A Relationship between vascular endothelial cell senescence and cardiovascular disease

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Abstract: The vascular endothelial cell (VEC) is a single layer of flat squamous epithelium covering the intima of the blood vessel. It constitutes a biological barrier to the blood vessel wall. It is not only a protective barrier but also a producer of some autocrine secretion. The substance is used to regulate homeostasis and vascular tone and has a variety of biological functions. VEC senescence can lead to vascular dysfunction, which is a major risk factor for cardiovascular system (CVS) and has a close relationship with cardiovascular disease (CVD). However, the mechanism of VEC senescence and the effects of VEC senescence on vascular function are not fully understood. This review summarizes the characteristics of VEC senescence and describes age-related CVD.

1 Introduction

Vascular endothelial cells (VEC), located at the interface between blood and blood vessel wall/tissue, and being a protective barrier, are a single layer of flat squamous epithelial cells located on the inner surface of blood vessels [1]. The main function of VEC is to adjust systemic blood flow and tissue perfusion by combining underlying smooth muscle cells with surrounding cells to sense changes in blood vessel diameter and vascular tension [2]. In addition, a large number of molecules that regulate platelet activation and coagulation can be released on the surface of VEC, so as to maintain blood flow and prevent thrombosis after vascular injury [3].

VEC remains stationary under the physiological conditions of the vascular system. However, under the pathophysiological conditions of wound healing, vascular inflammation and tumorigenesis, VEC can proliferate, but the proliferation of VEC is limited. When it proliferates to a certain number, the VEC ages and stops growing. Aging VEC impairs vascular function and vascular homeostasis, leading to disruption of vascular integrity [4]. VEC aging causes a decrease in the production of nitric oxide (NO). The functions of NO include inducing vascular smooth muscle cell relaxation, inhibiting platelet aggregation, and blocking the adhesion of neutrophils/monocytes to VEC [5]. Decreased NO causes vascular homeostasis dysfunction, thrombosis and the development of atherosclerosis [6]. In addition, many studies have shown that the aging mediators that induce VEC (such as oxidized low-density lipoprotein, AngII, advanced glycation end products, oxygen free radicals, etc.) can promote the formation of atherosclerosis and that the factors that inhibit the aging of VEC (such as statins, NO, antioxidants, etc.) can prevent the formation of

atherosclerosis [7]. It can be seen from the aforementioned studies that VEC aging plays an important role in the formation and development of atherosclerotic plaques, and contributes to the development of age-related CVD such as atherosclerosis. This article aims to summarize and explain the characteristics of VEC aging and its molecular mechanism, and to explore the correlation between VEC aging and CVD.

2 The characteristics of senescence of vascular endothelial cells

The aging of human beings is accompanied by the degradation of various tissues, leading to major changes in the structure and function of the organization. After VEC senescence, the morphological manifestation is that the intercellular space widens, the cells are flat and wide, and the nucleus and nucleoli are enlarged [8]. In terms of function, studies have found that the production of NO and the release of endothelin-1 (ET-1) were increased in the early stage of VEC aging. The late stage of VEC senescence also showed decreased expression of vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1), and increased nuclear factor κ B (nuclear factor- κ B, NF- κ B) activation [9,10]. Moreover, the function and activity of ICAM-1 are also significantly related to changes in age. VEC aging is characterized by changes in eNOS function, leading to dysfunction of various mechanisms including oxidative stress, and reducing the bioavailability of NO. At the same time, the change of eNOS function leads to an increase in the production of superoxide. This change is called "eNOS uncoupling". eNOS uncoupling is not only related to cell senescence, but also plays an important part in promoting the development of CVD. In short,

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eNOS is considered to be one of the most important mechanisms of age-related CVD [1]. Therefore, VEC senescence leads to the dysfunction of VEC, and can enhance the migration of monocytes to the blood vessel wall, leading to the development of CVD [12,13].

3 Age-related cardiovascular disease

3.1 Atherosclerosis

Atherosclerosis, a multifactorial and progressive cardiovascular disease, is commonly found in elderly patients [14]. The causes of atherosclerosis include lipid deposition, inflammatory cell infiltration and plaque formation. The aging process can accelerate changes in the structure and molecular composition of atherosclerosis [15]. The infiltration of oxidized lipoprotein into the subendothelial space of arteries often causes atherosclerosis as well. Kolodgie et al. [16] have shown that atherosclerosis is related to pathological thickening of the vascular intima, loss of vascular smooth muscle cells, lipid deposition and macrophage infiltration. There are two kinds of Cellular senescence: replication disorders and stress-induced premature senescence. The replication disorder is the shortening of telomeres induced by DNA damage. This damage may be caused by increased ROS content [17]. Biomarkers such as senescence-associated β galactosidase (SA β G) are found in the aging process of human cells. Atherosclerotic lesions and a large number of SA β G positives in old blood vessels confirm the link between atherosclerosis and aging. In lesions with abnormal endothelial function, white blood cells, vascular smooth muscle and platelets are components of atherosclerotic plaques. VEC recruit monocytes and macrophages by releasing colony stimulating factors [18]. Although monocytes and macrophages can remove potentially harmful compounds, they can also promote extracellular matrix protein deposition and vascular smooth muscle cell proliferation and migration through the release of inflammatory factors [19].

The latest advances in cell research provide new possibilities for the drug treatment of atherosclerosis. It has been proposed that antigens can be used as a vaccine to prevent atherosclerosis. However, anti-inflammatory drugs that may cause cardiovascular disease, such as rofecoxib (cyclooxygenase-2 inhibitor), need to be used with caution in patients with cardiovascular disease. Therefore, the treatment of atherosclerosis still needs to be improved [20].

3.2 Vascular calcification

With age, the calcium in the axial bone will gradually transfer to the cardiovascular structure, resulting in a decrease in the calcium content in the axial bone and the deposition of calcium in the cardiovascular structure. More than 60% of adults over the age of 60 have at least one major vascular bed, such as calcium deposits in the

carotid artery, coronary artery and thoracic aorta [21]. The degree of calcified aortic valve stenosis reflects the degree of vascular aging in CVS. Strong human genetic data also suggests that lipoproteins are involved in vascular calcification. In spite of the preliminary findings, clinical trials have not confirmed that statin therapy can limit the progression of vascular calcification [22]. Studies have shown that inflammation is clinically related to cardiovascular calcification [23]. Calcified aortic stenosis can cause many clinical manifestations in elderly patients. In the larger aorta, medial calcification can lead to increased pulse wave velocity and systolic hypertension. There is a need to better understand the molecular mechanisms of cardiovascular calcification and preventive measures to alleviate it. Once the cardiovascular structure is calcified, it may be difficult to ameliorate the cardiovascular structure and function through treatment [24].

3.3 Heart failure

Heart failure with preserved ejection fraction (HFpEF) is a serious factor that can reduce the quality of life of elderly patients [25]. The risk of HFpEF increases with age. As a matter of fact, left ventricle (left ventricle, LV) hypertrophy and fibrosis in the elderly patients may impair their appetite. Medical staff generally come to realize that the number of people suffering from HFpEF is increasing. The little attention paid by elderly patients and the poor prognosis of the elderly patient population have reduced the quality of life of elderly patients and led to a waste of resources [26]. The aging heart undergoes a series of changes to maintain its resting contractile function, including LV thickening, cardiomyocyte hypertrophy, and reduced β -adrenergic stimulation [27]. In addition, further damage from ischemic diseases increases with age. Aging is the main reason to promote the development of HFpEF, which is a subtype of disease that is difficult to treat, so new preventions and treatment strategies are essential.

4 Conclusions

VEC aging leads to changes in the structure and function of blood vessels, and is regarded to be the main risk factor for the occurrence and development of CVD such as atherosclerosis. As the first line of defense in blood vessels, VEC is a major participant in maintaining the stability of the cardiovascular environment. The aging of VEC leads to VEC dysfunction and increases the risk of various CVD [28]. However, the current regulation mechanism of VEC function, the effect of VEC aging on vascular function and its related molecular mechanisms are still unclear. Further exploration of its mechanism will provide new ideas for the prevention and treatment of CVD.

Fig. 1 Molecular mechanism of vascular endothelial cell senescence

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