

Progenitor Endothelial Cells in Pulmonary Arterial Hypertension

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Abstract

Pulmonary artery hypertension (PAH) is common cardio-pulmonary phenomenon associated with higher risk of premature death and disability. Several previous studies have shown that decreased number of circulating endothelial progenitor cells (EPCs) correlated well with vascular remodeling and impaired pulmonary artery function. Moreover, a deep deficiency of EPC characterized a poor clinical outcomes in PAH individuals. There is large body of evidence regarding that the EPCs could be not just biomarker of endothelial dysfunction, but a target of PAH therapy. However, improvement of PAH severity associated with increasing number of circulating EPC with angiopoietic phenotype accompanying sildenafil care. The short communication is depicted the predictive role of EPCs in risk stratification in PAH patients and possibilities to use EPC-based care aimed improving clinical outcomes.

Keywords: Pulmonary artery hypertension; Endothelial progenitor cells; Stratification; risk; Biomarkers.

Short Communication

The pulmonary arterial hypertension (PAH) is common cardio-pulmonary phenomenon that occurs due to primary remodeling of small-to-moderate pulmonary arteries associated with vascular hypertrophy, perivascular fibrosis and stiffening, endothelial dysfunction and vascular occlusion, which lead to right ventricle heart failure and developing of multi organs insufficiency [1]. Prevalence of PAH has been demonstrated steadily growth worldwide and characterized increased mortality rate and disability rate [2]. According to current clinical statement PAH is defined as elevated mean pulmonary artery pressure ≥ 25 mmHg at rest with simultaneously evidence of the presence of pre-capillary hypertension (end-expiratory pulmonary artery wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance >3 Wood units) measured during right heart catheterization [3]. Current conception of the pathogenesis of PAH based on an idea regarding self-supporting vascular remodeling and the thickness due to proliferation of smooth muscle cells with contractile phenotype, infiltration of intima and sub-intima with inflammatory and antigen-presenting cells (T lymphocytes, natural killer cells, activated macrophages/mononuclears), developing of dysfunction of the endothelial cells and fibroblasts, which are resulted in uncoupling intracellular signal systems (calcium signaling, type II bone morphogenetic protein receptor gene-dependent signals, Akt/endothelial nitric oxide synthases pathway, Jak-STAT and NOD-like receptor signaling) and their metabolic regulators (hypoxia, ischemia, inflammatory cytokines, autoantibodies) [4]. In this context, epigenetic dysregulation of DNA methylation, histone acetylation, and microRNAs co-existing PAH nature evolution is considered a leading factor in shaping of mitochondrial dysfunction that contributes to modification of cells involved in the vascular wall repair [5]. Therefore, chemical mediators of vasoconstriction, such hypoxia-inducible factor-1, endothelin-1, angiotensin-II, 5-hydroxytryptamine, and endotoxins, cause increasing vascular resistance, reducing pulmonary

blood perfusion and directly trigger vascular remodeling and worsening vascular repair. The endothelial progenitor cells (EPCs) are key player in restoring of structure and function of vasculature, because they produce unique ability to (trans-) differentiate into cells with different phenotypes including mature endothelial cells and vascular wall smooth muscle cells and attenuate endothelial function [6]. Although EPCs are considered an important component of endogenous vascular repair system, epigenetic modification failed their angiopoietic capabilities and promotes progressive vascular injury [7].

Circulating endothelial progenitor cells (EPCs) are defined as CD45(-) progenitors that obligatory express endothelial cell antigens on their surface, i.e. CD31 (platelet/endothelial cell adhesion molecule-1), CD144 (vascular cadherin), CD309 (VEGF-receptor-2), and CD133 (prominin-like 1) [8]. According to ability to appear in fibronectin coated dish all EPCs were divided into early outgrowth EPCs or late outgrowth EPCs. The late outgrowth EPCs originated from peripheral blood mononuclears demonstrated CD31(+)/CD146(+)/CD105(+) and / or CD309(+) immune phenotype and had functional properties suitable for mature endothelial cells. EPCs are able to synthesize and realize a wide range of active molecules (E-selectin, P-selectin), peptides and growth factors (vascular endothelial growth factor, fibroblast growth factor, granulocyte-macrophage colony-stimulating factor) that modulate angiogenesis and improve vascular integrity and function [9]. It has established that there are several populations of EPCs with different proliferative activities and angiopoietic potencies that can be seized upon biological markers of vascular reparation, vessel injury and endothelial dysfunction.

PAH is characterizes endothelial cell dysfunction associating with decreased number and poor function of circulating EPCs with angiopoietic phenotypes that corresponds to a modulation of inflammatory genes, which are involved in vascular remodeling, fibrosis and hypertrophy (i.e., interleukin-6, TNF-alpha, Gal-3, growth-differentiation factor-15) [10-12]. Although there were strong positive association between exercise tolerance and circulating number of EPCs in PAH patients, there was not found significant relations

between concentration of EPCs and clinical status or hemodynamic features [13]. However, the successful treatment of PAH with sildenafil corresponds to increased circulating number of EPCs in PAH [14]. Therefore, EPC-mediated therapy improves endothelial function, leads to decreasing of mean pulmonary artery pressure and index of pulmonary artery resistance and thereby ameliorates PAH [15]. Thus, identification of phenotypes of EPCs could be useful for prediction of poor clinical outcomes in PAH [16]. Additionally, the efficacy of PAH therapy could be assay with continuous monitoring of EPC number in peripheral blood, although the issue requires to be confirmed in large clinical trials.

In conclusion, deficiency of circulating EPCs associates with severity and prognosis of PAH and it could be predictive biomarker is patients suspecting PAH. Therefore, circulating levels of EPCs can consider as a target of PAH therapy, while this issue requires to be confirmed in large clinical trials.

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