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REVIEW

The Role of Endothelial Progenitor Cells in Ischemic Cerebral and Heart Diseases

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Ischemic heart and cerebral diseases are complex clinical syndromes. Endothelial dysfunction caused by dysfunctional endothelial progenitor cells (EPCs) is thought to play a major role in pathophysiology of both types of disease. Healthy EPCs may be able to replace the dysfunctional endothelium through endogenous repair mechanisms. EPC levels are changed in patients with ischemic cerebrovascular and cardiovascular disease and EPCs may play a role in the pathophysiology of these diseases. EPCs are also a marker for preventive and therapeutic interventions. Homing of EPCs to ischemic sites is a mechanism of ischemic tissue repair, and molecules such as stromal-derived factor-1 and integrin may play a role in EPC homing in ischemic disease. Potentiation of the function and numbers of EPCs as well as combining EPCs with other pharmaceutical agents may improve the condition of ischemia patients. However, the precise role of EPCs in ischemic heart and cerebral disease and their therapeutic potential still remain to be explored. Here, we discuss the identification, mobilization, and clinical implications of EPCs in ischemic diseases.

Key words: Endothelial progenitor cells; Stroke; Ischemic heart disease; Therapy

INTRODUCTION

Infarction or ischemia occurring in the brain or heart is a common cause of clinical illness. Occlusion of blood flow from the supplying artery leads to ischemia, oxygen deprivation, and associated cell injury to organs. The consequences of ischemia depend on the tissue area involved in the occlusion, the presence of collateral circulation, and the vulnerability of a given tissue to hypoxia (19). Neurons and myocardial cells undergo irreversible damage when deprived of blood supply, and persistent ischemia causes irreversible tissue injury and necrosis. Cell necrosis triggers an inflammatory response and a degradation of the extracellular matrix. However, the high number of cells with the capacity for proliferation and regeneration in highly differentiated organs, such as the brain and the heart, means that there is potential for self-renewal in these organs (19).

Stem cells have the capacity to self-renew and develop into functionally specialized cells. There is much evidence that human peripheral blood contains bone marrow-derived progenitor cells, which have the capacity to differentiate into mature endothelial cells, termed endothelial progenitor cells (EPCs) (75). Certain surface membrane markers, including the endothelial marker vascular endothelial growth factor receptor-2 (VEGFR-2) and the hematopoietic progenitor cell markers CD34 and CD133, are expressed on the surface of EPCs after vascular trauma (8,30,45). EPCs have the potential to form into new blood vessels (postnatal vasculogenesis) to repair ischemic injury (8,52,87). This process contrasts with the sprouting of new vessels from existing ones in the area (angiogenesis) to relieve ischemia. Vasculogenesis and angiogenesis are different in many aspects. Vasculogenesis begins from the assembling of EPCs and formation of a primary vascular plexus (36). In angiogenesis, new vessels are produced from preexisting vessels during which endothelial cells replicate,

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sprout, and make new lumen (37). In angiogenesis, pericyte detachment is the first step to form the new vessels. Endothelial cell replication and degradation of surrounding extracellular matrix happen thereafter. Many molecules act as mitogens of endothelial cells, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and many other proteins whose secretion is induced by ischemia (37,38).

EPCs can migrate to the site of blood vessel injury to help repair the damage and differentiate into mature endothelial cells (50,83). Restoration of the endothelial lining and maintenance of vascular homeostasis are two of the main functions of EPCs, but EPCs also promote vascular growth by releasing factors that act in a paracrine manner to support local angiogenesis and mobilize tissue-residing progenitor cells (39,76,99). Therefore, EPCs may restore dysfunctional endothelium by an endogenous repair mechanism.

In this article, we summarize the current concepts in the biology of EPCs, focusing on their role in ischemic cerebral and cardiovascular disease and their clinical implications.

IDENTIFYING ENDOTHELIAL PROGENITOR CELLS

EPCs have several origins such as bone marrow (BM), peripheral blood, and tissue-derived stem cells (15,71,77) and are characterized by the expression of cell surface markers CD34, CD133, and VEGFR-2 (KDR/Flk-1) (6,42). Additionally, two types of EPCs (early and late) have been identified sequentially from the same donors during the culture of total mononuclear cells from human peripheral blood (43). Therefore, EPCs have heterogenous cell populations of various origins and different phenotypes that have the ability to differentiate into functionally competent endothelial cells. EPCs also have the ability to transdifferentiate: Badorff and colleagues found that when EPCs from healthy volunteers and coronary artery disease (CAD) patients were cocultured with rat cardiomyocytes, they transdifferentiated in vitro into functional, active cardiomyocytes. They concluded that cell-to-cell contact, but not cellular fusion, mediates EPC transdifferentiation (11).

The identification, isolation, and purification of EPCs is troublesome because EPCs have the same surface markers as hematopoietic stem cells (HSCs), which hampers the interpretation of research and comparisons between studies (42). More specific endothelial markers and validated functional assays are needed to confirm the characteristics of isolated endothelial cells. Currently, EPCs and circulating endothelial cells (CECs) are mostly defined by the expression of CD34 and VEGFR-2 (KDR/Flk-1), although the $CD34^+KDR^+$ fraction is also expressed by HSCs (119). HSCs and EPCs both express CD133 and c-kit (CD117), whereas CESs do not. HSCs express CD38, but generally do not express VE-Cadherin or fibroblast growth factor receptor (FGFR), in contrast to EPCs, which express all three. Burger and colleagues proposed the following phenotype for EPCs: $CD34^+FGFR^+CD38^+$VE-$Cadherin^+$c-kit^+CD31^+ KDR^+CD133^+, which is generally compatible with the definitions of several other investigators (17,67,119). If necessary, distinction between EPCs and CECs can be made by expression of CD146 on CECs and by CD133 on EPCs (90). Activated CECs may be distinguished by expression of CD105 (endoglin), the receptor for transforming growth factor-β1, which is a recognized regulator of angiogenesis. Currently, it is acceptable to measure the number of circulating EPCs by flow cytometry using the markers CD34, VEGFR-2, and CD133. However, the functional and clonogenic capacity of EPCs need to be evaluated using colony-forming unit assays (111). A summary of the different markers to differentiate EPCs (early and late), CECs, and HSCs is provided in Table 1.

ENDOTHELIAL PROGENITOR CELL MOBILIZATION

Accumulating evidence suggests the existence of a common precursor cell for both blood and endothelial cells in adult life. This precursor might be the adult equivalent of the hemangioblast that has been identified in embryonic development (21,69,96). Additionally, a population of primitive cells has been described with an even larger multipotent differentiation potential: the multipotent adult progenitor cells (MAPCs). These cells are able to differentiate into mesenchymal cells, and into

Table 1. Characterization of Circulating Endothelial Cells (CECs), Endothelial Progenitor Ccells (EPCs), and Hematopoietic Stem Cells (HSCs)

Cell Types	Markers	Origins
CECs	CD34, KDR, CD146, VE-cadherin, TM, vWF	Mature endothelium
Early EPCs	CD133, CD34, KDR, CD31, VE-cadherin, CD117, CD38, FGFR	Bone marrow, peripheral blood, vascular parenchyma
Late EPCs	CD34, KDR, CD105, VE-cadherin, vWF, CD146, CD31	Early EPCs
HSCs	CD34, KDR, CD133, CD117	Bone marrow

KDR: kinase-inserted domain containing receptor (VEGFR-2); TM: thrombomodulin; vWF: von Willebrand factor; FGFR: fibroblast growth factor receptor.

cells with neuroectoderm, endoderm, and visceral mesoderm characteristics (i.e., endothelial cells) in vitro. These MAPCs, identified in long-term culture of human adherent bone marrow cells, confirm the existence of primitive cells in adult life (78,105). Currently, HSCs and EPCs for transplantation purposes are generally acquired from mobilized peripheral blood, not bone marrow.

Several growth factors, cytokines, and chemokines have been found to mediate mobilization of EPCs. In both animal and human studies, stimulation by the growth factors VEGF, stromal derived factor-1 (SDF-1), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), angiopoetin-2, fibroblast growth factor, placental growth factor (PlGF), platelet-derived growth factor-CC, stem cell factor (SCF), interleukin (IL)-2, IL-3, IL-6, IL-8, and IL-1β, which are all known to mobilize HSCs, have also been shown to result in an increased number of EPCs (4,42,59). This conformity between the EPC and the HSC response might reflect the common origin of these cells (i.e., hemangioblast), or a common physiological mechanism for the mobilization of progenitor cells from bone marrow. HSCs and EPCs may show concomitant mobilization due to the physiological need of synergistic interactions between these cells in the processes of angiogenesis and vasculogenesis (42). In this respect, it is thought that VEGF-A, PlGF, and SDF-1, released by blood platelets and monocytes, activate metalloproteinase-9 (MMP-9), which mediates a joint mobilization of HSCs, EPCs, and other cell types. The interactions between these cells and EPCs, which may contribute to the revascularization process, are illustrated in Figure 1. Endothelial nitric oxide synthase (eNOS) activity has also been suggested to account for the mobilization of EPCs in response to injury (56). Impaired mobilization of EPCs from bone marrow was observed in eNOS knockout mice (3). Increased NO availability is required for statin-induced mobilization of EPCs (53). EPC mobilization was also inhibited by C-reactive protein (CRP), which interferes with NO production (106). NO produced by eNOS also interacted with SDF-1 and the CXCR4 signaling pathway to induce mobilization and homing of EPCs (116).

ENDOTHELIAL PROGENITOR CELL HOMING

Progenitor cells such as EPCs are highly migratory and seem to be attracted to injured brain areas such as ischemic regions (2,20). While stem cell homing to bone marrow has been widely studied (64), the molecular basis of stem cell pathotropism is not well understood. Further identification of the mechanisms involved would pave the way for the development of treatments to enhance endogenous mobilization of stem cells in disease states, perhaps using small molecules. EPCs express a wide variety of receptors that may enable them to respond to many chemotactic signals that emanate from brain pathologies. Chemokine and cytokine production is a common feature of many brain lesions, including stroke, which suggests that these factors could be important in mediating the responses of stem cells to injuries. Recent studies have demonstrated that integrin-mediated adhesion and transmigration are involved in the homing of transplanted EPCs to bone marrow (66), as well as the recruitment of EPCs to sites of angiogenesis (102).

Stromal Cell-Derived Factor-1 (SDF-1) and CXC Chemokine Receptor-4 (CXCR-4)

Mutual, reciprocal SDF-1/CXCR4 interactions between HSCs, EPCs, and bone marrow stromal cells regulate human stem cell migration and development, as reviewed comprehensively by Dar and coworkers (23). The chemokine SDF-1 (also known as CXCL12) and its receptor CXCR4 are reported to be involved in regulation of migration, survival, and development of multiple cell types, including HSCs, EPCs, and stromal stem cells (54). During steady-state homeostasis, CXCR4 is expressed by hematopoietic cells and also by stromal cells, which are the main source for SDF-1 in the BM. Stress will increase SDF-1 and CXCR4 levels, which stimulate recruitment of immature and maturing leukocytes from the BM reservoir to damaged organs as part of host defense and repair mechanisms (1,49). Additionally, trafficking of SDF-1 is mediated by CXCR4, expressed by endothelial and various stromal cell types in the BM, but not by hematopoietic cells (23). Transcytosis of functional SDF-1 to the BM also occurs in the stem cell-rich endothelium and endosteum regions, regulating HSCs, EPCs, and stromal interactions in the stem cell niche. Dynamic expression of SDF-1 and CXCR4 induces proliferation of HSCs, EPCs, and mesenchymal progenitors, recruitment of osteoclasts, osteoblasts, neutrophils, and other myeloid cells, leading to leukocyte mobilization (23). In one study, the role of a recipient's EPCs in the repair process was studied using wild-type donor female heart transplanted into male rat abdominal cavity (109). Induced male EPCs migrated into the cardiac allograft and SDF-1 mRNA levels increased significantly. CXCR4 was also strongly expressed. The authors concluded CXCR4 overexpression enhances vascularization in the damaged myocardium, and that the SDF-1/CXCR4 axis is important in EPC chemotaxis, homing, engraftment, and retention in damaged myocardium (109).

The correlation between platelets and EPC homing has also been discussed. Platelets induce differentiation of HSCs or EPCs into foam cells and endothelial cells (24). Platelets could be involved in progenitor cell recruitment and differentiation via specific adhesion re-

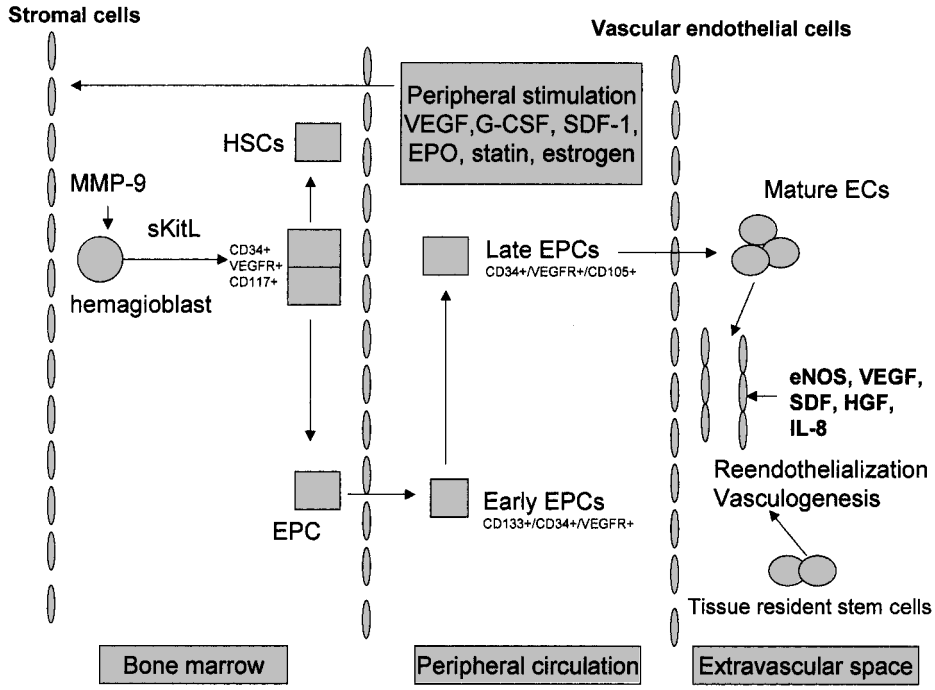

Figure 1. The mechanism of mobilization of endothelial progenitor cells (EPCs) by various stimuli. ECs: endothelial cells, HSCs: hematopoietic stem cells, eNOS: endothelial nitric oxide synthase, EPO: eryothropoietin, G-CSF: granulocyte colony-stimulating factor, HGF: hepatocyte growth factor, IL-8: interleukin-8, sKitL: soluble Kit ligand, MMP-9: matrix metalloproteinase-9, SDF-1: stromal cell-derived factor-1, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor.

ceptors such as P-selectin/P-selectin glycoprotein ligand-1 (PSGL-1) and integrins. This interaction may be the central mechanism for homing of EPCs to vascular injury sites (24,57). Sphingosine-1-phosphate (S1P) can also influence migration and proliferation of EPCs through the S1P receptor and supports SDF-1-induced migration and BM homing of $CD34^+$ progenitor cells (108).

Integrins

Integrins are heterodimeric transmembrane molecules consisting of α and β subunits that mediate cell adhesion and migration (22). Homing of progenitor cells such as EPCs to BM or ischemic tissue may follow the paradigm of mature leukocytes migrating to inflammatory tissue (61). We have shown that peripheral blood stem cell (PBSC) intracerebral transplantation can significantly improve neurological function following chronic cerebral ischemia in rats, accompanied by increased local cortical cerebral blood flow and β1-integrin expression in the ischemic hemisphere (89). The neurological improvement in this study was blocked by β1-integrin inhibitor (synthetic RDG peptide) (89). These results reveal that β1-integrin is necessary for neuroplasticity after intracerebral stem cell transplantation, possibly through the enhanced angiogenesis by homing of stem cells to ischemic sites (89).

β2-Integrins also mediate the adhesion and transmigration of EPCs as well as hemopoietic stem/progenitor cells in vitro (18,68). β2-Integrins are involved in the homing of hematopoietic progenitor cells to sites of ischemia and are critical for their neovascularization capacity in vivo (18). Preactivation of β2-integrins on adult EPCs has been shown to significantly augment the in vivo neovascularization capacity of EPCs, whereas $\beta2^{-/-}$ animals display a neovascularization defect in a model of hindlimb ischemia (18).

Whether β2- and β1-integrins play the same cellular role or whether different cell types use distinct mechanisms for homing remains to be determined. Further studies are still needed to elucidate whether there is a synergism between other adhesion molecules and their counterligands in the multistep recruitment of EPCs to ischemic tissue (62). Modulation of these integrins may provide novel opportunities for treating cerebral and cardiac ischemic disease.

ENDOTHELIAL PROGENITOR CELLS IN MYOCARDIAL INFARCTION

Myocardial ischemia and the cellular events that ensue may ultimately result in cardiomyocyte death and a reduction in cardiac performance (65). The vascular endothelium provides a one-cell-thick barrier for the blood vessels of the body and endothelial breakdown has been implicated in many disease processes, such as atherosclerosis (81). Circulating endothelial progenitor cells contribute to blood vessel formation at ischemic sites and are released into circulation after myocardial infarction (7,33,94). The relation between EPCs and ischemic heart disease is illustrated in Figure 2. A significant correlation between endothelial function and the number of endothelial progenitor cells was found in healthy volunteers, which reflects an increased endothelial turnover by the proliferation and differentiated of EPCs into endothelial cells after endothelial injury (41). Endothelial dysfunction and cardiovascular disease have also been shown to be inversely correlated to levels of circulating endothelial progenitor cells (41). Intravenous injection of human endothelial progenitor cells into rats following left anterior descending coronary artery ligation resulted in improved ventricular function, and endothelial progenitor cell accumulation in areas of infarction and in foci of neovascularization (46). Additionally, endothelial progenitor cells have shown a higher expression of antioxidative enzymes, such as catalase, glutathione peroxidase, and manganese superoxide dismutase, which allow for increased protection against oxidative stress (25).

Transplantation of EPCs with autologous harvesting eliminates immunorejection; however, mobilization and supply remain problems (6). Therefore, use of cytokines to increase maturation and migration of endogenous EPCs has been investigated. VEGF levels rise in conjunction with increased levels of circulating endothelial progenitor cells after myocardial infarction (73). G-CSF injection therapy induced growth and migration of endothelial progenitor cells from the bone marrow, and subsequent neovascularization of the ischemic tissue (44, 86,94). Studies in rat models showed that G-CSF could recruit endothelial progenitor cells to sites of myocardial ischemia, improve ventricular function, and promote neovascularization (47). Several studies suggest that NO production from eNOS is reduced in ischemic heart disease (84,98,116). Nitric oxide is essential for EPC-induced neovascularization (3,34).

Oxidative stress also plays roles in the initiation and progression of cardiovascular dysfunction associated with ischemic heart disease (115). Reactive oxygen species produced by xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and mitochondrial enzymes have been proposed to impair endothelial function by scavenging NO and yielding peroxynitrite in patients with ischemic heart disease (115). EPCs also have a higher expression of antioxidative enzymes, which enable them to resist oxidative stress (25).

Inflammatory stimuli may also induce a rapid release of EPCs into the circulation in humans (74,114). IL-1β, IL-6, and TNF-α were elevated in heart failure caused by coronary artery disease and hypertension (97). IL-1β is also able to mobilize EPCs and promote neovasculari-

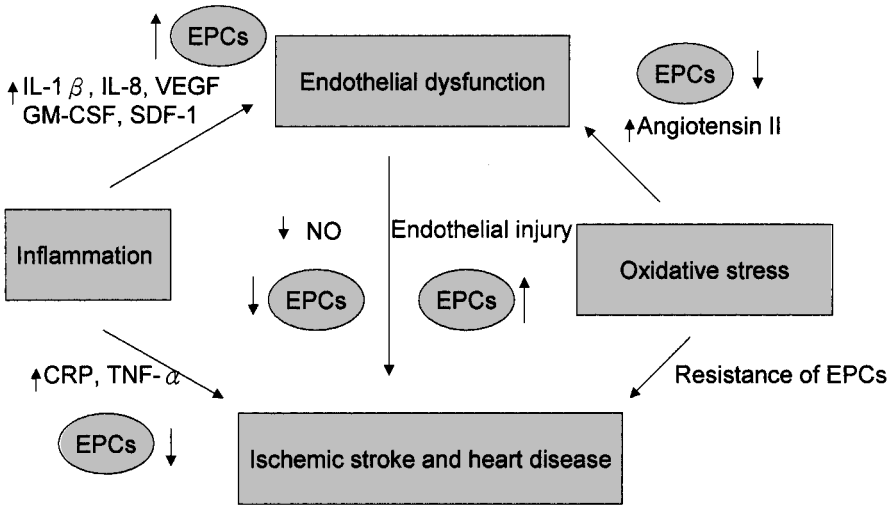

Figure 2. Relation between endothelial progenitor cells (EPCs) and ischemic heart and cerebral disease. CRP: C-reactive protein, eNOS: endothelial nitric oxide synthase, IL-1β: interleukin-1β, NO: nitric oxide, SDF-1: stromal cell-derived factor-1, TNF-α: tumor necrosis factor-α, VEGF: vascular endothelial growth factor, GM-CSF: granulocyte macrophage colony-stimulating factor.

zation through a VEGF-dependent pathway (5). Elevated levels of CRP have been associated with endothelial dysfunction in the form of inappropriate vascular constriction or relaxation, which contribute to the progression and adverse prognosis of myocardial infarction (28,82,92). Human recombinant CRP, at concentrations known to predict adverse vascular outcomes, directly inhibits EPC differentiation, survival, and function, expression of the key components of angiogenesis, and the response of EPCs to chronic ischemia and additionally induced EPC apoptosis in vitro (106). This occurs in part via CRP reducing EPC eNOS expression.

Therapeutically, the reduction of EPC number and the decreased functional activity of EPCs in patients with coronary artery disease were improved by 3-hydroxy-3-methylglutaryl coenzymeA (HMG-CoA) reductase inhibitors (statins), VEGF, erythropoietin (EPO), estrogen, and exercise (9,26,40,56,91,94). HMG-CoA reductase inhibitors increased the number and functional activity of EPCs in vitro, in mice, and in patients with stable coronary artery disease (26,59,105). Statin therapy also accelerated reendothelialization after balloon injury by improving mobilization and incorporation of bone marrow-derived EPCs (107,112). Regulation of EPC number and function was also affected by the lipid-lowering effect of statin therapy. Statins also increased the expression and activity of eNOS, contributing to increased mobilization and functional activity of EPCs (55). Several studies have shown that the prosurvival phosphatidylinositol-3-kinase (PI3K)/Akt pathway may play an important role in endothelial cells and EPCs (10,51). Thus, statins, VEGF, EPO, estrogen, and exercise (shear stress) are well known to augment the PI3K/Akt-pathway (101). Based on the finding that eNOS is essential for mobilization of bone marrow-derived stem and progenitor cells (3), these stimuli may increase progenitor cell mobilization by PI3K/Akt-dependent activation of the NOS within the bone marrow stromal cells (101).

ENDOTHELIAL PROGENITOR CELLS IN STROKE

Acute ischemic stroke caused by occlusion of a cerebral artery leads to sudden interruption of blood flow to parts of the brain, resulting in loss of neurons, astrocytes, and oligodendrocytes. Despite advances in medical and surgical treatment, stroke is still a leading cause of death and disability worldwide (103), and only a minority of patients can be rescued by systemic thrombolytic therapy. A growing amount of data suggests that EPCs are relevant to vascular homeostasis (41,100). Taguchi and coworkers reported that $CD34^+$ cells and $CD133^+$ cells, as an EPC-enriched population, provided a marker of cerebrovascular function (93). They demonstrated that circulating EPCs increased after the onset of stroke and peaked after 7 days. Ghani and colleagues also reported a reduction in EPCs in patients with cerebrovascular disease, when compared with healthy control subjects (32). They recruited 88 people who were divided into acute stroke, stable ischemic cerebrovascular disease, and control groups. EPC colony counts in each well of culture dishes differed significantly between the acute stroke (4.75), stable disease (7.25), and control groups (15.5). The level of EPCs also significantly correlated with the Framingham coronary risk score ($p = 0.002$). They concluded that the low EPC levels may play a role in the pathophysiology of cerebrovascular disease. In our previous study, we also demonstrated that intracerebral injection of peripheral blood stem cells ($CD34^+$) can enhance angiogenesis via β1-integrin in chronic stroke rats (89). In this study, $CD34^+$ cells differentiated into glial cells, neurons, and vascular endothelial cells. At the site of $CD34^+$ cell injection, the expression of neurotrophic factors was increased. Finally, the behavior of stroke animals injected with $CD34^+$ cells improved faster than those of control animals.

Because stroke is well known to be associated with endothelial abnormalities, it is reasonable to speculate that CECs are also increased in patients with this condition, and that CEC levels correlate with other indices of endothelial dysfunction. There have been two studies investigating CEC quantification in stroke. Freestone and coworkers (29) looked at patients with atrial fibrillation (AF) and stroke as part of a broader study of CECs in AF. They found higher levels of CECs in patients with concurrent AF and a history of stroke than in healthy controls with normal sinus rhythm, and that CECs correlated with von Willebrand factor (vWF). Nadar and colleagues (63) studied 29 patients presenting with stroke and hypertension (but no AF), and compared them with 30 high-risk hypertensive patients and 30 normotensive controls. Compared with the other two groups, the patients with acute ischemic stroke had significantly higher numbers of CECs per milliliter in venous blood and higher levels of vWF and soluble E-selectin. In addition, the numbers of CECs correlated with both vWF and soluble E-selectin (16).

Angiogenesis also occurs in stroke conditions. As ischemic tissue usually depends on collateral blood flow from newly produced vessels, acceleration of angiogenesis should be of therapeutic value to ischemic disorders. Indeed, therapeutic induction of angiogenesis reduced tissue injury in myocardial and limb ischemia (12,95). In ischemic stroke, on the other hand, angiogenic factors often increase vascular permeability and thus may deteriorate tissue damage (60). In order to safely apply therapeutic angiogenesis for ischemic stroke treatment, elucidating its precise mechanism is mandatory (37).

Upregulation and increased phosphorylation of eNOS

improves endothelium- dependent vasodilation (35,48). Clinical and experimental evidence suggests that brain ischemia promotes the formation of new vessels (110). In general, neovascularization can take the from of angiogenesis, arteriogenesis, or postnatal vasculogenesis mediated by mobilization of stem and progenitor cells (80). EPCs may promote vascular repair, neovascularization, and improve endothelial function (56,94). However, the functional role of EPCs in the formation of vessels, cerebral blood flow (CBF), and tissue recovery in the ischemic brain remain to be elucidated (3,14,72,118). Recently, increased EPCs and enhanced neovascularization through an eNOS-dependant pathway was reported (31,56). Tissue ischemia-induced eNOS activity is also critical for ischemic remodeling and for mobilization of stem and progenitor cells, and even upregulates neurogenesis in the brain (3,56,117). Several studies have also found that eNOS improved angiogenesis and cerebral blood flow in ischemic stroke animals (31,79,88).

CLINICAL IMPLICATIONS AND FUTURE PROSPECTS

EPCs as a Marker of Disease Prognosis and Severity

A lot of evidence shows that EPCs may be a valuable tool for clinical health providers. EPC number and function correlates with the risk of cardiovascular and cerebrovascular disease (32,41) and EPCs play a role in the process of vasuloprotection (26); EPCs can be used as a marker of vascular function. Two recent studies monitored EPC level to monitor the progression of atherosclerotic disease and to identify patients at high risk of adverse cardiac events (85,111). Both studies clearly demonstrated that the level of circulating EPCs predicts the occurrence of cardiovascular events and cardiovascular death. A reduced number of EPCs could represent both a causative factor and a marker of atherosclerosis, and seems to provide a link between endothelial dysfunction and clinical cardiovascular events (6). As a consequence, evaluation of EPC number and function may be used to assess endothelial dysfunction and risk in patients with ischemic heart and cerebral disease. While the number and function of EPCs may well provide more predictive and prognostic information than currently gained from traditional biomarkers, the use of EPCs for clinical diagnosis needs to be investigated further before it is adapted as a routine tool.

EPCs for Therapeutic Use

Quantitative and qualitative improvement of host EPCs could be of benefit to patients with ischemic disease. EPCs can be expanded in vitro for therapeutic use (13,89,113,118). Recent studies show increased number and functionality of EPCs may be achieved by targeted pharmacological strategies alone (27,70) or in combination with proangiogenic cytokines (4,58). In addition, statins have been demonstrated to augment EPC number and function (26), and other factors that affect the function of EPCs (e.g., angiotensin II, glucose, and low-density lipoprotein) are potential drug targets (6). As EPCs have also been shown to play an important role in endothelial cell regeneration, they may also be of benefit in a range of other vascular disorders.

Future Research on EPC Mobilization

Long-term clinical studies examining drug-mediated mobilization and functional modification of endogenous EPCs are not available. One focus of future research should be the elucidation of the molecular pathways regulating EPC levels and the function and genetic modification of EPCs leading to improved functional capacity. The development of pharmacological and genetic strategies for targeting EPCs will be necessary in the future (6).

CONCLUSION

Endothelial dysfunction, neurohumoral activation, inflammation, and increased oxidative stress may play a role in the pathophysiology of ischemic heart and cerebral disease. The mechanism of mobilization and homing of EPCs is a complex process. EPCs could be a potential pharmaceutical target. Future studies should explore the role of EPCs in ischemic heart and cerebral disease along with their potential therapeutic roles.

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