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Epigenetically Modified Endothelial Progenitor Cells in Heart Failure

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Abstract

Heart failure is a global health and medical problem that increases burden of cardiovascular (CV) disease. By now, there is not completely recognition regarding the reasons of various phenotypes of HF development, distinguish in CV risk, clinical outcomes and prognosis. It has suggested that epigenetic modification of several cell components of endogenous repair system might determine phenotypical response of the failing heart and contributes to nature evolution of HF. Moreover, epigenetically modified endothelial progenitor cells playing a central role in the tissue reparation and angiogenesis may link aging, genetic predisposition, co-morbidities, traditional CV risk factor and HF progression. The editorial comment devotes the consideration of the role of epigenetic in manifestation of progenitor endothelial cell dysfunction and perspectives to restore its reparative ability in HF individuals.

Keywords: Heart failure; Progenitor cells; Endothelial dysfunction; Epigenetics; Prediction

modification of cells involved in endogenous reparation [10]. Endothelial progenitor cells (EPCs) with angiogenic capability are the main players in the endogenous repair mechanisms counteracting endothelial dysfunction [11], which is a clear predictive value for CV mortality. It is known that worsening of recruitment and deregulation of epigenetic features of EPCs might play a pivotal role in HF progression and prognosis [12,13]. Indeed, recently it has been shown that EPC dysfunction is frequently found in patients at higher risk of cardiac dysfunction, as well as in the patients with known HF [14,15]. Moreover, progressively impaired functional capacity of angiogenic EPCs has closely associated with progression of HF [16], left ventricular ejection fraction, serum level of NT-pro-brain natriuretic peptide, higher sensitive C reactive protein concentration [17] and, that is important, EPC dysfunction was found a predictor of HF-related death, admission and CV outcomes [18-21].

DNA methylation, histone modifications, and differential expression of specific non-coding microRNA (miRNAs) are widely involved in the epigenetic modification of EPCs leading to detrimental impact on structural progenitors, worsening of their recruitment and differentiation [22]. Hypoxemia, matricellular proteins (osteoprotegerine, osteopontine), inflammatory cytokines (interleukin-6, C-reactive protein), growth factors (vascular endothelial growth factor, Tie-2, heterochromatin protein 1 α , SDF-1 α), chemokines (CXC chemokine receptor-4) and other active molecules (angiogenin, angiopoietin-1 and -2, soluble cellular adhesion molecules and soluble apoptosis signaling molecules) are discussed the leading factors, which could mediate epigenetic modification of EPCs and occur dysfunctional phenotype of progenitors [23,24]. It has suggested that the molecular target for these factors could be Janus kinase-2, p38 MAP kinase, Akt/STAT signaling and senescence-associated β -galactosidase [25-27]. Through these target molecules, mentioned above factors can also decrease expression of progenitor cell marker genes (i.e., CD133, CXCR4) and deactivate angiogenic gene (i.e., cadherin-5, and angiopoietin-like-2) expression. As a result in the deregulation of angiogenic gene transcription by interacting with chromatin that is modified by epigenetic factors, worsening of recruitment and differentiation of EPCs may occur.

Selective impairment of EPC function in the bone marrow and in the peripheral blood may contribute substantially to an unfavorable cardiac remodeling process, microvascular

Editorial

Despite the prevalence of heart failure (HF) is not more than 1% of all CV diseases, the impact of this disease on life duration, quality of life, and well-being in various patient populations is decisive and exists beyond initial cause of cardiac impairment [1,2]. Acute, acutely decompensated and chronic HF are the leading causes of mortality in patients with known cardiovascular (CV) disease [1]. The development and progression of HF involves several universal pathogenically mechanisms affected cardiac remodelling, vascular dysfunction, neuropathy/myopathy, renal structure/functionality, metabolic disorders predominantly due to neurohumoral and inflammatory activation, oxidative stress, and cell energy loss [3-5]. Up to date, these factors contribute to cardiac failure irrespective its aetiology [6], while aging, genetic predisposition, and co-existing co-morbidities might determine the phenotypic response of failing heart, contribute to HF progression, and clinical outcomes [7-9].

In this context, the direct link between structure changes of target cells/tissues and functional modalities of several systems including CV could be mediated through epigenetic

inflammation, dysfunction of endothelial repair and neovascularization capacity [24,28].

There is evidence that microRNA/gene expression signatures of EPCs rather than chromatin modifications may play a key role in epigenetically modified progenitor cells. Riedel S et al. (2015) [29] have shown that miR-126 and miR-21 in EPCs may protect of endothelium through stimulation of NO generation by endothelial cells and attenuation of vasodilator function. Qiang L et al. (2013) [21] reported that reduced expression of proangiogenic miRNAs (miR-126 and miR-508-5p) in EPCs are independently associated with the outcome of HF. Overall, epigenetic changes in EPCs affecting miRNA expression may reduce number and functional capacity of progenitors in HF leading to increased CV risk [30,31].

It is not clear whether the epigenetically induced EPC dysfunction is the risk factor of HF or it is result in nature evolution of the failing heart induced several causes. Probably, EPC dysfunction may not only predict HF manifestation and development, but it could be exhibited a causative impact on cardiac dysfunction and vascular remodeling linking etiological factors, co-morbidities, and endogenous repair system. On this way, the principal reversibility of EPC dysfunction under treatment, which could be attenuated epigenetically changes, is considered as novel approach of HF therapy. However, there is evidence regarding that the aerobic exercise may acutely reverse dysfunction of circulating angiogenic cells in chronic HF [13,29]. The results of similar investigations explain the positive effect of recently known methods of aerobic training on survival in HF individuals. What the role of medical care in epigenetically induced EPC dysfunction is not fully clear and it is required to be defined in large clinical investigations.

Conclusion

In conclusion, progenitor endothelial cell dysfunction plays a pivotal role in HF manifestation and progression, but it was found as predictive biomarker in HF. The epigenetic changes affecting presentation of angiogenic genes in EPCs may produce detrimental effect on endogenous repair system, which contribute to cardiac remodeling and endothelium integrity/functionality. The perspectives to implement in the routine clinical practice several methods toward restore of epigenetically modified EPC structure/function appear to be promised, while the evidence of this approach are very limited.

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