Transplantation of Endothelial Progenitor Cells as Therapeutics for Cardiovascular Diseases

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With better understanding of endothelial progenitor cells (EPCs), many therapeutic approaches to cardiovascular diseases have been developed. This article will review novel research of EPCs in promoting angiogenesis, vasculogenesis, and endothelialization, as a design for future clinical treatment. Cell therapy has the potential to supply stem/progenitor cells and multiple angiogenic factors to the region of ischemia. The efficacy of EPC transplantation may be impaired by low survival rate, insufficient cell number, and impaired function in aging and diseases. Combination of EPCs or cells primed with growth factors or genetic modification may improve the therapeutic efficacy. The molecular mechanism involved in EPC repairing processes is essential. Thus, we have also addressed the molecular mechanism of mobilization, homing, and differentiation of EPCs. The potential of therapeutic neovascularization, angiogenic factor therapy, and cell transplantation have been elucidated. Based on past experience and actual knowledge, future strategies for EPC therapy will be proposed in order to fully exploit the potential of EPC transplantation with clinical relevance for cardiovascular disease applications.

Key words: Endothelial progenitor cells (EPCs); Cardiovascular diseases; Angiogenesis; Cell therapy

INTRODUCTION

Cell therapy is currently attracting growing attention as a potential issue of improving the prognosis of patients with cardiovascular diseases (22,52,77,97,113). Cell-based therapy to stimulate postnatal vasculogenesis or to repair the integrity is being evaluated for cardiovascular diseases with excess morbidity and mortality, including the ischemic heart disease, in-stent restenosis, pulmonary hypertension, and peripheral arterial occlusive disease (3,39,79). To date several clinical studies have suggested the potential efficacy of several different cell types (6,67,77,79). Endothelial progenitor cells (EPCs) have been studied as a novel tool to assess the severity of cardiovascular disease and as a new strategy in regenerative medicine (21,77,113).

In response to ischemic injury, EPCs are mobilized from the bone marrow. The infusion or injection of stem or progenitor cells has been shown to improve neovascularization and heart function after ischemia in various experimental studies and clinical trials (46,52,106). EPCs can migrate to the site of blood vessel injury to help repair the damage and to differentiate into mature endothelial cells (37). Therefore, it can be therapeutically useful for treating ischemic injury. Studies have described reduced EPC numbers in diabetic patients who suffered a stroke (115). A report also indicated that EPC number correlated with the level of stromal derived factor-1 (SDF-1) from patients with the coronary disease or ischemic cardiomyopathy (33). Because EPCs are involved in neovascularization, enhancing the number and/or activity of EPCs could improve the recovery of

patients who experience ischemic injury. They might also be useful as autologous vectors for delivering genes to sites of vascular growth in regenerating tissues (59).

Applications associated with cardiovascular diseases depend on the functional activity of EPCs (39,77,115). EPCs from type II diabetes patients exhibit impaired proliferation, adhesion, and reduced angiogenic potential in vitro (26). Similar functional alterations have been indicated in EPCs isolated from aged patients with coronary artery disease or ischemic cardiomyopathy (35,47). However, controversial issues on EPC phenotypes, origins, and functions of endothelial repair still exist. For example, the potential limitation for cell therapy is a low rate of engraftment and persistence of cells in the ischemic tissue.

The present review focuses on the role of EPCs in repairing the vessel wall during the development of cardiovascular disease. We address the recent developments in EPC functionality for cell therapy and the efficiency of EPCs on the maintenance of endothelial integrity, endothelialization, and angiogenesis from in vitro to in vivo study after cell transplantation.

CLINICAL TRIALS OF EPC THERAPY IN CARDIOVASCULAR DISEASES

Much evidence has shown that EPCs may be a valuable tool for clinical health providers (25,55,80). Importantly, EPC function and number now have been highly correlated with the risk of cardiovascular disease (7,57). A recent study showed that the level of circulating EPC expression level predicted the occurrence of cardiovascular events and vascular tissue injury (2). Interestingly, a study indicated that the increased number and functionality of EPCs may be achieved by targeted pharmacological strategies alone (85) or in combination with proangigenic cytokines (17). Other factors can affect the function of EPCs, such as angiotensin II, glucose, and low density lipoprotein (30,53,110). Therefore, EPCs exhibit an important role in endothelial cell regeneration, which may be a benefit in repair of cardiovascular disease (15,89,93). Recently, experimental studies and early phase clinical trials tended to support the concept that cell therapy may enhance cardiovascular repair (24). In addition, intramyocardial VEGF-A165 gene transfer followed by bone marrow stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) seemed to be safe in improving the homing of stem cells and inducing angiogenesis in patients with severe chronic ischemic heart disease (76).

Studies have also suggested that the implantation of endothelial progenitor cells could be safe and effective for achievement of therapeutic angiogenesis for patients with limb ischemia (107). In an alternate study, percutaneous coronary intervention utilizing a new EPC anti-body-coated stent have been evaluated as a replacement to currently available drug-eluting or bare metal stents (63). The treatment with G-CSF, which mobilizes EPCs from bone marrow, can safely improve the clinical outcomes of patients with atherosclerotic peripheral artery disease (PAD) (83). Moreover, implantation of EPCs and bone marrow cells may result in increase in atherosclerotic plaque size and composition in apolipoprotein E knockout mice (30). Besides, the obvious therapeutical potential of blood-derived progenitor cells in patients indicates that the application is safe, feasible, and may improve both functional and clinical indices with peripheral arterial occlusive disease and critical limb ischemia (48). Additionally, the ability of G-CSF to mobilize functional EPCs in patients with coronary artery disease has been tested in a clinical trail (1,74,104).

Evidence showed that the transplantation of EPCs resulted in a significant increase in myocardial viability and perfusion (4,23). Alteration in progenitor cell proangiogenic function may participate to the hypertension-induced impairment in postischemic revascularization (111). When systemically applied, spleen-derived mouse mononuclear cells (MNCs) and EPCs home to the site of vascular injury, resulting in enhanced reendothelialization associated with decreased neointima formation after angioplasty (101,102). Alternatively, the enhanced regenerative activity of EPCs by human telomerase reverse transcriptase transfer will provide novel therapeutical strategies for postnatal neovascularization in severe ischemic disease patients (65). Indeed, ex vivo expanded EPCs can incorporate into the foci of myocardial neovascularization and have a favorable impact on the preservation of left ventricular function (45).

THE TRANSPLANATION OF EPCs FOR DISEASE IN ANIMAL MODELS

It is important that the damaged endothelial cells have to be replaced by the adjacent intact endothelium for vessel regeneration (88). Stem cells can differentiate into a variety of cells to replace dead cells or to repair damaged tissues. Recent evidence indicates that stem cells are involved in the pathogenesis of transplant arteriosclerosis (28). Several studies have highlighted that the increase in the number of circulating progenitors, induced by cell transfusion or enhanced mobilization, can also enhance restoration and integrity of the endothelial lining, suppress neointimal formation, and increase blood flow to ischemic sites (5,87).

In patients, the number of EPCs is poorly correlated with the severity of atherosclerosis (36). Indeed, in various animal models, transplantation of bone marrow-derived progenitor cells could sufficiently rescue organ function and enhance vascular repair and tissue regeneration (16,49,90). The incorporation of circulating EPCs into

the vessel wall was observed in animal model (28,90). In another model of transplantation, it was found that the endothelial monolayer in a vein graft postsurgery was completely lost and subsequently replaced by circulating EPCs (61). These progenitor cells can improve vascular repair and reduce vascular injury.

An important report indicated that the intravenous infusion of spleen-derived mononuclear cells seemed to improve the endothelium-dependent vasodilatation in atherosclerotic mice (101). It is thus more convincing that progenitor cells play an important role in repairing the vascular injury (60,102). In addition, EPCs derived from spleen homogenates also enhanced reendothelialization and reduce neointima formation after induction of endothelial cell damage using the carotid artery animal model (102). Besides, rapid repair of the endothelium with reduced activation of smooth muscle cells and neointima formation has been found in vivo after the implantation of EPCs using a ballon injury model (68,105). The transplantation of EPCs into mice after balloon injury could induce endothelial nitric oxide (eNOS) overexpression and accelerate the endothelial repair (96). In an alterative study, EPCs reduced the proinflammatory properties and the IL-10 expression in the atherosclerosis plaque site in mice model (19).

The infusion of EPCs or isolated hematopoietic progenitor cells promotes neovascularization of ischemic myocardium and improves the ventricular function after myocardial ischemia in both human and animal study (40,62,69). In a canine model, circulating endothelial progenitor cells could be a substitute source of endothelial cells for endothelialization on small-diameter-vessel prostheses to ensure nonthrombogenicity (109). A novel hybrid cell-gene therapy based on the phagocytosing action of EPCs was explored as a new therapeutic strategy for the treatment of pulmonary hypertension (66). Alternatively, a possible role of SDF-1 in the homing of stem cells to damage areas has been noted in the animal models of liver, limb, heart, and brain injury (42,64,95,108). Overall, it seems that proper mobilization of EPCs may lead to the repair of vascular injury. The application of endothelial progenitor cells on various cardiovascular diseases is summarized by Figure 1.

MECHANISM UNDERLYING THE THERAPEUTIC EFFECTS OF ENDOTHELIAL PROGENITOR CELLS

As highlighted by several reports, the functional repair properties of EPCs derived from different sources, including bone marrow and non-bone marrow organs such as the spleen, may vary with the maturation state of the cells (112). Thus, understanding the molecular mechanisms involved in EPC-repairing processes is essential. Here, we will review the mechanism for mobili-

zation, homing, and differentiation of EPCs in vascular diseases.

In most studies, many biochemical factors such as growth factors (SDF-1, G-CSF, GM-CSF, FGF, PIGF) (44,56,70,104), cytokines (IL-12, IL-3, IL-6, IL-8, and IL-1β) (43,71,81), erythropoietin (EPO) (101,103), angiopoietin-2 (94), and heme oxygenase-1 (HO-1) (58) that are well known to mobilize human stem cells have been found to increase the number of EPCs in arterial remodeling during ischemic damage. An increase in the number of circulating progenitor cells, induced by cell transfusion or enhanced mobilization, can also enhance the restoration and integrity of the endothelial lining, suppress neointimal formation, and increase the blood flow to ischemic sites (8,31,72,98). However, the beneficial outcome of EPC infusion depends on the growth and differentiation factors within the tissue, cell-to-cell interactions, and the degree of injury (75,112).

Experimental studies have provided novel options for improving survival and function by transduction of stem or progenitor cells with prosurvival genes (e.g., Akt or telomerase) (18,38,78). Pretreatment of cells with small molecules, such as statins, p38 inhibitors, or endothelial nitric oxide synthase (eNOS) enhancers, has been used to enhance cell homing, migration, and functional recovery after the induction of ischemia (18). Several studies have shown that the prosurvival phosphatidyl-inositol-3-kinase (PI3K)/Akt pathway may play an important role in endothelial cells and EPCs (20,114). Thus, statins, VEGF, EPO, estrogen, and shear stress have also been also reported to modulate the PI3K/Akt pathway (20,27, 41,51,86,100). Recently, the increased number of EPCs and enhanced neovascularization through an eNOS-dependent pathway were also reported. The activity of eNOS is essential for ischemic remodeling, and to mobilize EPCs and even modulate the neurogenesis in brain. Besides, reports also addressed that eNOS improved angiogenesis and cerebral blood flow in the stroke animal model (13,14). Increased nitric oxide (NO) availability is required for the statin-induced mobilization of EPCs (73). NO produced by eNOS also correlates with SDF-1 and the CXCR4 signaling pathway to induce the mobilization and homing of EPCs (114).

Although the importance of SDF-1 in stem cell recruitment to the injured tissue is well established, the underlying mechanism of SDF-1 in ischemic tissue still needs to be elucidated. Furthermore, SDF-1 gene expression is regulated by the transcription factor hypoxic-inducible factor-1 (HIF-1) in endothelial cells, resulting in selective in vivo expression of SDF-1 in ischemic tissue (44). SDF-1 is the only chemokine family member known to be regulated by HIF-1 (10). It seems reasonable that HIF-1-regulated SDF-1 expression may be important in a number of regenerative pathways. Thus, ex-
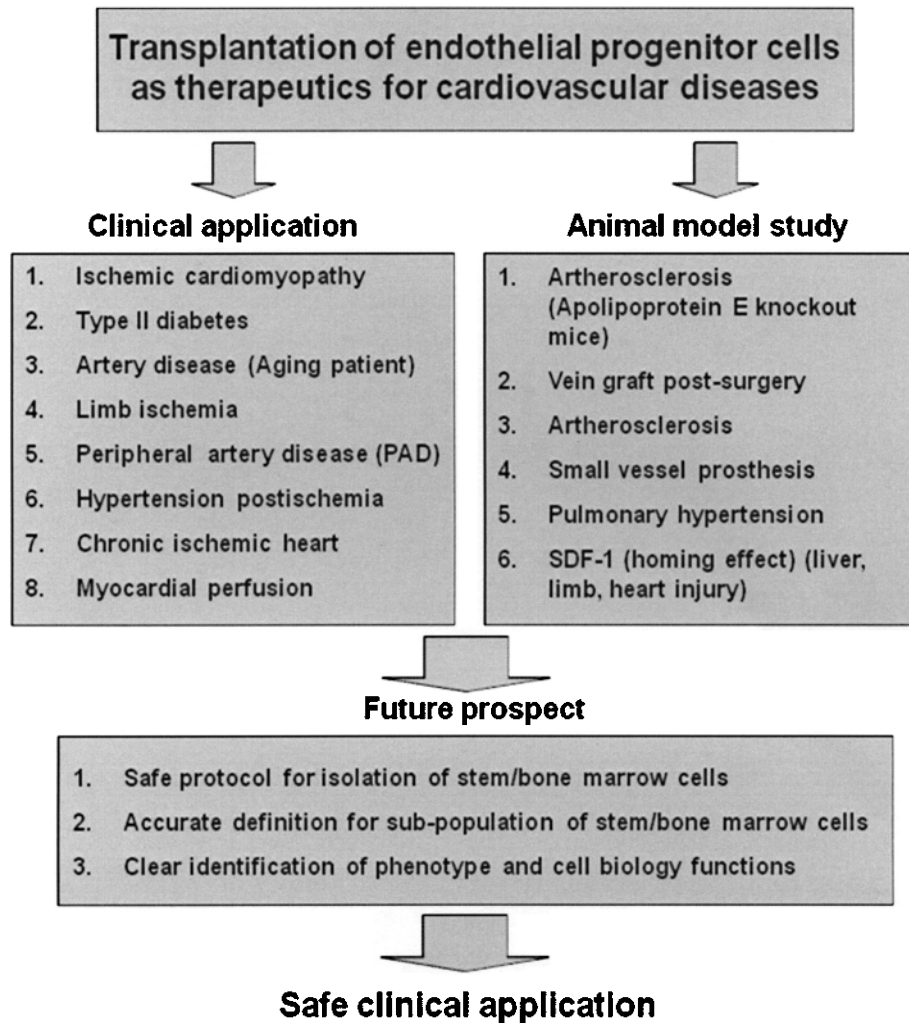
Figure 1. Schematic representation of the endothelial progenitor cells as therapeutics for cardiovascular diseases.

pression of HIF-1 activity may be a useful approach to improve the regenerative potential after ischemic injury (44). Integrins are crucial transmembrane molecules that mediate cell adhesion, migration, and the homing of progenitor cells such as EPCs to ischemic tissue, possibly through the enhanced angiogenesis by homing stem cells (54). The β2-integrins are involved in the homing of EPCs to the site of ischemia and are essential for their neovascularization capacity in vivo (11). The activation of β2-integrin on EPCs has been shown to significantly improve the neovascularization capacity in vivo in a model of hindlimb ischemia (9). Whether integrins play an important role for the mechanism of repair in cardiovascular disease remains to be determined in the future. Besides, further studies are still required to elucidate whether there is a synergism between adhesion mole-

cules in the recruitment of EPCs to ischemic tissue. The knowledge may provide novel opportunities for clinical cardiovascular disease applications. A summary of the possible mechanisms between EPCs and cardiovascular disease is shown in Figure 2.

FUTURE EXPLORATION

Cell-based transplantation strategies have the potential to become a major therapeutic advance for cardiovascular disease. There are still controversial issues regarding the active potency of EPCs for proliferation, differentiation, and migration in vitro, therapeutic neovascularization and reendothelialization in vivo of the EPC-based treatments. Although available clinical studies of EPC transplantation show beneficial results in terms of improvement in cardiovascular disease and re-

modeling after myocardial infarction (91), these studies still encounter some difficult issues that need to be solved in the future.

Clear characterization of the specific subpopulation of stem/bone marrow cells that have the most beneficial properties is important for vascular repair (12,29,32). Thus, it is also necessary to develop a safe protocol and hope to isolate sufficient numbers of EPCs that can continuously maintain their angiogenic potential and be used to treat patients in clinical trails with damaged vascular tissues. Ideally, a specific cell population or combination needs to be accurately determined. It is important to note that most preclinical and clinical studies testing the therapeutic effects of EPCs were based on introducing either whole bone marrow cells or a crude bone marrow cell population containing EPCs, hematopoietic cells, and irrelevant pluripotent cells, with some animal experiments using purified "EPCs," such as CD34^{+} hematopoietic stem cells (HSCs) (34,84).

Alternatively, a major problem was also observed in the clinical trail of EPCs. EPCs are relatively rare cells, and expansion of sufficient number of a definite subpopulation from peripheral blood is hardly possible. Additionally, the therapeutic implantation is associated with a change in phenotype and differentiation and the risk of cell biology, and may need other activation or stimulation (50,99). Besides, the ability and functional properties of EPCs in aging adults are really limited, especially in those with cardiovascular disease where a further reduction of EPCs was shown (82,92).

CONCLUSION

Stem cell therapy is feasible, moderately effective, and does not expose patients to high risk. The therapeutic effects of EPCs are well performed in several studies, but there are things remaining obscure. A combined cell therapy comprising EPCs is also a promising option, but issues regarding the types of patients, the types of used cells, and the therapeutic outcomes all complicate the wide use of cell therapy. There is also the necessity of
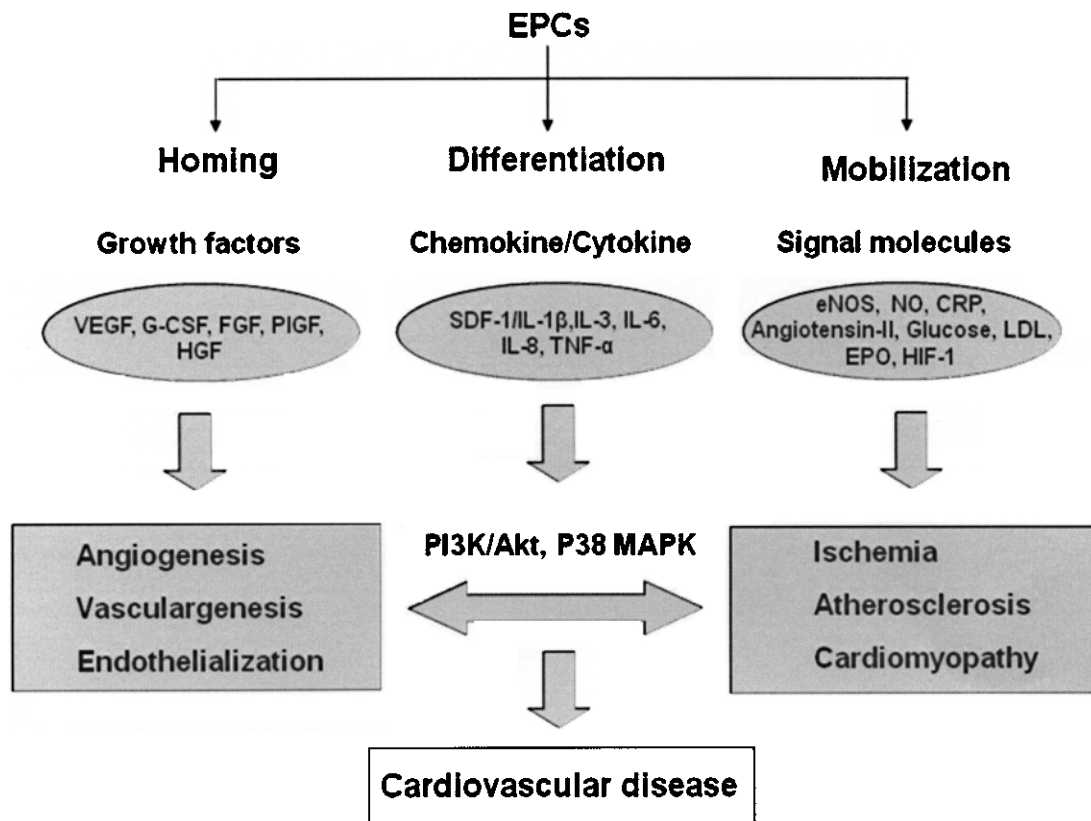

Figure 2. Possible molecular mechanism between EPCs and cardiovascular diseases. VEGF, vascular endothelial growth factor; G-CSF, granulocyte colony-stimulating factor; FGF, fibroblast growth factor; PIGF, placenta growth factor; HGF, hepatocyte growth factor; SDF-2, stromal derived factor 1; IL-1β, interleukin-1β; IL-3, -6, -8, interleukin-3, -6, -8; TNF-α, tumor necrosis factor-α; eNOS, endothelia nitric oxide synthase; NO, nitric oxide; CRP, C-reactive protein; LDL, low density lipoprotein; EPO, eryothropietin; HIF-1, hypoxia inducible factor.

establishing a safe isolation protocol in favor of cell differentiation and mobilization. The functions of EPCs are influenced by many factors such as cytokines and a large group of biological products as well as drugs including the statins-coated drug delivery. The mechanism of mobilization and homing of EPCs to a site of interest is a complex process. Future studies should also explore the functional mechanism of EPCs in cardiovascular diseases along with their potential therapeutic roles. Many issues remain to be understood before safe clinical application can be realized. Once accomplished, the therapeutic potential of transplanted EPCs may bring true benefit to patients with cardiovascular disease.

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