Endothelial progenitor cells in cardiovascular diseases

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Abstract
Cardiovascular diseases (CVDs) are the leading cause of death in both developed and developing countries. Endothelial progenitor cells (EPCs) are derived from hematopoietic stem cells with powerful function of angiogenesis. There are many studies on the relation between coronary heart disease and circulating EPCs. In this review, we discuss biological characteristics of endothelial progenitor cells, some influencing factors of the number and function of EPCs, and the role of EPCs in the treatment of cardiovascular disease. At last, we bring some perspectives on the future of endothelial progenitor cell therapy.

KEYWORDS
cardiovascular diseases, endothelial dysfunction, endothelial progenitor cells, EPC therapy

1 | INTRODUCTION

In the past few decades, cardiovascular diseases (CVDs) are one of the most common important causes of death in both developed and developing countries. Many CVDs, such as atherosclerosis, hypertension, and chronic heart failure, are closely related to endothelial dysfunction, which may reduce arterial elasticity, and eventually leading to CVDs. Under the circumstances, a great number of studies have been done on endothelial tissue and angiogenesis, which show us that different kinds of molecular, cellular, and functional changes in the endothelium tissue may affect the process of angiogenesis. Blood vessel formation is the basic process of the regeneration and development of organisms and tissues. More and more studies demonstrate that circulating endothelial progenitor cells (EPCs) derived from the bone marrow conduct to angiogenesis and normal vascular homeostasis. Therefore, transplantation of exogenous EPCs has gradually turned into a novel cell therapy for CVDs.

2 | ENDOTHELIAL PROGENITOR CELLS (EPCs)

2.1 | Characteristics of EPCs

It was considered that differentiation of mesodermal cells to angioblasts and subsequent endothelial differentiation was a specific process occurring in embryonic development for a long time. This concept was overthrown in 1997 when Asahara et al. demonstrated that CD34-positive hematopoietic progenitor cells isolated from adults could be differentiated into endothelial phenotype in vitro. There is no explicit definition of EPCs, but in general, EPCs, formed in the bone marrow or nonhematopoietic tissues, can be conceptually considered a heterogeneous group of cells, with a characteristic of being detected at different phases of endothelial differentiation in the peripheral blood.

There are lots of studies on the markers for identification of EPC populations. In general, EPCs in bone marrow have a mixed phenotype of early progenitor cells and endothelial cells and they mainly express CD34, a highly glycosylated transmembrane protein, vascular endothelial growth factor receptor 2 (VEGFR2), a receptor for vascular endothelial growth factor and CD133/AC133, and glycosylated transmembrane peptides binding cholesterol. However, CD34, VEGFR2, and CD133 are not the specific markers of EPCs. For example, VEGFR2 can also be expressed in dendritic cells, macrophages, or T lymphocytes while CD34 is expressed in mature endothelial cells as well. Some other studies indicated that there were other additional markers of circulating EPCs such as CD31, CD45, CD105, CD117, and CD146. Among them, CD31 can be seen in mature endothelial cells, CD45 can be tracked on neutrophils, monocytes, dendritic cells, and lymphocytes,
CD105 and CD117 are expressed on hematopoietic stem cells, and CD146 can be found on memory lymphocytes. When EPCs enter into peripheral blood, they have gradually lost the immature hematopoietic precursor marker CD133, but remaining CD34 and VEGFR-2 to express. Therefore, the expression of surface antigen can also be used to track the differentiation and maturation of EPCs. Still, specific EPC markers need further research and discovery.

Endothelial progenitor cells in a study group were different from those of other researches, suggesting that EPC is not a single type of cell population. There are two different types of EPCs: early and late EPCs. Early EPCs, shaping like a spindle, grow fastest at 2-3 weeks and die after 4 weeks, while late EPCs, with cobblestone shape, grow frantically at 4-8 weeks and have a lifespan of about 12 weeks. The study showed that the gene expression profiles of two kinds of EPCs were different, including VE-cadherin, Flt-1, KDR, and CD45, which indicated early EPC was a heterogeneous group of cells that differentiated from hematogloiblasts to mature cells, whereas late EPCs are homogeneous and well differentiated. In terms of function, though early EPCs secreted angiogenic cytokines (vascular endothelial growth factor, interleukin 8) more than late EPC, both types of EPC showed comparable vasculogenic capacity in vivo.

2.2 Mobilization and homing of EPCs

The initial vascular plexus is then remodeled and refined through proliferation and migration of endothelial cells to form new vessels from the preexisting ones during angiogenesis. During the process, ECs are tightly held together to form the inner lumen of blood vessels. Owing to the close junction, ECs can control paracellular permeability and the entry and exit of molecules. Besides, ECs are also involved in immune surveillance and blood flow control and maintaining the stability of intravascular environment.

EPCs are mainly located in the bone marrow. The bone marrow contains a large number of hematopoietic stem cells and bone marrow stromal cells. In such a microenvironment, the progenitor cells differentiate into different stages and become different subsets of cells. Under normal physiological conditions, EPCs account for only 0.01% of circulating monocytes. When affected by various sorts of factors including physiological or pathological and endogenous or exogenous, such as estrogen, statins, physical exercise, acute ische-mia after myocardial infarction, unstable angina pectoris, and the state of hypoxia, EPCs are stimulated and reach the effect site. During the process of mobilization and homing of EPCs, some molecular including the cytokines of granulocyte colony-stimulating factor (G-CSF), matrix metalloproteinases-9 (MMP-9), VEGF, SDF-1, endothelial nitric oxide synthases (eNOS), and nitric oxide (NO) play important roles. Under the action of these molecular, EPCs are released from bone marrow through endothelial sinusoid and travel into the blood circulation to work.

3 Influencing factors of the number and function of EPCs

Vascular endothelial cell is a layer of cell covering the inner side of vascular wall and plays an essential role in almost all vascular functions. A variety of factors may damage endothelial cells, which include physical injuries, biochemical injuries, and immune-mediated damages. When these happen, ECs are disabled to maintain the homeostasis, which is named as endothelial dysfunction and may lead to cardiovascular diseases. The pathophysiology of endothelial dysfunction is very complicated, and many mechanisms are related to it. Among them, oxidative stress is recognized by the most people. In the state of oxidative stress, the production of reactive oxygen species (ROS) exceeds the ability of endogenous oxygen radicals scavenging enzyme systems, causing the reduction in NO, a substance produced by endothelial cells through eNOS activation. NO takes effect both in EPC mobilization and in EPC migration and proliferation and promote angiogenesis.

In the treatment of coronary artery disease, the balance between endothelial damage and repair should be paid high attention. Under physiological conditions, endothelial cells are not only responsible for the metabolic exchange of blood and tissue fluid, but also synthesize and secrete a variety of bioactive substances to ensure the normal contraction and relaxation of blood vessels, maintain the vascular tension, regulate blood pressure, and keep the balance between coagulation and anticoagulation. If the balance is destroyed, endothelial cells will not be able to deal with all kinds of injury factors, thus leading to the disease.

It is due to the ability of EPCs to assemble and repair at the site of vascular damage that there are an increasing number of researches involving angiogenesis in the therapeutic use of EPCs. In patients with CAD, as the severity of the disease increases, the number of EPCs and circulating EPCs gradually decreases. This may be the result of endothelial dysfunction in patients with CAD.

The coronary artery of the patients with coronary heart disease has endothelium-dependent vasodilatation, which not only involves the coronary artery, but also often involves the peripheral arteries. Therefore, the elastic function of the peripheral arteriole can be clearly defined by the detection of the radial pulse wave, which reflects the function of the vascular endothelium itself. It is a new index to evaluate the function of vascular endothelial cells. This study shows that the vascular endothelial function is closely related to the number and activity of circulating endothelial progenitor cells. The decrease in EPCs suggests the decline of endothelial repair ability and impairment of function, resulting in the injury of arterial elasticity, which may lead to the occurrence of coronary heart disease. On this basis, factors relating to arterial elasticity and EPCs may lead to changes in vascular endothelial function and body physiology, such as age, fluid shear force, physical exercise, smoking, hypertension, endothelial microparticles, miRNA, berberine, nitric oxide synthase, nitric oxide production and release, oxidative stress, and signaling pathway (CXCR4/JAK-2, BMP4/ID2, CXR7/PEKK, etc.).
drugs (Losartan, Ramipril, Nifedipine, statins), 25-hydroxycholesterol, and gene transfer.

Aging is a major risk factor for clinical cardiovascular disease, and this relationship is mainly driven by the development of endothelial dysfunction.\textsuperscript{42,43} Tao et al\textsuperscript{44} found that the number of circulating endothelial progenitor cells in healthy elderly decreased progressively, and the number of circulating endothelial progenitor cells was positively correlated with arterial elasticity. Endothelial progenitor cells participate in the endothelial repair and endothelial function regulation, and as a result, aging leads to decreased arterial elasticity and the changes in the function and structure of the artery wall. In the process of aging, the production of free radicals is not balanced with the effectiveness of antioxidants.\textsuperscript{30} Increased ROS level will potentially stimulate chronic inflammation, eventually leading to impaired EPCs mobilization.\textsuperscript{30} Vascular senescence is an important factor in the aging of the human body.

Fluid shear stress is the frictional tangential force imposed on the vessel wall when blood flow through a vessel.\textsuperscript{45} Obi et al\textsuperscript{46} demonstrated that when cultured EPCs are exposed to shear stress in a flow-loading device, their bioactivities increased significantly in proliferation, anti-apoptosis, migration, production of bioactive substances, and antithrombosis. Xia et al\textsuperscript{47} showed that shear stress preconditioning reinforced the migration, adhesion, and re-endothelialization competencies in both young and elderly EPCs, which suggested that the upregulation of the shear stress contributes to the enhancement of endothelialization ability of endothelial progenitor cells.

Physical exercise is another risk factor for CAD, and it causes increased NO production. Gando et al\textsuperscript{48} reported that regular physical exercise could delay the age-related decline in arterial elasticity in the healthy people. Laufs et al\textsuperscript{49} demonstrated that physical exercise increased the number of EPCs in bone marrow and peripheral blood, and the upregulation of EPC in exercise depended on NO and VEGF. In conclusion, physical exercise is a significant method to improve vascular function and prevent vascular diseases.\textsuperscript{50}

Cigarette smoking, both active and passive, is one of the leading causes of morbidity and mortality in cardiovascular disease. Mobarrez et al\textsuperscript{51} found that cigarette smoking had an acute effect on endothelial cells, platelet and leukocyte function, and injury to vascular wall.

Hypertension is a common risk factor for the incidence of vascular disease. Wang et al\textsuperscript{52} indicated that impaired endothelial function and decreased arterial elasticity persist in the human body though blood pressure of hypertensive patients was controlled through drugs. Therefore, the optimal therapy for patients with hypertension is not just to lower blood pressure, but also to improve vascular damage.\textsuperscript{52}

MicroRNAs are recently discovered key regulators of gene expression. Wang et al\textsuperscript{53} experimented on type 2 diabetic mice and proved that miR-27b can rescue and protect impaired bone marrow-derived endothelial cells.

Elevated circulating endothelial microparticles (EMPs) are associated with endothelial dysfunction. Wang et al\textsuperscript{54} found that the decrease in the circulating CD3+/CD42 particles caused by berberine contributed to the improvement of endothelial function in healthy subjects by contrasting the healthy subjects whether using berberine therapy or not. Decreasing EMPs may become a novel therapeutic target for improving endothelial dysfunction in humans.

## 4 | THE ROLE OF EPCs IN THE TREATMENT OF CARDIOVASCULAR DISEASE

Since EPCs have many effective characteristics, including easiness to gain from the peripheral blood, powerful angiogenic and vasculo-genic effects, and the stability of the lineage and a reduced risk of tumorigenicity, EPCs is more and more used in the clinic.\textsuperscript{55,56}

### 4.1 | Endothelial progenitor cell capture stent

One of the major applications of EPCs is a device called EPC capture stent, which can repair damaged arterial endothelium using the characteristics of bone marrow–derived EPCs. EPC capture stent is a kind of stainless steel stent with the surface of EPC antibody, which makes up a covalently coupled polysaccharide intermediate coating with anti-human CD34 antibodies.\textsuperscript{36} With the stent, circulating EPCs will be attracted by the anti-human CD34 antibodies, differentiate into mature endothelial cells, and aggregate together to form a special blood vessel. Randomized clinical trials conducted on the EPC capture stents showed that they were safe, and there was no evidence of increasing risk of heart disease after market surveillance.\textsuperscript{56} EPC capture stents are feasible and safe, and the major adverse cardiac events are reported to be between 4.2% and 16%. However, some studies have shown that endothelial progenitor cells have adverse effects on stent implantation in the treatment of acute ST-segment elevation myocardial infarction compared with traditional stents. The most dangerous and common one is thrombogenesis, although this finding is still controversial.\textsuperscript{57-60}

### 4.2 | Endothelial progenitor cell therapy

Based on the previous studies, it is widely known that through mobilization and homing of bone marrow–derived EPCs, the process of angiogenesis can be started and tissue ischemia for CAD can be alleviated.\textsuperscript{36} Since this new treatment is at the emerging stage, many studies have discussed EPCs as a cellular candidate for regenerative therapies, and more data from the ongoing trials will help to establish the safety of EPC treatment.\textsuperscript{56} However, questions still remain with regard to safety and efficacy and further research is needed.

## 5 | CONCLUSIONS AND PERSPECTIVES

Endothelial progenitor cells are important therapeutic targets in the field of regenerative medicine. Since the discovery of EPCs in adult blood circulation, the mechanism of recruitment, mobilization,
homograft and differentiation has been gradually recognized. Nevertheless, further research on its molecular biological process will help clarify how to optimize biological conditions to improve angiogenesis in patients. In the current situation, genetic modification of EPCs before transplantation may become a new research hot spot. Although there are still many problems ahead, we have reason to believe that EPCs can be applied to the clinical treatment of coronary heart disease in the near future.

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