

Endothelial progenitor cells: what use for the cardiologist?

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Abstract

Endothelial Progenitor Cells (EPC) were first described in 1997 and have since been the subject of numerous investigative studies exploring the potential of these cells in the process of cardiovascular damage and repair. Whilst their exact definition and mechanism of action remains unclear, they are directly influenced by different cardiovascular risk factors and have a definite role to play in defining cardiovascular risk. Furthermore, EPCs may have important therapeutic implications and further understanding of their pathophysiology has enabled us to explore new possibilities in the management of cardiovascular disease. This review article aims to provide an overview of the vast literature on EPCs in relation to clinical cardiology.

Introduction

Maintenance of endothelial integrity and functioning is vital to the preservation of a healthy vasculature [1]. Thus, the impairment as well as insufficient recovery potential of the endothelial cell monolayer is believed to be a critical factor during the initiation and progression of atherosclerosis [2]. Indeed, endothelial damage/dysfunction has been proved to be involved in the pathogenesis of atherothrombotic vascular disease, with important prognostic and therapeutic implications.

Although the possibility that adult endothelial precursors may exist was suggested more than four decades ago, Asahara et al. first reported isolation of putative adult endothelial precursors which we now recognize as endothelial progenitor cells (EPCs), only in 1997 [3, 4]. Endothelial progenitors were able to differentiate into mature endothelial cells and promote repair of damaged endothelium [5-8]. Progressively increasing number of studies has been devoted to these enigmatic cells in the recent years and their close association with multiple markers of cardiovascular health is now well-recognised.

Apart from a diagnostic and prognostic role, EPCs may be attractive target for treatment and, at the same time, be used themselves in an attempt to stimulate angiogenesis, vasculogenesis and cardiac

performance. As an example, CD34 antibody coated stents designed to attract EPCs to the healing endothelium are under intensive clinical trial investigation. However, the precise role of EPCs in vascular pathology still needs to be further clarified as results of some currently available studies in the literature are controversial.

This article aims to provide an overview of the vast literature on EPCs in relation to clinical cardiology.

EPCs ageing and physical activity

Physiological factors and conventional risk factors for atherosclerosis are associated with variations of the number and activity of endothelial progenitors and may be the bridge linking EPCs to common cardiovascular disorders such as coronary artery disease (CAD), myocardial infarction and heart failure.

EPC characteristics are closely associated with the presence of various cardiovascular risk factors (Table 1). EPC numbers or function - or both - may be affected. For example, smoking contributes towards reducing the number of circulating EPCs, whilst hypertension reduces migratory capacity [9]. Serum LDL cholesterol levels, a positive family history of CAD, and age have all been shown to influence the number and migration of circulating CD34⁺ cells and EPCs [9].

Table 1

Effects of cardiovascular risk factors on EPC number and function

Cardiovascular risk factors	Effect on EPC number and function	EPC category	References
Hypercholesterolemia	Reduced EPC number, impaired EPC migratory capacity	Circulating EPCs (CD133, 34, 45)CFU-ECs	[9, 23]
Diabetes Mellitus	Reduced EPC number, impaired EPC migratory capacity	Circulating EPCs (CD31, 34, KDR)CFU-ECs	[26, 27, 29, 30]
Hypertension	Inverse relationship of EPC number with systolic blood pressure	Circulating EPCs (CD133, 34, KDR)	[9, 34]
Smoking	Affects EPC number in a dose-dependent manner	Circulating EPCs (CD133, 34, KDR)CFU-ECs	[35, 36]
Ageing	Reduced migration and proliferation	Circulating EPCs (CD133, 34, 45)CFU-ECs	[10-14, 113]
Exercise	Increased EPC number and function	Circulating EPCs (CD133, 34, 45)CFU-ECs	[15, 17-20]

EPC - endothelial progenitor cells

There is an age-related quantitative decline in bone marrow cells expressing endothelial progenitor markers [3]. Jie et al analysed the number of circulating CD34⁺/KDR⁺ EPCs in healthy subjects aged from 1 to 81 years old, and an inverse relationship with age was observed [10]. The progressive reduction in different progenitor cell populations with age was also confirmed by Shaffer et al, both in healthy donors and in patients with peripheral arterial disease [11]. Impairment of the functional activity of endothelial progenitors also parallels downregulation of their numbers [12]. This decline in EPC clonogenic capacity appears to occur at an earlier age, followed by a decline in migratory activity.

Admittedly, some controversy still exists on the relationship of age to EPC levels. For example, Pelliccia et al failed to find any difference in absolute numbers of CD34⁺, CD133⁺, CD105⁺, and CD14⁺ cells in older patients with CAD indicating a strong impact of factors other than age for the presence in atherosclerosis and re-emphasising the necessity of having a precise definition of EPC populations studied [13]. The decrease in EPC recruitment in the elderly may be associated with downregulation of tissue hypoxia-inducible factor 1 or insufficient local expression of VEGF, one of the key attractors of EPCs [14]. Furthermore, over an individual's lifetime, long-lived cells such as bone marrow endothelial precursors incur repeated exposures to oxidative stress; initially, EPCs may compensate by increasing their antioxidant responses to prevent oxidant injury. Over time, oxidant damage is likely to accumulate, thus diminishing the functional properties of EPCs.

Physical activity effectively promotes EPC health in terms of quantity, functional capacity and the prevention of apoptosis [15]. This effect is rapid and sustained, at least for 4 weeks [15]. Importantly, physical activity positively affects both bone marrow and peripheral EPC levels [15].

Furthermore, studies in animals have shown that physical activity enhances replacement of the dysfunctional endothelium by bone marrow-derived cells [16].

A rapid increase of EPC numbers following physical exertion may be attributable to acute mobilisation of the bone marrow EPC pool or a shear stress-induced release into circulation of vessel-wall resident EPCs [17, 18]. Again, NO-dependent mechanisms may be involved, given that physical exercise increases NO bioavailability [19]. The effect of physical activity on EPCs may be reduced by inhibition of endogenous NO synthase [20].

EPCs and cardiovascular risk factors

Hypercholesterolemia negatively affects both EPC number and function. Indeed, EPC count has an inverse relationship with total cholesterol and LDL-cholesterol levels [9]. Enhanced oxidative stress associated with dyslipidaemia may at least be partly involved in the dysregulation of EPC mobilisation, maturation and survival. Of note, circulating EPCs are very sensitive to oxidized LDL, resulting in premature apoptosis [21, 22].

Enhanced endothelial dysfunction and damage may result in higher tissue demand for EPCs and their increased turnover. Hypercholesterolaemia may also directly affect the bone marrow, resulting in depletion or exhaustion of the bone marrow pool of endothelial progenitors, with a consequent limited supply of EPCs released into circulation [23]. Also, LDL cholesterol levels have an inverse relation with EPC migratory capacity [23]. Elevated LDL cholesterol and oxidized LDL levels impair EPC migration, via a VEGF-mediated pathway, and oxidized LDL blocks VEGF-induced EPC migration through the inhibition of NO production [24, 25].

Reduced levels of EPCs have been described in both type 1 and type 2 diabetes mellitus [26]. EPC recruitment for re-endothelialization after vascular injury is impaired in patients with diabetes, and as a

consequence of such EPC dysfunction, the vascular regenerative potential of this disease group may be reduced - thus, contributing to the development of vascular complications [27]. Indeed, decreased numbers and functional activity of early EPCs are significantly associated with the pathogenesis of vascular complications in either type 1 or type 2 diabetes [26, 27].

Hyperglycemia significantly reduces eNOS production by EPCs with a corresponding decline in nitric oxide (NO) bioavailability [31]. The effects of high glucose could be ameliorated by co-incubation of EPCs with the NO donor sodium nitroprusside or p38 mitogen-activated protein kinase inhibitor, and deteriorated by eNOS inhibitor [28]. In contrast, antioxidants including vitamin C, N-acetylcysteine and polyethylene glycol-conjugated superoxide dismutase, and polyethylene glycol-catalase have no significant effects on EPCs [28]. This suggests that the inhibitory effects of high glucose on EPC could be reversed by NO donors, but not by various antioxidants.

Systolic blood pressure has a negative correlation with the number of circulating EPCs, but the clonogenic potential (number of CFU-ECs) is not impaired by arterial hypertension [9]. Angiotensin II accelerates the onset of EPC senescence, leading to impaired proliferation of EPCs; this seems to be inhibited by treatment with the angiotensin II type 1 receptor blocker, valsartan [29]. Ramipril also improves the proliferation and migration of EPCs, as well as *in vitro* vasculogenesis in patients with CAD [30].

These observations were confirmed in the Endothelial Progenitor Cells in Coronary Artery Disease (EPCAD) study, demonstrating that angiotensin-converting enzyme inhibitor treatment was associated with increased numbers and improved clonogenic potential of circulating EPCs, when compared with patients who were not taking angiotensin-converting enzyme inhibitors [31].

Whilst smoking leads to a reduction in EPC counts, nicotine itself may have a positive effect on EPC numbers and functional activity at low concentrations [32, 33]. This is supported by the finding that the use of nicotine patches slightly increases the magnitude of the rise in EPC levels after smoking cessation [32]. However, higher

nicotine levels will have cytotoxic effects on EPCs, indicating complex effects of nicotine on EPCs [33]. Indeed, the number of EPCs is reduced in chronic smokers, whilst cessation of smoking leads to rapid restoration of EPC levels [32]. In contrast, smoking cessation leads to rapid recovery of the circulating EPC population, especially amongst light smokers [32].

Recent studies have established a clear link between levels of circulating EPCs and the cumulative cardiovascular risk profile [8]. For example, Hill et al [8] hypothesized that EPCs derived from the bone marrow have a role in ongoing endothelial repair and thus, the depletion of these cells contributes to cardiovascular disease progression. Also, the number of CFU-EC colonies from peripheral blood correlates closely with endothelial function. Thus, EPC levels could be used as a 'biological marker' (or biomarker) for vascular function and the relationship to cumulative cardiovascular risk.

Although mechanisms linking cardiovascular risk factors and the impairment of EPC mobilization and function are not sufficiently well understood, the number of studies strongly indicates that chronic inflammation and oxidative stress may play a critical role, despite substantial resistance of endothelial progenitors to oxidative burden [34-36].

EPCs and cardiovascular pathology

Therapeutic modification of EPCs

Transplantation of EPCs

The available data that demonstrate angiogenic properties of EPCs and favorable outcomes of animal studies have encouraged clinical trials in patients with ischemic heart disease, particularly in the AMI setting [94]. However, results of human studies have proved to be controversial with some trials reporting significant improvement in cardiac vascularisation and performance while others failing to show any benefits. Results of randomized clinical studies are on cardiac transplantation of cells with endothelial progenitor potential are summarized in table 4.

Table 4

Randomized clinical studies on transplantation of cells which include endothelial progenitors

Study/year	Disorder	N	Delivery route	Cells delivered	Follow-up (months)	Effectiveness
Strauer et al. (2002) [117]	AMI	20	Intracoronary	BM-MNCs	4	Effective
Kang et al. MAGIC (2004) [92]	AMIOld MI	27	Intracoronary	PB-MNCs and G-CSF	6	Effective, but high rate of in-stent re-stenosis
Schachinger et al. TOPCARE-AMI (2004)	AMI	59	Intracoronary	PB-MNCs or BM-	12	Effective

Study/year	Disorder	N	Delivery route	Cells delivered	Follow-up (months)	Effectiveness
[118]				MNCs		
Ruan et al. (2005) [119]	Acute MI	20	Intracoronary	BM-MNCs	6	Effective
Strauer et al. IACT (2005) [120]	Chronic CAD	36	Intracoronary	BM-MNCs	3	Effective
Bartunek et al. (2005) [111]	Recent MI	35	Intracoronary	CD133+	4	Effective
Erbs et al. (2005) [112]	Chronic CAD	26	Intracoronary	Cultured PB-EPCs	3	Effective
Assmus et al. (2006) [111]	Chronic CAD	53	Intracoronary	BM-MNCs	3	Effective
Meyer et al. BOOST (2006) [104]	Acute MI	60	Intracoronary	BM-MNCs	18	Effective at 6 month, ineffective at 18 month
Hendrikx et al. (2006) [121]	Heart failure	20	Intramyocardial	BM-MNCs	4	Ineffective
Janssens et al. (2006) [105]	MI	67	Intracoronary	BM-MNCs	4	Ineffective
Kang et al. MAGIC Cell-3-DES (2006) [60]	Acute MIOld MI	82	Intracoronary	PB-MNCs and G-CSF	6	Effective
Schachinger et al. REPAIR-AMI (2006) [106, 122]	AMI	201	Intracoronary	BM-MNCs	12	Effective
Ge et al. TCT-STAMI (2006) [95]	MI	20	Intracoronary	BM-MNCs	6	Effective
Meluzin et al. (2007) [122]	Acute MI	60	Intracoronary	BM-MNCs	12	Effective

AMI - acute myocardial infarction, BM - bone marrow, CAD - coronary artery disease, G-CSF - granulocyte-colony stimulating factor, MI - myocardial infarction, MNC - mononuclear cell, PB - peripheral blood.

The majority of completed randomized trials have demonstrated some benefits of stem cells treatment, and studies uniformly report the safety of this approach with no specific adverse events observed (including proarrhythmia, oncology or excessive inflammatory burden)[95, 96]. High rate of in-stent restenosis in the MAGIC study where cell therapy was combined with G-CSF administration has been discussed above [59]. In the BOOST trial, intracoronary implantation of bone marrow cells did not provide long-term benefit on left ventricular systolic function after AMI compared to a randomized control group; however, stem cell therapy was associated with acceleration of left ventricular recovery [97].

In the study by Janssens et al [98], transfer of bone marrow stem cells to the coronary artery in 67 patients with AMI did not contribute to improvement of the global left ventricular function, but did favorably affect infarct remodelling at 4 months follow-up, with a reduction in infarct size. In the double-blind, placebo-controlled multicentre REPAIR-AMI trial, 204 patients with MI were randomized to bone marrow-derived cells or placebo [99]. At 12 months, the pre-specified cumulative endpoint of death, myocardial infarction, or necessity for revascularization was significantly reduced in the stem cell-therapy group

compared with placebo; of note, stem cells therapy was an independent predictor of a favorable clinical outcome in this study [99].

Alternative to intracoronary infusion routes of stem cell delivery such as intramyocardial implantation (either during cardiac surgery on NOGA system) have also been tested [100, 101]. In the only randomised with percutaneous transendocardial injections of CD34+ cells to patient with severe intractable angina, this method was found to be feasible and safe and is being extended into a larger ongoing phase IIb study [102].

Given the controversy of trial results, important issues have arisen about the factors affecting the efficacy of such therapy. In addition to route of administration, the time of stem cell delivery (ie. after AMI), origin and number of cells used may be critical. In fact, the majority of studies have used unselected mononuclear cells with unknown but evidently very low proportion of endothelial progenitors but with progenitors of other origins (eg. mesenchymal stem cells), this could be potentially favorable for cardiac recovery. Indeed, when either bone marrow or circulating mononuclear cells were delivered to infarct-related coronary arteries, treatment with bone marrow cells resulted in a better improvement of left ventricular contractility, when compared to peripheral blood

cells [103]. Several studies with selected CD34+, CD133+ cells or cultured peripheral blood EPCs have been successfully performed but large controlled studies are required to evaluate their clinical utility [102, 104, 105].

Although different factors may impair EPC-mediated vascular repair (for example, abnormality in their mobilisation from bone marrow and homing to the damaged vascular tissues, and exhaustion of their bone marrow niche), the available data strongly indicate functional characteristics of circulating endothelial progenitors are relevant. Accordingly, appropriate genetic modification of EPCs before their implantation may be a way to improve their angiogenic potential. The feasibility of this approach has been demonstrated by genetic inhibition of glycogen synthase kinase-3 β signaling in human EPCs that was associated with significant enhancement of their angiogenic properties in an animal model of ischaemia [106]. Additionally, the angiogenic potential of EPCs can be improved by non-genetic ex-vivo stimulus (for example, by exposure to hypoxia). However, the clinical relevance of these approaches needs further investigation [107].

Understanding of EPCs - where we are now?

Despite more than a decade of very intensive research and many studies devoted to the problem of understanding EPC biology, their potential clinical role is still largely limited by lack of a consensus on the phenotypic and functional definition of endothelial precursors [108]. At present, a single term 'EPC' refers to a very diverse group of cells of different lineages which appear to have some angiogenic potential, but not necessarily the ability to differentiate into functional endothelial cells, as expected from their name. Accordingly, a booming number of new publications on 'EPCs' may have limited scientific impact without a clear

Conclusion

Since the discovery of EPCs, there has been a rapid proliferation of research data on the relation of EPC to cardiovascular risk, pathology and treatment. So far, EPCs have been implicated in the whole cardiovascular disease process, and many conventional therapies have been shown to alter

understanding what type of cell is actually being analysed.

Currently only so-called 'outgrowth endothelial cells' (or 'late' EPCs) are known to uniformly give origin to functional endotheliocytes. Indeed, CD34 or CD133 and alone or in different combinations (often with KDR) are the most popular markers used to define 'circulating EPCs'. This popularity stems from initial reports showing that CD34+/KDR+ cells could form endothelium-like cells in vitro [4, 109]. Although many studies have employed CD34+/CD133+/KDR+ cells as their definition of 'true EPCs' their ability to generate endothelial cells has never been reliably proved. Furthermore, these cell populations probably represents a subset of CD45+ haematopoietic progenitors but do not form endothelial cells in vitro [110]. Inclusion of any additional markers in the definition of 'EPC' may hamper a holistic approach towards EPC analysis even further and should only be based on robust data confirming the functional identity of the cells analysed.

The problem with the identification of functional EPCs is also present with approaches based on cell culture. For example, markers previously used to prove endothelial identity of putative progenitors, such as CD31, lectin binding or LDL accumulation are now known to be non-specific for the endothelial lineage, but also characteristic for cells of haematopoietic origin [111, 112]. In fact, the majority of so called 'early' EPCs represent populations of monocytes and lymphocytes which co-express 'endothelial' markers and possess some degree of angiogenic capacity [36]. This reemphasises that the initiation of any new clinically-relevant study on EPCs should only be based on clear understanding of type of cells being analysed.

EPC number and function. More recently, attempts to utilise the clinical potential of EPCs such as in the form of CD34-antibody coated stents, has been attempted. Further challenges will be to develop simple techniques to measure EPCs numbers and function accurately and quickly, as these cells may help determine cardiac risk and outcomes for patients with heart disease.

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