Translational Medicine

Berezin, Transl Med (Sunnyvale) 2016, 6:3
DOI: 10.4172/2161-1025.1000176

Short Commentary Open Access

Progenitor Endothelial Cell Dysfunction in Heart Failure: Clinical Implication and Therapeutic Target?

Alexander E Berezin*

Internal Medicine Department, State Medical University of Zaporozhye, Ukraine

***Corresponding author:** Alexander E Berezin, Internal Medicine Department, State Medical University of Zaporozhye, UA-69035, Ukraine, Tel: +380612894585; E-mail: dr_berezin@mail.ru

Received date: May 09, 2016; **Accepted date:** May 17, 2016; **Published date:** June 01, 2016

Abstract

Chronic heart failure (HF) is a leading clinical and public problem affected higher risk of morbidity and mortality in different population. There is emerging evidence regarding that the epigenetic regulation may have a clue in the pathogenesis of HF. Epigenetic modifications including DNA methylation, ATP-dependent chromatin remodeling, histone modifications, and microRNA-related mechanisms, may involve in the endothelium reparation and injury through mobbing and differentiation of endothelial progenitor cell (EPCs). Recent clinical studies have shown that cardiovascular risk may contribute to epigenetic regulation of structure and functionality of EPCs leading to EPCs' dysfunction and worsening of endothelium repair. The short commentary is represented current available evidence regarding an implication of epigenetic modifications in development of EPC dysfunction and its importance for use as a target for HF treatment.

Keywords: Heart failure; Epigenetic modifications; Endothelium; Endothelial progenitor cell dysfunction; Prediction

Short commentary

Endothelial cell dysfunction plays a pivotal role in the pathogenesis of heart failure (HF) [1]. In HF patients there is a sufficient difference between presentation of CV risk factors in HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF) [2-4]. Various molecular and cellular mechanisms are involved in the development and progression of both HF phenotypes [5-7]. 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 [8].

Epigenetics is defined as emerging changes in the regulation of gene activity and expression that are not dependent on gene sequence [9]. 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 [10]. Indeed, DNA hypermethylation have been associated with various CV diseases including HF [11,12], histone post-translational modifications have also been implicated in atherosclerosis, endothelial dysfunction, inflammation, HF [13-15], ATP-dependent chromatin remodeling and microRNA-related mechanisms are necessary of cardiomyopathies, endothelial dysfunction and HF [16].

Recent studies have confirmed the CV risk factor may impact negatively on number and functionality of circulating bone marrow-derived endothelial progenitor cells (EPCs) [17-20]. Moreover, there is evidence regarding a relationship between decreased number of EPCs and the risk of HF advance and occurring HF outcomes [21,22]. The changes in number and functionality of EPCs originated from bone marrow and circulating mononuclear progenitors in CV disease have recently defined as an "impaired phenotype" of EPCs [19,23]. It has deemed that "impaired phenotype" of EPCs might appear prior to cardiac dysfunction and relates to CV risk factors mediating being a specific setting "incompetence" in endogenous reparation affected endothelium.

Focusing on current insight into the cellular and molecular mechanisms underlying EPC dysfunction, it has suggested that CV risk links CV disease development through epigenetic modifications of EPCs [14]. Indeed, epigenetic modulation of adhesion molecules in endothelial cells regulates the aggregation and adhesion of leukocyte to the vessel wall [24]. Moreover, the effect is induced by inflammatory signals, thrombomodulin, and low-density lipoproteins [24, 25]. Probably, microRNAs as triggered signal transductors might play a pivotal role in the cross-talk regulation among epigenetic factors and repair capability of endothelial progenitor cells [26]. Whether altered signature of miRNA, DNA methylation, ATP-dependent chromatin remodeling, and histone modifications are considered a clue for cardiac hypertrophy and dysfunction, low number of direct clinical evidence regarding specifically endothelial dysfunction development relating to epigenetic modulation remains a part of scientific discussion [27]. However, there is a large body of evidence that post-transcriptional regulation of endothelial nitric-oxide synthase plays a central role in redox signaling, injury of endothelial cells, and worsening of reparative capability of EPCs [28-32].

Whether progenitor endothelial cell dysfunction can improve CV risk prediction, HF risk development and be useful as predictive biomarker in patients with known HF is yet not completely clear. However, understanding the central role of endothelium repair system may provide novel insights into pathophysiology of HF [33]. Although several drugs might regulate the various epigenetic mechanisms in the target cells including EPCs in HF (angiotensin-converting enzyme inhibitors, mineralocorticoid antagonists, angiotensin-receptor/neprilysin inhibitors), the clinical significance of similar approaches are not fully defined due to serious limitation of obtained data and it

has been continued to be under active investigations. All these findings open the novel possibilities for the HF prevention and appear to be promised for target therapy of the HF in future.

In conclusion, the clinical implications of progenitor endothelial cell dysfunction in HF require more investigations in large clinical studies. The molecular regulators of epigenetic modifications as a novel therapeutic target for restoring endothelial cell function in HF is promising aim for primary and secondary endothelial therapy.

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