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BIOLOGICAL PROPERTIES OF ENDOTHELIAL PROGENITOR CELLS (EPCS) AND THEIR POTENTIAL FOR CELL THERAPY

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Abstract

Recent studies indicate that portions of ischemic and tumor neovasculature are derived by “neovasclogenesis”, whereby bone marrow (BM)-derived circulating endothelial progenitor cells (EPCs) home to sites of regenerative or malignant growth and contribute to blood vessel formation. Recent data from animal models suggest that a variety of cell types, including unfractionated BM mononuclear cells and those obtained by ex vivo expansion of human peripheral blood or enriched progenitors, can function as EPCs to promote tissue vasculogenesis, regeneration and repair when introduced in vivo. The promising preclinical results have led to several human clinical trials using BM as a potential source of EPCs in cardiac repair as well as ongoing basic research on using EPCs in tissue engineering or as cell therapy to target tumor growth.

Keywords

EPC; angiogenesis; vasculogenesis; cell therapy; tumor; ischemia

Introduction

The seminal observations by the late Jeffrey Isner and colleagues that established the existence of endothelial progenitor cells (EPCs) derived from the bone marrow (BM) and their participation in newly forming blood vessels after wounding altered our way of thinking about therapeutic angiogenesis[1]. Their study showed that BM cells were able to function as EPCs by homing from the peripheral circulation into ischemic foci and incorporating into microvasculature[1].

The finding that progenitor cells home to sites of neovascularization and differentiate into endothelial cells in situ is consistent with vasculogenesis, a mechanism previously believed to

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be restricted to development of blood vessels in the embryo [2]. The discovery of EPCs has changed that paradigm and introduced the notion of cellular therapy as a novel approach to therapeutic angiogenesis. The ability of EPCs to promote revascularization of injured and ischemic tissues or as cellular therapy to target cancer growth is being pursued in both preclinical models and, more recently, human trials to treat ischemia [3–8].

Additionally, the levels of circulating EPCs have been shown to be modulated during ischemic injury, disease states, aging and with certain pharmacologic agents [9–13]. Several studies have examined the numbers of circulating CD34+/VEGF-Receptor 2(R2)+ (also called flk-1) cells, as a marker for the endogenous EPCs, or enumerated the number of early outgrowth EPC colonies from human peripheral blood and have shown correlation of either assay with cardiovascular risk[11,14,15]. In this review, we will focus on the biological properties of EPCs, whereas the study and progress of using EPCs as a biomarker for disease progression or drug response will not be further discussed in this review.

Phenotype of the EPC

Initial studies identified EPCs by the expression pattern of cell-surface markers, which included VEGFR2, AC133, CXCR4, CD34, and c-Kit and the absence of markers of more committed hematopoietic lineages (lin-) [1,16,17]. Human-derived EPCs have been isolated from the CD34+/lin- or CD34+/VEGFR2+ (AC133 co-expression can also be used in lieu of, or in addition to, VEGFR2[17]) population; after administration to mice they have been shown to differentiate in vivo into endothelial cells associated with vessels that expressed the endothelial markers PECAM (CD31) or von Willebrand factor (vWF) [5]. Intravenous administration of mature endothelial cells (i.e. HUVECs) failed to result in engraftment into foci of neovascularization [1]. In this manner, mature endothelial cells were shown to be functionally distinct from BM-derived EPCs.

As with the hematopoietic or mesenchymal stem cells, several groups have attempted ex vivo expansion of EPCs [18–22]. At least two types of EPCs can be obtained by ex vivo culture of peripheral blood, an early and late outgrowth population (Figure 1). In most strategies, EPCs were generated by in vitro expansion of unmobilized human peripheral blood mononuclear cells (PB-MNCs) on fibronectin-coated tissue culture plates[18,21–26]. Human PB-MNCs or BM-MNCs cultured in endothelial growth media generated within 4–7 days spindle-shaped cells, which expressed endothelial markers such as VEGFR2 and VE-cadherin[18,23,26]. These early outgrowth, culture-expanded EPCs have limited proliferative capacity, can be maintained in culture for a short time (30–40 days) and co-express myeloid (e.g., CD14), pan-leukocytic (CD45) and endothelial markers (e.g., VE-cadherin and VEGFR2) [26,27]. However, continued culture of this population (>30 days) results in the loss of hematopoietic marker co-expression and uniform expression of endothelial lineage markers[26]. It has been proposed that this population resulted from the transdifferentiation of myeloid progenitors to endothelial-like cells; myeloid origination of early outgrowth EPCs has been demonstrated by multiple, independent laboratories [26–34]. Although there is controversy regarding whether both early and late myeloid precursors can acquire an endothelial phenotype, recent data suggest that this occurs with higher frequency with less mature or specific subsets of myeloid precursors [25,26,35]. Functionally, this population of early outgrowth EPCs homed and incorporated into both ischemic and tumor neovasculature after intravenous administration [26,28,36,37]. Moreover, this population was able to stimulate significant endogenous angiogenesis[5,18,29,37–39]. The combination of EPC contribution to neovasculature and their indirect stimulation of host blood vessel formation have resulted in significant therapeutic benefit in rodent hindlimb ischemia models[18,29,39–41]. The majority of the studies examining direct EPC contribution to neovasculature have analyzed early time points (<2 weeks) [18,39,41]. Although aspects such as persistence, remodeling and expansion of

engrafted EPCs have not been directly addressed, the data in tumor models suggest that these early outgrowth, peripheral blood-derived EPCs engraft transiently in vivo [26,38].

The late-outgrowth EPCs do not emerge until 2–3 weeks of culture of peripheral blood or BM and rapidly grow out thereafter to greater than 100 population doublings until eventually undergoing senescence [27,38,42,43]. Interestingly, the culture of highly purified BM hematopoietic progenitor populations (e.g. CD34+/lin- or AC133+/VEGFR2+) generated attached cells expressing endothelial markers with similar kinetics, supporting the notion that the late outgrowth EPCs were derived from the CD 14-(non-myeloid) population and resulted from aggressive expansion of the early progenitor (CD34+/AC133+/VEGFR2+/lin-) populations [26,27,38,42,43]. Similar to direct administration of purified progenitor populations or early outgrowth EPCs, administration of the late outgrowth human EPCs to immunodeficient, ischemic mice resulted in their incorporation into new vessels, and promoted overall angiogenesis [18,19,44–49]. Although there have been no direct comparisons reported of therapeutic outcome among purified progenitors with the various culture-expanded populations, a recent study compared the therapeutic efficacy of early and late outgrowth EPCs. The data suggested that while intramuscular injection of either population of culture expanded EPCs was able to promote neovascularization, the administration of a mixture of the two resulted in enhanced engraftment of both populations and improved neovascularization of hindlimb ischemia in immunodeficient mice [50]. Since only small populations of CD34 (~2%) or AC 133 (~0.5%) progenitors are present in BM, and even lower numbers (<20–100 fold) in peripheral circulation [5], ex vivo expanded EPCs have been widely used in many experimental studies and may be a feasible source of EPCs for clinical cell therapy [7,23,51]. Some studies suggested that other BM stroma-derived cells, such as multipotent adult progenitor cells (MAPCs) (Figure 1) or mesenchymal stem cells (MSCs) can also be differentiated into endothelial-like cells in culture that function as EPCs in mouse models of ischemia or tumor growth [45,48,52]. Despite greater elucidation of the phenotype of the distinct EPC populations derived after ex vivo culture expansion, our understanding of their relative efficacy in tissue vasculogenesis/repair as well as the nature of the endogenous EPC population(s) remains incomplete.

The Role of EPCs in Ischemic Injury

A growing body of preclinical data suggest that introduction of exogenous vascular progenitors, either unselected BM-MNCs, enriched AC133+ progenitors or ex vivo expanded early outgrowth EPCs, may promote revascularization and improve organ function [53]. Vascular trauma (e.g., limb ischemia, myocardial infarct) releases signals into the circulation such as VEGF and SDF-1 that promote the mobilization of EPCs into the circulation [53]. Moreover, local concentrations of VEGF and SDF-1 are elevated in ischemic foci and contribute to EPC recruitment from the circulation to the site of injury [54,55]. Other cytokines such as G-CSF and GM-CSF also promote EPC mobilization and downstream endothelial regeneration [53,56]. Hence, these agents may be developed to augment both the circulating levels as well as tissue recruitment of endogenous BM-derived vascular progenitors to promote organ repair.

Intravenous administration of both early and late outgrowth culture-expanded EPCs after ischemic injury resulted in their selective recruitment to ischemic sites [18,50,57]. However, the efficiency of recruitment is reduced if cells are introduced into the systemic venous circulation due to sequestration in the lung and other tissues [26,50,58,59]. Data suggested that a more targeted delivery, e.g., into the coronary arteries for cardiac therapy, improved cell engraftment [26,50,58,59]. This approach may also help avert EPC recruitment to unwanted sites of neovascularization.

In preclinical studies, direct EPC contribution to vessels ranged from 1–25%, depending on the model system or disease[60]. However, the rate of total vascular density (angiogenesis) was also increased. These observations suggest that incorporated progenitor cells may also promote neovascularization and tissue regeneration by releasing factors which act in a paracrine manner to support local angiogenesis, mobilize tissue residing progenitor cells, and/or improve host cell survival, thereby creating a permissive environment that enables rapid revascularization, proliferation, and survival of damaged cells[59].

The encouraging results using EPCs in animal models to stimulate angiogenesis and improve recovery of ischemic tissue led to a number of clinical studies. The human trials have utilized two general designs: intracoronary delivery to patients with recent myocardial infarctions or catheter-based intramyocardial injections into patients with chronic ischemic disease[53]. Due to the relative scarcity of the hematopoietic stem cell (CD34+/AC133+/VEGFR2+), the majority of the recently completed studies have used unfractionated BM-MNCs[8] in small scale, uncontrolled and non-randomized clinical trials. Most of the trials found a moderate improvement in heart function, documented by an increase in left ventricular ejection fraction, a decrease in end-systolic volume, shrinkage of the infarct size, thickening of the LV wall and improvement in exercise capacity without serious adverse events, such as inflammation (as measured by leukocyte count or serum C-reactive protein levels), emboli, arrhythmia, or death [52,53,61,62].

The encouraging results from the first, small-scale clinical studies led to larger, randomized, placebo-controlled, or double blind trials. Patient numbers ranged from 40 to 200 per study with average age between 55 to 60 years old. Three trials used intracoronary infusion of $0.7\text{--}2 \times 10^8$ autologous, bone marrow-derived MNCs 4–8 days after acute MI [63–65], whereas one trial enrolled patients with stable ischemic heart disease who had MI at least 3 months before cell therapy[66]. The remaining trials aimed on mobilizing endogenous stem cells by subcutaneous injection of G-CSF over a time period of 5–6 days after percutaneous coronary intervention [67–69]. Most trials showed no substantial benefits, except a modest increase in ejection fraction^{3,7} or infarct size and reperfusion¹ indicating that straightforward administration of unfractionated BM-MNCs, or mobilization of autologous BM stem cells might not be effective in the clinic [52,53,61,62,64,66,67,70]. It is also possible that the patient group, timing, cell dose or enhanced engraftment might be critical parameters in cell therapy.

EPCs Target Angiogenic Sites Within Growing Tumors

Thus far, the study of tumor neovascularization has focused primarily on the angiogenesis mechanism [71]; however, a growing body of studies has demonstrated that vasculogenesis may be an alternate, important mechanism of the tumor angiogenic switch[26,51,55,58,72–76]. The study that first identified a potential role of EPCs in tumor neovascularization utilized an adult immunodeficient mouse model engrafted with BM from mice carrying a transgene expressing β -galactosidase (lac Z) from endothelial-specific promoters [77]. In this model, donor-derived cells stained positive with X-gal at sites of tumor xenotransplants. Rafii and colleagues further studied the role of BM-derived EPCs in tumor growth utilizing Id-deficient (Id1+/-Id3-/-) mice that were unable to support growth of implanted tumors due to defects in angiogenesis[78]. However, susceptibility of Id mice to tumor challenge was restored after BM transplantation from wild-type mice [78]. Examination of these tumors revealed that >90% of the endothelium was BM-derived, suggesting that, at least in this model, vasculogenesis played an overwhelming role in tumor neovascularization. However, estimation of the physiologic role of vasculogenesis in tumor neovascularization in this mouse was confounded by the genetic impairment of angiogenesis in Id deficient mice [78].

Other studies in wild-type hosts confirmed that EPCs generated from mouse embryos or embryonic stem cells, culture-expanded EPCs or human BM-derived mesenchymal cells, preferentially home and contribute to tumor vasculature[26,55,72,79,80].

Efforts to quantify tumor reliance on vasculogenesis suggested wide variation in tumor vasculogenesis in mouse models, ranging from 0 to >90% [73,78,81]. Most murine orthotopic tumor models, however, suggested a low level (less than 5%) of vasculogenic-derived vessels [3,51,78,81,82]. The wide variation in the degree of tumor vasculogenesis may be the result of different model systems, e.g., different reporter constructs and types of tumor, or in the method of tissue sampling (e.g. vasculogenic vessels are not uniformly distributed but occur in 'hotspots') [81,83,84]. The role of vasculogenesis in human tumors has recently been assessed in one study of 6 patients who developed tumors after BM transplantation from donors of the opposite sex by colocalizing sex-chromosome specific probes with markers of endothelial cells [74]. The mean contribution of BM-derived endothelial cells to human tumors was 4.8% and ranged from 1–12%[74]. Future studies to examine location and numbers of BM-derived cells during tumor progression are necessary to further our understanding of the importance of tumor vasculogenesis. However, current evidence suggests that although angiogenesis is overwhelmingly the most widely studied process, it is not the only mechanism of blood vessel formation within a tumor.

Various types of exogenous EPCs have been shown to preferentially target tumor tissues[58, 79]. These observations, as well as reports which suggest that EPCs demonstrated a predilection for ischemic vasculature, led to the hypothesis that EPCs may be utilized as a delivery vehicle for tumor gene and/or cell therapy[18,85,86]. Wei and colleagues demonstrated that mouse embryonic EPCs stably expressing a suicide gene were able to reduce tumor volume and the number of lung metastases[58]. Furthermore, their degree of tumor inhibition supported a role for EPC-directed bystander cytotoxicity[58]. It will be important to establish if human genetically modified, ex vivo-expanded EPCs can have similar anti-tumor effects.

The phenotype of the endogenous, tumor-infiltrating EPCs is unclear. Several reports have observed that myeloid subsets can co-express endothelial markers, such as VE-cadherin, P1H12, or Tie2, and constitute significant leukocyte populations within tumors[26,75,82,87, 88]. These bi-phenotypic "vascular leukocytes" were shown to contribute to vasculogenesis in some model systems [26,75,82,88], whereas in other instances they did not directly contribute to tumor vessels but promoted angiogenesis in a paracrine manner[87,89]. Interestingly, a recent study suggested that BM-derived lymphatic EPCs contributed to new lymphatic vessels and may have differentiated from the inflammatory myeloid cells that circumscribe areas of new lymphatic growth[90]. This hypothesis was supported by demonstrating that CD14+ myeloid cells upregulated a number of specific markers of lymphatic endothelium such as VEGF-C, podoplanin, and LYVE-1 during in vitro culture to generate lymphatic endothelium [90]. These studies further strengthened the observations that myeloid populations can be induced to express markers of blood vessel endothelium in vitro and in vivo and that myeloid to endothelial transdifferentiation may contribute to tumor progression. These bi-phenotypic myeloid/endothelial (i.e. vascular leukocytes) populations may be isolated from circulation or derived ex vivo for use as tumor cell therapy[26,87,88]. Alternatively, this proangiogenic vascular leukocyte population may itself be a target to selectively retard tumor neovasculture [87].

Other Potential Applications

Another direction of cell therapy may be the application of EPCs in the construction of endothelial-coated vascular grafts in the context of tissue engineering. The poor patency rate of small diameter prosthetic bypass grafts has been largely attributed to thrombosis caused by delayed endothelialization of their lumen[91–93]. Autologous, vessel-derived endothelial cells

have been used to seed these grafts, but lack of sufficient number of cells has limited its clinical utility [94].

It had been shown that BM-derived cells served as a significant source of endothelialization of Dacron vascular grafts in dogs [95]. Furthermore, seeding grafts with CD34+, BM-derived progenitor cells dramatically increased endothelialization[96]. Supporting this observation was the report that G-CSF treatment, which mobilized leukocytes (including CD34+ cells) from the BM into the peripheral circulation, enhanced spontaneous endothelialization of vascular grafts [97]. More recently, sheep peripheral blood late outgrowth EPCs were used to seed decellularized porcine iliac vessels [4]. Seeded grafts remained patent for 130 days, >8-times longer than non-seeded grafts[4]. EPC-seeded grafts demonstrated contractile properties and nitric-oxide-mediated relaxation similar to native vessels [4]. Further studies are needed to compare the utility of different leukocyte subsets or culture expanded EPC populations in promoting vessel endothelialization in vitro and in vivo.

Finally, the observation that EPCs can be incorporated into growing vasculature introduces the theoretical possibility of correcting congenital diseases. Using BM transplant models, it was shown that vasculogenesis occurred during normal organ growth only in the early neonatal period[6]. The absence of vasculogenesis during adult organ growth was also confirmed by others[98]. However, it has not yet been reported if ex vivo expanded cell populations can engraft into growing neovasculature. Further work is necessary to define the window of organ vasculogenesis after birth, the efficacy of various EPC populations, and persistence of engrafted cells.

Vasculogenesis may be an essential cascade for tissue and organ regeneration following pathological damage in various diseases. EPCs can participate directly in neoangiogenesis by differentiating in situ into endothelial cells, but growing data suggest that they also affect tissue repair through paracrine mechanisms that are not well defined. The ease of obtaining human peripheral blood EPCs after ex vivo expansion as well as unfractionated BM cells as a source of EPCs make it possible to aggressively pursue efforts to develop them as cellular therapy to potentially augment vascularization in ischemic areas (i.e. after myocardial infarction), in bioengineering, or alternatively, to carry an anti-tumor gene to sites of tumor neo vascularization.

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Figure 1.

Model of characterized culture-expanded EPC populations. Early outgrowth EPCs co-express myeloid/pan-leukocyte and endothelial markers and cannot be expanded with serial passage in contrast to late outgrowth EPCs. Despite the heterogeneity in the origin and differentiation of these cell types, the in vivo vasculogenic and therapeutic efficacy appears similar.