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Review

Epigenetic regulation of cardiac fibrosis

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ABSTRACT

Cardiac fibrosis is characterized by excessive extracellular matrix accumulation that ultimately destroys tissue architecture and eventually abolishes normal function. In recent years, despite the underlying mechanisms of cardiac fibrosis are still unknown, numerous studies suggest that epigenetic modifications impact on the development of cardiac fibrosis. Epigenetic modifications control cell proliferation, differentiation, migration, and so on. Epigenetic modifications contain three main processes: DNA methylation, histone modifications, and silencing by microRNAs. We here outline the recent work pertaining to epigenetic changes in cardiac fibrosis. This review focuses on the epigenetic regulation of cardiac fibrosis.

Contents

1. Introduction

Most cardiac diseases are associated with cardiac fibrosis [1]. Cardiac fibrosis is often present in end-stage heart failure and is caused by various factors, such as ischemia, pressure overload, and so on [2,3]. Cardiac fibrosis, is a scarring process which is characterized by fibroblast accumulation and excess deposition of extracellular matrix (ECM) proteins, which leads to distorted organ architecture and function [4,5]. It is worth noting that cardiac myofibroblasts are characterized by α-smooth muscle actin (α-SMA) expression and appear to play a major role in the pathogenesis of fibrosis by secreting numerous cytokines, growth factors, and ECM proteins [6]. Excessive collagens, produced and deposited in the heart, lead to cardiac fibrosis. Cardiac fibroblasts are at the heart of cardiac function and are the principal determinants of cardiac fibrosis [7,8]. Activated cardiac fibroblasts are the major source of ECM. It is currently believed that along with these cellular key players, a number of regulatory factors also have substantial effects on fibrosis and may be responsible for inter-organ variability of fibrotic manifestations [9]. Cardiac fibrosis impedes both contraction and relaxation and impairs electrical coupling of cardiomyocytes, it is the important pathological basis for heart failure, fatal arrhythmia and cardiac sudden death [10]. Thus, prevention of cardiac fibrosis is an

Abbreviations: ECMs, extracellular matrix; α-SMA, α-smooth muscle actin; TGF-β1, transforming growth factor-β1; Ang-II, angiotension II; DNMTs, DNA methyltransferases; 5-Aza-dC, 5-Aza-2′-deoxycytidine; EZH2, Enhancer of zeste homolog 2; HDAC, histone deacetylases; HAT, histone acetyltransferase; HMT, histone methyltransferase; TSA, Trichostatin A; MiRNA, MicroRNA; IGF-IIR, insulin-like growth factor-II receptor; PPARγ, Peroxisome proliferator-activated receptor γ; MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; PI3K, Phosphoinositide 3-kinase inhibitor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

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important therapeutic target to treat various heart diseases. However, there is no therapy for cardiac fibrosis in general, largely because the underlying basis of cardiac fibrosis is unclear.

Epigenetics refers to heritable changes in gene expression, which are not a result of changes in the DNA sequence, but rather due to alterations related to the packaging or translation of genetic information [11,12]. These alterations in gene expression are achieved by changes in the tertiary structure of the DNA strand and thus the accessibility of the DNA for molecules which effect gene expression [13]. Even though epigenetic variability of genetic information is part of normal development and differentiation it also underlies exogenous stimuli [14]. Important alterations encompassing epigenetic changes are DNA methylation, histone modifications, microRNAs (miRNA) [15–17]. These modifications result in a variable expression of identical genetic information based on the surrounding conditions leading to enhanced expression or silencing of genes [18].

Recent evidence has suggested that differentiation of resident fibroblasts occurs in response to TGF-β1, Ang-II, which are all likely to play key roles in this process [19]. Many genes have been demonstrated to be involved in the pathogenesis of cardiac fibrosis [20,21]. Gene expression changes are quite dramatic and involve large numbers of genes, generally around the order of a few thousand differentially expressed genes. Epigenetic regulation of gene expression plays a large role in determining cellular identity [22,23]. The identification of the epigenetic regulators recruited by transcription factors to mediate gene expression changes during cardiac fibroblasts activation and proliferation. Emerging data suggest that these epigenetic modifications also impact on the development of cardiac fibrosis [24] (Fig. 1).

Despite intensive research and remarkable advances in our understanding of epigenetics, the mechanisms and regulators that trigger pathological epigenetic reprogramming in cardiac fibrosis remains poorly understood. The study of these alterations represents a fascinating avenue to further elucidate the underlying mechanisms of cardiac fibrosis. This review provides an introduction to epigenetic mechanisms such as DNA methylation, histone modifications and miRNA modifications as well as an outline of how these changes pertain to the development of cardiac fibrosis.

2. DNA methylation and cardiac fibrosis

DNA methylation plays an essential role in several epigenetic phenomena including genomic imprinting, X-chromosome inactivation, gene silencing and so on [25–27]. In mammalian DNA, the fifth position carbon of cytosine within cytosine guanine (CpG) dinucleotides can become methylated [28]. CpG dinucleotides exist throughout the genome and are usually heavily methylated and thus impede transcription of genes at those sites [29]. While these CpGs are relatively rare in the genome as a whole, they are often clustered in short stretches of DNA of 300–3000 base pairs (CpG islands) [30]. Most CpG islands are sites of transcription initiation [31]. CpG islands are estimated to occupy 50–70% of human gene promoters and under most conditions, methylation of CpG islands at gene promoters is associated with gene silencing [32]. CpG islands are also present outside of genes, primarily in conserved intergenic regions [33]. The function of these CpG islands is not well established [34]. Because their methylation pattern resembles that of CpG island promoters, it has been suspected that they may be part of distal regulatory regions and enhancers.

DNA methylation is catalyzed by at least three different DNA methyltransferases (DNMTs): DNMT1, DNMT3A and DNMT3B [35]. DNMT1 is primarily known as a maintenance DNMT having a greater specificity for hemi-methylated DNA and is important for maintaining the DNA methylation patterns during replication [36]. DNMT3A and 3B are considered primarily de novo methyltransferases [37]. While the enzymes that carry out DNA methylation have been relatively well characterized, much less has been understood regarding how DNA undergoes demethylation. Cytosine methylation is enzymatically driven by a transfer of a methyl group from the methyl donor S-adenosylmethionine to the carbon-5 position of cytosine [38]. Methylation of cytosine in CpG islands is associated with transcriptional repression by impeding the binding of transcription factors to *cis*-DNA binding elements present in the promoter regions of genes [39]. During this process, methyl groups of methylated CpG dinucleotides intercalate into the major groove of the DNA helix [40]. In normal tissue CpG islands are more commonly unmethylated, allowing for gene transcription to take place [41]. However, in fibrosis, the reverse can be seen with abnormal DNA methylation of CpG islands that impede transcription of important genes [42,43]. Methylation of DNA can interfere with the accessibility and recruitment of transcription factors to their DNA-binding [44]. This mechanisms lead to the transcriptional silencing of the methylated genes [45]. Recently, a family of methyl-CpG binding proteins has also been recognized that specifically bind to methylation marks, thereby contributing to transcriptional repression by recruiting histone modifying proteins [46]. These methyl-CpG binding proteins are able to recruit large protein complexes which control the accessibility of DNA through modification of the chromatin structure [47].

Phenotypic alterations during cardiac fibroblast proliferative and phenotypical characteristics may be explained by exposure to adverse environmental conditions [48]. Selenium deficiency led to reactive

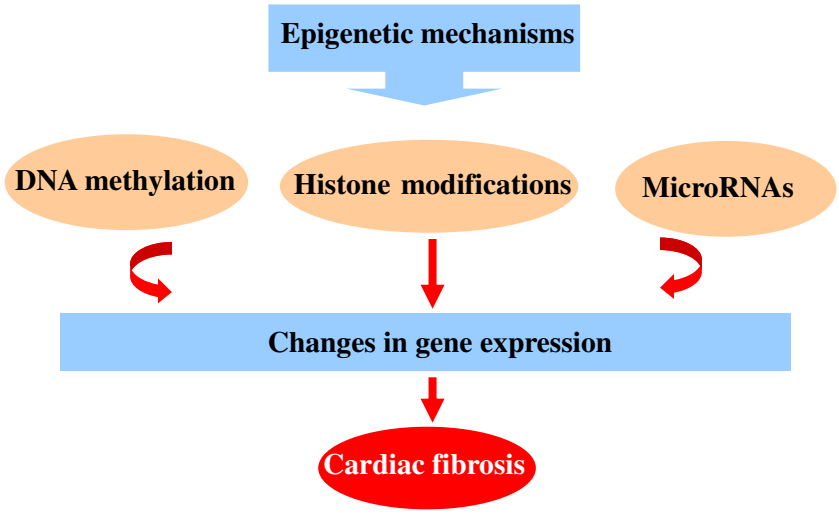

Fig. 1. Epigenetic modifications play a key role in the development of cardiac fibrosis. Important alterations encompassing epigenetic changes are DNA methylation, histone modifications, microRNAs.