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Endothelial Progenitor Cell in Cardiovascular Diseases

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1. Introduction

The last decade has seen a huge interest in the field of regenerative biology, with particular emphasis on the use of isolated or purified stem and progenitor cells to restore structure and function to damaged organs. Circulating endothelial progenitor cells (EPCs) have been studied as a potential cell source that contributes to neovascularization via postnatal vasculogenesis (Asahara et al., 1997). EPCs are reported to naturally home and integrate into sites of physiological vessel formation *in vivo* and incorporate into the vasculature of tumors, ischemic skeletal and cardiac muscle (Asahara et al., 1999). Furthermore, Accumulating evidence demonstrates a relationship between the frequency of circulating EPCs and cardiovascular disease risk (Hill et al., 2003). In the following, we will review the putative role of EPCs in endothelial repair and provides evidence for their influence on atherosclerosis.

2. Identification of EPCs

Despite the availability of effective preventive measures, coronary artery disease (CAD) remains a leading cause of morbidity and mortality in most industrialized countries. Convincing evidence indicates that the integrity and functional activity of the endothelial monolayer play an important role in atherogenesis. Traditional view suggests that endothelium integrity is maintained by neighboring mature endothelial cells which migrate and proliferate to restore injured endothelial cells. However, a series of clinical and basic studies prompted by the discovery of bone marrow-derived EPCs have provided new insights into these processes and demonstrate that the injured endothelial monolayer is regenerated partly by circulating EPCs. Putative circulating endothelial progenitors were first described in the adult human by Asahara *et al.* (Asahara et al., 1997) in 1997. They used the presence of CD34 to sort cells from the adult peripheral blood mononuclear component, based on the knowledge that this antigen is carried by both the angioblasts and haemopoietic stem cells responsible for vasculogenesis in embryonic life. By culturing MNCs (mononuclear cells) enriched or depleted in these CD34+ cells, they showed that the CD34+ component is able to give rise to spindle-shaped cells after 3 days, which become attached to fibronectin. Such culture led to an up-regulation of endothelial lineage markers such as CD31, Flk-1 and Tie2, and loss of the pan-leucocyte CD45 antigen, in these attaching cells. Asahara *et al.* (Asahara et

al., 1999) went on to deliver labelled, CD34^{+}-enriched, MNCs into mouse and rabbit models of hindlimb ischemia and demonstrated neovascularization in the relevant limb with apparent incorporation of labelled cells into capillary walls. In separate experiments, they delivered murine labelled-MNCs enriched for Flk-1 and similarly found incorporation into capillaries and small arteries in the mouse hindlimb ischemia model. Carriage of CD31 and lectin binding was observed in these incorporated cells. These landmark studies suggest that circulating EPCs in adult peripheral blood could differentiate into cells of endothelial lineage and enhance revascularization through vasculogenesis.

3. Issues of definition for EPCs

Since these important findings, an enormous amount of research has been undertaken into EPCs; however, in attempting to collate and interpret these results, a major limiting factor is that no simple definition of EPCs exists at the present time, and various methods to define EPC have been reported. This pertains to the unresolved issue of how EPCs should best be defined.

3.1 Antigen-based definitions of EPC

The first method of classification of EPC is based on expression of cell-surface antigens, typically using flow cytometry to quantify relevant populations. Endothelial cells (EC) display a characteristic combination of such antigens, including CD34, KDR (kinase insert domain-containing receptor, a type of VEGFR2), VE-cadherin, vWF (von Willebrand factor) and E-selectin. In order to distinguish mature endothelial cells from circulating endothelial progenitors, some groups have additionally used other antigens which are lost during maturation of endothelial lineage cells, most commonly CD133 (also termed AC133) (Hristov & Weber, 2004). The combination of CD34, KDR and CD133 has been used by several investigators, although many others have used only two of these three. Unfortunately, even with use of all three, this phenotype is not entirely specific, since this same cluster of antigens may also be found on haemopoietic stem cells (Adams & Scadden, 2006; Verfaillie, 2002). This relates to the probable origin of haemopoietic and EC lines from a common precursor, termed the haemangioblast. As haemopoietic stem cells differentiate, CD34, KDR and CD133 antigens are down-regulated and disappear. Furthermore, the use of CD133 to make the distinction from mature ECs will also lead to the exclusion of 'more mature' EPCs which may have lost this marker, while not yet being terminally differentiated. To complicate matters further, while the use of antigenic combinations may have logical appeal, whether this approach actually identifies a group of precursors capable of producing ECs has recently been challenged (Case et al., 2007).

3.2 Culture-based definitions of EPC

The second commonly employed definition for EPCs derives from *in vitro* culture work. Asahara *et al.* described *in vitro* culture of CD34-enriched MNCs leading to the formation of spindle-shaped attaching cells within 3 days (Asahara et al., 1997). Co-culture of CD34-enriched and CD34-depleted cells gave rise, within 12 hours, to multiple clusters, containing round cells centrally and sprouts of spindle-shaped cells at the periphery. This cluster appearance was reminiscent of the blood islands previously described, wherein angioblasts surround hematopoeitic stem cells as the initial stage of vasculogenesis (Flamme & Risau,

1992). Various culture preparations have been used to encourage endothelial lineage proliferation from human blood-derived MNCs. There has been a considerable variation in the details of techniques used: for example, some have replated the adherent cells after 2 days initial culture, whereas others have used the non-adherent cells at this time (Vasa, 2001). Then, endothelial cell lineage was confirmed by indirect immunostaining with the use of DiI-acLDL and co-staining with BS-1 lectin. However, controversy exists with respect to the identification and the origin of EPCs, which are isolated from peripheral blood mononuclear cells by cultivation in medium favoring endothelial differentiation.

4. Early and Late outgrowth EPCs

EPCs can be isolated, cultured, and differentiated ex vivo from the circulating mononuclear cells (MNCs) and exhibit characteristic endothelial properties and markers. Currently, two types of EPCs, namely early and late outgrowth EPCs, can be derived and identified from peripheral blood. The early EPCs appear after 3-5 days of culture, are spindle-shaped, have peak growth at approximately 2 weeks and die by 4 weeks. These have been variously termed 'early EPCs' by Gulati et al. (Gulati et al., 2003) and Hur et al. (Hur et al., 2004), 'attaching cells' by Asahara et al. (Asahara et al., 1997) and CACs (circulating angiogenic cells) by Rehman et al. (Rehman et al., 2003). The second type of EPCs appears only after longer culture, of approximately 2-3 weeks, forming a cobblestone monolayer with near-complete confluence, and can show exponential population growth without senescence over 4-8 weeks and live for up to 12 weeks. These were termed 'late EPCs' by Hur *et al.* (Hur et al., 2004) or OECs by Lin *et al.* (Lin et al., 2000) and Gulati *et al.* (Gulati et al., 2003). Early and late outgrowth EPCs (OECs) share some endothelial phenotype similarities but show different morphology, proliferation rate, survival features, and functions in neovascularization. For clarity, we will use the terms early EPCs and OECs in the present review.

Early EPCs, in contrast, do not participate in tube-forming assays, have only weak invasive ability on gels and produce only low levels of NO. They do, however, demonstrate some features in keeping with an endothelial lineage such as acetylated LDL uptake and lectin binding. In addition, early EPCs do not develop into OECs upon prolonged culture. Among antigenic markers, CD14 (a monocytic marker) has been found by several groups on early EPCs (Romagnani et al., 2005; Urbich et al., 2003). Early EPCs lack the impressive replicative ability of OECs, but are prolific producers of several growth factors, cytokines and chemokines, including VEGF, HGF (hepatocyte growth factor), G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte/macrophage colony-stimulating factor). The lineage origin of these two culture-derived endothelial-type cells has been examined. Expression of the pan-leucocyte antigen CD45 is relatively greatest in MNCs, lower in early EPCs and lowest in OECs. It appears that early EPCs are mostly derived from a CD14+ population of MNCs, implying a monocytic, rather than true endothelial, lineage (Yoon et al., 2005). In contrast, OECs derive exclusively, or almost exclusively, from the CD14⁻ population of MNCs (Yoon et al., 2005). It has been suggested that the MNCs from which OECs are derived may represent a 'true' circulating endothelial precursor (angioblasts).

OECs have many similarities to mature ECs, in terms of surface antigens (including KDR, vWF, and VE-cadherin) and high levels of NO (nitric oxide) production by eNOS (endothelial NO synthase). They are able to participate effectively in tube-forming assays *in vitro*. However, OECs differ from mature ECs in having far greater proliferative ability *in*

vitro and greater angiogenic potential *in vivo*. A small population of OECs with the highest proliferative potential was able to produce more than 200 progeny per replated cell. Based on these findings, these features make OECs attractive candidates for therapeutic use in ischemia-related neovascularization.

5. Endothelial progenitor cells and atherosclerosis

The discovery of endothelial progenitors within adult peripheral blood presents another possible means of vascular maintenance, namely a reservoir of circulating cells which can home to sites of injury and restore endothelial integrity thus allowing continued normal function. Hill *et al.* (Hill et al., 2003) studied men without known cardiovascular disease but with varying degrees of estimated cardiovascular risk. Endothelial function was determined by using brachial artery flow-mediated vasodilation, and EPC numbers were measured using their CFU assay in study subjects. An inverse correlation was found between numbers of CFUs and the overall Framingham risk score of the participants. Furthermore, they found a positive correlation between the number of EPCs and endothelial function as assessed by brachial artery reactivity of the subjects. These findings are compatible with the hypothesis that an adequate pool of EPCs in the blood may be a key requirement for appropriate endothelial function. It appears that bone marrow-derived EPCs play a pivotal role in the maintenance of adult vascular endothelium. However, the basis of this correlation between EPC levels and endothelial function remains to be determined.

Although the critical role of circulating EPCs in the pathogenesis of atherosclerotic diseases is substantiated by several observations, the relationship between circulating EPCs and coronary artery disease (CAD) remains a subject of debate. Several studies have examined the association between circulating EPCs and CAD or risk factors predisposing to coronary artery disease. Vasa *et al.* reported that the circulating EPCs levels were significantly reduced in patients with CAD compared to those without CAD (Vasa et al., 2001). Wang and coworkers indicated that decreased number and activity of EPCs were observed in patients with stable CAD, and EPC levels were negatively correlated with the severity of coronary stenosis assessed by Gensini score (Wang et al., 2007). Fadini *et al.* also reported that EPCs were significantly reduced in subjects with increased intima-media thickness (Fadini et al., 2006), implying that depletion of EPCs may be an independent predictor of subclinical atherosclerosis. However, Guven *et al.* showed that increased EPCs levels were associated with the presence of significant CAD, and EPC numbers correlated with maximum angiographic stenosis severity (Guven et al., 2006). The apparent conflicting results between different studies may have many explanations, including fundamental differences in the methodologies used to identify circulating EPCs in different studies; heterogeneity of patient population, and effect of the disease stage on biological properties of circulating EPC levels. Based on the angiographic classifications by Syntax score, our recent work has shown that severe CAD patients (with higher Syntax Score) have decreased circulating EPCs numbers than mild CAD patients and subjects with normal angiographic results (unpublished data). Moreover, circulating EPC levels were shown to be negatively correlated with the SXscore in patients with angiographic evidence of CAD. These findings are consistent with a recent study showing that lower level of circulating EPCs predicts CAD progression (Briguori et al., 2010), suggesting the critical role of EPCs in the pathogenesis of CAD.

6. Anti-atherosclerotic actions of EPC

Rapid and complete restoration of endothelial integrity and function prevents development and growth of a neointimal lesion; however, inadequate response to injury will instead allow the formation of an atheromatous lesion. The discovery of circulating endothelial progenitors has led to the theory that they are important mediators of this repair arm, and hence that a depletion or dysfunction in these cells would result in an imbalance between endothelial injury and repair, favoring atherosclerosis. Schmidt-Lucke *et al.* (Schmidt-Lucke et al., 2005) followed up a group of 120 individuals, comprising normal subjects and also patients with either stable or unstable coronary artery disease. They found that major cardiovascular events, CABG (coronary artery bypass grafting) or ischemic stroke were significantly more frequent in the subgroup with lower levels of circulating CD34/KDR double-positive cells at baseline. This association persisted after accounting for conventional cardiovascular risk factors. Werner *et al.* (Werner et al., 2005) studied CD34/KDR double-positive cell numbers in a cohort of 519 patients diagnosed with coronary artery disease by angiography. After adjustment for confounding variables, higher levels of EPCs were associated with a reduced risk of death from cardiovascular causes and of occurrence of a first cardiovascular event at 12 months follow-up. The authors followed up the outcomes when patients were grouped by baseline levels of CFUs (i.e. a culture-based definition of colony formation). Higher CFU formation was associated with a reduced occurrence of a first major cardiovascular event and reduced revascularization at follow-up. However, as discussed above, recent work on the CFU assay suggests that it is assessing the *in vitro* activity of cells which may be relevant to vascular function, but which are not actually EPCs themselves (Rohde et al., 2007; Hur et al., 2007).

Moreover, there is relevant animal-based work in this area of progenitor cells and endothelial function. Wassmann *et al.* (Wassmann et al., 2006) studied endothelial function in ApoE-knockout mice, on a high-cholesterol diet, with atherosclerotic plaques and demonstrable endothelial dysfunction of aortic rings *ex vivo*. They showed that the intravenous administration of spleen-derived MNCs improved endothelium-dependent vasodilation. In addition, Gulati *et al.* (Gulati et al., 2003). used a rabbit model of balloon injury to the carotid arteries. They cultured peripheral blood MNCs in endothelial growth medium for 2 weeks, producing endothelial-phenotype cells carrying CD31 and eNOS, and delivered these culture-modified cells immediately after balloon injury. They found that, compared with saline-treated controls, local treatment with EPCs led to accelerated re-endothelialization and improved endothelial function. Whether the improvement in endothelial function is directly due to increased numbers of new ECs or an indirect effect on pre-existing cells or a papacrine effect by implantation of EPCs remains unclear; however, an increase in vascular NOS activity was documented and is likely to mediate the effect.

7. Therapeutic implications and perspective

A crucial target in the treatment or prevention of atherosclerosis is to promote and maintain the integrity and health of endothelium. Since EPCs play a role in maintaining an intact and functional endothelium, decreased and dysfunctional EPCs may contribute to endothelial dysfunction and susceptibility to atherosclerosis. Enhancement of the regenerative capacity of the injured endothelium seems one way to reduce the incidence of atherosclerotic lesions (Hristov & Weber, 2007). Transplantation of human cord blood-derived EPCs was reported

to contribute to neovascularization in various ischemic diseases, and EPC transplantation on diabetic wounds has a beneficial effect, mainly achieved by their direct paracrine action on keratinocytes, fibroblasts, and endothelial cells, rather than through their physical engraftment into host tissues (vasculogenesis). In the TOPCARE-AMI (i.e., "Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction") trial (Assmus et al., 2002), intracoronary infusion of cultured human EPCs in patients with recent myocardial infarction was associated with improvements in global left ventricular function and microvascular function. In addition, an EPC-conditioned medium was shown to be therapeutically equivalent to EPCs, at least for the treatment of diabetic dermal wounds (Kim et al., 2010).

There are several ways to increase levels of circulating EPCs and improve their function by pharmacological strategies and lifestyle modification. Notably, it was shown that the angiotensin-converting enzyme (ACE) inhibitors such as ramipril (Min et al., 2004), and angiotensin II (AT II) inhibitors, like valsartan (Bahlmann et al., 2005) increased EPC levels in patients, probably interfering with the CD26/dipeptidylpeptidase IV system. Our recent data showed that moderate intake of red wine significantly enhanced circulating EPC levels and improved EPC functions by modifying NO bioavailability (Huang et al., 2010). Other studies indicated that either the phosphatidylinositol 3-kinase/Akt/endothelial nitric oxide synthase/NO (*PI3K/Akt/eNOS/NO*) signaling pathway or the interaction between hyperglycemia and hyperlipidemia in diabetic patients who have vascular diseases, are potential therapeutic targets for abolishing the impaired function of EPCs (Wang et al., 2011). Neutralization of the p66[ShcA]gene, which regulates the apoptotic response to oxidative stress, prevented high glucose-induced EPC impairment *in vitro* (Di et al., 2009). The existence of molecules acting on EPCs can be used to positively condition cultured EPCs before therapeutic transplantation. Thus, because it is known that chemokine SDF-1α is able to mobilize EPCs, and because EPCs are known to have receptors for SDF-1α, it was demonstrated that SDF-1α - primed EPCs exhibit increased adhesion to HUVEC, resulting in more efficient incorporation of EPCs into sites of neovascularization (Zemani et al., 2008).

8. Conclusions

In conclusion, EPCs are biomarkers of endothelial repair with therapeutic potential, since low EPC levels predict endothelial dysfunction and a poor clinical outcome. Various studies have focused on the important role of EPCs in vasculogenesis and angiogenesis of ischemic tissue in peripheral artery disease as well as acute myocardial infarction, but only a few studies have concentrated on the role of EPCs in the prevention and therapy of atherosclerosis.

9. Acknowledgements

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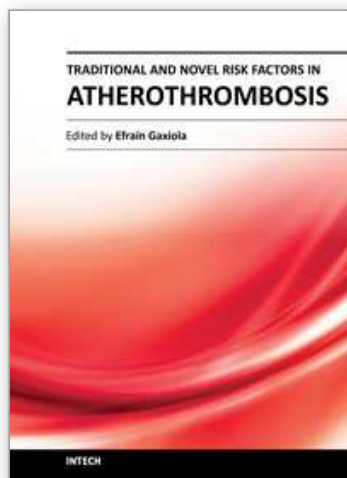
Traditional and Novel Risk Factors in Atherothrombosis

Edited by Dr. Efrain Gaxiola

Atherothrombosis has reached pandemic proportions worldwide. It is the underlying condition that results in events leading to myocardial infarction, ischemic stroke and vascular death. As such, it is the leading cause of death worldwide manifested mainly as cardiovascular/cerebrovascular death. The complex and intimate relationship between atherothrombosis and traditional and novel risk factors is discussed in the following chapters of Traditional and Novel Risk Factors in Atherothrombosis - from basic science to clinical and therapeutic concerns. Beginning with pathology and pathophysiology of atherothrombosis, plaque rupture/disruption, this book continues with molecular, biochemical, inflammatory, cellular aspects and finally analyzes several aspects of clinical pharmacology.

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