Endothelial progenitor cells for postnatal vasculogenesis

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Asahara, Takayuki, and Atsuhiko Kawamoto. Endothelial progenitor cells for postnatal vasculogenesis, Am J Physiol Cell Physiol 287: C572–C579, 2004; 10.1152/ajpcell.00330.2003.—In the past decade, researchers have defined committed stem or progenitor cells from various tissues, including bone marrow, peripheral blood, brain, liver, and reproductive organs, in both adult animals and humans. Whereas most cells in adult organs are composed of differentiated cells, which express a variety of specific phenotypic genes adapted to each organ’s environment, quiescent stem or progenitor cells are maintained locally or in the systemic circulation and are activated by environmental stimuli for physiological and pathological tissue regeneration. Recently, endothelial progenitor cells (EPCs) were isolated from peripheral blood CD34, Flk-1, or AC133 antigen-positive cells, which are considered to include a hematopoietic stem cell population, and were shown to be incorporated into foci of neovascularization. This finding, that circulating EPCs may home to sites of neovascularization and differentiate into endothelial cells in situ, is consistent with “vasculogenesis,” a critical paradigm for embryonic neovascularization, and suggests that vasculogenesis and angiogenesis may constitute complementary mechanisms for postnatal neovascularization. Previous reports demonstrating therapeutic potential of EPC transplantation in animal models of hindlimb and myocardial ischemia opened the way to the clinical application of cell therapy: the replacement of diseased or degenerating cell populations, tissues, and organs. In this review, we summarize biological features of EPCs and speculate on the utility of EPCs for vascular and general medicine.

Identification of the Endothelial Progenitor Cell (EPC) was an introductory emergence of stem cell biology in the field of vascular biology. Evidence accumulated since our first publication on an isolation of EPCs has elucidated the significance of a postnatal vasculogenesis mechanism for neovascularization and vascular remodeling. This unique cell fraction among peripheral blood mononuclear cells (MNCs) derived from bone marrow has a similar profile to that of an embryonic angioblast, which proliferates and/or migrates in response to angiogenic growth factors and differentiates into mature endothelial cells (ECs) in situ for blood vessel formation. Considering the importance of blood vessel development on organogenesis, vasculogenesis by EPCs may be an essential cascade for tissue and organ regeneration following pathological damage in various critical diseases.

Stem Cell Biology for Regeneration

Tissue regeneration for organ recovery in adults has two physiological mechanisms. One is the replacement of differentiated cells by newly generated populations derived from residual cycling stem cells. Hematopoietic cell regeneration is a typical example of this kind of mechanism. Whole hematopoietic lineage cells are derived from a few self-renewal stem cells by regulated differentiation under the influence of appropriate cytokines and/or growth factors. The second mechanism is the self-repair of differentiated functioning cells, preserving their proliferative activity. Hepatocytes, ECs, smooth muscle cells, keratinocytes, and fibroblasts are considered to possess this ability. After physiological stimulation or injury, factors secreted from surrounding tissues stimulate cell replication and replacement. However, regenerative activity of these fully differentiated cells is still limited because of finite proliferation by senescence and because of their inability to incorporate into remote target sites.

Whereas most cells in adult organs are composed of differentiated cells, which express a variety of specific phenotypic genes adapted to each organ’s environment, quiescent stem or progenitor cells are maintained locally or in the systemic circulation and are activated by environmental stimuli for physiological and pathological tissue regeneration. In the past decade researchers have defined the stem or progenitor cells from various tissues, including bone marrow, peripheral blood, brain, liver, and reproductive organs, in both adult animals and humans (Fig. 1).

Among these stem/progenitor cells, the EPC has been identified recently and investigated to elucidate its biology for therapeutic applications. Because recent reports demonstrate that endothelial lineage cells play a critical role in the early stage of liver or pancreatic differentiation before formation of functioning blood vessels (38, 44), the significance of vascular...
development in organogenesis has become a crucial issue in regenerative medicine.

EMBRYONIC EPCs

Embryonic stem cell researchers in this decade have opened a novel door for vascular biology, as for any medical field, to elucidate the history of vascular development. Embryonic EPCs, or angioblasts, for blood vessel development arise from migrating mesodermal cells. EPCs have the capacity to proliferate, migrate, and differentiate into endothelial lineage cells but have not yet acquired characteristic mature endothelial markers. Available evidence suggests that hematopoietic stem cells (HSCs) and EPCs (46, 54) are derived from a common precursor (hemangioblast) (16, 27, 68). Growth and fusion of multiple blood islands in the yolk sac of the embryo ultimately give rise to the yolk sac capillary network (52); after the onset of blood circulation, this network differentiates into an arteriovenous vascular system (51). The integral relationship between the elements that circulate in the vascular system (blood cells) and the cells that are principally responsible for the vessels themselves (ECs) is implied by the composition of the embryonic blood islands. The cells destined to generate hematopoietic cells are situated in the center of the blood island and are termed HSCs. EPCs are located at the periphery of the blood islands.

The key molecular players determining the fate of the hemangioblast are not fully elucidated. However, several factors have been identified that may play a role in this early event. Studies in quail/chick chimeras showed that fibroblast growth factor-2 (FGF-2) mediates the induction of EPCs from the mesoderm (48). These embryonic EPCs express Flk-1, the type 2 receptor for vascular endothelial growth factor (VEGFR-2), and respond to a pleiotropic angiogenic factor, VEGF, for proliferation and migration. Deletion of the Flk-1 gene in mice results in embryonic lethality, lacking both hematopoietic and endothelial lineage development, supporting the critical importance of Flk-1 at that developmental stage, although the steps regulating differentiation into endothelial vs. hematopoietic cells had not yet been defined at the time of those studies. The Flk-1-expressing mesodermal cell has also been defined as an embryonic common vascular progenitor that differentiates into endothelial and smooth muscle cells (69). The vascular progenitors differentiated to ECs in response to VEGF, whereas they developed into smooth muscle cells in response to platelet-derived growth factor (PDGF)-BB. It remains to be determined whether embryonic EPCs or vascular progenitor cells persist with an equivalent capability during adult life and whether these cells contribute to postnatal vessel growth.

POSTNATAL EPCs

The identification of putative HSCs in peripheral blood and bone marrow and the demonstration of sustained hematopoietic reconstitution with these HSC transplants have constituted inferential evidence for HSCs in adult tissues (5, 35, 58). Recently, the related descendants, EPCs, have been isolated along with HSCs in hematopoietic organs. Flk-1 and CD34 antigens were used to detect putative EPCs from the mononuclear cell fraction of peripheral blood (2). This methodology was supported by former findings that embryonic HSCs and EPCs share certain antigenic determinants, including Flk-1, Tie-2, c-Kit, Sca-1, CD133, and CD34. These progenitor cells have consequently been considered to be derived from a common precursor, putatively termed a hemangioblast (16, 27, 68) (Fig. 2).

In vitro, these cells differentiated into endothelial lineage cells, and in animal models of ischemia, heterologous, homologous, and autologous EPCs were shown to incorporate into sites of active neovascularization. This finding was followed by diverse identifications of EPCs by several groups (20, 23, 39, 47, 59) using equivalent or different methodologies. EPCs were subsequently shown to express VE-cadherin, a junctional molecule, and AC133, an orphan receptor that is specifically expressed on EPCs but whose expression is lost once the EPCs differentiate into more mature ECs (47). Their high proliferation rate distinguishes circulating marrow-derived EPCs in the adult from mature ECs shed from the vessel wall (17). Thus far, a bipotential common vascular progenitor, giving rise to both endothelial and smooth muscle cells, has not been documented in the adult.
These findings have raised important questions regarding fundamental concepts of blood vessel growth and development in adult subjects. Does the differentiation of EPCs in situ (vasculogenesis) play an important role in adult neovascularization, and would impairments in this process lead to clinical diseases? There is now a strong body of evidence suggesting that vasculogenesis does, in fact, make a significant contribution to postnatal neovascularization. Recent studies with animal bone marrow transplantation (BMT) models in which bone marrow (donor)-derived EPCs could be distinguished have shown that the contribution of EPCs to neovessel formation may range from 5 to 25% in response to granulation tissue formation (10) or growth factor-induced neovascularization (45).

IDENTIFICATION OF EPCs AND THEIR PRECURSORS

Since the initial report of EPCs (3), a number of groups have set out to better define this cell population. Because EPCs and HSCs share many surface markers, and because no simple definition of EPCs exists, various methods of EPC isolation have been reported (2, 3, 10, 20, 23, 39, 45, 47–50, 52, 59, 61, 63, 68, 69). The term “EPC” may therefore encompass a group of cells existing in a variety of stages ranging from hemangioblasts to fully differentiated ECs. Although the true differentiation lineage of EPCs and their putative precursors remain to be determined, there is overwhelming evidence in vivo that a population of EPCs exists in humans.

Lin et al. (39) cultivated peripheral MNCs from patients receiving gender-mismatched BMT and studied their growth in vitro. In that study, they identified a population of bone marrow (donor)-derived ECs with high proliferative potential (late outgrowth); these bone marrow cells likely represent EPCs. Gunsilius et al. (23) investigated a chronic myelogenous leukemia model and disclosed that bone marrow-derived EPCs contribute to postnatal neovascularization in humans (23). Reyes et al. (50) recently isolated multipotent adult progenitor cells (MAPCs) from bone marrow MNCs, which differentiated into EPCs. These findings strongly proposed MAPCs as the origin of EPCs (49). These studies therefore provide evidence to support the presence of bone marrow-derived EPCs that take part in neovascularization (Fig. 2).

EPC KINETICS FOR REGENERATION

Given the result of common antigenicity, bone marrow has been considered the origin of EPCs as HSCs in adults. The BMT experiments have demonstrated the incorporation of bone marrow-derived EPCs into foci of physiological and pathological neovascularization (2). Wild-type mice were lethally irradiated and transplanted with bone marrow harvested from transgenic mice in which constitutive LacZ expression is regulated by an EC-specific promoter: Flk-1 or Tie-2. Histological examination of the tissues in growing tumors, healing wounds, ischemic skeletal and cardiac muscles, and cornea micropocket surgery after BMT has shown localization of Flk-1- or Tie-2-expressing endothelial lineage cells derived from bone marrow in blood vessels and stroma around vasculatures. The similar incorporation was observed in physiological neovascularization in uterus endometrial formation after induced ovulation as well as estrogen administration (2). A source of EPCs other than bone marrow has never been identified because of the lack of appropriate animal models.

Previous investigators have shown that wound trauma causes mobilization of hematopoietic cells, including pluripotent stem or progenitor cells in spleen, bone marrow, and peripheral blood. Consistent with EPC/HSC common ancestry, recent data from our laboratory have shown that mobilization of bone marrow-derived EPCs constitute a natural response to tissue ischemia (26). The former murine BMT model presented the direct evidence of enhanced bone marrow-derived EPC incorporation into foci of corneal neovascularization after the development of hindlimb ischemia. Light microscopic examination of corneas excised 6 days after micropocket injury and concurrent surgery to establish hindlimb ischemia demonstrated a statistically significant increase in cells expressing β-galactosidase in the corneas of mice with, versus those without, an ischemic limb (63). This finding indicates that
circulating EPCs are mobilized endogenously in response to tissue ischemia, after which they may be incorporated into neovascular foci to promote tissue repair. This was confirmed by clinical findings of EPC mobilization in patients with coronary artery bypass grafting, burns (22), and acute myocardial infarction (60).

Having demonstrated the potential for endogenous mobilization of bone marrow-derived EPCs, we considered that iatrogenic expansion and mobilization of this putative EC precursor population might represent an effective means to augment the resident population of ECs that is competent to respond to administered angiogenic cytokines. Such a program might thereby address the issue of endothelial dysfunction or depletion that may compromise strategies of therapeutic neovascularization in older, diabetic, and/or hypercholesterolemic animals and patients. Granulocyte macrophage colony-stimulating factor (GM-CSF), which stimulates hematopoietic progenitor cells and myeloid lineage cells as well as nonhematopoietic cells including bone marrow stromal cells and ECs, has been shown to exert a potent stimulatory effect on EPC kinetics: mobilization from bone marrow, incorporation into sites of neovascularization, and proliferation and differentiation in culture (63). Such cytokine-induced EPC mobilization could enhance neovascularization of severely ischemic tissues as well as de novo corneal vascularization (63).

The mechanisms whereby these EPCs are mobilized to the peripheral circulation are in the early stage of definition. Among other growth factors, VEGF is the most critical factor for vasculogenesis and angiogenesis (6, 15, 57). Recently collected data indicate that VEGF is an important factor for the mobilization of EPCs from bone marrow, as well. Our studies performed first in mice (2) and subsequently in patients undergoing VEGF gene transfer for critical limb ischemia (32) and myocardial ischemia (32) established that a previously unappreciated mechanism by which VEGF contributes to neovascularization is via mobilization of bone marrow-derived EPCs. The similar EPC kinetics modulation has been observed in response to other hematopoietic stimulators, such as granulocyte colony-stimulating factor (G-CSF) (20), angiopoietin-1 (24), and stroma-derived factor-1 (SDF-1) (47).

This therapeutic strategy of EPC mobilization has recently been implicated not only by natural hematopoietic or angiogenic stimulants but also by recombinant pharmaceuticals. The statins inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the synthesis of mevalonate, a rate-limiting step in cholesterol biosynthesis. The statins rapidly activate Akt signaling in ECs, thereby stimulating EC bioactivity in vitro and enhancing angiogenesis in vivo (37). Recently, we (41) and Dimmeler and colleagues (12, 67) demonstrated a novel function for HMG-CoA reductase inhibitors that contributes to postnatal neovascularization by augmented mobilization of bone marrow-derived EPCs through stimulation of the Akt signaling pathway. With regard to its pharmacological safety and effectiveness on hypercholesterolemia, one of the risk factors for atherogenesis, the statin might be a potent medication against atherosclerotic vascular diseases.

**THERAPEUTIC POTENTIALS OF EPC TRANSPLANTATION**

The regenerative potential of stem cells is presently under intense investigation. In vitro, stem and progenitor cells possess the capability of self-renewal and differentiation into organ-specific cell types. In vivo, transplantation of these cells may reconstitute organ systems, as shown in animal models of diseases (1, 3, 14, 17, 32, 40). In contrast, differentiated cells do not exhibit such characteristics. Human EPCs have been isolated from the peripheral blood of adult individuals, expanded in vitro, and committed into an endothelial lineage in culture (2). The transplantation of these human EPCs has been shown to facilitate successful salvage of ischemic hindlimb and to improve blood perfusion in ischemic limbs of nude mice, whereas differentiated ECs (human microvascular ECs) failed to accomplish limb-saving neovascularization (32) (Fig. 3).

These experimental findings call into question certain fundamental concepts regarding blood vessel growth and development in adult organisms. Postnatal neovascularization was...
Invited Review

ENDOTHELIAL PROGENITOR CELLS FOR POSTNATAL VASCULOGENESIS

previously considered synonymous with proliferation and migration of preexisting, fully differentiated ECs resident within parent vessels, i.e., angiogenesis (18). The finding that circulating EPCs may home to sites of neovascularization and differentiate into ECs in situ is consistent with vasculogenesis (51), a critical paradigm for establishment of the primordial vascular network in the embryo. While the proportional contributions of angiogenesis and vasculogenesis to postnatal neovascularization remain to be clarified, our findings together with recent reports from other investigators (25, 59) suggest that growth and development of new blood vessels in the adult are not restricted to angiogenesis but encompass both embryonic mechanisms. As a corollary, augmented or retarded neovascularization, whether endogenous or iatrogenic, likely includes enhancement or impairment of vasculogenesis.

We therefore considered a novel strategy of EPC transplantation to provide a source of robust ECs that might supplement fully differentiated ECs thought to migrate and proliferate from preexisting blood vessels according to the classic paradigm of angiogenesis developed by Folkman (19). Our studies indicated that ex vivo cell therapy, consisting of culture-expanded EPC transplantation, successfully promotes neovascularization of ischemic tissues, even when administered as “sole therapy,” i.e., in the absence of angiogenic growth factors. Such a “supply side” version of therapeutic neovascularization in which the substrate (ECs as EPCs) rather than the ligand comprises the therapeutic agent was first demonstrated in the hindlimb ischemia model of immunodeficient mouse, using donor cells from human volunteers (32). These findings provide novel evidence that exogenously administered EPCs augment naturally impaired neovascularization in an animal model of experimentally induced critical limb ischemia. Not only did heterologous cell transplantation improve neovascularization and blood flow recovery, but important biological consequences, notably limb necrosis and autoamputation, were reduced by 50% compared with mice receiving differentiated ECs or control mice receiving media in which harvested cells were expanded ex vivo before transplantation.

A similar strategy applied in a model of myocardial ischemia in the nude rat demonstrated that transplanted human EPCs incorporated into rat myocardial neovascularization, differentiated into mature ECs in ischemic myocardium, enhanced neovascularization, preserved left ventricular (LV) function, and inhibited myocardial fibrosis (34).

Recently, Shatteman et al. (56) conducted local injection of freshly isolated human CD34+ MNCs into diabetic nude mice with hindlimb ischemia and showed an increase in the restoration of limb flow. Kocher et al. (28) attempted intravenous infusion of freshly isolated (not cultured) human CD34+ MNCs (EPC-enriched fraction) into nude rats with myocardial ischemia. This strategy resulted in preservation of LV function associated with inhibition of cardiomyocyte apoptosis. These experimental findings obtained using immunodeficient animals suggest that both cultured and freshly isolated human EPCs have therapeutic potential in peripheral and coronary artery diseases.

Induction of angiogenic diseases, such as diabetic retinopathy and malignant tumors, is a possible deleterious effect of EPC transplantation. Such harmful events should be carefully monitored in future clinical trials, although no adverse effects have ever been reported in previous basic and preclinical studies.

IMPACT OF CLINICAL PHENOTYPE ON EPCs

Preliminary clinical findings in patients with critical limb ischemia indicated that the response to phVEGF gene transfer was most robust and expeditious in young patients with premature atherosclerosis involving the lower extremities, so-called Buerger’s disease (28). This clinical observation was supported by experiments performed in live animal models, specifically young (6–8 mo) vs. old (4–5 yr) rabbits and young (8 wk) vs. old (2 yr) mice. In both cases, native neovascularization of the ischemic hindlimb was markedly retarded in old vs. young animals. Retardation of neovascularization in old animals appeared in part to result from reduced expression of VEGF in tissue sections harvested from the ischemic limb (54).

Endogenous cytokine expression, however, is not the only factor contributing to impaired neovascularization. Older, diabetic, and hypercholesterolemic animals, like human subjects (7, 8, 13, 21, 30, 42, 62, 65), also exhibit evidence of age-related endothelial dysfunction. Although endothelial dysfunction does not necessarily preclude a favorable response to cytokine replacement therapy, indexes of limb perfusion fail to reach ultimate levels recorded in wild-type animals, reflecting limitations imposed by a less responsive EC substrate (9, 54, 55, 66).

It is then conceivable that unfavorable clinical situations (such as aging) might be associated with dysfunctional EPCs, defective vasculogenesis, and, thus, impaired neovascularization. Indeed, preliminary results from our laboratory indicated that replacement of native bone marrow (including its compartment of progenitor cells) of young mice with bone marrow transplanted from old animals leads to a marked reduction in neovascularization following corneal micropocket injury, compared with young mice transplanted with young bone marrow (53). These studies thus established evidence of an age-dependent impairment in vasculogenesis (as well as angiogenesis) and the origin of progenitor cells as a critical parameter influencing neovascularization. Moreover, analysis of clinical data in older patients at our institution disclosed a significant reduction in the number of circulating EPC both at baseline and after VEGF165 gene transfer (31); specifically, the number of circulating EPCs of younger patients with critical limb ischemia was five times more than the number in older individuals. Impaired EPC mobilization and/or activity in response to VEGF may thus contribute to the age-dependent defect in postnatal neovascularization. Recently, Tepper et al. (64) reported that proliferation and tube formation of EPCs was impaired in patients with type 2 diabetes compared with normal subjects.

GENE THERAPY OF EPCs

Given these findings, together with the limited quantity of EPCs available even under healthy, physiological conditions, one must consider a strategy that addresses this shortfall and mitigates the possibility of dysfunctional EPCs for therapeutic vasculogenesis in ischemic disorders complicated by aging, diabetes, hypercholesterolemia, and/or hyperhomocysteinemia. Genetic modification of EPCs to overexpress angiogenic growth factors, enhance signaling activity of the angiogenic
response, rejuvenate the bioactivity, and/or extend the life span of EPCs constitutes one potential strategy that might address these limitations of EPC transplantation and thereby optimize therapeutic neovascularization (Fig. 3).

Our recent findings provide the first evidence that exogenously administered, gene-modified EPCs augment naturally impaired neovascularization in an animal model of experimentally induced limb ischemia (29). Transplantation of heterologous EPCs transduced with adeno-virus encoding VEGF not only improved neovascularization and blood flow recovery but also had meaningful biological consequences: limb necrosis and autoamputation were reduced by 63.7% compared with controls. The dose of EPCs used in the current in vivo experiments was subtherapeutic; i.e., this dose of EPCs was 30 times less than that required in previous experiments to improve the rate of limb salvage above that seen in untreated controls. Adenoviral VEGF gene transfer of EPC, however, accomplished a therapeutic effect, as evidenced by a functional outcome, despite a subtherapeutic dose of EPCs. Thus VEGF gene transfer of EPC constitutes one option to address the limited number of EPCs that can be isolated from peripheral blood prior to ex vivo expansion and subsequent autologous readministration.

EPCs in other fields

EPCs have recently been applied to the field of tissue engineering as a means of improving biocompatibility of vascular grafts. Artificial grafts first seeded with autologous CD34+ cells from canine bone marrow and then implanted into the aorta were found to have increased surface endothelialization and vascularization compared with controls (4). Similarly, when cultured autologous ovine EPCs were seeded onto carotid interposition grafts, the EPC-seeded grafts achieved physiological motility and remained patent for 130 days vs. 15 days in nonseeded grafts (33).

EPCs also have been investigated in the cerebrovascular field. Embolization of the middle cerebral artery in Tie-2/LacZ/BMT mice disclosed that the formation of new blood vessels in the adult brain after stroke involves vasculogenesis/EPCs (70). Similar data were reported by investigators using gender-mismatched wild-type mice transplanted with bone marrow from green fluorescent protein-transgenic mice (26). However, whether autologous EPC transplantation would augment cerebral revascularization has yet to be examined.

To date, the role of EPCs in tumor angiogenesis has been demonstrated by several groups. Davidoff et al. (11) showed that bone marrow-derived EPCs contribute to tumor neovascularization and that bone marrow cells transduced with an anti-angiogenic gene can restrict tumor growth in mice. Lyden et al. (43) recently demonstrated the critical role of bone marrow-derived EPCs in tumor neovascularization. Id-mutant (Id1−/−/Id3−/−) mice are angiogenic defective and tumor-resistant double-mutant mice in which implanted tumors rapidly regress in association with poor development of tumor neovessels. BMT from wild-type mice, not from Id-mutant mice, restored the tumor neovascularization and growth in Id-mutant mice (43). These data demonstrate that EPCs are not only important but also critical to tumor neovascularization. Although it is not known whether local administration of exogenous EPCs may augment tumor neovascularization, this issue should be carefully considered for clinical application of EPC cell therapy to treat cardiovascular diseases.

In conclusion, EPCs isolated from adult species, which have characteristics similar to those of embryonic angioblasts, have the capacity to proliferate, migrate, and differentiate into endothelial lineage cells but have not yet acquired mature endothelial markers. EPCs are mobilized from bone marrow into the circulation and then home to the site of neovascularization in response to physiological and pathological stimuli, thereby contributing to postnatal neovascularization. Since animal experiments on EPC transplantation proved the therapeutic potential of the cell-based strategy, the application of EPCs for regenerative medicine has been watched with keen interest. The clinical impact of EPC regenerative properties will be evaluated in a phase I-II trial being started at our institution.

However, a number of issues remain to be addressed in this research field. Some of the future perspectives are as follows: 1) identification of a specific marker for EPC with which other lineage cells do not share; 2) evaluation of EPC transdifferentiation in vitro and in physiological, pathological, and iatrogenic regeneration of tissues and organs; 3) methodological optimization of EPC purification, expansion, gene transfer, and administration to improve the efficacy of EPC transplantation; and 4) comparison of the therapeutic impact between purified EPCs and total bone marrow MNCs.

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