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Review Article

Endogenous Endothelial Repair System in Heart Failure: Focus on Progenitor Endothelial Cell Dysfunction -

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ABSTRACT

Heart Failure (HF) a leading cause of premature death in patients with established Cardio Vascular (CV) disease. Although the global burden of HF is increasing, there is no evidence regarding promising results that improves long-term clinical outcomes especially for HF with preserved and mid-regional pump function. In this context, determination of the vulnerable populations at higher risk of HF development and progression is very promising. Endothelial Dysfunction (ED) plays a central role in the manifestation of HF regardless its phenotypes. There is a large body of evidence regarding that the Endothelial Progenitor Cells (EPCs) as a component of endogenous vascular repair system could be modified by several stimuli including epigenetic factors and thereby they are involved in the pathogenesis of ED. However, there is unclear whether EPC dysfunction is only whiteness of HF or it could be a factor of HF manifestation in vulnerable population. The short communication is depicted the uncertain role of EPC dysfunction in pathogenesis of HF.

Keywords: Heart failure; Biomarkers; Endothelial Progenitor Cells; Prediction.

INTRODUCTION

Heart Failure (HF) remains a leading cause of mortality in patients with established Cardio Vascular (CV) disease [1,2]. There is a strong trend toward reducing death rate due to HF associated with steady increased frequencies of newly manifested HF in developed countries, although in developing countries the HF mortality rate appears to be exaggeratedly high [3]. Identification of the vulnerable populations at higher risk of HF development and progression has now based on the early diagnosis of CV disease (atherosclerosis, hypertension, coronary heart disease, peripheral artery disease, and vasculitis) and metabolic states including diabetes, abdominal obesity, thyroid dysfunction, as well as other CV risk factors which may pre-exist CV diseases and particularly HF [4]. The short communication is depicted the uncertain role of EPC dysfunction in pathogenesis of HF.

Endothelial dysfunction in HF

Endothelial Dysfunction (ED) is considered an integral state in the development of HF regardless its phenotypes [5] and even contributes in clinical outcomes across all stages of CV continuum [6]. There is a large body of evidence regarding that the exhausted reparative ability of vasculature in resulting in several factors including pre-existing co-morbidities, some severe diseases that had appeared prior HF manifestation (trauma, infections, inflammatory diseases), and traditional CV risk factors could be primary reasons for loss of endothelial cell integrity and shaping ED [7-9]. In this context, Endothelial Progenitor Cells (EPCs) that are mobbed from bone marrow precursors and peripheral tissue residences and involved in reparative processes through differentiation and turn-into mature endothelial cells are promising biomarkers of ED with possible predictive value [10,11].

Endothelial progenitor cell dysfunction: definition and role in HF

EPC dysfunction is determined as weak function and / or decreased circulating number of endothelial precursors [12]. Indeed, decreased number of circulating EPCs was found a strong predictor of CV death, CV outcomes and HF-related events in HF patients with reduced and preserved left ventricular ejection fraction independently etiology of the disease [12-14].

On the other hand, EPCs that circulate in the peripheral blood in patients at higher risk of HF and in individuals with established HF presented lowered survival ability and partially inconvenience to be differentiated to mature endothelial cells under influence of essential innate stimuli including transforming growth factor-beta, tumor necrosis factor-alpha (TNF- α) and other inflammatory

cytokines [15,16]. This phenomenon was previously described as EPC dysfunction and it was widely diagnosed in the patients with diabetes, abdominal obesity, hypertension and other CV risk factors [17]. Interesting, that all these factors promote oxidative stress and mitochondrial dysfunction in target cells including EPCs that is suitable for different pathophysiological stages of HF.

EPC dysfunction as a central player in HF risk development

Although number and functionality of EPCs have validated to be strong predictors of HF risk development and advance, it had been remained unclear whether EPC dysfunction is only whiteness of HF or it could be a factor of HF manifestation in vulnerable population. However, recent clinical trials have not confirmed ability of EPC collected from the patients with established HF having recovered function after treatment including cardiac rehabilitation programs, while a number of circulating EPCs may recover completely in some cases [18-20]. It has been suggested that the altered immune pattern of EPCs, which could be determined prior HF, is central player in worsening vascular / endothelial repair and contributes in ED [21]. Probably EPC functionality could be regulated by some epigenetic factors influencing on ability of precursors to differentiate into mature cells including endothelial cells. Moreover, it has noted that there is possibility to change of endothelial cell immune phenotype to cardiac cell phenotype in animal model [22]. Whether similar effects trigger structure and functional abnormality in cell precursors that involve in the pathogenesis of HF is not well established, although accumulation of reactive oxygen species leading to the swelling and fragmentation of mitochondria of EPCs has now described as factor of decreased repair ability of precursors [23]. Indeed, enhancement of oxidative stress and mitochondrial dysfunction of EPCs may negatively effect of number and function of one's (mobbing, proliferation, regeneration, apoptosis, differentiation, cell-cell interaction, survival) through intracellular signaling pathways (Akt/nitric oxide, PI3K/nitric oxide), which may operate in signal-regulated kinase and the inflammatory genes expression, such as interleukin-6 and TNF- α , and synthesis of specific mi RNAs (-126, -128, -130) [24,25]. Finally, epigenetically modified EPCs are not able to maintain the homeostasis of vasculature and trigger inadequate endothelial responses that realize ED and micro vascular inflammation. Probably, this model may be taken into consideration for creating novel molecular biomarkers of HF and target for personal treatment of the disease.

CONCLUSIONS

Evidence emerging from both animal and clinical studies has shown that EPC dysfunction may be crucial for pathogenesis of HF and however it is not excluded that worsening endogenous vascular repair system including EPCs could play a pivotal role in the



manifestation and progress of HF regardless etiology of the disease. Biomarker strategy based on determination of EPC dysfunction in patients at higher risk of HF development and in individuals with established HF maybe promising for HF diagnosis and stratification in future, while this conception requires more investigations for understanding.

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