

Epigenetic Modifications the Development of Different Heart Failure Phenotypes

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Abstract

Heart failure (HF) remains a leading cause of death in patient population with known cardiovascular disease. Within last two decades there are evidences regarding decline to determine new cases with HF with reduced ejection fraction (HFrEF) in developed countries, whereas the frequency of newly-diagnosed HF with preserved ejection fraction (HFpEF) exhibits dramatically rise. Epigenetic modification is considered a modification of the non-DNA sequences related heritable changes in gene expression of target cells. Epigenetic modifications affect several molecular mechanisms, i.e., DNA methylation and deacetylation, ATP-dependent chromatin remodeling, histone modifications, and microRNA regulation. The short commentary is clarified the implication of epigenetic modifications in development of different HF phenotypes.

Keywords: Heart failure; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction; Epigenetics

Short Communication

Heart failure (HF) is a sufficient medical problem and social burden that associates with increased morbidity/mortality rate and disability rate in the developed countries [1]. Within last decades there is progressively decrease of prevalence of HF with reduced left ventricular ejection fraction (HFrEF) [2]. In opposite, the frequency of newly-diagnosed HF with preserved left ventricular ejection fraction (HFpEF) appears to be raised [3]. These changes in presentation of HF phenotypes might relate to advance in contemporary of HF medical care [4], impact of age-related comorbidities and socioeconomic status [5-8]. Despite the implementation in routine clinical practice modern pharmacological strategy and none-drug therapy including implanted devices for mechanical support and pacing [8-10], the clinical outcomes in subjects with HFrEF and HFpEF remain similar [11].

In this context, the discovery of several biomarkers reflecting various pathophysiological stages of HF appears to be promised. Currently available clinical guidelines have been recommended to use a limited numerous of biomarkers for risk stratification of the patients with of HF (brain natriuretic peptides, soluble ST2, galectin-3, and higher sensitive cardiac troponins). However, not all these biomarkers have exhibited higher predictive value of manifestation and development of HFpEF [4,12,13]. Interestingly, the most biomarkers are considered a prognosticators in symptomatic patients with known HFpEF or HFrEF, but their role in concerning the risk of HF development in individuals at higher risk of cardiac dysfunction is not yet clear [14]. It is suggested that the age-related co- morbidities and ischemic/non-ischemic etiology are the factors, which might sufficiently limit both diagnostic and predictive utility of currently used biological markers [15].

Recent studies have shown the pivotal role of cardiovascular remodeling, immune dysfunction, low-grade microvascular

inflammation, hypercoagulation/thrombosis, endothelial dysfunction, autonomic nervous system and neurohumoral abnormalities in the pathogenesis of HF beyond initially occurred etiology factors [16,17]. However, both HF phenotypes may distinguish in etiological factors (ischemic/none-ischemic), aging (older vs. younger) and sex presentation, pre-existing co-morbidities (i.e., hypertension, lung and rheumatic disease, diabetes, obesity), as well as predominantly intracellular mechanisms, which are involved in the pathogenesis of cardiac dysfunction. There is not only hypothetically possibilities, but large body of evidence with respect to the tremendous impact of epigenetic modifications (i.e., DNA and histone modifications, ATP-dependent chromatin remodeling, and microRNA-related signals and processes) on phenotypic response regarding failing heart and leading to form either HFrEF, or HFpEF [18,19].

Theoretically, the post-translational modification of DNA may link chromatin repair, transcription, translation, cell signaling, and cell death in the failing heart specifically mediating phenotypic response neither HFrEF, or HFpEF. Various reprogramming of gene expression, including downregulation of the alpha-myosin heavy chain gene, homeobox gene Pitx2c, angiotensin II gene, cardiac troponin T gene, cardiac actin and myosin binding protein C genes, alpha-tropomyosin and myosin light chains genes, sarcoplasmic reticulum Ca²⁺ ATPase genes, estrogen receptor-alpha, estrogen receptor-beta and reactivation of specific fetal cardiac genes including atrial and brain natriuretic peptides are involved in the phenotypic response in failing heart [19,20].

Recent animal studies have shown that histones acetylation/methylation rather DNA modification could be the important mechanisms of epigenetics determined failing heart response through miRNA signaling [21,22]. Indeed, sirtuins have been involved into DNA damage reparation, inhibition of inflammation and fibrosis [23]. Down-regulated sirtuin-1, sirtuin-2, sirtuin-3 and sirtuin-6 have been implicated in the cell death/survival process, oxidative stress, sensitivity to ischemic injury, and they may induce cardiac hypertrophy, accumulation of extra cellular collagens, microvascular

inflammation [21]. All these factors contribute to failing heart development and may mediate HFpEF [24]. The nicotinamide adenine dinucleotide-dependent histone deacetylase (HDAC) was found as a regulator of cellular processes, including gene silencing, longevity, and DNA damage repair. In animals the inhibition of endogenous HDAC-II has primarily caused cardiac myocyte hypertrophy and also induced modest cell death [22]. In contrast, inhibition of class I HDACs presented anti-hypertrophic effect [25]. Moreover, induced expression of class II HDAC in cardiomyocytes mimics hypertrophic growth in an Akt-dependent manner [26].

In clinical settings it has found a sufficient difference in DNA methylation in promoters of up-regulated genes, but not down-regulated genes in severe HF [27]. Xiao et al. [28] reported that increased DNA methylation might have a causative role in programming of heart hypertrophy and reduced global cardiac contractility function. Probably epigenetic modifications identified in failing heart might affect cardiac function directly through regulation of structure protein synthesis and indirectly via increased activity of cardiac fibroblasts. However, the role of DNA methylation in the development of both phenotypes of HF beyond inherited forms is not yet clear.

The ATP-dependent chromatin remodeling complexes are not able to directly modify DNA or histones, whereas they may use energy of ATP hydrolysis in processes regarding destabilize, eject or restructure of nucleosomes and play a pivotal role in HF development [29]. Several triggers including metabolic factors, aging, oxidative stress, and hemodynamic stress may impact on the HF phenotype presentation through ATP-dependent chromatin remodeling-dependent mechanisms.

Histone modification represents a dynamic process affected histone proteins that are composed in the nucleosomes and mediated by several enzymes [30]. Recent studies have shown that histone modification predominantly methylation is closely regulates inflammatory and metabolic disorders, as well as links CV disease and vascular homeostasis [31]. There is evidence that altered redox signaling might mediate trimethylation of histones and links an oxidative stress pathway with biochemical mechanisms underlying HFrEF development [32].

MicroRNAs (miRNAs) are small non-coding RNAs that exert their function by both transcript degradation and translational inhibition, resulting in changes in target genes and proteins' expression [33]. It has been suggested that reactivation of a fetal microRNA program substantially contributes to alterations of gene expression in the failing human heart. The recent studies have shown that the increased expression of miRNA-1, miRNA-21, miRNA-29b, miRNA-129, miRNA-133, miRNA-208, miRNA-210, miRNA-211, miRNA-212, and miRNA-423, and miRNA-499 miRNA503 [34]. Theoretically, there is well-described signature of cardiac-specific miRNAs, which may involve in cardiac remodeling forming HF phenotypes [35]. On this way, signature of miRNA expression (especially miRNA-7, miRNA-123, miRNA-378) has been allowed to differ healthy and failing hearts and depended on reactivation of a fetal gene program. Indeed, these miRNAs have been displayed different expression levels in HF at early and end stage failing hearts [36]. However, low number of direct clinical evidence regarding specifically HF phenotypes' development relating to miRNA signature remains a part of scientific discussion [37].

Conclusion

In conclusion, the current available data preliminary clarify that epigenetic modifications might be discussed as a key factor forming different phenotypes in HF, whereas there is no strong evidence regarding epigenetic signatures represent causal pathways leading to specific forms of cardiac remodeling associated with HFrEF or HFpEF.

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