

## Enhancing endothelial progenitor cell for clinical use

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endothelial dysfunction and cardiovascular risk factors. However, translation of basic research into the clinical practice has been limited by the lack of unambiguous and consistent definitions of EPCs and reduced EPC cell number and function in subjects requiring them for clinical use. This article critically reviews the definition of EPCs based on commonly used protocols, their value as a biomarker of cardiovascular risk factor in subjects with cardiovascular disease, and strategies to enhance EPCs for treatment of ischemic diseases.

**Key words:** Endothelial progenitor cells; Cell therapy; Enhancing function and number; CD34; Clinical trials

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**Core tip:** Circulating endothelial progenitor cells (EPCs) have important potential for use in the treatment of ischemic diseases. However, their clinical application is limited by the lack of unambiguous and consistent definitions. This article reviews the definition of EPCs, their status in subjects with cardiovascular disease and discusses strategies to enhance EPCs for treatment of ischemic diseases. In patients with cardiovascular conditions who may require EPC administration, EPC numbers are low and EPCs are dysfunctional. Augmenting these cells may eventually improve their clinical efficacy.

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### Abstract

Circulating endothelial progenitor cells (EPCs) have been demonstrated to correlate negatively with vascular

### INTRODUCTION

Circulating endothelial progenitor cells (EPCs) are bone marrow - derived mononuclear cells that have the capacity to migrate, proliferate, and differentiate into mature endothelial cells (ECs)<sup>[1]</sup>. Asahara *et al*<sup>[2]</sup>,

reported that CD34<sup>+</sup> hematopoietic progenitor cells from adults can differentiate *ex vivo* to an endothelial phenotype, expressing EC markers and incorporating into neovessels. Since then, many publications have demonstrated the phenotype and function of these cells and use them in animal models and clinical studies<sup>[3-7]</sup>.

## HETEROGENEITY OF EPC

The translation of basic research into the clinical practice of EPCs has been limited, in part, by the lack of unambiguous and consistent definitions of EPCs. In general, two methods have been used to isolate EPCs: (1) cell selection based on surface markers; and (2) cell culture and then selection. Besides CD34, a variety of cell surface markers have been shown to be associated with EPCs.

Both CD14<sup>+</sup> monocytic and CD14<sup>-</sup> non-monocytic mononuclear cells have been used as the starting population for cultivation of EPCs<sup>[6]</sup>. Fernandez Pujol *et al.*<sup>[8]</sup>, demonstrated that CD14<sup>+</sup> monocytic cells underwent a morphological transformation to oval cells and showed a clear expression of EC markers after 1 wk. These markers include von Willebrand factor (vWF), VE-cadherin, CD105, acetylated low-density lipoprotein (ac-LDL)-receptor, CD36, vascular endothelial cell growth factor receptor-1 (VEGFR-1, Flt-1), and VEGF receptor-2 (VEGFR-2 or KDR). However, Urbich *et al.*<sup>[6]</sup>, showed that CD14<sup>-</sup> non-monocytic mononuclear cells also expressed endothelial marker proteins and were able to form colonies. CD14<sup>-</sup> cells were found to incorporate into vascular structures of nude mice after hind-limb ischemia and significantly improved neovascularization.

Kalka *et al.*<sup>[9]</sup>, cultured human peripheral blood mononuclear cells and characterized adherent EPCs. EPCs were able to up-take ac-LDL and expressed endothelial surface markers such as vWF, VEGFR-2, VE-cadherin, CD146, and CD31. In a similar approach, Hill *et al.*<sup>[10]</sup>, found that colonial formation EPCs expressed KDR, CD31, and Tie2.

Interestingly, Hur *et al.*<sup>[3]</sup>, identified two types of EPCs from the same source and labelled them as early EPC and late EPC. They expressed different level of VE-cadherin, Flt-1, KDR, and CD45 markers. Late EPC produced more nitric oxide, incorporated more into human umbilical vein ECs monolayer, and are able to better form capillary tube than early EPC<sup>[3]</sup>. However, early EPC secreted more angiogenic cytokines (VEGF and interleukin-8) than late EPC at culture<sup>[3]</sup>. These suggest that two types of EPC might have different roles in neovascularogenesis.

More recently, besides CD34, CD133, KDR and Ac-LDL up-take have been used more frequently as EPC markers for selection<sup>[11-14]</sup>. CD34 is a stem cell marker, CD133 an early EPC marker, KDR a marker for ECs, and Ac-LDL up-take, an endothelial function. Controversy remains on what are the most suitable makers for selecting EPC and what type of EPCs are most optimal for clinical application of cell therapy. Regardless of their

cell surface markers, EPCs shall have the capacity to form tubular structure on Matrigel<sup>[3,4]</sup>, take up Ac-LDL<sup>[3,4]</sup>, form colonies<sup>[4-6]</sup> and have the capacity to form vessels *in vitro*<sup>[2,9,15,16]</sup>.

## EPC NUMBER AND FUNCTION IN CARDIOVASCULAR DISEASES

Clinical studies documented a decreased number of circulating EPCs in coronary artery disease (CAD) patients, suggesting that levels of circulating EPCs might be associated with vascular endothelial function and cardiovascular risk factors<sup>[17-21]</sup>. Hill *et al.*<sup>[10]</sup> measured colony-forming units of EPCs from patients with different degrees of cardiovascular risk but without history of cardiovascular disease. A strong correlation was found between the number of circulating EPCs and the subjects' Framingham risk factor score and between the endothelial function and the number of EPCs. It was also found that EPCs from subjects at high risk for cardiovascular events had higher rates of *in vitro* senescence than cells from subjects at low risk.

Subsequently, it was demonstrated that reduced level of circulating EPCs independently predicts atherosclerotic disease progression and development of cardiovascular events<sup>[17-19]</sup>. Sen *et al.*<sup>[17]</sup>, suggested that EPC determines the quality of the coronary collateral circulation. Georgescu *et al.*<sup>[18]</sup> found that hypertension with hypercholesterolemia is accompanied by the alteration of vascular tone, the expression of pro-inflammatory molecules by the vessel wall, and reduced circulating EPC number.

However, contrasting results were reported, by Güven *et al.*<sup>[22]</sup> and Werner *et al.*<sup>[23]</sup>, on the association between the level of circulating EPCs and severity of CAD. Similarly, contrasting reports were also published in patients with peripheral arterial disease (PAD)<sup>[13,24-26]</sup>. This difference might be explained by different sampling time during the studies at different part of the disease process<sup>[27]</sup>. Higher circulating EPC may indicate early stage of CAD and PAD, while lower circulating EPC indicates more severe and late stage of disease, and is associated with poorer outcome of these patients. It become clear that EPC cell number and function are reduced in subjects with cardiovascular risk factors and more severe cardiovascular disease<sup>[28-32]</sup>. These are also subjects whom may benefit from EPC harvest for autologous transplantation. Thus it is important to enhance EPC cell number and function for clinical use.

## STRATEGIES TO ENHANCE EPC POTENCY

Though animal studies of autologous EPC transplantation is feasible in both coronary and peripheral artery diseases, clinical application of these therapies are limited. Asai *et al.*<sup>[33]</sup> demonstrated that topical Sonic hedgehog (*Shh*) gene therapy enhanced wound healing

by promoting recruitment of bone marrow derived EPCs. Besides migration, Shh also enhances EPC proliferation, adhesion, and tubule formation. In contrast, Jujo *et al.*<sup>[34]</sup>, showed that AMD3100, a CXCR4 antagonist, enhanced neovascularization and functional recovery after myocardial infarction through enhanced mobilization of EPC. Interestingly, the combinational therapy of Shh gene transfer with AMD3100 improved cardiac functional recovery by enhanced progenitor cell mobilization<sup>[35]</sup>.

Yao *et al.*<sup>[12]</sup>, modified EPCs with tissue kallikrein (TK) and found that TK protected EPCs from oxidative stress-induced apoptosis *via* inhibition of activation of caspase-3 and -9, induction of Akt phosphorylation, and secretion of vascular endothelial growth factor<sup>[12]</sup>. Moreover, Fu *et al.*<sup>[36]</sup>, demonstrated that TK can enhance EPC migration and adhesion by up-regulating the expression of integrin- $\alpha$ 3. Thus, TK-modified EPCs may be another strategy to enhance therapeutic potency of EPC for tissue repair.

Other agents such as statin, adiponectin, thymosin  $\beta$ 4 (T $\beta$ 4), losartan, aliskiren, hydrogen sulfide, GTP cyclohydrolase I, and ephrin-B2/Fc have been used to enhance EPC<sup>[37-42]</sup>. Among these, statin, losartan, aliskiren, and T $\beta$ 4 have good potential to improve quality and quantity of EPCs in patients with diabetes. Statins, a commonly used class of drugs to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, have pleiotropic beneficial effect on EPC<sup>[37,43]</sup>, atorvastatin increased circulating EPC after just 4 wk of administration in patients with ischemic heart failure<sup>[37]</sup>. Rosuvastatin mobilized EPC which is shown to be Akt/endothelial nitric oxide synthase dependent<sup>[43]</sup>.

Besides statins, losartan, an angiotensin II receptor antagonist drug, commonly used in hypertension, significantly improved impaired EPC function in hypertensive patients<sup>[42]</sup>. T $\beta$ 4, an actin sequestering protein, is found to possess angiogenic activity<sup>[44,45]</sup> and anti-diabetic property<sup>[46]</sup>. T $\beta$ 4 is angiogenic and can promote EC migration and adhesion, tubule formation, aortic ring sprouting, and angiogenesis<sup>[44,45]</sup>. T $\beta$ 4 ameliorates hyperglycemia and improves insulin resistance in mouse model of type 2 diabetes<sup>[46]</sup>. We showed that EPCs derived from Zucker diabetic fatty rat have reduced angiogenic potential. Treatment with T $\beta$ 4 *in vitro* improved EPC function and survival. It also appears to be beneficial *in vivo* (unpublished results). T $\beta$ 4 is a potential drug that can improve function of diabetic EPCs for cell therapy.

Clinically, EPC has been used in clinical trials<sup>[7,21,47]</sup>. In early phase clinical trials using EPCs for intramyocardial transplantation in subjects with refractory angina, Losordo *et al.*<sup>[7,48]</sup> used G-CSF to mobilize bone marrow cells and selected CD34<sup>+</sup> cells using magnetic beads post-apheresis. Subsequently these are injected into the ischemic myocardium without enhancing the cells<sup>[7,48]</sup>. Feasibility and safety appears to be established. However, efficacy remains to be demonstrated in sizeable clinical trials, preferably in a randomized and blinded manner. As subjects who need EPC therapy has lower EPC numbers and more dysfunctional EPC, these cells may need to be

augmented prior to autologous transplantation. There are already several agents discussed above, which can enhance mobilization (*e.g.*, AMD3100) and function of these cells. For the latter, post-processing after harvesting, may be employed. However, it will be important to make sure the cells improve and no adverse effect on these cells as a result. *In vitro* assays and animal experiments appear to show enhancement. Whether these strategies can be translated into clinical use remain to be demonstrated. It is also important to define relevant clinical end-points and surrogate parameters. Beyond statistical significance in improving markers, these need to be clinical significance. Thus, EPC migration may increase by a few millimeter *in vitro* in a dish or the left ventricular longitudinal strain may increase by a couple of percent, it is important to show clinical relevance in translation. Besides autologous strategies, allogeneic transplantation, which has been used in animal models, may also be considered for clinical use<sup>[45,49]</sup>.

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