Editorial

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Endothelial Repair in Diabetes: The Causative Role of Progenitor Cells Dysfunction?

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Abstract

Diabetes mellitus (DM) is considered a leading cause of premature cardiovascular (CV) mortality and morbidity in general population and in individuals with known CV disease. Recent animal and clinical studies have shown that reduced number and weak function of endothelial progenitor cells (EPCs) may not only indicate to higher CV risk, but contribute to the impaired heart and vessels reparation in patients with DM. Moreover, EPCs having a protective impact on the vasculature may mediate the functioning of other organs and systems. EPCs dysfunction is probably promising target for DM treatment strategy, while the role of restoring of EPCs number and functionality in CV risk diminish and reduce of DM-related complications is not fully clear. The aim of the short commentary: to elucidate the causative role of EPCs dysfunction in DM patients.

Keywords: Diabetes mellitus; Endothelial progenitor cells; Reparation; Vasculature; Heart; Epigenetics

Editorial

Diabetes mellitus (DM) is a worldwide epidemic metabolic disease associated with increased cardiovascular (CV) complications, premature CV death, and a higher incidence of disability leading to social and economic burden [1]. DM was found as the important cause of atherosclerosis, coronary artery disease, chronic renal disease, and heart failure [2-5]. It is suggested that hyperglycemia, lipotoxicity and hypoxia are essential factors contributing in the microvascular inflammation, endothelial dysfunction and endothelium injury [6]. On this way, worsening of intracellular signaling, activation of alternate polyol pathways, increment of growth factors (growth-differentiation factor-15, vascular endothelial growth factor, and accumulation of advanced glycation end products, activation of protein kinase C, activation of the renin-angiotensin-aldosterone system, inducting of oxidative stress and apoptosis, and decreased nitric oxide bioavailability were found an independent causes of weakened endothelium repair ability and worsening of endothelial integrity [7-10]. Finally, co-acting endothelial injury, incompetence in vascular reparation mechanisms and existing co-morbidities (i.e. hypertension, obesity, hyperuricemia, dyslipidemia) may lead to endothelial dysfunction, acceleration of atherosclerosis, senescence, thereby they may negatively influence on CV risk and development of CV disease [11-13].

The key role in the endothelial repair, vasculogenesis, neovascularization and attenuation of vasculature function plays endothelial progenitor cells (EPCs) derived from bone marrow and peripheral blood [14]. In contrast to recently proposed local “response to endothelium injury hypothesis” EPCs, which are mobilized or released into systemic circulation in response to specific stimuli, contribute vessel formation and endothelium reparation directly and through involvement of several paracrine mechanisms [15,16].

In this context, dysfunction of EPCs defined as weak EPCs functionality (i.e., reduced ability to proliferation, differentiation, adhesion, migration, incorporation into tubular structures, and survival) and / or lowering EPCs’ count in the circulation might be a critical step in the initiation of any cause-related vasculopaty that links etiological factors, co-morbidities, aging and clinical events [9]. Nevertheless, EPCs dysfunction may be a useful predictive tool for evaluating the risk of death in general population and among subjects with known CV and DM.

Alteration of structure and function of the EPCs in type 1 and type 2 DM may regulate through epigenetic changes [17]. It has suggested that glucose toxicity, lipid toxicity and reactive oxidative species via enhancing inflammation induce DNA methylation and histone modification in EPCs [6,9,18]. Although maturation and mobbing of the EPCs are under control of growth factors, such as chemokine stromal cell-derived factor-1, vascular endothelial growth factors, granulocyte colony-stimulating factor, and alpha-chemokine that binds to G-protein-coupled CXCR4, epigenetic changes in EPCs are considered an important mechanism, which links hyperglycemia, lipid toxicity and metabolic memory [9,19]. Thus, weak functionality of EPCs in type 1 and type 2 DM is resulting mutual related molecular mechanisms affected cellular signal systems, paracrine regulation and epigenetic modification [20,21]. Therefore, poor differentiation, mobbing and proliferation of EPCs lead to decreased circulating pool of primitive cells and worsening reparative capability [22-24].

Conclusion

In conclusion, reduced number and weak function of EPCs may not only indicate to higher CV risk, but contribute to the impaired heart and vessels reparation in patients with DM. EPCs dysfunction is probably promising target for DM treatment strategy, while the role of restoring of EPCs number and functionality in CV risk diminish and reduce of DM-related complications requires more investigations.

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