

Preconditioned Endothelial Progenitor Cells as Biomarker of Vascular Repairation?

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Citation: Berezin AE. Preconditioned Endothelial Progenitor Cells as Biomarker of Vascular Repairation? Insights in Biomed. 2017, 2:1.

Abstract

The endothelial progenitor cells (EPCs) have defined as cells positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers predominantly VEGF receptor-2 (VEGFR2) cumulatively. Therefore, there are at least two types of EPCs labelled as early outgrowth EPCs and late outgrowth EPCs probably distinguished their vascular protective ability. Recent animal and clinical studies have shown that reduced number and weak function of EPCs may not only indicate to higher CV risk, but contribute to the impaired heart and vessels repairation. Interestingly, there are some subpopulations of EPCs especially recruited from peripheral blood cells, which may exhibit very variable pro-angiogenic effect and endothelial repair capacity and they are called "preconditioned" EPCs. The aim of the short commentary is depicted the possibilities to use of measurement of traditionally labeled EPCs as biomarker of cardiovascular risk.

Keywords: Cardiovascular disease; Precondition; Endothelial progenitor cells, Vascular complications; Angiogenesis; Repairation

Received: January 10, 2017; **Accepted:** February 24, 2017; **Published:** February 27, 2017

Introduction

Endothelial progenitor cells (EPCs) have determined primitive cells originated from precursors found in the bone marrow and peripheral blood [1]. The ability of EPCs for self-renewal and differentiation into mature endothelial cells has recently been under intense investigation [2] and remains of high interest for regenerative medicine [3]. The recent pre-clinical and clinical studies have shown a key role of bone marrow EPCs in the endothelial repair, angiogenesis, neovascularization and attenuation of vascular function, whereas EPCs derived from peripheral blood cells including circulating mononuclears are under tight epigenetic control, and several paracrine and metabolic mechanisms and they are considered a central mechanism of immediate reparative response of injury [4-6]. There is a large body of evidence regarding that the both subpopulations of EPCs are mobilized or released into systemic circulation in response to specific stimuli [7-9].

Formerly EPCs were defined as cells positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers predominantly VEGF receptor-2 (VEGFR2) cumulatively [1]. Later an expression of other hematopoietic stem cells markers (CD133, AC133) and some endothelial markers (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 found [10-13]. Therefore, some subsets of EPCs may express mononuclear antigens, i.e., CD14, CD11b, CD11c, together with CD34 or VEGFR2, CD45, Tei2 and Flt-1 [14] and shape so called "non-classical" phenotypes. All these EPCs remain vascular protective capacity and may differentiate into mature endothelial cells under effect of microenvironment, paracrine regulators and appropriate growth factors (e.g., VEGF, fibroblast growth factor).

Additionally, there are at least two types of EPCs labelled as early outgrowth EPCs and late outgrowth EPCs and isolated from similar source [15]. Both subpopulations of EPCs have expressed CD144, Flt-1, KDR (VEGFR2), and CD45 markers in different manner. 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 [16]. Early EPC secreted more pro-angiogenic cytokines (VEGF and interleukin-8) than late EPC at culture [17]. Moreover, early EPCs intervened in the monolayer of human umbilical vein endothelial

cells (HUVEC), but more late EPCs were incorporated to HUVEC [18]. Overall both subpopulations of EPC might distinguish one another in ability to differentiate into circulating angiogenic cells (referred as early EPCs), shaping endothelial colony cells (referred as late outgrowth EPCs), and inducing vasculogenesis [19].

Whether early and late outgrowth EPCs mediate similar effect on vascular protection and tissue repair is uncertain [20]. There is large evidence that the EPCs especially recruited from peripheral blood cells may exhibit very variable pro-angiogenic effect and endothelial repair capacity and they are called "preconditioned". Indeed, pro-inflammatory cytokines realizing into circulation from mononuclear cells following direct vascular endothelial injury after stenting and angioplasty procedures via NO/cGMP/p38 MAPK and Notch4 signaling pathways are involved in precondition of wild-type EPCs and increase an ability of EPCs to neointima formation [21,22]. In contrast, some metabolites, i.e., creatinine, phosphates, glucose, and cytokines (interleukin [IL]-2beta, IL-8, tumor necrosis factor-alpha) negatively reprogram the early EPCs suppressing their maturation and leading to weak differentiation into mature endothelial cells [23-26]. Finally, growth dynamics, lipoprotein transport, and gene expression of EPCs are actively modified by secretomes of different cells involving in the pathogenesis of cardiovascular (CV) and metabolic disease.

All these claim a fact that not only a lower level of circulating EPCs, but reduced EPC functionality are powerful factor of increased CV risk [27-30]. Indeed, recent animal and clinical studies have shown that reduced number and weak function of EPCs may not only indicate to higher CV risk, but contribute to the impaired heart and vessels reparation [31-33]. In a way it has suggested that impaired differentiation, proliferation and migration of EPCs as well as exhaustion of endogenous endothelial repair mechanisms involving EPCs may contribute to vascular dysfunction, inflammation, thrombosis and impairing and fibrinolysis and re-

endothelialisation. Consequently, CV risk factors may influence on EPC morphology and function shaping impaired secretory phenotype and altered expression of regulatory factors [34]. On the one hand, all these mediate inadequate response of endothelial repair system toward vascular injury. On the other hand, preconditioned by CV risk factors EPC are discussed a main modulator of vascular reparation and restoring endothelial functions [35].

Discussion

In this context, measurement of circulating preconditioned EPCs' level might be much more pretty accurate biomarker of CV risk and CV outcomes in various diseases. Consequently, a simple measurement of circulating EPC number showing potential for improved endothelial function based on labeling of specific antigens might be wrong step to determine the regenerative ability of EPCs. Probably, we have precious many investigations with controversial results regarding predictive role of EPC count in peripheral blood in CV disease and diabetes [36-41]. However, lack of accessible and affordable approved methods regarding an assay of ability to survive, moving, differentiation, and colony forming of preconditioned EPCs is challenge for use of this approach in routine clinical practice, although there are data that the even simple measurement of EPCs in circulation might be useful for CV risk predicting in patients with acute coronary syndrome, atherosclerosis, heart failure and diabetes [42,43].

Conclusion

Large clinical studies are required to re-assay the role of circulation EPC number measurement in CV risk prediction. Probably, novel methods regarding exam of functionality preconditioned EPCs are needed in future.

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