

Endothelial Progenitor Cells are Affected by Medications and Estrogen

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Endothelial dysfunction is the main road to the development of atherosclerosis. The paradigm today is that lack of endothelial progenitor cells is a major limitation to vascular regeneration and leads to endothelial dysfunction. Studies have shown the association and positive correlation between endothelial function and the ability to build colonies of endothelial progenitor cells-colony-forming units (EPC-CFU). EPCs are defined as cells that have a positive receptor to a hematopoietic stem cell marker such as CD34 as well as endothelial cell markers like vascular endothelial growth factor receptor 2 (VEGFR2), together with an immature hematopoietic stem cell marker CD133 (an endothelial cell marker that is absent on mature endothelial cells, which is the main reason for using this marker for identifying EPCs) [1].

It is believed that these cells – CD34+/CD133+/VEGFR2+ cells – are immature progenitor cells, while CD34+/VEGFR2+ cells are shed cells of the vessel wall [2]. There are at least two types of EPCs: early and late. Early EPCs are characterized as an angiogenic population of cells that can be grown on culture within 4–7 days in vitro [3] and have a spindle shape, while late EPCs (outgrowth EPCs) have different growth patterns and are grown in culture for at least 2–3 weeks in vitro [4] and have a cobblestone appearance. Early EPCs form colony-forming units and have endothelial cell receptors like CD31, TIE2 and VEGFR2 [3]. Late EPCs have other endothelial receptors, such as VE-cadherin, von Willebrand factor, as well as CD31, CD133, CD34 and VEGFR2 [4]. The late EPCs have been shown to be able to differentiate into mature endothelial cells for angiogenesis and vasculogenesis.

Studies have demonstrated that EPCs (mainly early EPCs) can be used as a marker of endothelial function, and some

researchers suggest using these cells as a biological marker for risk assessment of cardiovascular disease.

Hill et al. [5] demonstrated a negative correlation between EPCs and the Framingham risk score, and a positive correlation between colony-forming units of early EPCs and brachial artery flow-mediated diameter dilatation (the most physiological non-invasive tool to estimate endothelial function). Endothelial dysfunction has been shown to lead to the development of atherosclerosis and a grave cardiovascular outcome [6], while other studies found that a reduced number of early EPCs was

associated with a significantly higher incidence of cardiovascular events [7]. On the other hand, higher levels of EPCs were associated with fewer

cardiovascular events, including death and a major cardiovascular event or revascularization and hospitalization, in a group of 519 patients with known coronary artery disease [8]. It has been shown that isolated early EPCs have an impaired function, an impaired migratory response, as well as a negative correlation of EPCs with coronary artery disease (CAD) severity [9]. It could be that the impaired migratory response is due to down-regulation of VEGF (observed in patients with CAD), or to an intrinsic pathway within the EPCs. The consequences are decreased number and function of PECs in patients with CAD [10-14]. More than that, circulating EPCs are further inhibited in patients with more severe CAD [13,14]. Possible mechanisms

to explain these effects in patients with severe coronary artery disease include exhaustion of endothelial progenitor cell production in the bone marrow and mobilization from the niches in the bone marrow, or reduced availability of nitric oxide due to oxidative stress and/or enhancement of free oxygen radical in the blood [12].

Endothelial progenitor cells are one of the cornerstones of blood vessel regeneration

EPCs are affected by acute and chronic diseases like vascular events and infections

PHARMACOLOGICAL INTERVENTION IN PATIENTS WITH CAD

Recent studies have shown that circulating EPCs can be enriched by short-term culture of steady-state peripheral blood mononuclear cells [15] and used as a reliable marker of endothelial function and integrity. Cardiovascular medications are used

to increase overall numbers and function of EPCs in patients with cardiovascular risk factors.

ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

Several studies in animal models have shown enhanced EPC number and function following treatment with ARBs [16-18]. Possible mechanisms involving inhibition of oxidative stress [19,20], through activation of the peroxisome proliferator activated receptor-gamma (PPAR-γ), have been suggested [21].

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

A positive trend towards improvement in EPC numbers and function [22] was observed in patients with stable coronary artery disease. It is believed that this improvement occurs through the bradykinin B2 receptor pathway, which activates endothelial nitric oxide synthase (eNOS), which in turn enhances EPC mobilization, number in the peripheral circulation and function [22].

CALCIUM CHANNEL BLOCKERS (CCB)

Studies have shown that CCBs have a favorable effect on EPC number and function [23,24]. The mechanism might be through increased VEGF secretion from vascular smooth muscle cells within the vessel wall [24]. Another possibility is the result of greater resistance to free oxygen radicals and less apoptosis; both are possibly induced by CCBs [24].

HMG-COA REDUCTASE INHIBITORS

Several studies have documented the favorable effect of statins on EPCs; they induce EPC proliferation and function [25-27] even after 3 weeks of treatment at different doses. EPC proliferation and differentiation were induced by statins through the Akt pathway. This mechanism may induce eNOS activation and VEGF-induced endothelial cell migration [28].

THE ENDOCRINE SYSTEM AND EPCS

INSULIN GROWTH FACTOR SYSTEM

Insulin growth factor 1 (IGF1) has a favorable effect on EPC number and function, a phenomenon that decreases with age. These decreased effects (with aging) could be reversible with growth hormone (GH) treatment [29]. It has been shown that IGF1 stimulates differentiation, migration and vascular network formation of EPCs in elderly subjects through activation of IGF1 receptor. IGF1 increases eNOS expression, activating PI3 kinase/Akt. Growth hormone induces augmentation of IGF-1, NO bioavailability, and EPC number [30]. Endothelial function measured by flow-mediated diameter change was found to correlate with levels of IGF3 in serum [31]. Infusion of IGF1 increased the number of circulating EPCs and inhibited inflammation and oxidative stress in ApoE-null mice [32]. In a

porcine model, IGF1 that was secreted by EPCs induced myocardial repair of infarction [33], and IGF1 has been reported to repair endothelial damage via an NO-dependent pathway and increase EPC mobilization [34].

Angiogenesis starts with mobilization of EPCs that proliferate and form new vessels [35]. Hypoxia is one of the most potent triggers to start EPC recruitment and mobilization. Hypoxia inducible factors (HIFs) regulate transcription of key angiogenic genes, including the gene of VEGF [36]. Insulin-like growth factor binding protein 3 (IGFBP-3) is involved in retinopathy [37]. IGFBP-3 expression is regulated by hypoxia, promoting differentiation of EPCs to endothelial cells. It increases EPC migration, VEGFR1 and VEGFR2 expression, tube formation [38] and NO synthesis. Exogenous IGFBP-3 increased vessel regrowth possibly by promoting progenitor cell chemoattraction [38].

ESTROGEN AND EPCS

Estrogen has been shown to induce accelerated re-endothelialization of injured arterial segments within 7 days with a significant reduction in carotid medial thickness 14–21 days after injury [39]. This tremendous effect was observed following another observation: 3 days after the carotid artery injury a significant increase of circulating EPCs was documented in animals that received estrogen compared to others that did not receive estrogen. This mechanism, estrogen-mediated re-endothelialization with increased numbers of EPCs, was found to be nitric oxide dependent because estradiol did not accelerate re-endothelialization or augment EPC mobilization after injury in mice deficient in the enzyme nitric oxide synthase (eNOS^{-/-}). Estrogen induces mobilization of circulating EPCs from the bone marrow, and these cells help to build and restore injured/damaged endothelium, supporting re-endothelialization after arterial injury. This is dependent on eNOS expression and, in the absence of NO, estrogen does not affect EPCs. Estrogen induces proliferation and migration, and inhibits apoptosis of EPCs [39].

EPC number and function can be manipulated for therapeutic purposes

SUMMARY

EPCs constitute an essential cornerstone in the building and maintenance of the endothelial blood vessels, as well as the functioning of most of the systems of our body, including the endocrine, neurological, hematological, immune and inflammatory systems as well as organs such as kidney, heart, lungs and brain. Moreover, they serve as gatekeepers, preventing degenerative processes that affect every organ and tissue. It is important to know and understand that medications and hormones have an effect on these cells. This knowledge may help us to stimulate and maintain EPCs as well as plan future pharmacological interventions.

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“In war, truth is the first casualty”

Aeschylus (525-456 BC), Greek tragic dramatist