International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 7, No. 2, 2024

Research Progress in Prevention and Treatment of Atherosclerosis by Regulating Endothelial Cells with Traditional Chinese Medicine

Fang Fang

Shaoxing People's Hospital, Shaoxing, Zhejiang, 312000, China

Abstract: Atherosclerosis (AS)is an important pathological basis of cardiovascular and cerebrovascular diseases. Its pathogenesis is complex and involves many factors. Traditional Chinese medicine (TCM) has the advantage of multi-link and multi-target intervention in the prevention and treatment of AS, in which the regulation of endothelial progenitor cells (EPCs) is an important research direction. This article will review the research progress of TCM in preventing and treating AS by regulating EPCs.

Keywords: Atherosclerosis; Endothelial Progenitor Cells; Traditional Chinese Medicine.

1. Introduction

AS is a chronic systemic vasculitis disease, which leads to high incidence rate and mortality of cardiovascular diseases worldwide. AS begins with endothelial cell activation, followed by the accumulation of lipids, fibrous components, and calcification, triggering vascular narrowing and activation of inflammatory pathways [1]. EPCs are precursor cells of human vascular endothelial cells, which can be mobilized from bone marrow to peripheral blood to participate in the repair of damaged blood vessels under physiological or pathological stimuli [2]. The relationship between EPCs and AS has always been a focus of clinical research. This article is based on the impact of EPCs on AS and provides a review of the effects of TCM in preventing and treating AS by regulating EPCs. It is hoped that this will provide new ideas for future research.

2. Overview of Atherosclerosis

AS is mainly a chronic inflammatory vascular disease characterized by lesions in the intima of large and medium-sized arteries, lipid deposition in the vascular wall, and rich fibrous plaques [3-4]. Its pathogenesis may be related to endothelial cell dysfunction, lipid metabolism disorder, foam cells, inflammation and neovascularization, and increased platelet reactivity [3,5]. As inflammatory factors lead to endothelial function damage, adhesion factors expressed by endothelial cells combine with monocytes, while monocytes accumulated and deposited under the endothelium are transformed into macrophages under the effect of macrophage colony stimulating factor, swallow a large amount of oxidized low-density lipoprotein, degrade into foam cells, accumulate to form lipid stripes, foam cells eventually die, and form necrotic cores in the plaque. The toxic substances released by inflammatory stimuli can thin the fibrous cap, further accelerating the process of AS plaque rupture, bleeding, and thrombus formation [6].

3. EPCs and AS

EPCs originate from bone marrow and have the ability to differentiate into mature endothelial cells, which can play a role in repairing endothelial damage. In recent years, studies have found that changes in the number of EPCs can serve as biological markers for the formation and development of AS plaques [7]. Endothelial injury is the fundamental pathological damage of AS. In the case of endothelial damage, the vascular wall endothelium is repaired by various mechanisms, such as endothelial cell division near the damaged area. Under physiological conditions, EPCs can be considered as reserves for endothelial repair function. If the proliferation and migration of adjacent endothelial cells alone cannot meet the needs of endothelial repair, the differentiation of EPCs becomes a repair mechanism for repairing endothelial injury areas.

4. The Role of EPCs in AS and the Prevention and Treatment with TCM

(1) Repair vascular damage

Research has found that certain cytokines in ischemic tissue, such as vascular endothelial growth factor (VEGF), are elevated, stimulating the mobilization and release of bone marrow EPCs, and migrating to the damaged site under the mediation of inflammatory chemokines, limiting endothelial damage[8]. In addition, EPCs also promote the initiation of endogenous repair mechanisms. EPCs that migrate to the damaged site can release cytokines such as VEGF, fibroblast growth factor, hepatocyte growth factor, and epidermal growth factor to stimulate the proliferation of endothelial cells adjacent to the injury, further repairing the damage to the vascular endothelium [9]. Research has shown that EPCs can differentiate into mature endothelial cells, and in the event of vascular injury, EPCs can induce angiogenesis and vascular repair [10]. Under the action of ischemia or cytokines in the body, EPCs are mobilized to the peripheral circulation and homing to ischemic tissues, secreting angiogenesis related factors locally, differentiating and proliferating to form endothelial cells and neovascularization, promoting endothelial injury repair [11]. Research has also confirmed that patients with unstable angina often have coronary endothelial dysfunction, which is closely related to a decrease in the number of EPCs [12]. It can be seen that EPCs play an

important role in endothelial repair and angiogenesis.

(2) Inhibit platelet activation

There is a close relationship between platelet activation and atherosclerosis. Platelet activation can promote the proliferation of arterial intima, smooth muscle proliferation, and migration of extracellular matrix to intima, thereby accelerating the progression of atherosclerosis. When there is bleeding or rupture within atherosclerotic plaques, it can induce platelet aggregation and form blood clots. The damage to vascular endothelium and the release of inflammatory mediators such as C-reactive protein and plaque rupture lead to an increase in reactive oxygen species levels and exposure of collagen fibers, resulting in platelet aggregation and adhesion, thrombosis, and further damage to endothelial cells. Subsequently, the release of inflammatory mediators and adhesion molecules induces smooth muscle cell migration, proliferation, and accumulation, while EPCs can inhibit platelet activity at this time; In addition, platelets will aggregate and adhere to damaged endothelial areas in the early stages of AS, which can cause thrombosis in the damaged areas[13-16]. EPCs can inhibit the formation and development of thrombosis after endothelial injury by suppressing platelet activation, adhesion, and aggregation at damaged sites, thereby slowing down the progression of atherosclerosis and reducing the risk of plaque rupture [16]. The possibility of platelet activity consuming EPCs and reducing their quantity has become a hot topic in atherosclerosis research.

(3)Promote nerve cell repair

AS patients often have neurological dysfunction, such as peripheral neuropathy and autonomic dysfunction. These neurological impairments may lead to symptoms such as pain, sensory abnormalities, and motor disorders in patients, seriously affecting their quality of life. Research has found that transplantation of EPCs into stroke prone mice results in significant neurological recovery in the ischemic area, demonstrating that EPCs can protect the nerves in the damaged area and promote their recovery [17]. The role of EPCs in the recovery of neurological function in AS is mainly manifested in the following aspects:

Promoting angiogenesis: New blood vessels are generated through two mechanisms: one is the replication and recombination of pre-existing microvascular endothelial cells; the second is to re recruit EPCs, which are then incorporated into existing tissues and differentiated into mature functional endothelial cells [18]. EPCs can differentiate into endothelial cells and participate in the process of angiogenesis. EPCs promote angiogenesis in ischemic tissues by secreting cytokines such as VEGF, and participate in the re endothelialization and angiogenesis of damaged blood vessels through mobilization, migration, homing, and differentiation [19].

Antioxidant effect: EPCs have antioxidant properties and can eliminate free radicals in the body, reducing the damage of oxidative stress to neurological function. Research has found that infusion of EPCs during ischemia-reperfusion can achieve strong neuroprotective effects by reducing the activity of apoptotic protease 3 and hydroxyl radicals, increasing SOD and glutathione peroxidase, and inhibiting apoptosis and oxidative stress [20].

Promote the release of nerve growth factors. EPCs can secrete various nerve growth factors, such as brain-derived neurotrophic factor, nerve growth factor, etc. These nerve growth factors can promote the growth, differentiation, and regeneration of neurons, thereby facilitating the recovery of neural function. The study found that the treatment group showed significant improvement in neurological function recovery in ischemic stroke mice after joint transplantation of embryonic stem cells and EPCs, indicating that the survival of post-stroke neuroblasts depends on a mature vascular network system. EPCs not only provide a vascular rich microenvironment for damaged nerves, but also secrete cytokines that have a significant promoting effect on axonal reconstruction of damaged neurons [21]. Another study found that infusing EPCs 1 hour after stroke for 4 weeks can significantly reduce cortical atrophy and improve behavioral abilities such as walking on a crossbeam [22].

5. TCM Regulates EPCs to Intervene in AS

(1)Enhance the proliferation, migration, and adhesion capabilities of EPCs

EPCs are a group of endothelial cells that can proliferate and differentiate into mature blood vessels. The number, proliferation, and migration functions of EPCs in the circulation of patients with coronary heart disease undergo significant changes, and they play an important role in the occurrence and development of ischemic diseases such as coronary heart disease. Research has shown that the number of EPCs and cell colonies in peripheral blood of patients with coronary heart disease are significantly lower than those in the control group, and are negatively correlated with the extent and degree of coronary artery disease [23]. Research has found that curcumin in turmeric can increase the number of EPCs, improve their proliferation and NO secretion function, and upregulate the expression of e NOS [24]. The active ingredient tanshinone IIA in Danshen can enhance the proliferation, migration, and adhesion ability of EPCs, increase NO secretion, and improve the survival rate of EPCs [25-26]. Ginsenoside can enhance the proliferation, adhesion, migration, and angiogenesis of human EPCs, and promote their secretion of platelet-derived growth factor [27].

(2)Promote endothelial repair and regeneration

Research has found that tanshinone IIA upregulates the expression of VEGF and SDF-1, promotes the homing of ECPs, and promotes endothelial repair and regeneration[28]; Danshensu improves the survival of EPCs under hypoxic conditions by phosphorylating protein kinase B (Akt), and accelerates the pro angiogenic function of EPCs on cell migration and angiogenesis through the SDF-1 α/CXCR4 axis [29]. Saffron in safflower regulates the angiogenic effect of bone marrow-derived EPCs by upregulating the expression of vascular endothelial growth factor and its receptor VEGFR-2, basic fibroblast growth factor, and angiopoietin 1[30]. Previous studies have shown that Buyang Huanwu Tang not only promotes vascular endothelialization, but also increases the number of EPCs in the peripheral circulation of pig coronary stent models, and upregulates the expression of VEGF and bFGF, which is expected to play a key role in promoting stent endothelialization [31-32]. Research has shown that deer antler has the effect of promoting endothelial cell proliferation, migration, and improving endothelial cell function. It activates the PI3K/Akt signaling pathway to regulate the mobilization and homing of EPCs, promoting angiogenesis in rats with lower limb arteriosclerosis obliterans [33].

6. Conclusion

In summary, the repair mechanism of EPCs and the risk factors causing AS are in a dynamic balance in healthy individuals. EPCs therapy represents a new treatment method that promotes the repair of vascular endothelial damage by participating in angiogenesis and the re endothelialization of damaged vascular endothelium. Drug intervention in the treatment of EPCs is safe and has the advantage of mobilizing the endogenous repair mechanism of the body itself. Although the use of EPCs has been proved to slow down the process of atherosclerosis, many problems that may be brought about by the treatment of EPCs have not yet been solved, such as promoting the formation of new blood vessels and the promotion of the process of atherosclerosis caused by the interaction between EPCs and platelets, which are issues that need attention and further research in the treatment of EPCs. In addition, future research can further explore the protective mechanism of traditional Chinese medicine on EPCs and its application prospects in the prevention and treatment of AS. At the same time, it is also necessary to strengthen research on the integration of traditional Chinese and Western medicine, and explore more effective treatment methods.

Acknowledgments

The author gratefully acknowledges the financial support from Zhejiang Health Science and Technology Plan (2022KY1286), Zhejiang Province Traditional Chinese Medicine Science and Technology Plan (2023ZL730) and Shaoxing Science and Technology Plan Project (2022A140 17).

References

[1] Jebari-Benslaiman S, Galicia-Garcia U, Larrea-Sebal A, et al. Pathophysiology of Atherosclerosis [J]. Int J Mol Sci, 2022,23 (6):3346.

[2] WU Qianqian, FANG Tao, QI Guoxian. Advances in Research on Endothelial Progenitor Cells'Function on Stability of Atheromatous Plaque [J]. Adv Cardiovasc Dis,2014, 35(4): 488-491.

[3] LibbyP, BuringJE, BadimonL, et al. Atherosclerosis [J]. NatRevDisPrimers, 2019, 5(1):56.

[4] LusisAJ. Atherosclerosis [J]. Nature, 2000,407(6801): 233-241.

[5] Grootaert MJ, Roth L, Schrijvers DM, et al. Defective autophagy in atherosclerosis: To die or to senesce? [J]. Oxid Med Cell Longev,2018, 20(18):7687083.

[6] LU Meijun, YANG Guanlin, JIA Lianqun, et al. Exploration of Scientific Connotation of Treating Atherosclerosis with Phlegm and Blood Stasisfrom New Perspective of "Spleen−Intestinal Microflora-Pyroptosis"[J]. CHINESE ARCHIVES OF TRADITIONAL CHINESE MEDICINE, 2021, 39(11):46-49.

[7] Moon JH, Chae MK, Kim KJ, et al. Decreased endothelial progenitor cells and increased serum glycated albumin are independently correlated with plaque forming carotid artery atherosclerosis in type 2 diabetes patients without documented ischemic disease[J].Cire J. 2012. 76(9): 2273-2279.

[8] Jeong HS. Lee HK. Tark KC, et al. Effect of Endogenous Bone Marrow Derived Stem Cells Induced by AMD-3100 on Expanded Ischemic Flap [J]. J Korean Med Sei. 2014, 29(3):S837-948.

[9] Qi RuWang. Bao HeWang, Wen BiaoZhu, et al. An in Vitro Study of Differentiation of Hematopoietic Cells to Endothelial Cells [J]. Bone Marrow Res, 2011:846096.

[10] Morishita T, Uzui H, Ikeda H, et al. Association of CD34/CD133/VEGFR2-Positive Cell Numbers with Eicosapentaenoic Acid and Postprandial Hyperglycemiain Patients with Coronary ArterDisease [J]. International Journal of Cardiol,2016,221(7):1039-42.

[11] Zhao YH, Yuan B, Chen J, et al. Endothelial progenitor cells: therapeuticperspective for ischemic stroke[J]. CNS Neuroscience & Therapeutics, 2013,19(2):67-75.

[12] WATT J, KENNEDY S, AHMED N, et al. The relationship betweenoxidised LDL, endothelial progenitor cells and coronary endothelial function in patients with CHD [J]. Open Heart, 2016, 3(1):e342.

[13] Pesaro AE, Serrano CV Jr, Katz M, el al. Inflammation and circulating endothelial progenitor cells in patients with coronary artery disease and residual platelet reactivity [J]. Clinics (Sao Paulo), 2012 , 67(9): 1117-1121.

[14] Li YF., Ren LN, Guo G, et al. Endochelial progenitor cells in ischemic stroke: an exploration from hypothesis to therapy[J].J Hemaol Oncol,2015,11(8):33.

[15] Langer HP, Bigalke B, Seizer P, et al. Interaction of platelets and inflammatory endothelium in the development and progression of coronary artery disease [J]. Semin Thromb Hemost,2010, 36(2): 131- 138

[16] Abou-Saleh H, Yacoub D, Theoret JF, et al. Endothelial progenitor cells bind and inhibit platelet function and thrombus formation[J].Circulation, 2009,120(22):2230-2239.

[17] Nth LR, Deroide N, Lere-Dean C, et al. Neuroblast survival depends on mature vascular network formation after mouse stroke: role of endorbelial and smooth muscle progenitor cell co-administraion[J]. Eur J Neurosci, 2012, 35(8):1208-1217.

[18] Masuda H. Asahara T: Post-natal endothelial progenitor cells for neovascularization in tissue regeneration[J]. Cardiovasc Res ,2003,58:390-8.

[19] ZHANG M, MALIK A B, REHMAN J. Endothelial progenitor cells and vascular repair [J]. Curr Opin Hematol, 2014, 21(3):224-228.

[20] Qiu J, LL W, Feng SH, et al. Transplantation of bone marrow-derived endochelial progenitor cells attenuates cerebral ischemia and reperfusion injury by inhibiting neuronal apoplosis, oxidative stress and nuclear factor-kappa B expression [J]. Int J Mol Med, 2013, 31(1):91-98.

[21] Rosell A, Morancho A , Navarro-Sobrino MA, et al. Factors secreted by endothelial progenitor cells enhance neurorepair responses after cerebral ischemia in mice [J]. PLOS One, 2013, 8(9): e73244.

[22] Fan YF, Shen FX, Frenzel T, et al. Endothelial progenitor cell transplant-tation improves Long-Term stroke outcome in mice [J]. Ann Neurol,2010,67 (4) :488-497.

[23] FANG Yeqing, ZHANG Songrong, FANG Hongcheng et al. The Relationship Between Endothelial Progenitor Cells and Coronary Artery Stenosisin Patients of Coronary Heart Diseases [J]. Chin J Arterioscle, 2012, 20 (9):814-818.

[24] HUANG Meijian, ZHU Chengsheng, YAO Hangping, et al. Effects of curcumin on number and function of endothelial progenitor cells derived from peripheral blood of chronic obstructive pulmonary disease patients[J]. CHINESE JOURNAL OF CLINICAL PHARMACY, 2015, 24(3):147-152.

[25] Yan Fengdi, HeShenghu, Zhang Jing. Effects of salvianolic acid on human peripheral endothelial progenitor cells in

vitro[J]. Chin J Clinicians(Electronic Edition), 2014, 8 (24):4436-4439.

[26] ZHANG Juan, LYU Jiao-jiao, LI Hao, et al. Optimization of effective component formula of paeonol and salviol IIA combined with rhG-CSF on EPCs proliferation in rats using orthogonal design[J]. Chin Hosp Pharm J, 2018, 38(17):1777-1782.

[27] TAN Meixin, XIONG Wu, HUANG Dingling, et al. Effects of ginsenoside Rg1 on proliferation, adhesion, migration, tube formation ability and PDGF se-cretion of human endothelial progenitor cells [J]. Shandong Medical Journal, 2022, 62(08): 11-14.

[28] YANG Yan, CHEN Qingwei, CAO Guangyu et al. Efficiency of rat bone marrow−derived endothelial progenitor cells on VEGF and SDF−1expression with the aid of Tanshinone IIA [J]. LASER JOURNAL, 2012, 33(2):83-86.

[29] YIN Y, DUAN J L, GUO C, et al. Danshensu accelerates angiogenesisafter myocardial infarction in rats and promotes the functions of endothelial progenitor cells through SDF-1α/CXCR4 axis[J].European Journal of Pharmacology, 2017, 814：274-282.

[30] LIU Yu, YUN Qinghui, ZHU Yanrong et al. Proangiogenic Activities of Safflor Yellow A on Bone Marrow-derived Endothelial Progenitor Cells in Rats[J]. Pharm J Chin PLA, 2018, 34(4):305-308.

[31] WEN Zhihao, HUANG Deqing, HUANG Mingjian et al. Effect of Buyang Huanwu Decoction on the proliferation, migration and adhesion of endothelial progenitor cells in rats with acute myocardial infarction [J]. Journal of Hainan Medical University, 2021, 27(14):1041-1046.

[32] CHEN Tao, LIU Zongjun, GAO Junqing, et al. Effect of Buyang Huanwu Decoction on early stent endothelialization and endothelial progenitorcells after coronary artery stent implantation in pigs[J]. Shanghai J Tradit Chin Med, 2022, 56 (05):74-80.

[33] HAN Jie, LI Tingquan, LI Zijuan, et al. The Role of PI3K/Akt Signal Pathway in the Enhancement of Endothelial Progenitor Cell Activity and Cell Migration by Pilose Antler [J]. CHINESE JOURNAL OF INTEGRATIVE MEDICINE ON CARDIO-CEREBROVGASCULAR DISEASE, 2022, 20 (06): 997-1002+ 1007.