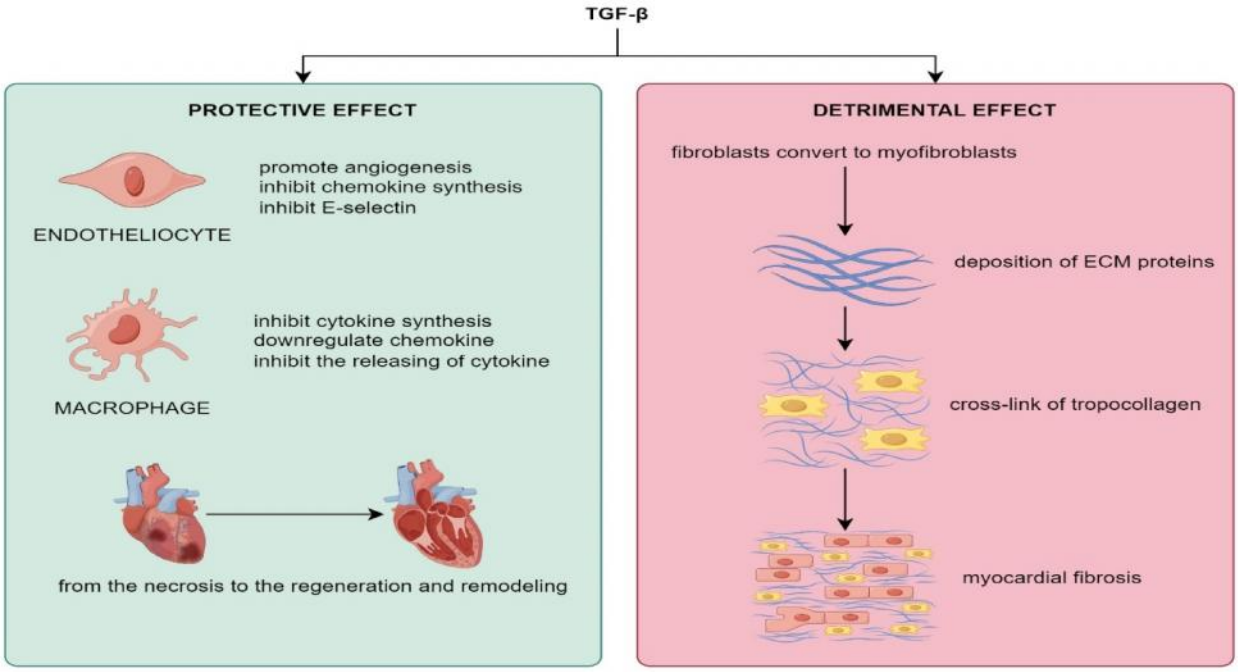

Fig.1. The protective effect ofTGF-β on cardiac was mostly seen in the inflammatory stage: with the activation of endotheliocytes and macrophages, the cytokine, E-selection and chemokine are inhibited, promoting the angiogenesis, cardiac regeneration and improving cardiac remodeling. The detrimental effect of TGF-β was seen in the fibrogenesis of myocardial: with the activation of TGF-β, fibroblasts convert to myofibroblasts, which aggravates the deposition of ECM proteins and cross-link of tropocollagen, ultimately leading to cardiac fibrosis.

3. Therapies

3.1 Gene therapy

Cardiovascular gene therapies target protein expression, angiogenesis, and cardiac regeneration[42]. Gene knockout, gene silencing, and gene overexpression are the most commonly used therapies[43]. When mice with MI underwent IncRNA-Safe knockdown, the formation of myofibroblasts and the secretion of ECM proteins were indirectly decreased[44]. The expression of TUG1 increased in TGF-β1 treated rats,and the knockdown of TUG1 suppressed the effects induced by TGF-β1 [45]. Despite Notch3 cDNA treatment alleviating cardiac damage, Notch3 siRNA promoted cardiac fibrosis *in vivo*[46]. In circular ribonucleic acid (circRNA) 010567 treated mice ,the structure and function of the heart significantly improved ,and the expression of TGF-β1 and Smad3 decreased remarkably[47]. When circHNRNPH1 was expressed in MI, it induced the expression of Smad7 (an inhibitory protein of TGF-β signaling pathway) and accelerated the degradation of TGF-β. As a result, knocking out circular HNRNPH1 may be an effective therapy for cardiac fibrosis[48]. By overexpressing long non-coding RNAs (lncRNAs), N1LR, the death rate of cardiomyocytes exposed to H2O2 was decreased, inflammatory factors were decreased, and cardiac fibrosis was alleviated by inhibiting of TGF-β/smad[49]. Decrin gene treatment also improved cardiac function and alleviated cardiac fibrosis in AMI mice by decreasing Smad2/3 activation[50]. Silencing of KLF5 (Kruppel-like factor 5) decreased cell and tissue damage by upregulating miR27a and decreased TGF-β in MI [51].

MicroRNA gene therapy plays an increasingly important role on cardiac fibrosis after MI, but the specific mechanism is unclear. MicroRNA-214 (the miR-214) inhibited the TGF-β signaling pathway in vivo and in vitro to prevent the expression of fibrosis gene[52]. Meanwhile, miR-130a, miR-34a, miR-202-3p, miR-212-5p, miR-195-5p, MiR-208b/miR-21 and miR-208 exerted their effects on fibrosis by regulating TGF-β Signaling Pathway[53-58].

3.2 Drug therapy

The traditional drugs for the secondary prevention of coronary artery disease are anti-platelet drugs, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (ACEI/ARB), statins, nitrates and β-receptor antagonists ,and most of them play important role in cardiac remodeling and the long-term prognosis after MI[59-62]. The effect of ACEI/ARB is undoubtable on alleviating the cardiac remodeling and fibrosis, but the mechanism needs to be further investigated, and here we just clarify the relationship with TGF-β signaling pathway. In ARB and ARB/ACEI combined treated rats, the expression of TGF-β/Smad mRNA decreased, indicating that the combined treatment is more effective than ACEI treatment on alleviating the cardiac remodeling[63]. Valsartan inhibited the expression of TGF-b/Smad, HIF-1 a (hypoxia inducible factor-1a) and proteins associated with Ang II-mediated cardiac fibrosis in MI rats[64]. At the same time,the level of TGF-β1 and TAK1 (TGF-activated kinase 1) decreased significantly in rats treated with simvastatin, and the expression of the inhibitory protein Smad7 markedly increased, indicating that simvastatin promoted the function and remodeling of the heart via the TGF-β signaling pathway[65]. N-Acetylcysteine also decreased the level of TGF-βtoo in MI[66].

For patients suffering from MI or HF, some new drugs are used to improve their long-term prognosis: sodium-dependent glucose transporters 2(SGLT-2), angiotensin receptor-neprilysin inhibitor (ARNI) such as sacubitril/valsartan, Dipeptidyl peptidase-4 (DPP-4) inhibitors, and so on.[67-74]. Sacubitril/valsartan, combining sacubitril and valsartan in 1:1 ratio ,is better than valsartan in improving the structure and function of cardiac, decreasing the expression of TGF-β1 and Smad3 protein by inducing the synthesis of myofibroblast[75]. In rats after MI, ARNI and ACEI combined decreased TGF-β expression compared to ACEI alone[76]. In non-diabetic rats treated with empagliflozin, cardiac fibrosis was improved by inhibiting the TGF-β1/Smad3 signaling pathway[77]. DPP4 inhibitor also alleviated cardiac fibrosis by inhibiting the expression of TGF-β1[78].

3.3 Metabolic process regulation

As a new research field to improve cardiac structure and function, the regulation of metabolic processes has gained great attention in recent years[79]. PGAM1(phosphoglycerate mutase 1), a key aerobic glycolysis enzyme, plays critical role in regulating molecular metabolic processes .The overexpression of PGAM1 may increase the TGF-β level and promote the inflammation [80]. In MI mice, deficiency of PGAM1 alleviated the inflammatory, apoptosis and fibrosis of cardiac by regulating TGF-β signaling pathway[81]. Similarly, inhibiting glycolysis weakened fibrosis in other organs[82,83]. METTL3 (methyltransferase complex), involved in many metabolic processes, the silenceing of which would improve the fibrosis induced by TGF-β1, may be a new targeted therapy in the future[84]. TNAP (tissue nonspecific alkaline phosphatase) also played an important role in cardiac fibrosis via the TGF-β signaling pathway[85]. SAHA (Suberoylanilide hydroxamic acid) exerted its cardiac protective effects by increasing the expression of DUSP4[86].

3.4 Herbal medicine

Herbal medicine, also referred to as botanical medicine, utilizes plants or plant extracts to treat a wide range of diseases, and here we just put emphasis on the mechanism of cardiovascular diseases related with TGF-β signaling pathway[87-89]. Many studies have verified the cardiac protective effects of quercetin in MI[90, 91]. Ghadeer M. Albadrani[92] found quercetin reduced the levels of Ang II, TGF-β and smad3 to exert its cardiac protective effects in MI rats, while Toshinobu Nakamura[93] found quercetin exerted its antifibrotic effect but had no obvious inhibition on the phosphorylation induced by TGF-β in idiopathic pulmonary fibrosis. In MI mice, puerarin also alleviated cardiac fibrosis by regulating MCP (monocyte chemoattractant protein)-1 and TGF-β1 signaling pathway[94].

Ursolic acid downregulated the expression of TGF-β, MMP-2(matrix metalloproteinase 2) and MMP-9 in MI rats[95]. Artemisinin is an extracted chemical product form artemisia, discovered by Dr. Tu Youyou in 1972 in China [96], which plays important role in antifibrotic in many organs like lung, kidney, liver and so on[96-100]. Artemisinin decreased the level of TGF-β, MMP-2,MMP-9,and Type I collagen in MI rats[101], which may be helpful on the treatment of cardiac fibrosis. Oxymatrine, resveratrol, zerumbone, lourerin B and calycosin also protected against myocardial fibrosis by modulating TGF-β/Smads signaling pathway in MI rats[102-106], while the specific mechanism needs to be studied in the future.

3.5 The others therapies

The inhibitory protein, Smad7, inhibits the TGF-β/Smads signal pathway by interfering the smad receptors[107]. Some people have clarified that its role involves regulating macrophage phenotypes, while the inhibitory effects were relatively limited in inflammation and repair in mice with MI [108]. Samd1 protected against adverse remodeling by regulating the TGF-β signaling pathway after MI[109]. And the expression of ALK4(activin receptor-like kinase 4) may be a new targeted therapy on cardiac fibrosis[110]. IL-6(inhibitor interleukin 6) and cytokine-Like 1 alleviated the cardiac fibrosis by regulating the TGF-β signaling pathway [111, 112]. Vitamin D supplementation also alleviated cardiac fibrosis by regulating TGF-β signaling pathway in MI rats[113]. All of them may be effective therapies for improving the cardiac fibrosis after MI.

4. The problems

The therapies aimed at improving cardiac fibrosis after MI are becoming increasingly popular as research deepens, but the potential side effects also need to be addressed. In mice treated with anti-TGF-β antibodies, mortality increased and the left ventricular structure worsened after MI[114]. Aortic aneurysms and cardiac fibrosis may be aggravated by interference with the TGF-β/Smad signaling pathway[115, 116] and these processes could also exacerbate asthma, cancer, and skeletal development issues[117-119]. Therefore, the mechanisms still need to be elucidated, and the widespread use of these therapies still has a long way to go in the future.

5. Conclusions

The development of cardiac fibrosis has a close relationship with TGF-β signaling pathway, while the widely used drugs in clinical are still relatively limited compared with the traditional secondary prevention drugs like ACEI/ARB, statin, and β-receptor antagonist, and even though there are so many new therapy methods. Fortunately, the safety of sacubitril/valsartan is sure in improving the cardiac remodeling. Other targeted therapies such as gene therapy, metabolic process regulation, and botanical medicine are the new hot areas and need to be further explored in the future.

Abbreviations

MI, myocardial infarctions; MACEs, major adverse cardiac events; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MAPK, mitogen-activated proteinkinase; TNF-α, tumor necrosis factor-α; a-SMA, alpha-smooth muscle actin; HIF-1a, hypoxia inducible factor-1a; TAK 1, TGF-activatedkinase 1; DPP4, Dipeptidyl peptidase-4; PGAM1, phosphoglycerate mutase1; TNAP, tissue nonspecific alkalinephosphatase; SAHA, Suberoylanilide hydroxamic acid.

Availability of Data and Materials

Data sharing is not applicable as no data were generated or analyzed

Author Contributions

T-t C and ML were mainly responsible for literature search and analysis, as well as drafting the initial manuscript. CL and J-l M coordinated and supervised the literature collection and analysis, and carried out the initial analyses. XL

and TW helped with interpretation of the results and language embellishment. HY, YS, X-f D, and R-j X reviewed and revised the manuscript, andprovided critical review of important intellectual content. YY was responsible for pre-submission review and provided important comments and suggestions during the revision process of the paper.All authors contributed to the conception and design of the study. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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