Editorial

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Epigenetic Mechanisms of Endothelial Progenitor Cell Dysfunction

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Abstract

Diabetes mellitus remains a leading factor contributing increased morbidity and mortality worldwide. The development and progression of DM associates with microvascular and macrovascular complications linked the DM with cardiovascular events. The impaired ability of endothelium to repair the injury and restore integrity depends in part on number and function of endothelial progenitor cells (EPCs). The mechanisms underlying EPC dysfunction in DM predominantly include weak bone marrow mobilization, decreased proliferation, and shortened survival. The weak function and lowered number of EPCs obtained from peripheral blood were recently found in 1 type and 2 type of DM. It has suggested that glucose toxicity, lipid toxicity, inflammation and oxidative stress may directly and indirectly via several molecular mechanisms worse of EPCs function and, however, lead to deficiency of circulating angiopoetic progenitors. Epigenetic changes are considered important key to understand whether EPCs dysfunction is reversible setting or not. The aim of editorial is to discuss around the role of epigenetic changes in EPCs in linking of DM with cardiovascular risk.

Keywords: Diabetes mellitus; Endothelial progenitor cells; Endothelial dysfunction; Endothelial injury; Impaired vascular reparation; Cardiovascular risk

Editorial

Diabetes mellitus (DM) is a major metabolic factor leading to increased mortality and morbidity associated with higher incidence of disability, huge social and economic burden [1, 2]. Recent basic and clinical studies have shown that development and progression of DM has impaired endothelium structure and integrity via several molecular mechanisms induced by glucose toxicity, lipid toxicity, oxidative stress, and inflammation [3-6]. On this way, epigenetic changes affected function and structure of endothelial-derived progenitor cells (EPCs) might lead to worsening of endothelium reparation [7]. Moreover, the EPCs dysfunction might be a clue in the initiation of DM-related microvascular and macrovascular complications [8,9] having a great predictive value [9].

EPCs originated from bone marrow cells and peripheral blood cells support endothelial homoeostasis and attenuate angiogenesis. The mechanisms underlying EPC dysfunction in DM predominantly include weak bone marrow mobilization, decreased proliferation, and shortened survival [10]. Importantly, the deregulation of epigenetic features of EPCs plays a key role in DM-induced vascular injury and endothelial dysfunction [11]. DNA methylation / hydroxymethylation / transmethylation, histone modifications, and differential expression of specific non-coding RNAs like microRNA (miRNAs) are discussed as causative mechanisms of epigenetic modifications [12]. Despite this, the early phases of epigenetically changes in EPCs are pre-diabetic situation affected mitochondrial injury upon hyperglycemic insult, oxidative stress activation, and lowering survival ability of cell organelles [13]. Indeed, lowered cell membrane protection against hyperglycemic endothelial damage through weak antioxidant effect and insufficient hexosamine biosynthetic pathway may independently increase oxidative stress, amplify endothelial inflammation, and impair endothelial and angiopoetic functions [14]. In this context, even transient hyperglycemia may induce long-lasting activating epigenetic changes in the promoter of the nuclear factor kappaB (NF-kappaB) subunit p65 in EPCs [15].

Moreover, it has found that both the epigenetic changes and the gene expression changes have been persisted for euglycemia and associated with NF-kappaB-induced increasing in monocyte chemoattractant protein 1 and vascular cell adhesion molecule 1 expression, and reducing mitochondrial superoxide production [16]. Interestingly, the up-regulated NFkappaB-p65 gene might be a determined prior hyperglycemia due to increased histone 3 lysine 4 di- and trimethylation-1 (H3K4m1) and histone demethylase LSD1 but not H3K4m2 or H3K4m3 [17]. Authors concluded that active transcriptional state of the NFkappaB-p65 gene is linked with persisting epigenetic marks, i.e. enhanced H3K4 and reduced H3K9 methylation, which appear to occur as a result of effects of the methyl-writing and methyl-erasing histone enzymes [18]. All these changes have negatively influenced on survival of EPCs inducing their apoptosis, as well as worse of progenitor angiopoetic capability and endothelium integrity [19].

Additionally, the dysregulation of epigenetic histone modifications in EPCs associated with increased H3K4m3 and reduced H3K9me3 may accompany to metabolic memory and

pro-inflammatory phenotype of resident cells via up-regulation of appropriate miRNAs such as miR-125b, mi34a [20,21]. Indeed, miR-125b mimics increased expression of inflammatory genes, monocyte chemoattractant protein-1, and interleukin-6, and reduced H3K9me3 at their promoters in target cells. miRNA34a overexpression led to a significantly increased EPC senescence, paralleled with an approximately 40% Sirt1 reduction [21]. Yet, dysregulation in H3K4m3 and H3K9me3 has been reported as a cause of increased eNOS expression, which promoters recruitment and differentiation of early EPCs [21].

Probably, pre-exiting higher susceptibility of target cells to hyperglycemia-induced oxidative stress in DM might be related to DNA methylation and / or hypomethylation that regulate angiogenic genes through heterochromatin expression. Maeng Y et al. (2015) [22] reported that overexpressed heterochromatin protein 1α (HP1α) HP1α in EPCs has promoted the differentiation and angiogenic activity of one in vitro and in vivo. This effect is mediated by increased expression of angiogenic genes (NOTCH1, cadherin-5, sirtuins, and angiopoietin-like-2), and decreased expression of progenitor cell marker genes (CD133, CXCR4, and C-KIT) [23-25]. Although DNA and histone methylation lead to distinguished repression of heterochromatin (stable long-term repression and local formation, respectively) [26], the crosstalk between SET domain histone methyltransferases and DNA methyltransferases is essential for relationship of both epigenetic pathways, which mediate reprogramming of EPCs in DM [27].

Thus, epigenetic changes are considered a causative factors contributing to apoptosis and senescence in proangiogenic EPCs in DM. Whether EPCs dysfunction in DM is potently reversible is not fully clear, however, there is growing number of evidence regarding early use of some antidiabetic drugs (i.e. metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and probably glucagon-like peptide-1 agonists) might prevent a metabolic memory phenomenon directly related to epigenetically modified EPCs [7].

Conclusion

In conclusion, EPCs dysfunction is discussed as a conductor of endothelial injury and vascular complications in DM. Epigenetic changes in EPCs are a clue for forming of the “impaired angiopoetic phenotype” of progenitors leading to increased cardiovascular risk. The any strategies appear to be promised to revers of EPCs dysfunction via epigenetic mechanisms might be discussed in context of improved survival and reduced disability in DM individuals.

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