

## Are Epigenetic Features Essential in Advance of Heart Failure Phenotypes?

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### Abbreviations

$\alpha$ -MHC: the alpha-myosin heavy chain gene;

CV: cardiovascular;

DNA: deoxyribonucleic acid;

ECREM: Epigenetic Code REplication Machinery;

HFrEF: heart failure with reduced ejection fraction;

HFpEF: heart failure with preserved ejection fraction;

miRNA: micro ribonucleic acid;

MHC: myosin heavy chain;

SPR-Ca<sup>2+</sup> ATPase: sarcoplasmic reticulum Ca<sup>2+</sup> ATPase genes.

### ABSTRACT

Chronic heart failure (HF) is a leading clinical and public problem affected higher risk of morbidity and mortality in different population. HF appears to be in both phenotypic forms: HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF). Although both HF phenotypes are distinguished in clinical features, co-morbidity status, prediction score, and treatment, the clinical outcomes in patients with HFrEF and HFpEF are similar. In this context investigation of various molecular and cellular mechanisms leading to development and progression of both HF phenotypes are very important. There is emerging evidence regarding that the epigenetic regulation may have a clue in the pathogenesis of HF. The review is represented current available evidence regarding an implication of epigenetic modifications in development of different HF phenotypes.

**Key words:** Heart failure with reduced ejection fraction; Heart failure with preserved ejection fraction; Epigenetic modifications; Chromatin remodeling

### INTRODUCTION

Chronic heart failure (HF) has remained to be a serious clinical and public problem<sup>[1]</sup>; despite the prevalence of chronic HF especially HF with reduced left ventricular ejection fraction (HFrEF) seems to have a tendency to decrease within the last decade in the development countries<sup>[2]</sup>. Contrary, a frequency of newly HF with preserved left ventricular ejection fraction (HFpEF) is on the rise and HFpEF is considered more common than HFrEF predominantly in the older population and among subjects with hypertension, diabetes, respiratory diseases<sup>[3]</sup>. Currently, more than 50% of patients with the clinical syndrome of HF might have a preserved left ventricular ejection fraction<sup>[4]</sup>. Nevertheless, recent clinical studies have shown a sufficient distinguish between presentation of both HF phenotypes (HFrEF or HFpEF) in individuals at risk for HF development in a primary care setting<sup>[5,6]</sup>. Although HFpEF patients might have lower levels of predictive biomarkers<sup>[7]</sup>, the clinical outcomes in HFpEF individuals, i.e. cardiovascular (CV) death, HF-related death, sudden death and readmission, are not better than in patients with HFrEF<sup>[8,9]</sup>.

Current clinical HF guidelines are recommended to use early identification and treatment of the underlying cause of cardiac

dysfunction to prevent HF manifestation<sup>[10,11]</sup>, whereas no evidence that HF phenotypes' development is preventable with specific medical care<sup>[12]</sup>. Taken together, all these data clarify the importance of stratification of individuals at risk of HF<sub>rEF</sub> or HF<sub>pEF</sub> development and progression<sup>[13,14]</sup>.

Various molecular and cellular mechanisms are involved in the development and progression of both HF phenotypes. There is emerging evidence regarding that the epigenetic regulation may take an important part in the pathogenesis of HF playing a pivotal role in phenotypic response of failing heart and prognosis<sup>[15,16]</sup>. There is experimental and clinical evidence that advance of HF might associate with autonomic imbalance with increased sympathetic nerve activity and a withdrawal of parasympathetic activity, with the target of involvement being the heart which may be of epigenetic origin<sup>[16-18]</sup>. The increase in angiotensin II signaling enhances sympathetic nerve activity through actions on both central and peripheral sites causing increased contractility of the heart, as an adaptation, during chronic HF<sup>[17]</sup>. Angiotensin II signaling is enhanced in different brain sites such as the paraventricular nucleus, rostral ventrolateral medulla and area postrema via neuregulin-brain natriuretic peptide release from these sites which influences the function of cardiomyocytes and the heart<sup>[18]</sup>. It is suggested that blocking angiotensin II type 1 receptors decreases sympathetic nerve activity and cardiac sympathetic afferent reflex when therapy is administered to the PVN which may be due to epigenetic modulation<sup>[19]</sup>.

Epigenetic modifications affected DNA methylation, ATP-dependent chromatin remodeling, histone modifications, and microRNA-related mechanisms are considered a sufficient factor contributing to adverse cardiac remodeling and preceding cardiac dysfunction<sup>[20]</sup>. Probably, in the future epigenetic modifications of cardiomyocytes would be a target for personalized management and much more effective tools for prevention of HF development<sup>[21]</sup>. The review is summarized the knowledge regarding implication of epigenetic modifications in development of different HF phenotypes.

## DEFINITION OF EPIGENETICS

A classical definition of epigenetics was proposed by Conrad Waddington in the 1950s, which believed that organism' phenotype arises from its genotype through so called "programmed epigenetic" event. Epigenetics was considered neither as the study of changes in states of any gene activity or inherited activity states only<sup>[22]</sup>. In some definitions, only those activity states that are inherited across cell division were defined<sup>[23]</sup>. In the Roadmap Epigenomics Project epigenetics is used as an emerging frontier of science that involves the study of changes in the regulation of gene activity and expression that are not dependent on gene sequence<sup>[24]</sup>. Accordingly Banbury Conference Center and Cold Spring Harbor Laboratory chromatin-based epigenetic trait has defined as a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence<sup>[25]</sup>. By now, it has been suggested that the basis of epigenetics is non-genetic cellular memory that expressed or non-expressed in specific developmental and environmental situations<sup>[26]</sup>.

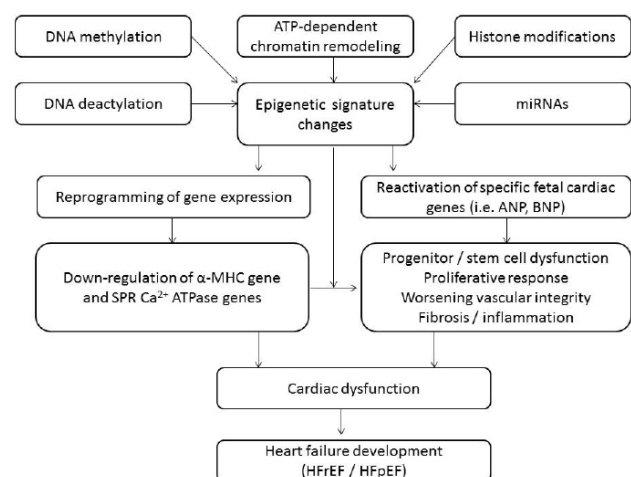
Berger SL *et al*<sup>[27]</sup> have suggested to use at least three categories of signals that modulate epigenetic state: "Epigenator", "Epigenetic Initiator" and "Epigenetic Maintainer". Authors suggested that signal that is proposed to name the "Epigenator" might be attribute of the environment and it could be a trigger an intracellular pathway. The signal that is called "Epigenetic Initiator", corresponds to "Epigenator" signal and is essential for define the precise arrangement of the epigenetic chromatin environment. Finally, "Epigenetic

Maintainer" signal is deemed as the chromatin environment contributing to the first and subsequent generations. The role of different classes of potential signals affected epigenetic modifications of chromatin is not well defined and is widely discussed.

In this context, discrete chemical modifications of DNA and primarily histones might regulate expression or repression of target genes and can be transmitted to the descent via epigenetic memory<sup>[28]</sup>. It has suggested that the macro-molecular complex, called "Epigenetic Code REplication Machinery" (ECREM), as being involved in the inheritance of the epigenetic code. The main the members of ECREM could be enzymes involved in epigenetic modification of chromatin, i.e. DNA methyltransferases, histone deacetylases, histone acetyltransferases, and sirtuins. Moreover, deregulated ECREM is considered a clue of cell reprogramming<sup>[27,28]</sup>. However, epigenetic events in various cells provide closely control of gene expression and genomic regulation through multiple generations leading to phenotypes' variability.

## EPIGENETICS IN FAILING HEART

Epigenetics are referred a modification of the non-DNA sequences related heritable changes in gene expression of target cells that is currently recognized as a key to understanding of pathogenesis CV diseases<sup>[29]</sup>. Epigenetic modifications are based on different molecular mechanisms, which affect DNA methylation and deacetylation, ATP-dependent chromatin remodeling, histone modifications, and microRNA regulation (Figure 1). All these processes coordinate modulating of chromatin structure and thereby might effect of modalities and expression of target genes<sup>[30]</sup>. It has been found the proliferative capability of human cardiac cells is under tight epigenetic regulation that mediates a dynamic adaptation of the structure and functionality of wide spectrum of cells, i.e. cardiomyocytes, fibroblasts, endothelial cells, progenitor cells, for environmental challenges and to respond to biochemical stress. It is suggested that dysregulation in epigenetic signals, messengers and molecular targets is a clue for pathological remodeling of heart and vessels, progenitor cell dysfunction, worsening of endogenous repair system, metabolic memory manifestation<sup>[31]</sup>. It is now becoming evident that cumulative effect of these factors may culminate in HF, cardiac hypertrophy, arrhythmia, dyslipidemia, atherosclerosis/atherothrombosis, and associates with increased



**Figure 1** The principal scheme regarding epigenetic regulations in heart failure development. Abbreviations: α-MHC: the alpha-myosin heavy chain gene; SPR-Ca<sup>2+</sup>ATPase: sarcoplasmic reticulum Ca<sup>2+</sup>ATPase genes.

risk of CV death<sup>[32-37]</sup>. Whether interactions between features of transcriptomics, proteomics and metabolomics are specifically for HF<sub>rEF</sub> and HF<sub>pEF</sub> remains still not clear. Moreover, different mechanisms of epigenetic modifications may relate to various HF-dependent settings, i.e. cardiac hypertrophy, myocardial infarction, atrial fibrillation, sudden death, and play controversial role (Table 1). However, the innate mechanisms regarding causal pathway to HF phenotypes' development are not fully understood and require more investigations<sup>[38]</sup>.

#### DNA methylation

DNA methylation is the most common epigenetic chromatin modification<sup>[39]</sup>. Movassagh M *et al*<sup>[40]</sup> suggested that there is distinct global pattern of the epigenome leading to regulate the expression of underlying genes. Authors investigated genome-wide maps of DNA methylation and histone-3 lysine-36 trimethylation enrichment for cardiomyopathic and normal human hearts. It has found a sufficient difference in DNA methylation in promoters of up-regulated genes, but not down-regulated genes in end-stage cardiomyopathy [40]. Furthermore, the process of DNA methylation was under regulation through several genetic pathways that are modulating by platelet/endothelial cell adhesion molecule 1, hypoxia-inducible factor-1alpha, angiominin-like 2, and Rho GTPase activating protein 24<sup>[40,41]</sup>. Authors suggested that epigenetic modifications identified in failing heart might affect cardiac function directly through regulation of structure protein synthesis and, however, indirectly via increased activity of cardiac fibroblasts due to prolonged hypoxia contributing to the pro-fibrotic nature of the ischemic milieu.

Contrary, satellite repeat element transcripts, a form of non-coding RNA that is heavily methylated in post-natal tissue, have putative functions in maintaining genomic stability and chromosomal integrity<sup>[42]</sup>. Moreover, the hypomethylation of satellite elements exhibited closely association with significant up-regulation of satellite transcripts<sup>[42]</sup>. Finally, there is evidence that methylation-regulated, alternative transcripts might express in a tissue- and cell type-specific manner and they may regulate intragenic promoter activity via enhancing transcription elongation efficiency<sup>[39,43]</sup>. Thus, DNA methylations may enhance transcription of the underlying satellite repeat element transcripts.

Xiao D *et al*<sup>[44]</sup> reported that increased DNA methylation might have a causative role in programming of heart hypertrophy and reduced global cardiac contractility function. Moreover, impaired contractility of the left ventricle has associated with an increase in the susceptibility to ischemic injury<sup>[44]</sup>. Contrary, Haas J *et al*<sup>[45]</sup> did not find evidence regarding participation of DNA methylation in genes suspected to HF development. However, DNA methylation has exhibited a causality role in diabetes-induced HF<sub>pEF</sub><sup>[46]</sup>. Unfortunately, the data regarding the role of DNA methylation in development of both phenotypes of HF beyond inherited forms in are very limited. More investigations are required to understand

the underlying mechanisms linked DNA methylation and HF presentation.

#### ATP-dependent enzymes in chromatin remodeling

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, which is functional unit of chromatin<sup>[47]</sup>. Because nucleosomes actively participate in transcription, chromosome segregation, DNA replication, and DNA repair, the chromosomal DNA packaging by nucleosomes is crucial for the regulation of these processes<sup>[48]</sup>. The dynamic access to DNA packaging performs by specialized chromatin remodeling complexes<sup>[49]</sup>. There are four different families of ATP-dependent chromatin remodeling complexes: switching defective/sucrose non-fermenting complexes (SWI/SNF), imitation switch complexes, chromodomain-helicase-DNA-binding complexes, and inositol-requiring eighty complexes<sup>[50,51]</sup>. All members of each family exhibit distinct unique domains that are served to histone-DNA contacts for DNA movement and chromatin restructuring<sup>[52]</sup>. The covalently modified histones are recognized by these domains of ATP-dependent chromatin remodelers and thereby regulate an expression of distinct gene programs tailored to specificity and biological functions of each family of chromatin remodeling complexes<sup>[53]</sup>.

#### Histone modifications

Histone modification represents a dynamic process affected histone proteins (H2A, H2B, H3, and H4) that are composed in the nucleosomes and mediated by several enzymes<sup>[54]</sup>. As a result, distinct histone amino-terminal modifications appear to be able to induce synergistic or antagonistic interaction affinities for chromatin-associated proteins, which in turn dictate dynamic transitions between transcriptionally active or transcriptionally silent chromatin states<sup>[55]</sup>. By now more than 150 post-translation modifications of histones have been reported, including methylations, acetylations, sumoylation, ubiquitinations, ADP-ribosylation, proline isomerization, and phosphorylations<sup>[56]</sup>. Appearance of conformational changes in the chromatin resulting in alteration due to histone modifications regulates gene expression depending on depending on whether DNA has been became accessible (defined as euchromatin) or inaccessible (called as heterochromatin) for further transcription process<sup>[57]</sup>.

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<sup>[58-60]</sup>. There is evidence that altered redox signaling might mediate trimethylation of histones H3K4 and H3K9 and thereby links an oxidative stress pathway with biochemical mechanisms underlying HF<sub>rEF</sub> development<sup>[61]</sup>. Probably, aging might affect on development neither HF<sub>pEF</sub> nor HF<sub>rEF</sub> through so-called "epigenetic drift" via markedly regulation of DNA and histone methylation<sup>[62]</sup>. However, further investigations are needed to explain in details the role of histone modification in impairment of cardiac structure and functionality.

**Table 1** The role of epigenetic modifications in HF development and progression.

Mechanisms of epigenetic modifications	Phenotypic response	References
Altered DNA methylation	Left ventricular dilatation	[44]
	Cardiac hypertrophy	[45]
	Reduced contractility function	[44-46]
ATP-dependent chromatin remodeling	Reduced contractility function?	[51]
Histone acetylation	Cardiac hypertrophy	[58-61]
	Endothelial dysfunction	[62]
Altered miRNA signature	Left ventricular dilatation	[66-70]
	Arrhythmogenesis	[69]
	Cardiac hypertrophy	[65, 69, 71]

## MICRORNA-DEPENDING MECHANISMS

MicroRNAs (miRNAs) are small non-coding RNAs that exert their function by both transcript degradation and translational inhibition, resulting in changes in target gene and protein expression<sup>[63]</sup>. It has been suggested that reactivation of a fetal microRNA program substantially contributes to alterations of gene expression in the failing

human heart. Indeed, 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 the reduced expression of miRNA-30, miRNA-182, and miRNA-526 are associated with HF development and progression<sup>[64-66]</sup>. Therefore, altered microRNA expression in human heart was found in ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis<sup>[67,68]</sup>. There is evidence that the disproportion between myocardial expressions of alpha- and beta-myosin heavy chain (MHC) might be associated with over-expression of heart-specific miRNA-208a leading to arrhythmia, fibrosis, and cardiac hypertrophy<sup>[69]</sup>. Nevertheless, miRNA-208a expression is under negatively control of MED13, a subunit of the mediator complex, which controls transcription by thyroid hormone and other nuclear hormone receptors<sup>[70]</sup>. The down-regulation of miRNA-1 and up-regulation of miRNA-195 are necessary for cardiac hypertrophy and HFpEF development, while the underlying molecular mechanisms of these effects are not still clear<sup>[65,71]</sup>. Finally, cardiac hypertrophy may associate with the activation of Nppa, Nppb, and Acta1 (skeletal  $\alpha$ -actin) fetal gene program<sup>[72]</sup>. It has deemed that the key components of cardiomyocyte hypertrophy mediator might be miRNA-dependent regulator of calcium signaling pathways<sup>[73]</sup>. Whether altered signature of miRNA is considered a clue for cardiac hypertrophy and dysfunction, low number of direct clinical evidence regarding specifically HF phenotypes' development relating to miRNA signature remains a part of scientific discussion<sup>[59]</sup>.

In conclusion, the current available data preliminary clarify that epigenetic modifications might be discussed as a clue of forming phenotypes of 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. More investigations are required to discover epigenetic regulation features, because of progress in this setting appears to be more much promised for individualized translation medical care.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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