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by Rahmawati Minhajat

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The Role of Endothelial Progenitor Cell in Cardiovascular Disease Risk Factors

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ABSTRAK

Endothelial progenitor cells (EPCs) adalah sel yang berasal dari sumsum tulang dan bersirkulasi di darah perifer. Sel ini memiliki karakteristik mirip stem cell (sel punca), tetapi dengan kemampuan berproliferasi dan berdiferensiasi yang lebih terbatas. Penemuan EPC telah mengubah paradigma lama dalam bidang biologi vaskular dan membawa implikasi besar dalam dunia kedokteran karena EPC dapat memediasi proses vaskulogenesis dan menjaga integritas pembuluh darah. Peningkatan jumlah EPC dalam sirkulasi menjadi penting karena berkorelasi positif dengan reendotelialisasi dan neovaskularisasi yang berhubungan erat dengan kesehatan kardiovaskular. Dengan demikian, EPC berpotensi digunakan untuk terapi penyakit akibat disfungsi endotel.

Kata kunci: *endothelial progenitor cell, disfungsi endotel, vaskulogenesis, reendotelialisasi.*

ABSTRACT

Endothelial progenitor cells (EPCs) are cell derived from bone marrow and the cells circulate in peripheral blood. These cells have characteristics similar to stem cells, but their ability to proliferate and differentiate is more limited. EPC discovery has changed the old paradigm in the field of vascular biology and it brings huge implications in medicine as EPCs can mediate the processes of vasculogenesis and maintain the vascular integrity. Increasing amount of EPC in the circulation is important since it has positive correlation with reendothelialization and neovascularization and they are closely linked to cardiovascular health. Thus, EPC could potentially be used for treatment of disease caused by endothelial dysfunction.

Key words: *endothelial progenitor cell, endothelial dysfunction, vasculogenesis, reendothelialization.*

INTRODUCTION

Endothelial progenitor cells (EPCs) are cells derived from bone marrow and they circulate in peripheral blood. The cells have characteristics similar to stem cells, but their ability to proliferate and differentiate is more limited, i.e. they only can differentiate into endothelial cells.[1,2]

In 1997, Asahara et al[3] has successfully isolated EPC from peripheral blood for the first time. The cells have positive surface antigen for mucosialin (CD34) and vascular endothelial growth factor receptor-2 (VEGFR-2/FLK-1). In vitro, the cells have a potency to develop into mature endothelial cells and in vivo, they have roles in neoangiogenesis. Shi et al[4] have demonstrated that mononuclear cells which contain bone-marrow-derived-CD34+ surface antigen can be mobilized to peripheral circulation

and can differentiate into mature endothelial cells. Since the discovery, mononuclear cells of peripheral blood which ha CD34+ surface antigen are believed to be derived from the bone marrow and the cells are originated from the same precursor of hematopoetic stem cells (hemangioblast) since both of them show the same surface antigen, i.e. which is positive to CD34, prominin-1 (CD133) and FLK-1.[3,5]

The EPC discovery has changed the old paradigm in the field of vascular biology, which believes that the process of vasculogenesis exclusively occurs only during embryogenesis. Some evidences indicate that postnatal neovascularization is not only derived from proliferation, migration and remodeling of endothelial cells on vascular wall (angiogenesis), but it also involve EPC recruitment from bone marrow, a process that has been known as vasculogenesis.[6-8] The discovery has brought huge implications in medicine as EPCs can mediate the processes of vasculogenesis and maintain the vascular integrity.[3]

Risk factors for cardiovascular diseases are smoking, hypertension, diabetes mellitus and dyslipidemia, which show reduced number of EPCs. Thus, EPC could potentially be used for treatment of ischemic disease by mechanisms of vasculogenesis through reendothelialization and neovascularization. Both are the key process to improve the quality of blood vessels and to repair tissue ischemia.[8,9]

MOBILIZATION, DIFFERENTIATION AND EPC HOMING

The main source of EPCs is bone marrow, but the cells can also be isolated from peripheral and umbilical blood. In normal condition, the number of EPCs from these various sources is very limited; while the mobilization from bone marrow and the number in the circulation are extremely affected by endogenous, exogenous factors as well as physiological and pathological conditions.[6,10,11]

The release of EPCs from bone marrow is affected by various growth factors, enzymes, ligands and surface receptors. The natural response of body tissues when there is hypoxia is increasing the production and secretion of factors that stimulate neovascularization in order to reduce hypoxia. In hypoxia state, the hypoxia-inducible transcription factor-1α (HIF-1α) induces transcription of various proangiogenic proteins such as VEGF, stromal cell-derived factor-1 (SDF-1) and monocytes chemotatic protein-1 (MCP-1), which will actively recruit EPCs from bone marrow to the circulation and then guide them to hypoxic site. Moreover, the local condition of bone marrow has important role in EPC mobilization. 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) induce mobilization by interfering the interaction between EPC and the stroma cells of bone marrow, which allow EPCs to be released from bone marrow through endothelial sinusoid and entering the blood circulation. The process is the initial phase of EPCs mobilization from the bone marrow.[12,13]

The process of EPCs differentiation into mature endothelial cells is still poorly understood. Various studies found that VEGF induces EPCs differentiation and the process of EPCs differentiation into mature endothelial cells has occurred gradually since the migration of EPCs from bone marrow to the systemic circulation.[10,14]

As a response to proinflammatory cytokines released by hypoxic tissue, endothelial cells will increase the expressions of adhesion molecules cells such as E-sellectin, intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and β1-integrin, which facilitate EPCs attachment to local endothelial cells. Next, the EPCs secrete MMPs and matrix metalloelastases (MMEs), which locally impair extracellular matrix and it initiates neovascularization.[12]

Morphologically, EPCs cannot be identified, but there are some specific markers that can be used. In the early phase, the cells showed positive response to CD133, CD34 and VEGFR-2. Cells that shows positive response to those three markers are mainly still in the bone marrow; while the cells which are already present in peripheral circulation show diminishing expression of CD133; however, the expressions

of CD34 and VEGFR-2 are still present. The next development is the advance phase of EPC (the mature endothelial cells), in which the expression of CD34 has diminished, but the VEGFR-2 is still positive and the expressions of vascular endothelial cadherin (VE-cad), platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) and von Willebrand factor (vWF) is initiated.[13-15] Markers of EPCs mobilization include SDF-1, MMP-9, GCS-F and eNOS. Marker which shows the quantity of EPCs is the expression of total CD34; while the marker for EPCs quality are viable CD34, VEGFR-2 and EPC culture cells.[13]

ENDOTHELIAL DYSFUNCTION AND THE ROLE OF EPC

Endothelial cell is a layer of cell covering the inner side of vascular wall. The cell responds to each physical or chemical stimulation by releasing appropriate substances to maintain vasomotor balance and vascular hemostasis. A condition, in which the endothelial cell loses its ability to maintain the balance and when the endothelial cells have lost its physiological capacity to promote vasodilation, fibrinolysis and antiagregation effect, is called as endothelial dysfunction.[14,15]

The pathophysiology of endothelial dysfunction is very complex and involves various mechanism through oxidative stress, i.e. a condition with increased reactive oxygen species (ROS) production and reduced antioxidant level. Increased ROS causes deprivation in NO availability, i.e. a substance produced by endothelial cells through eNOS activation.[16] Nitric oxide not only has a role in EPCs mobilization, but it also has a role in EPCs migration and proliferation.[16] Moreover, increased oxidative stress will initiate NF-κB that may lead to inflammatory process as a beginning of atherosclerosis process.[17]

There is a dynamic correlation between inflammation, oxidative stress and EPCs mobilization. Oxidative stress stimulates inflammatory process, in which proinflammatory cytokines will stimulate the production of growth factors such as VEGF, that will further stimulate EPCs mobilization to the circulation. Inflammation may have good and bad impacts on EPCs. The limited and temporary inflammatory response can stimulate EPCs mobilization; while excessive and continuous response will cause reduced EPCs in the circulation. An in vitro study has demonstrated that inflammation and oxidative stress may affect EPC mobilization. The presence of continuous factors causes damages or continuous endothelial dysfunction which may ultimately cause reduction or exhaustion in EPCs supply.[13]

The number of EPCs in the circulation has negative correlation with the degree of endothelial dysfunction in patients with various cardiovascular risk factors. There is a correlation between the number of EPCs and endothelial dysfunction, i.e. reduced number of EPCs can predict the incidence of cardiovascular disease in the future.[18,19]

The role of EPCs in vascular repair is through normalization of endothelial function and improvement of blood flow in injured vascular area. Since endothelial cells are mature cells which has poor capacity to proliferate, i.e. only about 0.01%,[20] therefore, EPCs play an important role in maintaining endothelial layer through reendothelialization and neovascularization. It also indicates that EPCs can be used as a potential therapy for treating endothelial dysfunction.[21]

CONDITION AND FACTORS AFFECTING THE NUMBER AND FUNCTION OF EPCS

The number of EPCs in the circulation of healthy individual is very limited, i.e. less than 1% of total bone marrow cells and less than 0.01% of total mononuclear cells in peripheral blood; however various factors and conditions can affect its number and function.[6] Evidences of some studies show that patients with cardiovascular risk factors such as age, sex, smoking habits, hypertension, diabetes mellitus (DM) and dyslipidemia have reduced number and function of EPCs. In contrast, some cytokines, hormones, medicines and physical activity can improve its number and function.[11] A study has demonstrated that the number of EPCs is increased significantly for a short of time after acute myocardium infarction (AMI) attack and it reaches peak level on the seventh day after the

attack and subsequently, the level decreases.[22] Another study that evaluated the number of CD34+ cells in patients with heart failure shows that there is increasing biphasic response, i.e. increased CD34+ cells in patients with Class I New York Heart Association (NYHA), but it is reduced in patients with Class IV NYHA and the number is even lower when compared with control.[23]

There are physiological conditions affect the number and function of EPCs, which include different age, sex and physical activity. Estrogen has been known as a rapid stimulator for endothelial NO production and eNOS activation. In addition, estrogen can also lower the level of endogenous asymmetric dimethylarginin (ADMA), which is the inhibitor of eNOS.[24] Fandini et al[25] have reported that the number of EPC is greater in fertile female than male subjects; however, the difference has not been found in postmenopausal women compared to men of the same age. The difference can represent the risk of cardiovascular risk in men and postmenopausal women, in which it is correlated to the low number of EPCs.

In aging process, there is also an imbalance between production of free radicals and the availability of antioxidant. There is a correlation between ROS, inflammation and age, i.e. increased ROS level will potentially stimulate chronic inflammation that ultimately will cause impaired EPCs mobilization. Thus, it has also been reported that there is reduced response of EPC migration to VEGF in elderly age as well as reduced clonogenic capacity of EPC that has begun starting from the middle age.[26] Heiss et al[27] have reported that the survival, migration and proliferation capacity of the EPCs are lower in those with older age. The findings show that there is a negative effect of age on EPC differentiation and proliferation, which is correlated to cardiovascular risk.

Physical exercise causes increased NO production. In a study that evaluate the effect of physical exercise on EPC in patients with stable coronary artery disease (CAD), it found that the number of EPC in the circulation increases significantly and the apoptosis is reduced after physical exercise for 28 days compared to the first day of exercise. Increased EPC number is correlated to higher NO availability after physical exercise. The study demonstrates that physical exercise increases the number of EPC in bone marrow and peripheral blood, in which the upregulation of EPC in physical exercise depends on NO and VEGF.[28]

Smoking is one of risk factors causing endothelial dysfunction. The high level of oxidative stress in smoker can potentially affect EPC mobilization and survival in vivo, in which there is 50% reduction of EPC number in smokers compared to the control.[29]

Hypertension is also characterized by endothelial dysfunction and reduced NO availability. Endothelial dysfunction in patients with early stage of hypertension can induce the development of EPCs mobilization factor as the mechanism of compensation in the body. In the advanced stage of hypertension, which has continuous process of oxidative stress and inflammation, it will give contrary effect, i.e. reduced quality and quantity of EPCs.[2,13] In patients with hypertension there is accelerated aging of EPCs and reduced activity of telomerase that affect vascular remodeling.[30]

Dysfunction of EPCs in hypertension causes endothelial repair and neoangiogenesis cannot take place and it will worsen the microvascular abnormality and atherosclerosis, which is the beginning of target organ damage in hypertension.[31] In a study of subjects with refractory hypertension, the number of EPCs is reduced to 76.7% compared to the control.[32] Angiotensin II accelerates the onset of EPCs aging through increased oxidative stress.[33] A clinical trial in CAD patients has demonstrated that ramipril can increase the number of EPCs 2-5 folds as well as its function.[34] Treatment using angiotensin II receptor antagonist also increases the number of EPCs significantly, in which olmesartan treatment can cause increased EPCs from 231±24 to 465±71; while irbesartan treatment increases the number from 196±15 to 300±8 after 4-week treatment.[35]

In patients with type 1 and type 2 DM, there is reduced number and function of EPC in circulation. Tapper et al[36] have demonstrated that isolated EPCs from peripheral blood of patients

with type 2 DM have reduced proliferation capacity in the culture up to 48% compared to normal individuals. Loomans et al[37] also have reported similar results in patients with type 1 DM, i.e. there is reduced EPCs number of 44% compared to the non-diabetics control group. There is a significant increase of EPCs number in DM patients who were treated with insulin or oral diabetic agents.[38] Insulin stimulates NO production; while in insulin resistance, there is an imbalance between endothelial damage and the ability of repair. This condition is correlated to reduced availability of NO, increased ROS production and PI3K/Akt down-regulation. It is potentially disrupt the process of vascular repair, which is the role of EPCs, including impaired EPC mobilization from the bone marrow.[39]

Increased plasma cholesterol level has significant correlation with endothelial damage and dysfunction. It has been proven that the number of EPCs is reduced significantly in patients with hypercholesterolemia and the number of EPCs has negative correlation with the level of total cholesterol and low density lipoprotein (LDL) cholesterol.[40]

Anti-inflammatory agents and antioxidants such as HMG-CoA reductase inhibitors(statin) have been proven to have positive effects on EPC. Statin increases mobilization and function of EPC through upregulation of PI3K/Akt. The effect of statin in mobilizing EPC to the circulation is correlated with increased reendothelialization and reduced neointima resulting in reduced restenosis.[41,42]

CLINICAL APPLICATION OF EPCs

Several studies have been conducted to sound out the application of EPCs in clinical settings. Although the basic biomolecular mechanism of EPCs has not been fully understood, some studies have shown promising results. Increasing EPCs number in the circulation is essential as it correlates positively with reendothelialization and neovascularization, which has strong association with cardiovascular health.[26]

The use of EPCs as target therapy is based on the results of some studies such as: local injection or infusion of fresh CD34+ cells isolated from human can accelerate the blood flow to the ischemic area in diabetic experimental animal model. In a clinical trial, EPCs transplantation to those with myocardium infarct, ischemia, coronary arterial disease and heart failure has been proven to be appropriate and safe.[43]

EPCs transplantation is one of promising strategies for restoring blood flow in ischemic diseases such as ischemic heart disease and peripheral artery disease (PAD).[44] In a study of transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI), EPCs was given by intracoronary infusion to 20 patients with acute myocardium infarction. The study shows that there is significant increase of ejection fraction, smaller area of infarction and better perfusion of myocardium.[45] As a target therapy, in addition to its benefit for additional vascularization in ischemic tissue, it can also be used to deliver anti- or pro-angiogenic agents.[3]

The very limited number of EPCs will limit the use of EPCs as a therapy. The number of EPCs needed for therapy in human adults is relatively large, i.e about $3x10^8$ to $6x10^8$ cells, which means that 8.5-120 liter of peripheral blood is necessary to generate adequate number of EPCs.[46] To overcome the limitation, we need an effort to expand the number of EPCs.

Some strategies that have been considered as applied EPCs for treatment are:[44] 1) In vivo expansion of EPCs. Some candidates can be used to induce EPC in vivo such as VEGF, GM-CSF and statin; 2) Ex vivo expansion of EPC. The strategy is performed by taking mononuclear cells from peripheral blood of healthy individual and then the cells are cultured. After obtaining sufficient number of EPCs, the EPCs are then injected to ischemic area; 3) Local injection of EPC. Local injection of SDF-1 can increase the accumulation of the transplanted EPCs resulting in increased neovascularization. Combination of SDF-1 local injection and EPCs transplantation is a potential strategy for neovascularization therapy; 4) EPCs modification through gen transfer. Various studies have been conducted and still on going to enhance the effort of EPC expansion including by genetic engineering, i.e by transferring human telomerase reverse transcriptase (hTERT) gene or coding genes for

proangiogenesis factor such as VEGF into EPCs.

THE PROGNOSTIC VALUE OF EPCs

There is a correlation between the number of EPCs and endothelial dysfunction, i.e. reduced number of EPCs can predict the incidence of cardiovascular disease in the future. The number EPCs isolated from the patients with cardiovascular risk factors has a significant negative correlation with the risk factor score based on the Framingham score.[47]

EPCs level is an independent predictor for mortality due to chronic heart failure, in which the level is not affected by the etiologies of heart failure, instead it is more correlated to clinical status of the patient evaluated by NYHA classification. EPCs level has been suggested to be an additional marker for clinical follow up of patients with chronic heart failure.[48]

The number of EPCs in the circulation is extremely reduced in patients with type 2 DM, metabolic syndrome and individuals with insulin resistance. In those with metabolic syndrome, the EPCs level has negative correlation with HOMA score. The level of EPC in patients with type 1 and type 2 DM also has negative correlation with HbA1C level.[47,28,62]

CONCLUSION

Endothelial progenitor cell can be isolated from peripheral blood, in which the cells undergo differentiation into mature endothelial cells and are involved in reendothelialization as well as neovascularization in endothelial dysfunction. The cells is usually identified through positive expressions of CD133, CD34 and VEGFR-2. EPCs mobilization from bone marrow and its number in circulation is extremely affected by endogenous and exogenous factors as well as physiological and pathological conditions. The cells have important roles in prevention and therapy of cardiovascular diseases. The higher the number of endothelial progenitor cells in circulation, the more protective it is for blood vessels, particularly reendothelialization and neovascularization of ischemic tissue and EPCs can be used as a predictor of cardiovascular disease in the future.

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