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Review Article

The role of TGF-β in cardiac fibrosis and heart failure: A review

Anil Kumar K. Prajapati[1], **Gaurang B. Shah**[2]*

[1]*Dept. of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India*
[2]*Dept. of Pharmacology, L.M. College Of Pharmacy, Ahmedabad, Gujarat, India*

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ABSTRACT

Chronic heart failure occurs when the heart's capacity to effectively pump blood becomes disrupted, resulting in insufficient oxygen and nutrient delivery to the body's tissues. Cardiac fibrosis, a common pathophysiological process in cardiovascular diseases like myocardial infarction and hypertension, results from the increased accumulation of extracellular matrix (ECM) by activated cardiac fibroblasts (CFs). The stimulation of fibroblasts is prompted by pro-inflammatory signaling molecules and neuroendocrine activators and ventricular wall stretch, which is observed in conditions such as pressure overload or injury following a myocardial infarction. These activated fibroblasts transform into myofibroblasts, which play a crucial role in ECM secretion and cardiac fibrosis. TGF-βs are multifunctional cytokines involved in regulating various cell processes, including inflammation, ECM deposition, cell proliferation, differentiation, and growth. TGF-β stimulation promotes myofibroblast differentiation and increases ECM protein synthesis. It also activates pro-fibrotic genes by increasing Smad2/3 while reducing inhibitory Smad 6/7 in myofibroblasts. Smad 2/3 activation has been observed in fibroblasts infiltrating remodeling hearts after injury. TGF-β further contributes to collagens I, III, and VI deposition, enhancing matrix protein expression in the heart. Despite some attempts to target TGF-β3 signaling at the ALK1-5 receptor activity level, the success has been limited. However, additional research is needed to explore and develop therapies focused on the TGF-β signaling pathway to address cardiac dysfunction and heart failure.

1. Introduction

Chronic heart failure occurs due to an inequity in the heart's ability to effectively pump blood, leading to insufficient delivery of oxygen and nutrients to the body's tissues. The primary symptoms of this complex condition are shortness of breath during exertion, difficulty breathing while lying flat (orthopnea), and sudden nighttime breathlessness (paroxysmal nocturnal dyspnea). Fatigue and swelling in the ankles are also common indications of chronic heart failure, resulting from irregularities in the filling and/or emptying of the left ventricle.[1] Cardiac fibrosis is a common pathological process observed in various cardiovascular diseases, including myocardial infarction (MI) and hypertension.[2] It results from an excessive extracellular matrix (ECM) buildup by cardiac fibroblasts (CFs), specialized spindle-shaped cells[3] found in the myocardial interstitial, epicardial, and perivascular regions. Unlike other cells in the myocardium, CFs are not associated with the basement membrane.[4] Functionally, CFs play a crucial role in maintaining the homeostasis of the ECM and can detect and respond to changes in their microenvironment. Depending on the specific stimuli they encounter, CFs can contribute to either physiological or pathological remodelling of the myocardium. In the context of heart failure, activated fibroblasts have been

* *Corresponding author*.
E-mail address: gaurang.shah@lmcp.ac.in (G. B. Shah).

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compared to fibroblasts in cancer that promote tumor growth through their proliferative activities.[5] Fibrosis occurs when fibroblasts are abnormally activated and can be categorized into reparative/replacement fibrosis and reactive fibrosis. Reparative fibrosis is triggered by the loss of cardiomyocytes, leading to the formation of scars to maintain the myocardium's structural integrity. Reactive fibrosis is not preceded by cardiomyocyte loss but starts when activated fibroblasts break down the existing tissue framework and excessively deposit fibrillar and non-fibrillar extracellular matrix (ECM) proteins, replacing the cardiomyocytes. This process ultimately reduces the myocardium's contractile capacity and compliance.[6] In the context of heart failure, the resident cardiac fibroblast within the tissue is the key driver of advancing cardiac fibrosis. These fibroblasts become activated and transform into myofibroblasts, leading to the progression of the condition. The stimulation of fibroblasts is prompted by pro-inflammatory signaling molecules and neuroendocrine activators, as evidenced in cases of pressure overload or injury subsequent to myocardial infarction.[7,8] Once converted into myofibroblasts, these cells are essential for the fibrotic process by producing and releasing an abundance of extracellular matrix (ECM) material. Moreover, they acquire contractile properties through the activation of genes like αSMA, enabling them to actively restructure the ECM or facilitate scar formation after MI.[9,10] Furthermore, myofibroblasts release growth factors that directly induce cardiomyocyte hypertrophy via a paracrine-dependent mechanism, another hallmark of heart failure. This interplay between activated cardiac fibroblasts and cardiomyocytes contributes significantly to developing and advancing fibrosis and heart failure.[11] Cardiac fibrosis initiates harmful mechanisms that result in the enlargement of heart chambers, thickening of the heart muscle, and increased apoptosis. These processes eventually progress to congestive heart failure (CHF), a condition where the heart's pumping ability is compromised, leading to fluid buildup in the lungs and other parts of the body.[12,13]

2. Fibroblast-to-Myofibroblast Transition

An essential process in both wound healing and fibrotic diseases is the transformation of fibroblasts into myofibroblasts, enabling them to evade quiescence or apoptosis.[14] The transformation of the phenotype from fibroblasts to myofibroblasts is termed Fibroblast-to-Myofibroblast Transition (FMT). FMT can be broadly categorized into two stages. Initially, fibroblasts undergo activation, transitioning into a proto-myofibroblast phenotype, and subsequently, in the second stage, they complete the transition into fully developed myofibroblasts.[15,16] In the initial stage of transition, it is challenging to differentiate between normal fibroblasts and proto-myofibroblasts (see Figure 1). However, if the tissue continues to experience elevated mechanical, physical, and biochemical stresses caused by injuries, the fibroblasts initiate the polymerization of stress fibers containing αSMA. The wound's mechanical tension and growth factors further promote the transition of fibroblasts into myofibroblasts.[17] Notably, the presence of growth factors can induce the formation of stress fibers, which enhance cell motility.[18] This observation suggests that environmental factors, such as humoral stimuli like TGF–β, essential in the conservation of Fibroblast-to-Myofibroblast Transition (FMT).[19]

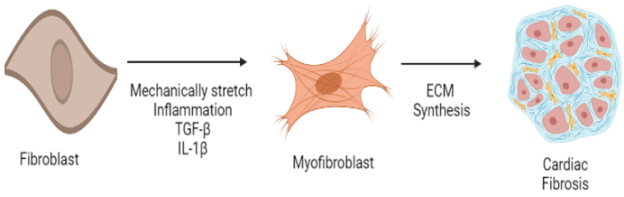

Figure 1: Fibroblast-to-myofibroblast transition

(Fibroblast is converted into myofibroblast through the mechanical stretch, Inflammation, TGF–β and IL-1β. Myofibroblast synthesized and secret the ECM, which is deposited in cardiac muscles and cardiac fibrosis.)

3. Introduction of TGF-β

TGF-βs are versatile cytokines known to play crucial roles in various cellular functions, including the regulation of inflammation, accumulation of interstitial matrix, cellular propagation, maturation, and development. In the context of mammalian biology, it is notable that there exist three closely homologous isoforms of Transforming Growth Factor-beta (TGF-β), specifically referred to as TGF-β1, TGF-β2, and TGF-β3. Each of these isoforms is encoded by distinct genetic loci.[20] The production of TGF-β occurs across a spectrum of cellular types and is initially sequestered in an inactive complex form, thereby precluding its interaction with corresponding receptors. The activation of TGF-β signaling pathways is primarily contingent upon the liberation of the biologically active TGF-β from its latent reservoir. Intriguingly, this latent complex is found to be prominently stored within various tissue types. It is worth noting that even a marginal proportion of activated latent TGF-β molecules is proficient in inducing a robust cellular response, thereby underscoring the efficiency of this signaling axis.[20] Certain proteases, such as plasmin, Matrix Metalloproteinase (MMP)-2, and MMP-9, can stimulate TGF-β. This process links the degradation of the extracellular matrix with the activation of a molecule that plays a central role in preserving matrix integrity and stability.[20–22] Additionally, reactive oxygen species,[23] matricellular proteins,[24] and integrin-mediated

interactions[25] can also trigger TGF-β activation. However, the exact role of these factors might differ based on the particular types of cells and the specific pathological situations implicated.[26]

4. Cellular effects of TGF-β

TGF-βs exhibit remarkable versatility, impacting diverse cell types significantly. Their pivotal roles encompass embryonic development, cell functions like growth, differentiation, proliferation, and survival. TGF-βs also regulate fibrosis, and have regulatory functions in the realm of inflammatory responses and tissue immunity, showcasing multifunctional capabilities.[26] TGF-β's pivotal role in fibroblast regulation is evident[27]. TGF-β triggers myofibroblast differentiation[28] and enhances interstitial matrix protein synthesis (refer to Figure 1). It also curtails Matrix Metalloproteinase (MMP) activity and boosts protease inhibitor synthesis, including PAI-1 and TIMPs, thus contributing significantly to matrix preservation.[27,29] Moreover, TGF-β acts as a potent inducer of Connective Tissue Growth Factor (CTGF), an agent in fibrogenesis that cooperates with TGF-β for sustained fibrotic processes.[30] Furthermore, TGF-β1 stimulation prompts cardiomyocyte enlargement and encourages the production of fetal contractile proteins.[28]

4.1. TGF- β signaling pathway in cardiac fibrosis

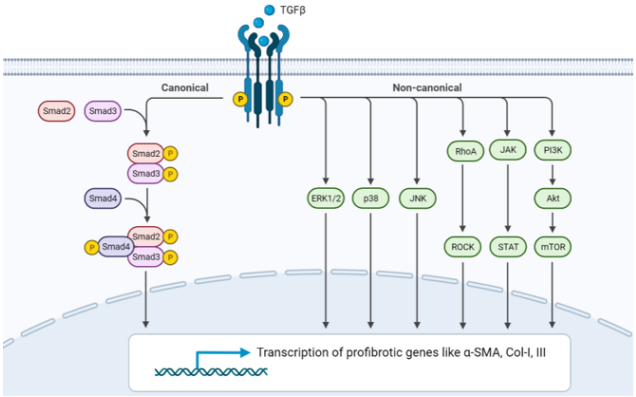

Figure 2: TGF- β signaling in cardiac fibrosis

TGF-β could induce signal transduction via the canonical (SMAD-dependent) and non-canonical (SMAD-independent) pathways (see Figure no. 2). In the canonical pathway, TGF- β 1 binds to and causes heterodimerization of TGF-β receptor type 1 (TBRI, also known as an activin-like kinase (ALK) 5) and the type II receptor (TBRII), leading to the phosphorylation of SMAD2/SMAD3, which subsequently form a complex with SMAD4 and translocate into the nucleus, acting as a transcriptional factor to regulate the fibrotic gene expression (e.g., αSMA, collagen I and III). SMAD6/7 are inhibitory SMADS to inhibit transcription of SMAD2 and SMAD3.[30]

5. The Role of TGF-β in Cardiac Fibrosis

Cardiac fibrosis is characterized by two main aspects: the disruption of the normal structure of the myocardium and the excessive production of extracellular matrix (ECM) proteins.[31] TGF-β plays a key role in this process by stimulating the activation of pro-fibrotic genes in myofibroblasts. This is achieved by increasing the levels of Smad2/3 while reducing the inhibitory Smad 6/7.[32] Moreover, fibroblasts infiltrating the remodeled heart after injury were found to have activated Smad 2/3.[33] TGF-β also increases the deposition of collagens I, III, and VI and enhances the expression of matrix proteins like ED-A fibronectin in myofibroblasts. This is achieved through the regulation of plasminogen activator inhibitors, tissue inhibitors of metalloproteinases, and pro-fibrotic cytokine expression.[32–34] Additionally, TGF-β inhibits the degradation of ECM proteins by controlling the expression of plasminogen activator inhibitor (PAI)-1 and tissue inhibitor of metalloproteinases (TIMPs). Furthermore, since TGF-β receptors are present in almost all inflammatory cells, TGF-β itself regulates the function of these cells during the fibrotic process.[35,36]

5.1. The role of TGF-β in the preclinical study of heart failure

In the preclinical study of heart failure, the production of TGF-β in the myocardium is significantly and consistently increased. This upregulation is linked to both enlargements in the heart and fibrosis. In the Coronary Artery Ligation experimental model of myocardial infarction, the regulation of TGF-β isoforms shows distinct patterns: TGF-β1 and β2 show initial increases, whereas TGF-β3 exhibit later and prolonged induction.[37,38] In the myocardium subjected to pressure overload during hypertrophic growth, there is a notable rise in the levels of TGF-β1.[39] The signaling of Angiotensin II plays a vital role in facilitating the increase of TGF-β in the myocardium affected by infarction and undergoing restructuring.[40,41] Angiotensin II causes Cardiac myocyte enlargement[42] and activates fibroblast propagation and the expression of extracellular matrix proteins[43] through AT1-dependent interactions. Abundant evidence confirms a clear association between the Renin-Angiotensin System (RAS) and TGF-β, suggesting that TGF-β functions in a subsequent step to Angiotensin II.[43] Stimulation with Angiotensin II leads to an increase in TGF-β mRNA and protein expression by both cardiomyocytes and cardiac fibroblasts.[44,45] Treatment with ACE inhibitors or AT1 receptor blockers significantly reduces TGF-β levels in enlarged heart[46] and infarcted heart.[41,47]

5.2. The connection between the RAS, TGF- β, and the β-adrenergic system in cardiac remodelling or in heart failure

Ang II as its predominant isoform, the renin-angiotensin-aldosterone system plays a significant role in various pathophysiological functions, including cardiac fibrosis.[48–50] Ang II, produced either systemically or locally, exerts its effects through two specific receptors: angiotensin type (AT) 1 and AT2. Through AT1, Ang II is involved in several biological processes, including cardiac fibroblast (CF) proliferation, migration, and activation, leading to the induction of extracellular matrix (ECM) protein synthesis and apoptosis.[51] The effects of Ang II on CF activation through AT1 are mediated via the activation of p38 MAPK, protein kinase C (PKC), and ERK cascades.[52,53] Moreover, Ang II interacts with TGF-β signaling in both cardiomyocytes and CFs, leading to the induction of cardiac hypertrophy and fibrosis (see Figure 3). The responsiveness of fibroblasts to Ang II is regulated by various mediators that influence AT receptor expression. For example, pro-inflammatory mediators like NF-κB, IL-1β, IL-6, and TNF-α can enhance fibroblasts' sensitivity to Ang II by promoting AT1 synthesis.[51–54] Recent research suggests that β-adrenergic signaling may also play a role in mediating the growth responses of the heart as a downstream mediator of Ang II/TGF-β.[55–57] Activation of the sympathetic nervous system plays a crucial role in the development of myocardial hypertrophy and heart failure, particularly by promoting cardiomyocyte hypertrophy (see Figure 3). While the hypertrophic effect of catecholamines on cardiac myocytes in vitro is solely mediated through the stimulation of β-adrenoceptors (ARs), in vivo, myocardial hypertrophy can also be induced by selective activation of β-ARs. In experiments with isolated perfused hearts, TGF-β overexpression enhances the isoprenaline-induced expression of hypertrophy-associated proteins, such as Atrial Natriuretic Factor (ANF). This effect specifically relies on the induction of ornithine decarboxylase (ODC), the rate-limiting enzyme of polyamine metabolism.[56] The findings suggest that β-adrenergic receptor (β-AR)-mediated growth responses might be involved downstream of Ang II/TGF-β1 in cardiac remodeling. The augmentation of β-adrenergic signaling by TGF-β might play a role in contributing to heightened catecholamine stimulation as stable hypertrophy transitions to heart failure. Thus, there may be a network connection between Ang II, TGF-β, and the β-adrenergic system in cardiac hypertrophy.

6. Conclusion

Myocardial infarction (MI) results in immediate cardiomyocyte death due to ischemia, leading to fibrosis and subsequent myocardial dysfunction, eventually culminating in heart failure. Fibrosis involves extracellular matrix (ECM) deposition, a process mediated by myofibroblasts formed from normal quiescent cardiac fibroblasts. TGF-β and its signaling pathways actively participate in this transformation. TGF-β is also responsible for cardiac fibrosis, cardiomyocyte apoptosis, and cardiac hypertrophy. The TGF-β signaling pathway involves binding to the TGF-βRII receptor, which recruits TGF-βRI receptors (ALK1-5). Canonical signaling triggers SMADs, which relocate to the nucleus for transcriptional reprogramming, fostering the creation of myofibroblasts and ECM generation. This progression ultimately results in cardiac fibrosis. In cases of myocardial infarction (MI), elevated TGF-β levels worsen myocardial injury. Efforts to target TGF-β signaling by modulating ALK1-5 receptor activity for therapeutic benefits have encountered limited success, prompting the need for additional exploration to devise potent treatments derived from the TGF-β signaling pathway, aiming to tackle cardiac dysfunction and heart failure.

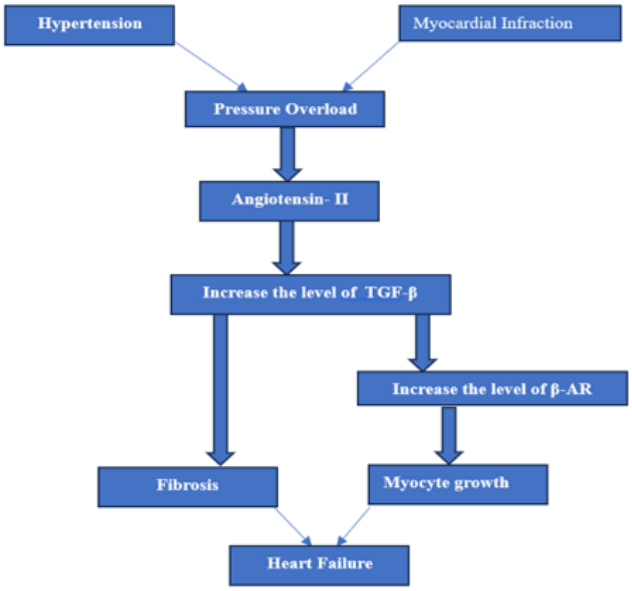

Figure 3: Flow diagram of the connection between the RAS, TGF-β, and the β -adrenergic system in cardiac fibrosis and heart failure.

6.1. Abbreviations

MI: Myocardial infarction, ECM: Extracellular Matrix, CFs: Cardiac Fibroblasts, αSMA: α-Smooth Muscle Actin, CHF: Congestive Heart Failure, FMT: Fibroblast-to-Myofibroblast Transition, MMP: Matrix Metalloproteinase, TGF-β: Transforming growth factor beta, PAI-1: Plasminogen Activator Inhibitor-1, TIMPs: Tissue Inhibitor of Metalloproteinases, CTGF: Connective Tissue Growth Factor, ALK: Activin-Like Kinase, IL: Interleukin, Col-I: Collagen I, NF-κB: Nuclear factor kappa B, TNF-α: Tumor necrosis factor-alpha.

AT 1: Angiotensin Type 1, AT2: Angiotensin Type 2, ACE inhibitors: Angiotensin-converting enzyme inhibitors.

ANF: Atrial Natriuretic Factor, β-AR: beta adrenergic receptor, RAS: Renin-Angiotensin-Aldosterone System.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Anil Kumar K. Prajapati, Research Scholar https://orcid.org/0000-0001-6068-0616

Gaurang B. Shah, Professor https://orcid.org/0000-0003-0769-3914

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