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MINIREVIEWS

Epigenetic regulation in cardiac fibrosis

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Abstract

Cardiac fibrosis represents an adoptive response in the heart exposed to various stress cues. While resolution of the fibrogenic response heralds normalization of heart function, persistent fibrogenesis is usually associated with progressive loss of heart function and eventually heart failure. Cardiac fibrosis is regulated by a myriad of factors that converge on the transcription of genes encoding extracellular matrix proteins, a process the epigenetic machinery plays a pivotal role. In this mini-review, we summarize recent advances regarding the epigenetic regulation of cardiac fibrosis focusing on the role of histone and DNA modifications and non-coding RNAs.

Key words: Cardiac fibrosis; Epigenetics; Endothelial cell; Fibroblast

Core tip: Cardiac fibrosis contributes to the increased accidence of sudden cardiac death, heart failure and arrhythmia. The molecular mechanisms underlying cardiac fibrosis remain obscure. Seminal studies have revealed complex pathways associated with cardiac fibrosis. How histone/DNA modifying enzymes and microRNAs fine-tune these events are actively pursued by investigators. This review provides an overview on recent advances regarding the epigenetic regulation of fibrosis.

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INTRODUCTION

The term "epigenetics" was coined in 1953 by Waddington CH and the following decades have witnessed great progress achieved in this field[1]. By consensus epigenetics is defined as stably inheritable phenotypes stemmed from changes of chromatin

without alterations in primary DNA sequences[2]. The nucleosome, the fundamental unit of eukaryotic chromatin, is composed of an octamer of four core histones (H2A, H2B, H3, H4) surrounding 147 bp of DNA. The amino-terminal tails of histones serve as a platform for diverse posttranslational modifications including methylation[3], acetylation[4,5], ubiquitination[6,7], O-linked N-acetylglucosamine (GlcNAc)[6], phosphorylation[5] and sumoylation[8] on specific residues catalyzed by histone-modifying enzymes. These covalent modifications are dynamic[7] and modulate gene regulation in a combinatorial manner upon exposure to different stimulus[5,9,10]. Histone modifications manipulate gene activation/repression by influencing the accessibility of transcriptional factors to chromatin or by recruiting and/or occluding of non-histone proteins, mostly co-factors, in contrast to promoter CpG island methylation for gene silencing[11]. Proper function of the epigenetic machinery, or lack thereof, is implicated in mammalian development[12], carcinogenesis[4] and cardiovascular diseases (CVDs).

Fibrosis or scarring in different organs, including the lungs[13], the kidneys[14], the liver[15], and the heart, is characterized by deposition of extracellular matrix (ECM) components, such as collagens, laminins and fibronectin, caused by diverse insults. Fibrosis can be deemed as erroneous ECM "turnover", *i.e.*, imbalance between ECM production (increased) and ECM degradation (reduced). Collagen is the most abundant component of the ECM in the heart including five types (types Ⅰ, Ⅲ, Ⅳ, Ⅴ and Ⅵ) identified in the myocardium. Among these, types Ⅳ and Ⅴ collagens are components of the basement membrane, while types Ⅰ and Ⅲ collagen are the main constituents of the ECM[16,17]. A number of different cell types in the heart are responsible for collagen synthesis: All cardiac collagen types are produced by fibroblasts, whereas endothelial cells synthesize all types except type Ⅵ. Degradation of collagen is mediated by both intracellular and extracellular pathways, the latter involving matrix metalloproteinase (MMPs) and tissue inhibitors of MMPs (TIMPs)[18].

Fibrosis is an evolutionarily conserved process that serves to facilitate host defense and wound healing. Deregulated fibrosis, however, is invariably associated with loss of organ function. For instance, cardiac fibrosis is correlated with elevated mortality in dilated cardiomyopathy[19], which is the most common cardiomyopathy globally and directly correlates with sudden cardiac death, heart failure and arrhythmia[20-22]. Despite numerous progress made in identifying molecular mechanisms and/or factors that contribute to hypertrophy over the past decades, the mechanistic underpinnings of cardiac fibrosis is poorly understood. Although an extensive body of evidence suggests that cardiac fibroblast may participate in the pathogenesis of cardiac fibrosis, other cell types involved remain to be determined, especially endothelial cells and macrophages[23-26]. This review summarizes our current understanding of the involvement of epigenetic machinery in cardiac fibrosis and attempts to identify some of the previously unaddressed questions that require further investigation. We only briefly discuss the pathways and transcriptional factors involved in cardiac hypertrophy because models used to study cardiac hypertrophy and fibrosis often overlap and excellent reviews on cardiac hypotrophy are available elsewhere[27,28].

SIGNALING CASCADE IN CARDIAC FIBROSIS

Cardiac fibrosis usually appears in patients with hypertrophic cardiomyopathy, hypertension and/or diabetes mellitus, suggesting that cardiac fibrosis may be secondary to these conditions[29-33]. Myocardial infarction (MI), aging, and mutation in cardiac fatal genes such as Mhy7, Troponin T and BNP can also trigger cardiac fibrosis[34-38]. Studies in animal models have revealed a convoluted network of signaling cascades and transcriptional factors. A body of evidence suggests that the calcineurin–nuclear factor of activated T cells (NFAT) circuit, the β-adrenergic–receptor signaling pathway, and the IGF-Akt signaling pathway all contribute to cardiac fibrosis by modulating the activities of such transcription factors as serum response factor, myocyte enhancer factor (MEF), and kruppel-like factor during development and in response to pathophysiological stimuli[29,30,39-43]. Meanwhile, evidence from different groups shows that extracellular-regulated kinases Erk1 and Erk2 (Erk1/2), downstream effectors of the mitogen-activated protein kinase cascades, play a prominent role in cardiac hypertrophy and fibrosis. ERK activation mediated by auto-phosphorylation at Thr188 enhances TAC-induced cardiac hypertrophy and fibrosis[26,39,40].

TGF-β is believed to play the most central role in cardiac fibrosis based on the fact that TGF-β is activated in different models of cardiac fibrosis, which in turn facilitates the synthesis of ECM proteins and contributes to endothelial-mesenchymal transition (EndMT)[33,44-47]. Meanwhile, TGF-β represses ECM degradation by suppressing the expression of MMPs[48] and by augmenting the levels of protease inhibitors such as plasminogen activator inhibitors and TIMPs[44,49]. TGF-β drives fibrotic process by binding to the heterodimeric membrane receptor, which results in phosphorylation and subsequently nuclear translocation of SMAD family of transcription factors[50]. Thus, inhibition of the specific cellular receptors, kinases and other mediators involved in the activation of TGF-β pathway may provide effective therapeutic targets for cardiac fibrosis.

HISTONE MODIFYING ENZYMES IN CARDIAC FIBROSIS

Numerous enzymes that catalyze specific residues

of core histones have been implicated in cardiac hypertrophy and fibrosis. For instance, p300, a histone acetyltransferase, accelerates left ventricular remodeling after MI[9,10]. Inactivation of Ezh2, the catalytic subunit of the Polycomb repressor complex 2 responsible for histone H3K27 methylation (H3K27me3), induces cardiac fibrosis[3,51]. These histone modifying enzymes influence cardiac fibrosis *via* the interaction with sequence-specific transcriptional factors to manipulate fibrosis-associated gene activation or repression. For example, p300 and GATA-4 synergistically activate GATA-4-dependent transcription of the *ET-1* and *ANF* genes[10] and Ezh2-mediated H3K27me3 on the promoter zones directly represses fetal gene expression[51].

Trivedi *et al*[52] show that the mice deficient in Hdac2, a class Ⅰ histone deacetylase (HDAC), are resistant to isoproterenol-induced cardiac hypertrophy and fibrosis. Mechanistically, Hdac2 deletion leads to the derepression of inositol polyphosphate-5-phosphatase f (Inpp5f). Consequently, glycogen synthase kinase 3β (GSK3β) is constitutively activation thereby causing the inactivation of cardiac fetal genes[52]. However, the authors did not address whether fibrosis is independent of GSK3β or GSK3β is responsible for both cardiac hypertrophy and fibrosis. Olson and colleagues report that class Ⅱ HDACs interact with MEF2 and repress its activity, acting as signal-responsive repressors of transcription of cardiac fetal genes[53]. This observation is verified by several complementary studies. First, inhibition of class Ⅰ and Ⅱ HDACs by trichostatin A (TSA) protects the mammalian heart from pressure overload-induced cardiac fibrosis and attenuates hypertrophy-associated protein expression[51]. Zhang *et al*[53] show that calmodulin binding transcription activator 2 (CAMTA2), transcriptional coactivator for Nkx2-5, is repressed by an interaction with class II HDAC. Activation of PKC/PKD signaling leads to phosphorylation of class Ⅱ HDACs, creating docking sites for 14-3-3 proteins to exclude HDACs from the nucleus and relieving the inhibition of CAMTA2, which proceeds to activate cardiac hypertrophy and fibrosis[54]. Recently, our laboratory has identified a histone H3K4 trimethylation-dependent pathway that contributes to cardiac fibrosis. Specifically, we have discovered that SET1, an H3K4me3 modifying enzyme, induces the transcription of endothelin (ET-1) in vascular endothelial cells. Once released into the circulation, ET-1 then serves as an angiocrine factor to induce cardiac fibrosis in response to chronic angiotensin Ⅱ infusion or mechanic stretch[55].

Histone modifying enzymes can communicate with each other or other branches of the epigenetic machinery to modulate cardiac fibrosis. A study by Eom *et al*[56] further highlights the role of crosstalk between HDACs and HATs and post-translational modifications of these proteins in cardiac hypertrophy and fibrosis. These authors propose that the acetylation status of HDAC2 and by extension its activity in regulating cardiac fibrosis is controlled by p300/CBP-associated factor and HDAC5[56]. Weng *et al*[57] have found that the H3K4 methyltransferase complex (COMPASS) can forge a dialogue with chromatin remodeling proteins BRG1 and BRM to transactivate ET-1, which in turn invokes a pro-fibrogenic response in the heart; depletion of either COMPASS or BRG1/BRM alleviates Ang Ⅱ-induced cardiac fibrosis in mice[57].

Overall, although there is abundant evidence supporting a role for histone modifying enzymes in cardiac fibrosis, the dataset appears to be fragmental with many outstanding issues awaiting resolution. For instance, what is the genome-wide role for any given histone modifying enzyme in cardiac fibrosis? How are different histone modifying enzymes are recruited to the chromatin? Is there a unique histone signature that defines cardiac fibrosis? How to differentiate histone modifications and non-histone protein modifications? These lingering questions will have to be addressed in future studies.

MICRORNA INVOLVED IN CARDIAC FIBROSIS

MicroRNAs (miRNAs), usually 20-30 nucleotide in length, are one major form of small non-coding regulatory RNAs that also include short interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs)[58]. In general, miRNAs act to silence gene expression by targeting specific mRNA at the posttranscriptional level. MiRNA expression profiles are widely used in cancer classification, diagnosis, therapy and prognosis[59], but mounting evidence shows that circulatory miRNAs, such as miR-29a and miR-21, may also be used as a diagnostic marker for cardiac fibrosis[60,61]. Numerous studies aimed to investigate the potential impact of miRNAs in the heart have demonstrated a key role for miRNAs in cardiac fibrosis in response to multiple injury stimulus.

It has been demonstrated that mice depleted of miR-212/132[62], miR-25[61,63], or miR-29[61] are protected from pressure-overload-induced cardiac fibrosis while miR-101[64] and miR-24[65] regulate fibrosis after MI. Knockdown of miR-133a[66] and cardiac-specific overexpression of miR-195 induces spontaneous cardiac hypertrophy and fibrosis. Thum *et al*[26] have shown that miR-21 silencing in fibroblasts decreases ERK-MAP kinase activity and curbs interstitial fibrosis. Follow-up studies have shown several different but not mutually exclusive mechanisms underlying the pro-fibrotic effect of miR-21. For instance, Roy *et al*[67] have found that miR-21 regulates fibroblast MMP-2 *via* targeting phosphatase and tensin homologue (PTEN). Alternatively, miR-21 also partly influences TGF-β-mediated EndMT *via* the PTEN/Akt pathway[68]. Conceivably, miR-21 might elicit a range of different pathways responsible for cardiac fibrosis at multiple levels. Cardiac-specific miR-208, transcribed from the a-myosin heavy chain (*a-MHC*) gene locus, regulates

stress-dependent fibrosis by negatively modulating expression of thyroid hormone receptor associated protein 1[69]. The role of miR-208 in cardiac fibrosis is further supported by the observation that inhibition of miR-208 by antisense oligonucleotide improves cardiac function and attenuates remodeling[70].

Sometimes miRNAs and their targets form feedback (forward or backward) loops to manipulate downstream pathophysiological events. For instance, da Costa Martins *et al*[41] have reported that pressure overload activates the calcineurin/NFAT axis to stimulate the expression of miR-199b. MiR-199b, once transcribed, targets dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a (Dyrk1a), which activates NFAT by phosphorylating and thereby excluding NFAT from the nucleus. Conceivably, reduced levels of Dyrk1a as a result of miR-199b activation will release NFAT from the cytoplasm, which will lead to increased expression of miR-199b[41].

Cardiac- and skeletal muscle–enriched miR-22 regulates cardiomyocyte hypertrophy and cardiac fibrosis in response to stress *via* targeting Sirt1 and Hdac4[71], supporting the possibility that microRNAs could communicate with other epigenetic factors by directly influencing their abundances. Meanwhile, miRNAs could also suppress fibrotic genes transcription. MiR-133 and miR-30 could reduce production of collagens by directly down-regulating connective tissue growth factor (CTGF) through specific binding to its 3′ untranslated region (3′-UTR)[72]. MiR-101a can restrain interstitial fibrosis in post-infarct rats by targeting c-Fos to repress downstream effectors of TGF[64]. Intriguingly, miR-18/19 and miR-34a dampen age-related cardiac remodeling by negatively regulating the CTGF and thrombospondin-1[73] expression and directly targeting protein phosphatase 1 nuclear-targeting subunit[38], respectively.

DNA METHYLATION IN CARDIAC FIBROSIS

Patterns of mammalian DNA methylation vary in time and space. Similar to histone modifications, levels of DNA methylation are dependent on the balance of methyltransferases (DNMTs) and demethylases. In general, DNA methylation modulates gene transcription *via* changing chromatin conformation and/or influencing the interplay between DNA and proteins[74,75]. Based on the structural and functional differences, the enzymes responsible for DNA methylation identified so far include two categories: DNMT1 and DNMT3a/3b. DNMT1 is responsible for maintenance of DNA methylation using hemimethylated DNA strand as substrate[76], while DNMT3a/3b catalyze de novo DNA methylation operating on two un-methylated "clean" DNA strands[77].

A recent investigation by Xu *et al*[78] showed that TGF-β induces aberrant methylation of RASAL1 (a Ras-GTPase) promoter and subsequently down-regulation of RASAL1, resulting in elevated Ras-GTP activity to enhance EndMT and cardiac fibrosis. Mechanistically, this process is associated with ten eleven translocation family enzyme (TET3)-mediated RASAL1 promoter hydroxymethylation (or demethylation) and reversal of EndMT[78]. A recent study indicates that mice with cardiac-specific knockout of DNMT3b, predominantly expressed in the heart, exhibit extensive interstitial fibrosis and myo-sarcomeric disarray[79]. Further exploration suggests that dysregulation of DNA methylation-induced alternatively spliced myh7 transcript may be accountable for these phenotypes, which is similar to the aforementioned effects of miR-208 derived from myh6[60].

Methylation of DNA is not an isolated event but instead forges crosstalk with non-coding RNAs and histone modifications. For instance, Wang *et al*[80] show that lysine demethylase (LSD1) interacts and demethylates DNMT1 to increase DNMT1 stability, indicating that LSD1 may coordinately modulate histone and DNA methylation by acting directly on both histones and Dnmt1. Meanwhile, DNMT3a/b are recruited to tri-methylated H3-K9 positions *via* interacting with heterochromatin protein 1 (HP1a)[81], synergistically silencing transcription at the pericentric satellite repeats[82]. Whether these interactions and/or cooperations function in the heart remain elusive. Dakhlallah *et al*[83] demonstrated that in lung fibroblasts from patients with idiopathic pulmonary fibrosis, there was a negative correlation between increased DNA methylation-induced repression of miR-17-92 cluster and DNMT1 expression. Several miRNAs from the miR-17-92 cluster, most prominently miR-19b, directly regulated DNMT1 expression by targeting seed sequences in the 3-UTR in a negative feedback loop. To further study whether this system function *in vivo*, Dakhlallah *et al*[83] use a classical murine model of pulmonary fibrosis. After the initiation of fibrosis, treatment with 5-aza-2-deoxycytidine in bleomycin-challenged mice alleviated lung fibrosis by decreasing *DNMT-1* gene expression while restoring miR-17-92 cluster expression[83]. These results are consistent with findings from Bechtel *et al*[84] that long-term TGFβ1 exposure induced RASAL1 hypermethylation depends on DNMT1, which is intimately linked to the perpetuation of kidney fibroblast activation and renal fibrosis. More importantly, 5-aza-2-deoxycytidine attenuated folic acid-evoked renal fibrosis by reducing DNMT1–induced methylation of RASAL1[84]. In the heart, whether miRNAs regulate DMNTs in a similar fashion needs to be addressed in the future study.

FUTURE DIRECTIONS IN CARDIAC FIBROSIS

The past two decades have seen a sea of groundbreaking discoveries in epigenetics fueling the research on CVD[85-88]. This mini-review only provides a snapshot

of how research on cardiac fibrosis has benefitted from epigenetic theories and tools. Many of the factors discussed here are enzymes, the activities of which can be manipulated *via* small-molecule compounds for therapeutic interventions. For instance, HDAC inhibitors have been successfully used to treat certain forms of cancer in the clinic[89,90]. The recent elucidation of the human functional genome has re-affirmed the notion that epigenetic regulation is the bedrock of human diseases[91]. In perspective, continued effort in investigating the epigenetic mechanisms underlying cardiac fibrosis will eventually bring cure to this debilitating pathology.

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