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Review

Epigenetic mechanisms underlying cardiac degeneration and regeneration ☆

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ABSTRACT

Epigenetic modifications which are defined by DNA methylation, histone modifications and microRNA mediated gene regulation, have been found to be associated with cardiac dysfunction and cardiac regeneration but the mechanisms are unclear. MicroRNA therapies have been proposed for cardiac regeneration and proliferation of stem cells into cardiomyocytes. Cardiovascular disorders are represented by abnormal methylation of CpG islands and drugs that inhibit DNA methyltransferases such as 5-methyl Aza cytidine are under trials. Histone modifications which include acetylation, methylation, phosphorylation, ADP ribosylation, sumoylation and biotinylation are represented within abnormal phenotypes of cardiac hypertrophy, cardiac development and contractility. MicroRNAs have been used efficiently to epigenetically reprogram fibroblasts into cardiomyocytes. MicroRNAs represent themselves as potential biomarkers for early detection of cardiac disorders which are difficult to diagnose and are captured at later stages. Because microRNAs regulate circadian genes, for example a nocturnin gene of circadian clockwork is regulated by miR122, they have a profound role in regulating biological clock and this may explain the high cardiovascular risk during the morning time. This review highlights the role of epigenetics which can be helpful in disease management strategies.

1. Introduction

Epigenetics has emerged as one of the important phenomena behind cardiac disorders and includes small non-coding RNAs like microRNAs, DNA methylation and histone modifications (Fig. 1). Epigenetics refers to changes in gene expression which are not due to change in the DNA sequence but attributed to chromatin alteration or packaging which changes the accessibility of DNA [1]. Epigenetic changes often are a result of gene environment interactions or surrounding conditions [2] leading to enhanced/decreased expression or silencing of genes e.g. in the case of diabetes, hypertension and obesity. DNA methylation are the most studied epigenetic modifications and mainly involve methylation of CpG islands in the promoter of genes. Diseased states such as cardiovascular disorders are represented by abnormal methylation of the CpG islands consequently leading to modifications in gene expression [3]. Movassagh et al. [4] have identified different patterns of DNA methylation in heart failure patients. Recently, homocysteine which is a marker for cardiovascular disease has been shown to play a crucial role in epigenetics [5,6]. Hyperhomocysteinemia has been reported to be associated with alteration in the DNA methyltransferase activities involving methionine, folic acid and cystathionine B synthase. DNA methylations can be transferred mitotically to next generations through cell divisions as they are quite stable. Histone modifications are another mechanisms to altered gene expression via chromatin remodeling by histone acetyltransferases or deacetylases which change the DNA accessibility. The role of histone regulatory proteins in heart disease has been demonstrated by Backs and Olson [7]. Furthermore, RNA based mechanisms like microRNAs and non-coding RNAs are also involved in altering gene expression of target genes and are studied extensively in cardiac disorders [8–11]. MicroRNAs have also been implicated in stem cell therapies e.g. miR133a has been reported to be involved in the differentiation of cardiogenic mesenchymal stem cells by targeting epidermal growth factors [12]. This review aims to elucidate epigenetic mechanisms underlying cardiac disorders and how these epigenetic mechanisms can be beneficially introduced for cardiac therapies.

Abbreviations: ABCA1, ATP binding cassette transporter A1; CAD, coronary artery disease; CREBP, cAMP (adenosine 3′5′ cyclic monophosphate) response element-binding protein; CVD, cardiovascular disease; DNMT, DNA methyltransferase; DOTIL, disruption of telomeric silencing protein; FHL1, four and a half LIM domains 1; GNASAS, guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide; HAT, histone acetyl transferase; HDAC, histone deacetylase; HF, heart failure; HSD11B2, hydroxysteroid (11-beta) dehydrogenase 2; IL-10, interleukin 10; INSIGF, insulin induced gene; JMJD, Jumonji domain; LIM1, Lin11/Isl1/Mec3 transcription factors; LINE-1, long interspersed nucleotide elements; MEG3, maternally expressed gene 3; MI, myocardial infarction; MTHFR, methylenetetrahydrofolate reductase; SRF, serum response factor; TBX5, T box 5; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome; VCAM-1, vascular cell adhesion molecule 1.

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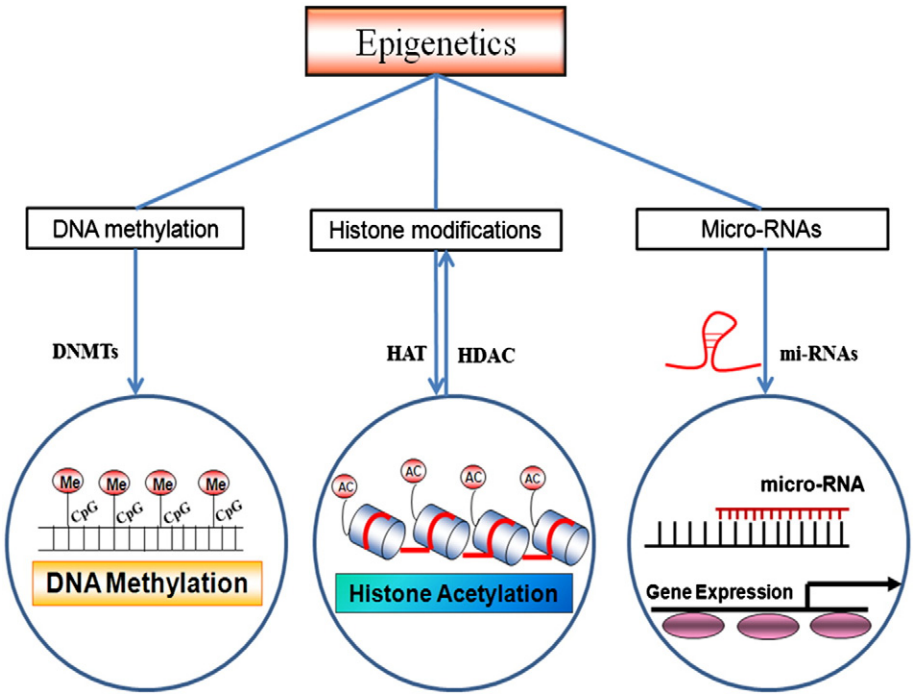

Fig. 1. Epigenetic mechanisms and role of DNA methylation, histone modification by acetylation and methylation and post-transcriptional control by microRNA. DNA Methyltransferase is involved in gene methylation. HAT and HDAC are involved in histone acetylation and chromatin remodeling. microRNAs are involved in post-transcriptional control of the genes.

2. Role of epigenetics in cardiac degeneration

2.1. Role of DNA methylation

The pathogenesis of cardiovascular disease is well studied but the role of epigenetics still needs to be explored. The epigenetic modifications in cardiomyopathy have been summarized in Table 1. Many studies have demonstrated with the help of animal models that DNA methylation plays an important role in atherosclerosis and cardiovascular disease [13]. DNMTs (DNA methyltransferases) and MTHFR (methylenetetrahydrofolate reductase) represent two important genes in DNA methylation and mice deficient in these genes show hypomethylation of their DNA [13,14]. Chen et al. have shown the formation of aortic fatty streaks in MTHFR deficient mice. In leucocytes of DNMT deficient mice, there is an increase in the expression of inflammatory mediators which represent hypomethylation [15]. In peripheral blood leukocytes, there are changes in DNA methylation in ApoE −/− mice, which lead to atherosclerosis promotion and dysregulation of inflammation [14].

The DNA methylation status is also affected by dietary folate and vitamin levels and providing these dietary supplements to female mice before conception causes higher methylation of CpG islands in the offspring [13]. Due to this the offspring has a characteristic phenotype of brown coat color, insulin resistance, cancers, lengthened life span and reduced susceptibility to obesity. The aortas of ApoE knockout mice represent a decrease in DNA methylation which can be detected at 4 weeks and any histological changes associated with atherosclerosis can be determined [16]. The estrogen receptors α and β show increased methylation at the promoter region in atherosclerotic tissues and the methylation of estrogen receptor increases with age. There is hypermethylation of the HSD11B2 gene, and loss of global methylation of genomic content in blood leukocytes of hypertensive patients [17]. In another report it was shown that in patients with atherosclerotic cardiovascular disease, there is lower DNA methylation in blood leukocytes [18]. Baccarelli et al. [19] have shown that incidence and mortality from ischemic heart disease and stroke can be predicted by lower LINE-1 (long interspersed nucleotide elements) methylation in peripheral blood leukocytes. LINE-1 have been evaluated as surrogate markers for global methylation status [20].

Hypertension which is associated with cardiac degeneration is influenced by global genomic methylation content in the peripheral blood leukocytes [17] of hypertensive patients. In Chinese individuals, elevated *Alu* methylation status in peripheral blood leucocytes has been related to the prevalence of cardiovascular disease and obesity [21]. Friso et al. [22] have linked hypermethylation of the HSD11B2 gene with blood pressure control. Impaired lipid metabolism and glucose metabolism, which lead to increased cardiovascular risk and diabetes, are represented by hypermethylation of MEG3, IL-10, GNASAS, ABCA1 and hypomethylation of IGF2 and INSIGF genes [23].

2.2. Role of microRNAs

MicroRNAs have emerged recently as one of the epigenetic mechanisms underlying cardiovascular diseases (Fig. 2, Table 2). In patients with atherosclerotic plaque, the elevated levels of miR127 lead to disruption of endothelium and subsequently, vascular senescence via inhibiting SIRT1 [24]. In animal models and patients with myocardial infarction, miR133b and miR499 have been shown to be upregulated and are potential candidates for biomarkers [8,25]. Additionally, in patients with coronary artery disease, the level of miR126 and miR145 is decreased profoundly [26]. Downregulation of miR126 indicates inflammation of vessel walls during the development of atherosclerosis by promoting the expression of VCAM-1 [27,28]. In unstable angina patients, the levels of miR134, miR370 and miR198, were found to be significantly increased and showed an increased risk of cardiovascular disease [29]. Sondermeijer et al. [30] reported that miR340 and miR624 were significantly increased in patients with cardiovascular diseases.

The role of miR21 in early phase MI is evident from an animal study, where acute MI created by left ventricular coronary artery ligation leads to a decrease in expression of miR21 in the infarcted area as compared to the surrounding area [31]. Wang et al. [8] found elevated levels of miR208a in CAD patients as compared to healthy subjects, where this