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Review article

Entanglement of GSK-3β, β-catenin and TGF-β1 signaling network to regulate myocardial fibrosis

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ABSTRACT

Nearly every form of the heart disease is associated with myocardial fibrosis, which is characterized by the accumulation of activated cardiac fibroblasts (CFs) and excess deposition of extracellular matrix (ECM). Although, CFs are the primary mediators of myocardial fibrosis in a diseased heart, in the traditional view, activated CFs (myofibroblasts) and resulting fibrosis were simply considered the secondary consequence of the disease, not the cause. Recent studies from our lab and others have challenged this concept by demonstrating that fibroblast activation and fibrosis are not simply the secondary consequence of a diseased heart, but are crucial for mediating various myocardial disease processes. In regards to the mechanism, the vast majority of literature is focused on the direct role of canonical SMAD-2/3-mediated TGF-β signaling to govern the fibrogenic process. Herein, we will discuss the emerging role of the GSK-3β, β-catenin and TGF-β1-SMAD-3 signaling network as a critical regulator of myocardial fibrosis in the diseased heart. The underlying molecular interactions and cross-talk among signaling pathways will be discussed. We will primarily focus on recent in vivo reports demonstrating that CF-specific genetic manipulation can lead to aberrant myocardial fibrosis and sturdy cardiac phenotype. This will allow for a better understanding of the driving role of CFs in the myocardial disease process. We will also review the specificity and limitations of the currently available genetic tools used to study myocardial fibrosis and its associated mechanisms. A better understanding of the GSK-3β, β-catenin and SMAD-3 signaling network may provide a novel therapeutic target for the management of myocardial fibrosis in the diseased heart.

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Abbreviations: AngII, angiotensin II; BAC, bacterial artificial chromosome; bHLH, basic helix-loop-helix; BMP, bone morphogenetic protein; CBP, CREB-binding protein; CF, cardiac fibroblast; Co-SMAD, co-mediator SMAD; CREB, cAMP-response element-binding protein; ECM, extracellular matrix; EMT, endothelial-mesenchymal transition; FSP1, fibroblast-specific protein 1; GRK2, G-protein coupled receptor kinase 2; GSK-3, glycogen synthase kinase 3; HF, heart failure; I/R, ischemia-reperfusion; I-SMAD, inhibitory SMAD; MEF, mouse embryonic fibroblast; MI, myocardial infarction; NF-κB, nuclear factor-kappa B; PI3K, phosphoinositide 3-kinase; PMCA4, plasma membrane calcium ATPase 4; R-SMAD, receptor-regulated SMAD; SIRT, Silent information regulator; SIS3, SMAD-3 inhibitor 3; SMAD, contraction of Sma and Mad (Mothers against decapentaplegic); TAK1, TGF-β-activated kinase 1; TCF21, transcription factor 21; TGF-β1, transforming growth factor beta 1; TNF, tumor necrosis factor; VICs, aortic valve interstitial cells; α-SMA, alpha-smooth muscle actin.

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1. Introduction

About 5.7 million adults in the United States have heart failure (HF) and half of the people who develop HF die within 5 years of diagnosis [1]. HF costs the nation an estimated $30.7 billion each year [2]. Clinical studies have identified a strong association of ongoing myocardial fibrosis and development of HF [3–5]. Almost every form of heart disease is associated with expansion and activation of the cardiac fibroblast (CF) compartment, suggesting fibrotic remodeling as a major cause of HF [6]. Circulating levels of the collagen I and III N-terminus propeptides in the blood plasma are considered strong predictive markers for HF [3–5]. Furthermore, approaches to prevent the excessive ECM turnover leads to a survival benefit in human HF patients. However, all these clinical studies are associative in nature and fail to answer the critical question of cause versus consequence. Thus, until very recently, there was a lack of direct evidence for the role of activated CFs and fibrosis in driving myocardial pathology. In the absence of direct evidence, CFs and fibrosis were often considered secondary effects of the disease process. The primary reason behind the lack of definitive evidence was the unavailability of well-characterized animal models to genetically manipulate the target gene specifically in the CFs. Thus, most of the existing knowledge about cardiac fibroblast biology was generated either from in vitro culture models or mouse models in which genetic manipulation was only made in cardiomyocytes (CM).

Recent studies from our lab and others have challenged this concept by demonstrating that fibroblast activation and fibrosis are not only the secondary consequences of a diseased heart but plays an essential role in mediating various myocardial disease processes [7–15]. Takeda et al. [8] were the first to demonstrate the driving role of CFs in the myocardial disease process. In this pioneering work, Takeda et al. [8], for the first time, used mouse lines in which Cre recombinase was driven by the periostin (*Postn*) promoter (CF–specific gene targeting) to demonstrate that CFs are essential for the adaptive response of the heart to pressure overload. Haploinsufficiency of the Krüppel-like factor 5 (*Klf5*) suppressed TAC (transaortic constriction)-induced cardiac fibrosis and hypertrophy, whereas CM-specific *Klf5* deletion did not lead to any cardiac phenotype. Furthermore, CF-specific *Klf5*-knockout mice developed severe heart failure when subjected to high-intensity pressure overload, suggesting a cardioprotective role of CFs. Thus, this report was the first to provide compelling evidence that CFs play a pivotal role in the myocardial pathophysiology. At this end, we employed periostin promoter driven cre model to demonstrate that CF-specific GSK-3β-knockout (KO) leads to hyperactivation of canonical TGF-β1-SMAD-3 signaling, resulting in adverse fibrotic remodeling and cardiac dysfunction in the ischemic heart. Acharya et al. [16] have developed a mouse model expressing Cre recombinase protein fused to two mutant estrogen receptor ligand-binding domains (MerCreMer) under the control of the endogenous *Tcf21* (transcription factor 21) gene locus. This mouse model has been successfully utilized for the fibroblast-specific gene manipulation and lineage tracing in multiple studies [12,15,17]. Studies with CF-specific genetically manipulated mouse models are listed in Table 1. Importantly, in several of these studies, the cardiac phenotype was only observed in CF-specific genetic manipulation and CM-specific genetic manipulation of the same gene did not lead to any cardiac phenotype, suggesting the driving role of CFs in mediating various myocardial disease processes [8,14]. Taken together, these studies have demonstrated successful utilization of CF-specific mouse models and also recognized the concept that CFs and fibrosis plays a driving role in the myocardial disease process. The emergence of these newly optimized CF–specific mouse models has led to an explosion of interest in fibroblast biology and fibrosis research in the past few years (Fig. 1).

In terms of a molecular mechanism, most studies have implicated the direct role of canonical SMAD-2/3-mediated TGF-β signaling as the primary mediator of fibrogenesis process. However, recent studies with newly optimized CF-specific mouse models have implicated the significant role of other signaling cascades in myocardial fibrosis or fibrosis in general [7,10,13,15,17]. As the new studies with CF-specific mouse models are emerging, it is becoming clear that the profibrotic pathways operate in a network, instead of being isolated entities. Recent studies have uncovered the multiple molecular interactions of the GSK-3β, β-catenin pathway with the canonical TGF-β1-SMAD-2/3 cascade to regulate the strength and duration of the profibrotic signal [7,10,18,19]. At the molecular level, several mechanisms have been proposed to define the biological effect of this signaling network, which includes: i)

Table 1
Cardiac studies with CF-specific genetically manipulated mouse models.

Target (gene/pathway)	Cre driver promoter	Type	Reference	Phenotype
Kruppel like factor 5 (Klf5)	Periostin	Injury inducible deletion	[8]	CF–specific *Klf5* deletion ameliorates TAC-induced cardiac hypertrophy and fibrosis. By contrast, CM-specific Klf5 deletion did not alter the hypertrophic responses.
β-Catenin	Col1a2	Tamoxifen- inducible deletion	[10]	CF-specific deletion of β-catenin impairs wound healing and decreases cardiac performance.
p53	Col1a2	Tamoxifen-inducible deletion	[11]	Loss of p53 in cardiac fibroblasts severely decreases the formation of fibroblast-derived endothelial cells, reduces post-infarct vascular density and worsens cardiac function.
GSK-3β	Periostin	Injury inducible deletion	[7]	Fibroblast-specific deletion of GSK-3β leads to hyperactivation of SMAD-3 resulting in excessive fibrotic remodeling and cardiac dysfunction after myocardial infarction.
GSK-3β	Col1a2	Tamoxifen-inducible deletion	[7]	FB-specific deletion of GSK-3β leads to hyperactivation of SMAD-3 resulting in excessive fibrotic remodeling and cardiac dysfunction after myocardial infarction.
Muscleblind-like protein 1 (MBNL1)	$Tcf21^{MCM}$ and $Postn^{MCM}$	Tamoxifen-inducible overexpression and deletion	[17]	MBNL1 overexpression promotes the transformation of fibroblasts into myofibroblasts. Conversely, deletion of MBNL1 abrogates transformation and impairs the fibrotic phase of wound healing in mouse models of myocardial infarction and dermal injury.
Plasma membrane calcium pump (PMCA4)	Periostin	Injury inducible deletion	[14]	Specific deletion of *Pmca4* in CFs reduces TAC-induced hypertrophy and cardiac dysfunction. Importantly, these phenotypes were not observed in CM-specific PMCA4 KOs.
Activated fibroblast	Periostin	Inducible targeting cell killing	[9]	Ablation of activated CFs (periostin expressing) results in significantly reduced cardiac fibrosis and improved cardiac function in response to Ang II and myocardial infarction.
Activated fibroblast	Periostin	Inducible targeting cell killing	[12]	Deletion of $periostin^{(+)}$ activated fibroblasts (myofibroblasts) reduces collagen production and scar formation after MI.
G protein-coupled receptor kinases (GRK2)	Col1a2	Tamoxifen-inducible deletion	[13]	Cardiac fibroblast GRK2 deletion enhances contractility and remodeling following ischemia/reperfusion injury.
p38	$Tcf21^{MCM}$ and $Postn^{MCM}$	Tamoxifen-inducible overexpression and deletion	[15]	CF-specific deletion of p38 attenuates myofibroblasts differentiation and fibrosis. This phenotype was also reproduced in a dermal wound healing model. Conversely, transgenic mice with CF-specific activation of p38 develops interstitial and perivascular fibrosis in multiple organs.

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