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Endothelial Progenitor Cells Dysfunction in Diabetes Mellitus

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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. Therefore, 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 review is summary of knowledge regarding endothelial progenitor cells (EPCs) dysfunction in DM patients.*

Keywords: *diabetes mellitus; endothelial progenitor cells,*

1. Introduction

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]. Basic studies have exhibited evidence regarding the innate complex mechanisms underlying changes that occur in the vasculature during DM and lead to CV risk associated with macrovascular and microvascular complications of DM. There are several biochemical, hemodynamic and endocrine mechanisms with a preponderant initial role in DM-related vascular dysfunction. 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 - VEGF), and accumulation of advanced glycation end products (AGE), activation of protein kinase C (PKC), activation of the renin-angiotensin-aldosterone system (RAAS), inducting of oxidative stress and apoptosis, decreased nitric oxide (NO) bioavailability, and leukostasis 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]. Low number and weak functionality of EPC were found in subjects with DM 1 and 2 types, as well as in patients with prediabetes including metabolic syndrome, obesity and insulin resistance [17, 18]. In this context, EPCs’ dysfunction is considered a marker of CV risk in general population and in subjects with known DM, as well as a cause of DM-related complications [19]. The aim of the review is summary of knowledge regarding endothelial progenitor cell dysfunction in DM patients.

2. Determination of Endothelial Progenitor Cells

There are some controversies regarding the definition, origin, determination and isolation of EPCs. Indeed, the definition of EPCs is not standardized completely [20]. On head EPCs were defined as cells positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers predominantly VEGF receptor-2 (VEGFR2) cumulatively [21]. VEGFR2 is kinase insert domain receptor (KDR) and in follow term “KDR-positive precursor” as a one of important determinations of EPCs has been remained to use optionally.

The later an expression of other hematopoietic stem cells (CD133 aslo known as AC133) markers and endothelial markers (i.e., platelet-endothelial cell adhesion molecule known as CD31, VE-cadherin also known as CD 144, caveolin-1, von Willebrand factor, and endothelial NO synthase) on the surface of EPCs was determined [22-26]. Interestingly, several subsets of EPCs may exhibit “non-classical” phenotype expressing CD45, Tei2 and Flt-1 markers [27]. However, it has been found that subset of circulating CD34(+) cells expressing VEGFR2 and CD133 was a phenotypically and functionally distinct population of circulating EPCs that may influence on the reparation and angiogenesis [28].

In the pioneer investigation provided by Hur J et al (2004) [23] two types of EPCs labelled as early EPCs and late outgrowth EPCs and received from the same source were identified. They have expressed different level of CD144, Flt-1, KDR (VEGFR2), and CD45 markers. Late outgrowths EPCs produced more nitric oxide, incorporated more into human umbilical vein ECs monolayer, and are able to better form capillary tube than early EPC. However, early EPC secreted more angiogenic cytokines (VEGF and interleukin-8) than late EPC at culture. Therefore, early EPCs intervened in the monolayer of human umbilical vein endothelial cells (HUVEC), but more late EPCs were incorporated to HUVEC [23]. These suggest that two types of EPC might have different roles in neovasculogenesis and neovascularizetion. Thus, by now to help classify EPCs, they have used their ability to differentiate into circulating angiogenic cells (referred as early EPCs) and forming endothelial colony cells (referred as late outgrowth EPCs) [28].

Recently investigations have shown that other population of EPCs distinguished from BM-EPCs and was found in the circulation and / or in the tissue (so called “tissue residential EPCs”) may express monocyte marker CD14, together with CD34 or VEGFR2 [29, 30]. Interestingly, early EPCs are able to express several monocyte markers, i.e. CD14, CD11b, CD11c, on their surface. Contrary, the populations of late outgrowth EPCs were determined as predominantly CD14-negative and they have usually expressed markers of mature endothelial cells [31]. This “non-classical” phenotype of EPCs has associated with vascular protective capacity and may differentiate into mature endothelial cells under influence of microenvironment in the presence of special growth factors (e.g., VEGF, fibroblast growth factor) and paracrine regulators [32, 33].

Despite the exact mechanisms by which EPCs provide cardiovascular protection are unknown [20], both populations of EPCs (early and late outgrowth) are probably to be equal in their ability to produce angiopoetic capacities [34]. However, there is evidence regarding early EPCs could be superior than late outgrowth EPCs to secret angiopoetic cytokines in vitro [23]. Overall, the controversies in heterogeneity of EPCs and their functional capabilities remain uncertain yet.

3. Definition of Endothelial Progenitor Cell Dysfunction

Because of EPCs originated from bone marrow cells and peripheral blood cells maintenance endothelial homoeostasis and attenuate the process of angiogenesis and neovascularization, a lot of investigators thought the EPCs as a component of endogenous repair system. Moreover, EPCs having a protective impact on the vasculature may mediate the functioning of other organs and systems [19, 20, 22, 29]. In this context, dysfunction of EPCs defined as wear 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 [35]. 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 metabolic disease including DM.

4. THE MOLECULAR MECHANISMS OF PROGENITOR ENDOTHELIAL CELL DYSFUNCTION IN DIABETES MELLITUS

Alteration of structure and function of the EPCs has identified in type 1 and type 2 DM [20]. The mechanisms underlying EPC reduction in diabetes predominantly include weak bone marrow mobilization, decreased proliferation, and shortened survival [36]. It has suggested that in DM glucose toxicity, lipid toxicity and reactive oxidative species (ROS) via enhancing inflammation may regulate proliferation BM-EPCs [6, 9, 20]. The key mechanism of this response is the activation of matrix metalloproteinase-9 (MMP-9) through intracellular signal systems, i.e. Akt / STAT and nitric oxide dependent signaling [37]. Maturation and mobbing of the BM-EPCs are under control of growth factors, such as chemokine stromal cell-derived factor-1 (SDF-1), VEGF, granulocyte colony-stimulating factor (G-CSF), and alpha-chemokine that binds to G-protein-coupled CXCR4 [38, 39]. Lataillade JJ et al (2000) reported that SDF-1 may stimulate the growth of EPCs' colonies, chemotaxis and cell expansion [39]. Nevertheless, SDF-1 is able to improve survival of the EPCs in culture through suppression of their apoptosis [40]. SDF-1 exerts pleiotropic effects regulating chemoattraction and adhesion of EPCs in CXCR4-dependend mechanisms playing an essential role in the trafficking of EPCs in various tissue including heart and vasculature [41]. It is importantly that SDF-1 gene expression in EPCs and endothelial cells is regulated by the transcription factor hypoxia-inducible factor-1 (HIF-1), which is under control of reduced oxygen tension in the tissues [42]. VEGF has exhibited autocrine action in EPCs suppressing apoptosis and protect a survival effect [43]. GM-CSF may accelerate re-endotheliazation and reduce microvascular inflammation through mobbing of EPCs [44]. There is evidence that “residence” EPCs originated from myeloid cells could trans-differentiate into endothelial cells in the same manner [34].

DM is characterized reduced expression of angiopoetic factors (SDF-1, VEGF, G-CSF, CXCR4) in heart and vasculature [18]. Moreover, differentiation and mobbing of EPCs after ischemia-reperfusion injury in DM is defective [46]. The initial role in these processes belongs to over-production of ROS, decreased superoxide dismutase activity, and probably SDF-1 genotype polymorphism [18, 42, 47], whereas epigenetic changes in EPCs are considered an important mechanism, which links hyperglycemia, lipid toxicity and metabolic memory [6, 9, 48]. Finally, 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. Therefore, poor differentiation, mobbing and proliferation of BM-EPCs and PB-EPCs lead to decreased circulating pool of primitive cells and worsening reparative capability [40].

5. ENDOTHELIAL PROGENITOR CELLS AND CV RISK

Reduced number and weak functionality of circulating EPCs have been demonstrated sufficiently correlation with vascular endothelial dysfunction and independently association with both traditional (aging, hypertension, hypercholesterolaemia, smoking, diabetes, C-reactive protein level) and non-traditional (insulin resistance, adipocyte dysfunction) CV risk factors, Framingham risk factor score [49-51], as well as frequency of major CV events, revascularization, hospitalization rate and death from CV causes [52-54]. Most importantly, EPCs isolated from peripheral blood of the patients with known CAD have exhibited an impaired migratory and weak proliferative response [50], which have confirmed being of “EPC impaired phenotypes” pre-existing in subjects with CV risk factors prior established CV disease [55, 56]. However, the circulating level of EPCs in patients with established higher CV risk is very variable and does not fully correlate with number of CV risk factors [57, 58], although number of BM-EPCs has closely predicted asymptomatic atherosclerosis [59, 60] and CV disease [61]. One found that lowered number of circulating EPCs originated from bone marrow have accompanied with hypercholesterolemia-induced expression of pro-inflammatory molecules by the vessel wall [62]. Additionally, the level of circulating CD34+KDR+ EPCs may help to identify patients at increased CV risk [55].

However, there are controversies regarding number and colony-forming ability of circulating BM-EPCs and PB-EPCs in individuals with established CV disease and metabolic disease, i.e. DM, metabolic syndrome, obesity. The first controversial reflects disproportion between circulating level of EPCs depending stage of CV disease. To update our knowledge, at the early stage of CV disease especially in patients with asymptomatic atherosclerosis, moderated increase of the EPCs' count in circulation was found [63]. In contrast, lowered level of EPCs might clarify a severity of atherosclerosis or DM-related vasculopathy [64, 65]. The next controversial relates to the level and functionality of EPCs in subjects with obese, metabolic syndrome and DM. Interestingly, at the early stage of metabolically inactive obesity ("not fully" metabolic syndrome) BM-EPCs number may increase and an ability of primitive cells to mobbing, differentiation and colony forming might be not distinguished healthy individuals [66]. In contrast, development of insulin resistance, metabolic syndrome and type 2 DM has closely associated with weak ability of EPCs to mobbing, and the lowered level of circulating EPCs was determined [67]. In contrast, Asnaghi V et al (2006) [68] have reported that clonogenic potential of circulating EPCs in patients with type 1 DM may increase. Finally, heterogeneity of EPCs and the variable changes in the EPCs' phenotypes at the different stages of CV disease and development of DM are limiting factors to determine the predictive value of count and functionality of EPCs in CV risk calculation.

6. The Concept of Impaired Cardiac and Vessel Reparation in Diabetes: Role of EPCs

EPCs are involved in the homeostasis of the heart and vessels, and their exhaustion or dysfunction may accelerate the course of DM-related CV complications. Because uncommitted progenitor cells can differentiate toward the several phenotypes (i.e. endothelial cell phenotype), it is possible that a broader derangement of immature EPCs predisposes to CV complications in DM [69]. Whether weak functionality and / or lower number of EPCs exist prior to both CV risk and established CV / metabolic diseases or they appear resulting in CV risk factors' influence on epigenetic mechanisms of immature progenitors is not fully clear. However, an ability of BM-EPCs and PB-EPCs to restore of structure and function of cardiac and vessels in DM is sufficiently impaired [70]. There is evidence regarding potent possibilities to improve the EPCs' capacity using various methods, i.e. aerobic exercise, lipid lowering drugs, ACE inhibitors, calcium channel blockers, antidiabetic drugs including metformin, sitagliptin [71-75]. Several mechanisms are involved in the attenuation of EPCs functionality by mentioned above approaches, i.e. increase of NO production via enhancing phosphorylated-AMP-activated protein kinase and phosphorylated-eNOS, down-regulation of high mobility group box-1 and AkT / STAT signaling leading to oxidative stress suppression, attenuation of DNA / histone methylation, inhibition of progenitor cells' apoptosis and NETosis through suppression of proprotein convertase subtilisin/kexin type 9 and Dll4/Notch signaling pathway [76-78]. Subsequently, improving function of EPCs in DM appears to be under control and the prevention of CV complication development could be associated with restoring of EPCs-dependent repair mechanisms.

Thus, the EPCs may enhance the balance between heart and vascular injury and repair that is critical for the maintenance of cardiac remodeling, heart function, intimal integrity, endothelial function, and prevention of CV complications [79]. All these findings elucidate that EPCs dysfunction could be an alternative therapeutic target to promoting heart and vessels repair in patients with DM. Despite these promising results received in animal and clinical studies, there is not clear whether the EPCs functionality could be restore completely and the circulating number of EPCs would be achieved the level of healthy individuals. By now, the results of the recently performed investigations have shown that EPCs dysfunction in DM remains to be unresolved yet. Probably, there is required more investigations to explain whether EPCs-dependent mechanisms of tissue repair could be exhibited clinically significant relevance or they are an attribute of nonspecific influence of recently known therapeutic approaches.

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.

7. Abbreviations

AGE - advanced glycation end products

BM-EPCs - bone marrow-derived endothelial progenitor cells

CAD – coronary artery disease

CV - cardiovascular

DM – diabetes mellitus

EPCs – endothelial progenitor cells

G-CSF - granulocyte colony-stimulating factor

HIF-1 - hypoxia-inducible factor-1 (

HUVEC - human umbilical vein endothelial cells

MMPs – metalloproteinases

NADPH - nicotinamide-adenine dinucleotide phosphate

NO – nitric oxide

PB-EPCs – peripheral blood-derived endothelial progenitor cells

PKC - activation of protein kinase C

RAAS - the renin-angiotensin-aldosterone system

ROS - reactive oxidative species

SDF-1 - chemokine stromal cell-derived factor-1

T2DM – type 2 diabetes mellitus

VEGF - vascular endothelial growth factor

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