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Short Communication

Endothelial Progenitor Cell Dysfunction in Diabetes Mellitus: New Biomarker for Risk Stratification?

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Abstract

Endothelial progenitor cell (EPC) dysfunction is defined as weak function and lowered number of endothelial precursors with pro-angiogenic phenotypes that are imbedded in vascular integrity maintenance, angiogenesis, and vascular reparation. There is large body of evidence that deficiency of EPC number in peripheral blood is considered as a marker of endothelial dysfunction, which is established risk factor and player in pathogenesis of cardiovascular disease. Moreover, recent clinical studies have shown that circulating EPCs had demonstrated vascular protection in several diseases including diabetes mellitus (DM). However, the role of EPCs in pathogenesis DM appeared to be uncertain. The short communication is dedicated the controversies in abilities of EPCs to have tissue protective and play a pivotal role in nature evolution of DM.

Keywords: *Diabetes Mellitus; Cardiovascular Risk; Endothelial Dysfunction; Endothelial Precursors; Prediction; Prognosis*

Endothelial progenitor cells (EPCs) are defined as various populations of primitive CD34+ endothelial precursors with different origin that additionally express CD31, CD133, CD144 and VEGFR2 antigens [1]. Although previous investigations, which had seized molecular characteristics of EPCs, have sufficiently been distinguished in hierarchy, colony-forming and proliferation capacities, as well as immune phenotypes [2,3], the most specific property of these cells remained an ability to be a source for renewal of mature endothelial cells [4]. Thus, EPCs are determined as a component of endogenous vascular repair system that supports vascular integrity, endothelial function, angiogenesis, neovascularization and reparation [5].

There is a large of body evidence that decreased number and/or weak function of EPCs known as EPC dysfunction frequently proceeded to developing cardiovascular (CV) disease and/or CV events and also accompanied CV risk factors [6-8]. Indeed, declined number of circulating EPCs was associated with CV complications, but restoring of a pole of angiopoetic endothelial precursors was related to an attenuation of vascular function, decreasing of a risk of CV events and improving of clinical outcomes [9,10]. It has been suggesting that EPCs were not just able to produce wild range of spectrum of angiopoetic factors contributing in the angiogenesis and vascularization (hormones, microRNAs, growth factors, active peptides and molecules), but they are directly imbedded in the differentiation into mature endothelial cells and smooth muscle cells of vascular wall supporting vascular integrity and function [11]. The regulation of autocrine EPC function is performed through several signal systems (Akt, nuclear factor-kappa B; STAT, and Notch signaling) and epigenetically via target genes (hey1, hes1, cdkn1c and il33) that mediate an activity of intracellular signal systems [12]. Key triggers for EPC activity were

pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-6), growth factors (vascular endothelial growth factor, transforming growth factor-beta, hypoxia inducible factor-1), hormones (angiotensin-II, renin, and endothelin-1), and oxidative stress components (oxidized lipids), which corresponded to insulin resistance and metabolic memory phenomenon [13].

Although EPCs dysfunction is considered as a key player in vascular complications in diabetes mellitus [14], at early stages of type 1 and type 2 diabetes mellitus, gestational diabetes as well as pre-diabetes circulating number of pro-angiogenic EPCs may be temporary increased [15,16]. However, impaired colony shaping, differentiation and migration abilities and survival in EPCs were dominated in diabetes across its nature evolution [17]. Indeed, hyperglycemia, insulin resistance and dyslipidemia are main triggers of putative EPC dysregulation by affecting the SDF-1/CXCR-4 and NO pathways and the p53/SIRT1/p66Shc axis that contribute to EPCs mobbing, migration, homing, differentiation and angiopoetic properties [18,19]. As a result altered balance between vascular injury and vascular reparation induces atherosclerosis, microvascular inflammation, pro-thrombotic state and thereby modulates target organ damages including retinopathy, renal disorders, cardiac failure, and peripheral artery disease [11]. Another way to regulate quantity and function of EPCs is epigenetic impact that is modulated through several stimuli, i.e. impaired glucose metabolism, inflammatory cytokines (TNF-alpha, interleukin-6), oxidative lipids (for instance, oxidized high-density lipoprotein [Ox-HDL]), growth factors (vascular endothelial growth factor, transforming growth factor beta 1), and adipocytokines' profile disturbance [20]. Indeed, epigenetic changes such as DNA methylation, histone modification and microRNAs expression are able to alter the functions of EPCs leading to reducing number of circulating angiopoetic cells and deteriorate NO metabolism [21,22]. Finally, altered molecular and cellular regulatory pathways lead to dysregulation in endogenous vascular repair system and deteriorating EPCs function and CV complication. In fact, deficiency of circulating number of EPCs strongly predicts atherosclerosis progression [23], restenosis and major adverse cardiac events in diabetics after PCI [24] and CV death [25]. Consequently, measure of quantity and detection of functionality of EPCs could a powerful diagnostic tool for CV risk stratification and prediction of CV events.

On the other hand, there are serious expectations regarding that the clinical outcomes in diabetics could be improved through modification of endothelial function and inducing cardioprotection via restoring number and function of EPCs with metformin therapy, glucagon-like peptide 1-receptor agonists (liraglutide, exenatide), dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin) and sodium glucose cotransporter-2 (SGLT2) inhibitors, which appeared to be effective in suppression of anti-angiogenic miRNAs [26-28]. Although exact protective mechanisms for the EPCs in pre-diabetes and diabetes remains elusive, EPCs dysfunction is promising target for improving clinical outcomes in diabetics.

In conclusion, the EPC dysfunction appears to be a promising biomarker of CV risk and adverse clinical outcomes in diabetics. However, abilities of EPC subsets expressed angiogenesis-related molecules require to be accurate identified and compared each other in clinical studies affecting several populations of the patients with established diabetes mellitus.

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