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**Review Article** 

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# Research progress of vascular endothelial cell injury and repair

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Abstract Vascular endothelial cells play a very important role in human tissues, which is an important link to determine health. As the covering cell of vascular intima, it not only has the function of regulating vascular pressure and phagocytosis of bacteria and senescent cells, but also has the function of releasing cytokines to regulate cell damage. The injury of vascular endothelial cells can lead to a variety of cardiovascular diseases. In recent years, it has been found that different vascular injury models can be established to simulate the reaction of cells in different pathological conditions. This facilitates the research and development of drugs to protect vascular cells and makes it possible to cure many cardiovascular diseases. Therefore, the damage and repair of vascular endothelial cells have become the focus of research.

## Keywords Vascular endothelial cells, Injury, Repair

## Introduction

Endothelial cells are specialized flattened epithelial cells that form the interface between the circulatory and lymphatic systems. Vascular endothelial cells are generally endothelial cells that cover the lining of blood vessels in a single layer. They appear as a tree along the blood vessels and are usually slightly elongated to serve as the interface between the blood vessel wall and the blood. It not only attaches to the inner wall of blood vessels, but also presents a single layer of longitudinal distribution in the heart and lymphatic lumens. Current studies have shown that vascular endothelial cells not only have resident vascular endothelial cells, but also circulating endothelial cells exist in flowing blood [1].

Endothelial cells act as a barrier between blood and vascular walls, filtering oxygen and water, and preventing white blood cells from accumulating. When vascular pressure changes, endothelial cells can secrete a large number of active substances involved in vascular tone regulation, including vasodilator nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin (PGI2). As well as angiotensin II (AngII), endothelin-1 (ET-1), prostaglandin A2 and prostaglandin-like thromboxane A2, which can cause vasoconstriction, so as to regulate vascular pressure and normal blood circulation [2]. When blood vessels are injured, platelets accumulate in large quantities. Studies have shown that thrombin regulatory protein, von willebrand factor and protein C receptor of vascular endothelial cells can maintain the dynamic balance between coagulation and fibrinolysis, thus maintaining normal blood flow [3]. When vascular lesions occur, it is easy to cause inflammation. Vascular endothelial cells have autophagy and can regulate the transport of neutrophils, thus stopping inflammation [4]. The endothelial cell layer is connected to the vascular smooth muscle layer, and when the blood vessel ruptures, the vascular endothelial cell signaling, allowing platelets and macrophages to release cytokines. Thus, smooth muscle cell migration and proliferation are promoted, resulting in the formation of new inner membrane and vascular remodeling [5]. In



conclusion, vascular endothelial cells can regulate metabolic level and endocrine function, and have a barrier function, regulate vascular tension, promote fibrinolysis, participate in inflammatory reaction, and cooperate with vascular smooth muscle to participate in vascular remodeling. This review focuses on the damage and repair of endothelial cells.

## Vascular endothelial cell injury

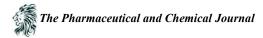
Vascular endothelial cells are an integral part of the body, serving as a barrier to contact with blood. Changes in blood flow velocity and blood composition can lead to corresponding changes in vascular endothelial cells. There are a lot of vascular endothelial cell injury factors, in addition to mechanical damage, and hydrogen peroxide  $(H_2O_2)$ , tumor necrosis factor alpha (TNF- $\alpha$ ), Ang II, lipopolysaccharides (LPS) can cause injury to the endothelial cells. These conditions can be used to make cell damage model and provide theoretical basis for the study of cardiovascular disease.

## $H_2O_2$

H<sub>2</sub>O<sub>2</sub> penetrates most cell membranes and reacts with intracellular iron. In normal cells, catalase catalyzes the decomposition of  $H_2O_2$ . When the amount of  $H_2O_2$  is too high, the catalytic decomposition is incomplete and a large number of free radicals are generated, which leads to oxidative stress reaction of vascular endothelial cells and damage to endothelial cells, leading to the occurrence of cardiovascular diseases, but the damage mechanism is still unclear. Studies have shown that H<sub>2</sub>O<sub>2</sub> can inhibit the expression of miR-122 in human umbilical vein endothelial cells (HUVECs). Overexpression of miR-122 can weaken the expression of ET-1 and increase the release of the vascular relaxation factor prostaglandin F1 $\alpha$ , which may restore the injury by regulating p53. Conversely, it can aggravate  $H_2O_2$ -induced oxidative stress injury and cell apoptosis, resulting in deep vein thrombosis [6].  $H_2O_2$  may damage HUVECs through the signaling pathway of phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT). CCK8 showed decreased cell viability, and IHC staining showed discontinuous and defective positive expression of eNOs, resulting in reduced NO synthesis, increased ET-1 level, and increased endothelial permeability, and thrombosis was formed [7]. It has also been reported that  $H_2O_2$  can induce the loss of mitochondrial membrane potential and produce a large number of reactive oxygen species (ROS), leading to the imbalance between ROS and NO, which may be the main cause of endothelial cell dysfunction in cardiovascular diseases [8]. As  $H_2O_2$  is easy to obtain and toxic, endothelial cells are sensitive to it, so the utilization rate of this model is high. However, different types of endothelial cells have different sensitivity to it, and  $H_2O_2$  also has the disadvantage of poor stability. Attention should be paid to the determination of ROS and the detection of  $H_2O_2$  effect when applying.

## TNF-α

TNF- $\alpha$  is mainly produced by activated monocytes and macrophages and is often used to construct cellular inflammatory models, which can induce apoptosis signals by activating caspase signaling cascades [9]. It can also induce anti-apoptotic signals by stimulating nuclear factor - $\kappa$ B (NF- $\kappa$ B) [10]. Current studies have found that this cytokine can change cell morphology and regulate cell permeability, and vascular permeability increases with the increase of TNF- $\alpha$  concentration, and the recovery time is also positively correlated with the concentration, but when the concentration of TNF- $\alpha$  is high enough, vascular permeability increases and does not recover, promoting endothelial cell apoptosis [11]. TNF- $\alpha$  can induce the overproduction of ET-1 in endothelial cells, resulting in a serious imbalance between NO and ET-1 in endothelial cells, which leads to endothelial cell injury [12]. TNF- $\alpha$ induces inflammation in HUVECs mainly through up-regulation of ICAM-1, e-selectin, IL-1 $\beta$ , IL-18, VCAM-1, IL-6, NLRP3, caspase-1 and ASC, and down-regulation of IL-10, providing a direction for future studies on inflammation [13]. In conclusion, TNF- $\alpha$  plays a key role in the cardiovascular inflammatory cascade and is usually used to explore the repair effect of Traditional Chinese medicine on vascular endothelial cells.



### AngII

AngII is an effector peptide in the renin-angiotensin system [14]. It constricts blood vessels and plays an important role in the cardiovascular system. It is often used to model hypertension to simulate the damage caused by hypertension to endothelial cells. The main pathological changes of hypertension are vascular endothelial dysfunction, which leads to more serious cardiovascular diseases. Studies have shown that AngII induced HUVECs senescence and apoptosis are related to PI3K/Akt signaling pathway [15]. AngII can increase autophagy and gradually induce autophagy, senescence and apoptosis of HUVECs. In the early stage of AngII injury to vascular endothelial cells, mild autophagy has a protective effect; without intervention, excessive autophagy will lead to vascular injury [16, 17]. AngII damages vascular endothelial cells, which is related to lncRNA AK094457 gene. When HUVECs is stimulated by AngII, the level of this gene is up-regulated, and the levels of ET-1, ICAM-1, McP-1 and VCAM-1 are also up-regulated, and the cell viability is decreased. When lncRNA AK094457 is knocked out, the expression of the above proteins is inhibited, and the cell viability is partially restored, which can alleviate the damage caused by AngII [18]. AngII damages endothelial cells and is also associated with downregulation of lncRNA-ATB gene, which can inhibit cell viability and promote apoptosis. However, overexpression of this gene can repair endothelial cell injury [19]. Endothelial cells are sensitive to AngII, so they are often used to construct endothelial cell injury models.

## LPS

LPS, as an endotoxin, is a proinflammatory factor, which acts on TLR4 receptor on the surface of endothelial cell membrane to show its damage effect. LPS is thermally and chemically stable, so it is often used to construct endothelial cell injury models. LPS was found to induce apoptosis and autophagy through JNK signaling pathway [20]. LPS can also up-regulate miR-34a-5p and promote the activation of Nrf-2/HO-1 pathway by targeting *FOXM1*, leading to vascular injury, in which miR-34a-5p can also serve as a marker for the diagnosis and treatment of sepsis induced endothelial cell injury [21]. When the TLR4 signaling pathway is activated by LPS, extracellular calcium influx can be induced, indicating that endothelial cell damage is related to calcium overload [22]. It has also been shown that caspase-11 rather than TLR4 is required when LPS stimulates endothelial cells to cause scorchdeath, and caspase-11 activates NLRP3 inflammasome and causes IL-1 $\beta$  release, which provides a new target for treatment of acute lung injury [23]. LPS can also produce excessive ROS in endothelial cells, resulting in oxidative damage, which is found to be related to the REDD1/TXNIP axis [24]. LPS was also associated with NF- $\kappa$ B signaling pathway and increased NF- $\kappa$ B P65 nuclear translocation. TNF- $\alpha$ , IL-1 $\beta$ , MCP-1 and IL-8 of HUVECs were upregulated, and the level of ICAM-1 was also increased, which plays a crucial role in inflammatory response as an adhesion factor that enables neutrophils to adhere to damaged endothelial cells [25]. In conclusion, LPS can damage vascular endothelial cells in many ways, and its mechanism needs to be further studied.

#### Others

The injury of vascular endothelial cells is multi-layered and multi-faceted. In addition to the above common models of inducing endothelial cell injury, there is also mechanical injury caused by physical methods [26]. When the limb is in the ischemic state, blood recovery will cause ischemia-reperfusion injury to vascular endothelial cells [27]. With the development of cardiovascular diseases, more and more vascular endothelial cells have been found to be damaged. Vasoconstrictor ET1 [28], estradiol [29], anticancer drugs [30], vascular endothelial growth factor (VEGF) [31], gabate mesylate [32], etc., can be used as the condition of endothelial cell injury. Even some disease factors such as corona virus disease 2019 [33], pregnancy-induced hypertension [34], uremia [35], and metabolic syndrome [36] can cause damage to vascular endothelial cells. Homocysteine has also been used to construct endothelial cell injury models in recent years [37]. With the development of time, more and more injury modes and injury pathways have been discovered, which provides a new theoretical basis for the study of endothelial cell injury repair, and provides a new direction and hope for the treatment of cardiovascular diseases caused by endothelial cell injury.



## Vascular endothelial cell repair

The etiology of vascular injury is complex, repair of vascular endothelial cells has become an important basis for vascular repair and treatment of cardiovascular diseases. Endothelial cells can synthesize and release various factors, and the changes of these cytokines can be used to determine the cause and condition, so that endothelial cells can be repaired in time. At present, in addition to drugs like atorvastatin [38] and aspirin [39]. Endothelial progenitor cells (EPCs), VEGF, mesenchymal stem cells (MSCs) and hyperbaric oxygen therapy (HBOT) can also be used to repair endothelial cells on the market. But these have certain limitations. Also, a good lifestyle can keep blood vessels healthy.

# EPCs

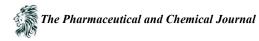
EPCs can be differentiated into vascular endothelial cells to replace and repair damaged cells, which exist not only in bone marrow but also in peripheral blood. Therefore, we subdivide them into resident EPCs and circulating EPCs. When blood vessels are damaged, platelets accumulate rapidly. Sdf-1 and VEGF secreted by platelets and activated endothelial cells up-regulate the expression of endothelial markers in EPCs. Moreover, the activation of EphB4 pathway in EPCs enhances the expression of PGSL-1, promotes the recruitment of circulating EPCs in vivo, and thus enhances its angiogenesis promoting ability [40]. In the case of endotoxic lung injury, vascular endothelial cell repair mainly relies on lung tissue resident EPCs rather than circulating EPCs [41]. Studies have shown that diabetes can lead to microvascular lesions and reduced NO utilization, leading to EPCs dysfunction [42]. In addition, wounds in diabetic patients are not easy to heal. By applying EPCs amplified in vitro to wounds in diabetic mice, it was found that wounds healed significantly, indicating that the therapeutic ability of EPCs can be used to repair wounds in diabetic patients [43]. EPCs provide a new hope for the treatment of cardiovascular diseases, and it has been proved to be beneficial for the treatment of diabetic foot ulcer [44]. However, our experience in the clinical application of EPCs such as in vitro amplification and transplantation is not rich enough, so we need to continue to explore.

# VEGF

VEGF is a cytokines that can make endothelial cells undergo mitosis and can induce angiogenesis and change vascular permeability [45]. VEGF family consists of VEGF-A, VEGF-B, VEGF-C, CEGF-D, VEGF-E and placental growth factor, among which VEGF-A is mainly involved in angiogenesis, which binds to VEGFR-2 and activates the PI3 kinase pathway and Akt/PKB phosphorylation to promote endothelial cell survival [46]. Studies have found that VEGF can differentiate cardiac stem cells into vascular endothelial cells by activating the PI3K/Akt signaling pathway, which provides a theoretical basis for the treatment of cardiac diseases [47]. VEGF plays a key role in brain injury recovery, increasing angiogenesis and improving neuronal injury and death [31]. The function of VEGF is not always positive, and in the case of acute pulmonary edema, the function of VEGF will become contradictory with the change of the disease, showing the duality of its role [48]. For patients with psoriasis, excessive VEGF in the skin can lead to vascular inflammation [49]. Now research suggests that the role of VEGF in main channel in addition to PI3K/AMPK/Akt/eNOS pathway and the VEGF/VEGFR2/Akt/eNOS/NO pathway, and found that calcium protease/PTP1B/VEGFR2 pathway can be used as a kind of negative feedback, control of VEGF physiological balance [50]. Tumor cells can also secrete VEGF to form new blood vessels and transport oxygen and other nutrients for cancer cells. Therefore, it is necessary to have a deeper understanding of the bioutilization response of VEGF, especially the control of its dose.

# MSCs

MSCs are a kind of pluripotent stem cells with multidirectional differentiation potential and immunosuppressive properties [51]. It is not only derived from bone marrow, but also can be extracted from umbilical cord and adipose tissue. It is an important cell that can repair tissue and fight inflammation [52]. Studies have shown that MSCs repair blood vessels mainly through paracrine mediated mechanisms [53]. Vascular injury is often studied with adipose-derived mesenchymal stem cells (ASCs), which promote endothelial regeneration and angiogenesis by producing



extracellular vesicles and growth factors. VEGF, growth transforming factor (TGF- $\beta$ ), hepatocyte growth factor  $\beta$ , fibroblast growth factor 2 and platelet-derived growth factor secreted by human ASCs are known to be important factors promoting angiogenesis [54]. TGF- $\beta$  supports the formation of vascular tubular structures. Studies have found that growth differentiation factor 11, as a member of TGF- $\beta$  superfamily, is widely present in various tissues and can enhance MSCs survival and angiogenesis in ischemic tissues, which can treat ischemic cardiovascular disease in diabetic patients [55]. Endothelial cell senescence can lead to vascular senescence, and exosomes secreted by MSCs can prevent endothelial cell senescence through miR-146a/Src pathway, and also prevent HUVECs senescence induced dysfunction, and increase the number of blood vessels in diabetic mice wounds [56]. Long-term culture of ASCs shows that the angiogenesis of aging ASCs is reduced [57]. The types and quantities of cytokines secreted by MSCs in different tissues and organisms are different, which should be verified in more detail before clinical application.

# нвот

HBOT allows patients to breathe pure oxygen or high concentration oxygen under high pressure, which has vasoconstriction, antibacterial and scavenging effects. It has been found that HBOT can increase the release of TGF $\beta$ 1 and TGF $\beta$ 2, and promote the proliferation of fibroblasts around the wound [58]. It also promotes VEGF/SDF-1 expression in fibroblasts and VEGFR/CXCR4 expression in HUVECs by activating HIF-1 $\alpha$  and NF- $\kappa$ B signaling, enhancing angiogenesis and improving wound healing in diabetic patients [59]. HBOT can also reduce inflammation at the wound site by changing the expression of neutrophils and endothelial cell adhesion molecules and reducing the aggregation of neutrophils [60]. HBOT can also improve the level of circulating EPCs, and Matrigel's analysis showed that angiogenesis was enhanced and blood flow in ischemic areas was improved after treatment [61]. Experiments have shown that HOBT can activate Nrf-2 oxidative stress pathway to protect cells and induce the growth of vascular endothelial cells [62]. HBOT directly and indirectly enables vascular endothelial cells to play a role in the treatment of vascular injury. Although HBOT is mostly used as an auxiliary means in the treatment of cardiovascular diseases, its clinical value has been affirmed.

## **Other Methods**

In terms of Traditional Chinese medicine, studies have shown that velvet antler can promote angiogenesis and repair vascular endothelial cells in rats with myocardial infarction [63]. Curcumin repaired aortic endothelial cells by upregulating eNOS activity [64]. Tetramethylpyrazine can inhibit apoptosis of vascular endothelial cells and promote angiogenesis [65]. In addition to pharmacological studies, unhealthy lifestyle habits such as smoking, obesity and excessive pressure in daily life can promote the damage of vascular endothelial cells, and a healthy lifestyle can prevent endothelial cell dysfunction [66]. In conclusion, the injury of vascular endothelial cells is reversible. There are many reasons for the injury of vascular endothelial cells, and there are different treatment methods for different injury modes.

# **Current situation and Prospect**

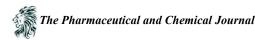
Vascular endothelial cells are a very important component of the body, and their homeostasis is crucial for cardiovascular disease. Endothelial cells in the body are prone to injury, and their repair depends on the balance of NO and ROS in blood vessels, as well as the regenerative ability of EPCs and other important cytokines to endothelial cells. This paper summarizes the physiological activity of vascular endothelial cells and the main methods of damage and repair. With the development of the times, more and more vascular endothelial cell injury principles and treatment pathways have been discovered, which has found new methods for the treatment of various vascular diseases such as hypertension, diabetes, coronary heart disease and so on. In particular, patients with diabetes tend to block distal limb blood vessels in the later stage, and suffer from diabetic feet. Studies can find that by making endothelial cells grow in the ischemic place, new blood vessels can be generated, improving blood flow, so that the feet of patients with diabetes will no longer ulcerate and reduce the probability of amputation. In



conclusion, restoring the injury of vascular endothelial cells can provide a new idea for the treatment of cardiovascular diseases, so we can predict that vascular endothelial cells have a broader development prospect.

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