Concise Review: Endothelial Stem and Progenitor Cells and Their Habitats

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ABSTRACT

Recent studies on the stem cell origins of regenerating tissues have provided solid evidence in support of the role of the resident cells, rather than bone marrow-derived or transplanted stem cells, in restoring tissue architecture after an injury. This is also true for endothelial stem and progenitor cells: local pools exist in the vascular wall, and those cells are the primary drivers of vascular regeneration. This paradigm shift offers an opportunity to rethink and refine our understanding of the multiple therapeutic effects of transplanted endothelial progenitor cells, focusing on their secretion, shedding, intercellular communicational routes, and other potential ways to rejuvenate and replenish the pool of resident cells. The dynamics of vascular wall resident cells, at least in the adipose tissue, may shed light on the origins of other cells present in the vascular wall—pericytes and mesenchymal stem cells. The fate of these cells in aging and disease awaits elucidation.

INTRODUCTION

For the past 15 years, investigations into the biology and therapeutic efficacy of endothelial stem and progenitor cells (EPCs) were largely driven by the initial observations of Asahara et al. [1]. This work suggested evidence for the existence of circulating EPCs (CD34+/H11001, VEGFR2+/H11001), which participate in angiogenesis. It also generated a substantial number of follow-up studies that, using various models of disease, broadened the view on the therapeutic efficacy of EPC transplantation. Recent advances in the field, however, have shifted the focus to local stem and progenitor cells for the endothelium [2–6], and although they do not refute the previous work, they require critical re-evaluation of the role of EPCs in the pathogenesis of disease, their precise cellular identity, and their beneficial effects in therapeutic interventions. In this brief overview, we first present existing and emerging evidence on the topography of EPCs and other stem cells in the vascular wall and their function in angiogenesis, focus on potential mechanisms of stem cell-mediated therapeutic effects, and then describe the mechanisms and consequences of premature senescence of EPCs. Because of space limitations, we are able to provide only a snapshot of this rapidly developing field of knowledge.

EARLY EMBRYONIC DEVELOPMENT

During early embryonic development, mesodermal cells migrate toward the extraembryonic yolk sac and create “blood islands.” The outer luminal layer of these islands contains endothelial precursors (angioblasts), whereas the inner mass consists of hematopoietic precursors [7, 8]. Subsequently, the dorsal aortic area, aorto-gonado-mesonephric region (AGM), which harbors EPCs, becomes the first hematopoietic organ because of the ability of EPCs to give rise to hematopoietic stem cells (HSCs), as well as mesenchymal stem cells (MSCs) [9, 10]. Notably, this ability is conserved in mammals throughout adult life, long after the disappearance of AGM. Temporarily restricted genetic cell fate tracing studies by Iruela-Arispe’s group have demonstrated in mice with an inducible vascular endothelial (VE)-cadherin Cre that its progeny migrates to fetal liver and later to bone marrow. AGM mesenchyme traced using myocardin Cre mice is incapable of hematopoiesis but is capable of generating endothelial cells (ECs) [9]. The process of embryonic endothelial-hematopoietic transition in zebrafish occurs through a unique Runx1-dependent mechanism of endothelial cell bending and escaping aortic ventral wall in the direction of subaortic space [11]. In fact, the mechanics of this process bears some similarities to the transition of endothelial cells into pericytes described in the adult adipose tissue [12, 13], where endothelial cells “dive” into the basement membrane and in the process undergo a transition to pericytes, which acquire the properties of MSCs and then the
properties of preadipocytes, while moving away from the capillary walls.

**ADULT MAMMALS**

In adult mammals, cells with EPC-like characteristics have been described in the bone marrow, circulation, and blood vessels [14–17]. In the vascular wall, solitary cells or small clusters of EPCs are represented in all three layers: adventitial, medial, and intimal. These c-Kit+/VEGFR2+/CD45− cells are clonogenic and can differentiate toward ECs, smooth muscle cells (SMCs), and fibroblasts [18]. Subsets of ECs from umbilical cord or peripheral blood or isolated from adult vasculature also show clonogenic potential [19, 20]. The most recent studies by Salven’s group describe a small subpopulation of c-Kit-expressing ECs (lin−CD31+CD105+Sca1+CD117/c-Kit+) that reside in the adult blood vessel endothelium and are capable of undergoing clonal expansion in vivo and in vitro, whereas other ECs have a very limited proliferative capacity [21, 22]. These c-Kit+ adult vascular endothelial stem cells (VESCs) make up only 0.4% of all adult vessel wall lin−CD31+CD105+ ECs. Cell transplantation experiments using isolated VESCs confirmed that a single c-Kit+ VESC can generate in vivo functional blood vessels that connect to host circulation. Self-renewal is a defining functional property of stem cells, which therefore have the ability to repeatedly respond to growth stimuli by giving rise to extensive numbers of proliferative daughter cells [23]. By performing repeated isolations and in vivo serial transplantation experiments, Salven and coworkers showed that VESCs also display long-term self-renewal capacity [21].

It has to be mentioned that studies of EPCs are riddled with uncertainty due to the lack of specific markers, diversity of protocols for their isolation, and differences in their experimental usage. In the literature, the collective term “EPCs” may indicate endothelial colony-forming cells (ECFCs), late outgrowth endothelial cells, or blood outgrowth endothelial cells. ECFCs have been characterized by their robust proliferative potential and de novo vessel formation in vivo [20]. It is also obvious that future availability of specific cell-surface markers and efficient isolation techniques will be central issues for the practical use of endothelial cell populations in tissue engineering and regenerative medicine. Alas, the situation is not much different from studies of other stem and progenitor cells. The subject has been comprehensively discussed elsewhere [6, 14, 16–19].

In addition to EPCs, the vascular wall harbors MSCs, HSCs, and possibly smooth muscle progenitor cells. Studies by Hu et al. [24] identified adventitial progenitor cells as Sca-1+/Fkhl1+/c-Kit+ in ApoE−/− mice and showed that they can migrate toward the injured intima to participate in neointimal formation of atherosclerotic lesions and differentiate toward SMCs. Originally thought to egress from the circulation, mast cells and macrophages found in the vasculogenic zone are currently proposed to originate from the resident precursors [25]. Hence, the vascular wall is richly endowed with various stem and progenitor cells, thus raising the question of their origins: Do they arise from a hemangioblast-like precursor and have an embryonic AGM origin? Or does each type of stem cell have an individual precursor(s)? If so, what is its location? No answers to these questions are available at the time of this writing.

In fact, a time-tested aortic ring model of angiogenesis provides serial snapshots of vascular wall resident cells participating in vascular sprouting, as comprehensively summarized by Nicolas [26]. The first cells migrating out of the vascular wall embedded in three-dimensional (3D) matrix are fibroblasts (which express vimentin, and some of them, such as myofibroblasts, also express a-smooth muscle actin) and macrophages (which express CD45, CD68, and CD163); the fibroblasts probably direct the future sprouts through generation of mechanical forces, and the macrophages provide chemotactic gradients for sprouting. These migrants are followed by endothelial cells, which later become surrounded by pericytes. The tip endothelial cells are highly migratory, whereas the cells in the base of vascular sprouts are highly proliferative. Endothelial cells are coated with the electron-dense, fluffy glyocalyx. Pericytes, usually considered a hallmark of capillary wall, emerge from the intimal layer of aortic vascular rings turned inside out prior to embedding into the 3D collagen matrix and are immunostained for desmin, calponin, proteoglycan NG2, and, in the presence of serum, a-smooth muscle actin (reviewed in [26]).

**AGING ANIMALS**

In aging animals, angiogenic competence is decreased. Mouse aortic rings obtained from these animals show a 40% reduction in vascular sprouting induced by vascular endothelial growth factor compared with young animals [27]. A similar defect occurs in prematurely senescent Klotho mice [28]. Of note, caloric restriction regimens rescue angiogenic competence of aortic rings obtained from 24-month-old rats by 45%–63% [29]. One of the downstream targets of caloric restriction, sirtuin-1, is robustly expressed in EPCs and ECs, and it declines with age and following application of cardiovascular stressors [30]. The mechanism of sirtuin-1 deficiency leading to premature senescence of EPCs is represented by the stress-induced loss of integrity of lysosomal membrane and leakage of cathepsins, which are capable of directly degrading this deacetylase, as shown in in vitro studies [30]. EPCs isolated from the bone marrow of mice genetically engineered to lack endothelial sirtuin-1 exhibit premature senescence and a higher rate of apoptosis even at a young age [30].

**EPCs and ECs Become Dysfunctional**

The idea that EPCs and ECs become dysfunctional in the course of a disease derives from the demonstration of their defective regenerative capacity, compromised clonogenicity, migration, and capillary formation. There are multiple examples of EPC incompetence developing in the course of a disease. Patients with systemic lupus erythematosus exhibit reduced levels of circulating HSCs and EPCs even during remission [31]. Aging is the most common cause of EPC dysfunction [32]. Recent studies from our laboratory showed that bone marrow-derived EPCs from db/db mice are functionally incompetent, whereas adoptive transfer of bone marrow-derived cells from syngeneic nondiabetic mice significantly improved vasculopathy and insulin sensitivity and partially improved renal function in db/db recipients [33]. Hyperglycemia has been reported to reduce survival and impair function of

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circulating EPCs [34]. EPC dysfunction has been also documented in type I and II diabetes, coronary artery disease, atherosclerosis, vasculitis with kidney involvement, and end-stage renal disease. In most cases, this incompetence is a result of stress-induced premature senescence of EPCs, and it is a significant contributor to the arrested regeneration and accelerated progression of diverse diseases. This concept underwrites the interest in exogenous and endogenous stem cell therapy.

Several recent studies are reshaping our understanding of the role of stem cells in general and EPCs in particular in regenerative processes. Using genetic fate tracing technology, Irving Weissman’s group has documented that bone marrow-derived or circulating cells do not contribute to regeneration of a distal phalanx in an adult mouse and that germ-layer and lineage-restricted stem/progenitors are responsible for the regeneration [4]. They also concluded that endothelial stem/progenitor cells involved in adult angiogenesis must be local, nonhematopoietic, and noncirculating but rather tissue-resident cells [4]. Salven’s group has demonstrated [20] the existence of a vessel wall-residing c-Kit+ adult VESCs. The importance of endothelial cells for tissue-regenerative processes has been illustrated in a study by Rafii’s group [35], which provides evidence for angiocrine signals generated during vascular regeneration through production of epidermal growth factor-like laminin fragments, and those foster growth of the pulmonary epithelia. Along these lines, dependence of adipogenesis on endothelial cells has been demonstrated by Spiegelman’s group [12] and Cinti’s group [13]. These studies show that endothelial cells undergo phenotypic transition to give rise to pericytes, which in turn serve as adipogenic progenitors. Whether similar processes take place outside adipose tissue remains unknown, although the appearance of pericytes in inverted aortic ring cultures (see above; [26]) may be suggestive. These new data dictate the necessity of reinterpreting the vast number of observations (reviewed in [36–38]) demonstrating beneficial effects of EPC transplantation, as well as the multitude of observations correlating the level of circulating EPCs with the progression and outcome of diverse diseases.

**Direct Incorporation of Stem Cells**

Direct incorporation of stem cells substituting for the damaged cells was initially advocated as a mechanism explaining beneficial effects of transplantation. Toward this end, incorporation into a defective intimal layer was suggested by the results of Asahara et al. [1]. EPC transplantation to diabetic mice resulted in vascular engraftment and restoration of blood flow in hind limb ischemia [39], Cross-grafting aortic segments between Balb/c and Tie-2/LacZ mice demonstrated chimerism of endothelial cells in the intimal layer, thus arguing in favor of EPC incorporation into the vessel [40]. This process may be facilitated and directed in part by platelet adhesion to the site of vascular injury, resulting in adhesion and maturation of circulating EPCs to endothelial cells [41]. However, the direct circulating EPC engraftment to the damaged vasculature is disproportionately low [42] or even undetectable [4]. There is growing concern whether bone marrow-derived EPCs actually repair vascular endothelium by the engraftment mechanism [43, 44], with the focus shifting toward progenitors within the vascular wall. Various pathways of indirect communication between these partners—circulating EPCs and damaged endothelium—are emerging.

**Paracrine Effects of Stem Cells**

Cultured peripheral vascular or bone marrow-derived cells give rise to at least two populations of cells that have been designated as EPCs: (a) early, VEGFR2+ and VE-cadherin+ cells coexpressing myeloid CD14 and pan-leukocytic CD45 (4–7 days) markers and (b) late outgrowth cells emerging after 2–3 weeks from CD14 nonmyeloid population and expressing CD34, VEGFR2, and AC133. Both populations are capable of inducing neovascularization, but the mode of action differs. Whereas early outgrowth EPCs have limited capacity for population doubling and induce only transient angiogenesis, late outgrowth EPCs can expand to more than 100 population doublings. Cell therapy with both populations results in the enhanced engraftment and neovascularization in hind limb ischemia [36–38]. Early outgrowth EPCs exert an angiogenic effect mainly by secreting products, whereas late outgrowth cells were thought to produce the effect by direct engraftment. The secretome of EPCs has been studied using combination of proteomic techniques. Pula et al. performed mass spectrometry screen of the secretome of colony-forming units and identified 272 nonredundant proteins, of which 124 were also found in cultured EPCs [45]. Among those were matrix metalloproteinase-9; interleukin-8; macrophage migration inhibitory factor; various cathepsins and protease inhibitors; s100 proteins A11, A8, and A4; plasminogen activator inhibitor-2; and apolipoprotein E; as well as a potent proangiogenic and prosurvival factor, thymidine phosphorylase. Thymidine phosphorylase also increased the number and dimensions of focal adhesions in mature endothelial cells and stimulated their migration and wound healing [45]. Another recent study identified prostacyclin as an angiocrine signal capable of repairing neuronal damage [46]. However, a growing body of evidence demonstrates that although they secrete paracrine proangiogenic growth factors and thus make an important contribution to angiogenesis, the cells described as circulating peripheral blood endothelial progenitor cells are hematopoietic cells, such as monocyte/macrophages and T lymphocytes [3, 5, 14, 47]. Therefore, Richardson and Yoder recently proposed that the term EPC be retired and the circulating cell subsets contributing to angiogenesis be referred to according to the terms already existent for each subset [6].

**Sheddome**

Sheddome, a fraction of the secretome represented by nonsecretory plasma membrane proteins appearing as a result of epitope shedding, is a subject of potential import. Shedding of syndecans (type 1 transmembrane heparin sulfate proteoglycans) is executed by several different sheddases belonging to the family of metzincins and mediated by growth factors (chemokines), conditions leading to cell stress and during wound healing (reviewed in [48]). Shedding of syndecan 1 is essential for the resolution of inflammation. Soluble endoglin (CD105), a cleavage product of a transmembrane coreceptor for transforming growth factor-β, which can inhibit angiogenesis, may contribute to preeclampsia. Among many other members of sheddome are the sonic hedgehog and monocyte-macrophase-specific scavenger receptor CD163, each contributing to regenerative processes. This potentially important field awaits in-depth exploration.
Cell-Cell Fusion

Two types of fusion exist: homotypic cell fusion between similar cells resulting in multinucleated cells, and heterotypic cell fusion between cells of different lineages (reviewed in [49, 50]). Both processes occur under physiological conditions and in chronic inflammatory processes, as for instance, in cell fusion of myelolymphoid cells with nonhematopoietic cells. Notably, this mechanism of repair may be partially responsible for “reprogramming” or “transdifferentiation,” which hitherto was attributed to stem cell plasticity, and may represent a rescue mechanism whereby genetic material is rejuvenated. However, little is known about cell fusion mechanism as an explanation for EPC-facilitated restorative processes.

Tunneling Nanotubes

Tunneling nanotube (TNT) formation between cultured cells has been described [51] and has proved to be a viable mechanism of organellar exchange between the cell partners. This mechanism has been shown to account for mitochondrial transfer between adult stem cells and somatic cells and rescue of their respiration [52]. TNT mechanism, although difficult to demonstrate in vivo and therefore studied in cultured cells, is believed to play a significant role in intercellular communication. When human umbilical vein endothelial cells (HUVECs) are presented with EPCs [53], each cell type labeled with differentially emitting fluorophores, TNT-mediated communication occurs under basal conditions. EPC-to-HUVEC flux, however, increases threefold after exposure of HUVECs to the cytotoxic drug adriamycin. TNT mechanism of organellar exchange may provide the means for the single EPC to exchange organelles with multiple endothelial cells, a multiplicative mechanism.

Microvesicles and Exosomes

Microvesicles (MVs) and exosomes represent yet another mechanism of information transfer between distant cells. By consensus, MVs are characterized as having a size of 100–400 nm in blood, whereas exosomes have a size of 50–100 nm. The former are better characterized as products of endothelial cells, the latter as immune and tumor cells (reviewed in [54]). Endothelial MVs surge in plasma of patients with diverse acute and chronic cardiovascular and renal disease and are characterized by surface markers CD54, CD62E, CD62P, CD31, CD106, CD105, CD144, and CD146 [55]. Detailed analysis of information transfer awaits elucidation.

CONCLUSION

Tectonic shifts occurring in the field of regenerative properties of stem cells have created repercussions in EPC biology of vascular regeneration. The paradigm that emerges from the recent work gives preference to the vessel-resident EPCs in accomplishing angiogenic demands of regenerating tissues (Fig. 1). This shift offers an opportunity to revise and refine our understanding of the role of these cells, either circulating, transplanted, or local, in tissue maintenance and regeneration. A host of questions are emerging, some formulated above, others as follows:  

- What is the fate of EPCs and ECs resident in the vascular wall? Does the example of the vasculature in adipose tissue [12, 13] extrapolate to other organs? How prevalent is the endothelial origin of pericytes and MSCs?  
- What are the stages of EPC differentiation toward mature endothelium? What are the drivers of the process? Could this process be diverted under pathological conditions?  
- How could the resident EPC pool become exhausted in disease states? How could it be rejuvenated and/or replenished?  
- What are the messages delivered by distant or circulating progenitors or mature cells to the local cells? Could these messages be “improved,” refined, or strengthened pharmacologically? Is it possible that disease processes are associated with an improper messaging system or inadequate interpretation of messages by recipient cells?

These and other issues have the potential to reshape our knowledge of vascular homeostasis in the years to come and improve therapeutic outlook for tissue regeneration.

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AUTHOR CONTRIBUTIONS

M.S.G. and P.S.: collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of the manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.
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