

Immune Phenotypes of Circulating Endothelial Progenitor Cells: A Biomarker of Cardiovascular Disease?

Alexander Berezin*

Professor, MD, PhD, Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University for Zaporozhye, 26, Mayakovsky Av., Zaporozhye, Postcode 69035, Ukraine

Abstract

Endothelial Progenitor Cells (EPCs) are recognized a circulating pool of primitive endothelial precursors of different origin from bone marrow or peripheral tissues, which express on their surface endothelial markers, i.e. CD45-, CD34+, CD144+, CD309 etc. There are at least two types of EPCs: early outgrowth EPCs and late outgrowth EPCs, which distinguish each other their structure, function, expression of CD markers and gene expression. Whether various immune phenotypes of circulating EPCs may play similar role in endothelial homeostasis acting as endogenous repair system is not fully understand. However, both immune phenotype EPCs are involved in the pathogenesis of CV diseases across all stages of CV continuum. The short commentary is depicted the possibility to use a dysfunction of different EPCs as a predictive biomarker of CV disease development with promising discriminative value to relate to CV clinical outcomes.

Keywords: Cardiovascular Disease; Endothelial Progenitor Cells, Prognosis; Outcomes

***Corresponding Author:** Alexander Berezin, Professor, MD, PhD, Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University for Zaporozhye, 26, Mayakovsky Av., Zaporozhye, Postcode 69035, Ukraine; Tel.: +38 061 2894585; Fax: +38 0612894585; E-mail: dr_berezin@mail.ru and aeberezin@gmail.com

Cardiovascular (CV) diseases including atherosclerosis, arrhythmia, myocardial infarction, heart failure remain to be a main cause of death worldwide [1]. Recent animal and clinical studies have shown that endothelium that widely involved in the

pathogenesis of CV diseases across all stages of CV continuum could coordinate both mutual counteracting processes, i.e. vascular injury and reparation [2, 3]. The pivotal role in the endothelium homeostasis plays endothelial progenitor cells (EPCs), which enhance angiogenesis, neovascularization and vascular function acting as endogenous repair system [4, 5].

Pioneer investigations of Asahara et al [6, 7] have been shown that EPCs located in a bone marrow and probably in peripheral tissues are able to migrate into injury sites and directly turning into mature endothelial cells and even into smooth muscle cells shaping new vessels. Therefore, EPCs may synthesize and secrete a broad spectrum of angiopoietic factors, i.e. Vascular Endothelial Growth Factor (VEGF), Stromal-cell-Derived Factor-1 (SDF-1), and Fibroblast Growth Factor (FGF), which attenuate angiogenesis and vascularization through epigenetic mechanisms affecting as endothelial precursors, as more mature endothelial cells [8]. Acting through several intracellular pro-survival regulators (hypoxia induced factor-1 α , Akt / eNOS signaling) EPC-depending cytokines are able to mediate cytoprotective effects on the target cells in injured tissues [9]. In this context, CV risk factors including diabetes, obesity, impaired fasting glucose, hypothyroidism, hyperurikemia may induce EPC dysfunction determined as lowering EPC number and weak their functionality [10-13]. As a result EPC dysfunction may precede manifesting endothelial dysfunction and CV diseases through worsening vascular repair capability [9, 14]. On the other hand, EPC dysfunction could preview CV diseases and even CV risk factors, although there is no clear explanation of the phenomenon [14-16]. Probably epigenetic dysregulation is a main cause leading to both lowered number and weak function of EPCs prior to influencing traditional CV risk factors [17]. Taken together it is

suggested that various CV risk factor may impact on structure, function, ability to colony forming and differentiation of different immune phenotypes of EPCs in a distinguish manner.

Recent studies performed *ex-vivo* with cultured EPCs allow recognizing two different phenotypes of EPCs labelled as early outgrowth EPCs and late outgrowth EPCs and isolated from similar source having similar markers expressing on their surfaces, i.e. CD144, CD309 (VEGF receptor - VEGFR), and CD45 [18, 19]. Late outgrowths EPCs may easily shape colony of endothelial cells than early outgrow EPC. Moreover, late outgrowths EPCs were able to produce more nitric oxide and got better attenuation of capillary structure when compared to early EPC [18]. Consequently, early outgrow EPCs may produce slightly broad spectrum of pro-angiogenic and angiopoietic cytokines including VEGF and interleukin (IL)-6 [19, 20]. Additionally, there was a considerable difference between early outgrow EPCs and late outgrow EPCs in gene expression profiles that affects their ability to express some intracellular signal systems, i.e. stem cell factor (SCF)/c-Kit, angiopoietin-1/Tie2, and SDF-1/CXCR4 [21]. It has postulated that the difference in gene expression in EPC populations could enhance their ability to realize variable effects affected secretion and differentiation. However, nowadays we do not exactly know whether both immune phenotypes of EPCs distinguishing their ability to shaping endothelial cell colony in culture. In this context, cytokine-triggered low intense inflammation as a common pathogenetic factor of CV diseases may up-regulate an expression of various genes leading to worsening survival ability of EPCs and number depletion of ones [22].

Indeed, an exhaustion of circulating number of EPCs labeled as CD34+ and / or CD133+, AC133+, endothelial cell markers (CD309, CD31, CD 144) was found in patient with atherosclerosis, cardiac dysfunction, myocardial infarction / acute coronary syndrome, hypertension, diabetes mellitus, thyroid dysfunction [14, 15, 23-25]. However, there are several controversies regarding the role of different immune phenotypes of EPCs in tissue reparation. Koller et al (2016) [23] reported that EPCs, defined as triple-positive cells (CD34+CD45-CD309+) was a significant and independent inverse predictor of mortality of heart failure as ischemic as well as non-ischemic etiology. There is evidence that the number of circulating non-hemopoietic EPCs with immune phenotypes CD14+CD309+ and

CD14+CD309+Tie2+ could demonstrate more pretty discriminative value in ischemia-induced cardiac failure than CD45+ CD309+ EPCs [24]. Therefore, lowered number of CD14+CD309+Tie2+ EPCs may suggest shaping systolic cardiac dysfunction, whereas hemopoetically originated EPCs did not exhibit predictive value in left ventricular hypertrophy and isolated diastolic function [14, 25]. Moreover, incorporation of number of CD14+CD309+Tie2+ EPCs as a predictive biomarker into biomarker risk score for cumulative CV events in heart failure patients may sufficiently improve sensitivity, specificity, reliability and final discriminative value of the scale [26]. Yang et al [27] reported that count of circulating EPCs with immune phenotype CD34-/CD133+/KDR+ (VEGFR+) may exhibit osteogenic potential and strong correlates with coronary atherosclerosis at the early stage. Whether increased number of CD34-/CD133+/KDR+ (VEGFR+) EPCs in individuals suspected to atherosclerosis could link to the risk of all-cause mortality is not fully understand. Similar results were received by Berezin A et al (2016) [28] in small cohort study. Authors reported that lowered number of non-classical EPCs with immune phenotypes CD14+CD309+ and CD14+CD309+Tie2+, but not CD34+ subsets of EPCs associated well with biomarker of atherosclerosis in individuals with type 2 diabetes mellitus. Finally, EPCs with classical CD34+CD133+CD309+ phenotype and non-classical CD34+Tie2+ phenotypes may sufficiently distinguish each other in ability to predict CV diseases and exhibit discriminative value for clinical CV outcomes. Further large clinical trials are required to explain the role of various immune phenotypes of circulating EPCs as a biomarker of CV disease with promising predictive value.

Conclusion

CV disease development associates with exhausting number of circulating EPCs and / or lowered functional ability of ones. CV risk factors are able to modulate innate features of circulating EPCs with different immune phenotypes, which correspond to a risk of CV events and CV mortality. However, there is no clear evidence regarding pretty predominance in useful of measurement of immune phenotypes of EPCs to predict CV disease that requires more clinical investigations.

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