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Application of vascular endothelial cells in stem cell medicine

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Abstract

Stem cell medicine is gaining momentum in the development of therapy for various end-stage diseases. The search for new seed cells and exploration of their application prospects are topics of interest in stem cell medicine. In recent years, vascular endothelial cells (VECs) have attracted wide attention from scholars. VECs, which form the inner lining of blood vessels, are critically involved in many physiological functions, including permeability, angiogenesis, blood pressure regulation, immunity, and pathological development, such as atherosclerosis and malignant tumors. VECs have significant therapeutic effects and broad application prospects in stem cell medicine for the treatment of various refractory diseases, including atherosclerosis, myocardial infarction, diabetic complications, hypertension, coronavirus disease 2019, and malignant tumors. On the one hand, VECs and their extracellular vesicles can be directly used for the treatment of these diseases. On the other hand, VECs can be used as therapeutic targets for some diseases. However, there are still some obstacles to the use of VECs in stem cell medicine. In this review, advances in the applications and challenges that come with the use of these cells are discussed.

Key Words: Vascular endothelial cells; Stem cell medicine; Angiogenesis; Atherosclerosis; Tissue defects; Refractory diseases

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Core Tip: Vascular endothelial cells (VECs) are involved in several physiological and pathological processes, including angiogenesis, control of blood pressure, and treatment-resistant diseases. Therefore, researchers have applied VECs in stem cell medicine and achieved beneficial results, demonstrating that these cells have a broad potential for application in many fields. This review discusses the functions, applic-

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INTRODUCTION

With the rapid development of medical science and technology[1,2], methods for the treatment of many diseases have been improved. However, there is still a lack of effective treatments for some refractory diseases, such as atherosclerosis[3], myocardial infarction (MI)[4], hypertension[5], malignant tumors[6], and diabetes[7]. Some of the current treatment methods are capable of exerting an effect, but most of them can only function to inhibit the disease without the ability to cure it. In recent years, with the understanding of stem cell biology deepening[8], researchers have found that stem cells, which are capable of self-renewal and differentiation, may provide new solutions for promoting recovery of body defects[9] and treating many intractable diseases[10,11]. The use of stem cells in the field of medicine has been an emerging topic in the past two decades. The main methods of stem cell medicine include using stem cells alone, coculturing stem cells with another type of cells, and the combination of stem cells with a variety of materials and cytokines. Therefore, the exploration of suitable seed cells attracts attention constantly in stem cell medicine. Vascular endothelial cells (VECs), a single layer of cells that lines the inner surface of blood vessels[12], have been widely studied in recent years. A large number of studies have shown the function of VECs in angiogenesis[13,14], the regulation of blood pressure, and the promotion of various pathological processes[15]. VECs have promising potential in stem cell medicine. VECs promote angiogenesis in tissue regeneration and transplantation, improve neural recovery, and act as therapeutic targets for a variety of diseases[16], including atherosclerosis, hypertension, diabetes, and malignant tumors. These recent studies have shown promise for the use of VECs in stem cell medicine. The research progress of VECs is remarkable and has attracted worldwide attention. Although there have been some reviews of VECs[15], the application of VECs in the field of stem cell medicine has been rarely reviewed. Therefore, a systematic description of the application scope and mode of VECs in stem cell medicine is urgently needed. This review aims to discuss the application of VECs in stem cell medicine and focuses on some existing problems, solutions, and aspects that need to be further studied.

SEPARATION, CULTURE AND IDENTIFICATION OF VECs

Sources of VECs

VECs come from a wide range of sources, including various organs from humans and animals. VECs derived from the human umbilical vein are most commonly used[17-21], because human umbilical vein endothelial cells (HUVECs) offer the advantages of sufficient sources, favorable cell activity, ability to obtain a large number of cells at one time, and importantly, availability without any major ethical controversy. In addition, the coronary artery and omentum are also donors for VECs. Shishkova *et al*[22] cocultured primary human coronary artery and internal thoracic artery endothelial cells and identified their mutually beneficial paracrine interactions. Wang *et al*[23] extracted mouse aortic endothelial cells, while Schwartz[24] cultured bovine aortic endothelial cells and Reckless *et al*[25] cultured rabbit aortic endothelial cells. Winiarski *et al*[26] explored strategies to extract microvascular endothelial cells from the omentum. These studies enriched sources of VECs.

To expand the source of VECs, scholars induced human pluripotent stem cells, including human embryonic stem cells and induced pluripotent stem cells, to differentiate into VECs[27]. Although it has been shown that VECs derived from pluripotent stem cells exhibit some characteristics of endothelial cells, the expression of some key

VEC genes is decreased in stem cell-derived VECs, and some epithelial genes are detected[28]. As a result, most researchers prefer tissue-derived VECs to pluripotent stem cell-derived VECs.

Separation of VECs

There are three classic methods for the isolation of VECs: (1) Mechanical scraping method[29]; (2) Tissue block adherent method[30]; and (3) Enzyme digestion method [31]. Because of its high efficiency, enzyme digestion is the most commonly used method. However, the cells obtained by enzyme digestion are of low purity and often contaminated by other cells. Therefore, many researchers have pursued purification methods of VECs. Abbot *et al*[32] first purified human synovial microvascular endothelial cells by magnetic bead sorting, which is still frequently used in recent years for its high purity. However, magnetic bead sorting could affect the activity of the cells. Density gradient centrifugation is another purification method that is based on the physical properties of endothelial cells[33]. It is an effective method for cell purification, but if the cells are mixed with other components of similar densities in the tissue, it is difficult to separate them. In addition, repeated centrifugation may impact the state of cells and increase the risk of cell damage. Fluorescence-activated cell sorting is another commonly used method[34] that is equipped with good reproducibility, high efficiency, and no effect on cell activity.

Culture of VECs

VECs are cultured adherently in most cases. However, there are still major differences between adherent culture methods and the *in vivo* microenvironment, and there is the disadvantage of low culture efficiency. Scholars have explored various methods for the culture of VECs in the pursuit of better culture conditions. Locatelli *et al*[35] cultured the HUVECs in microgravity and observed that the HUVECs made a series of adaptive changes in order to achieve a new equilibrium in this environment. Wang *et al*[27] applied VECs to three-dimensional (3D) culture in alginate saline gel and found that this method could provide a better environment for cells compared with 2D culture in terms of cell quantity and quality. Bartaula-Brevik *et al*[36] cultured HUVECs in a bioreactor system and found HUVECs in the bioreactor performed good abilities in angiogenesis. These studies provided the potential for some new culture methods to be applied in VECs culture.

Identification of VECs

Identification of VECs is not difficult and microscopic observation is the most common method. Although VECs from different sources differ microscopically, they all show a paving stone-like morphology. Mitotic, dikaryotic, and polykaryotic nuclei can be observed in the process of cultivation over time. To further identify VECs, scholars focused on exploring their specificity, including the expression of specific surface markers and biological factors. Flow cytometry and immunofluorescence are universal methods for identification and CD31 is the most commonly detected surface marker for VECs. Evaluation of certain biological factors is also helpful for identification of VECs, including VIII factor and von Willebrand factor[37].

ROLE AND MECHANISM OF VECs IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES

VECs function as a single layer of cells lining the inner surface of the cardiovascular system and play important roles in both physiological and pathological processes. First, VECs act as a barrier between blood and the surrounding tissues, which is especially important for penetration[38]. Second, VECs also serve as an endocrine organ in the body, capable of synthesizing and releasing various endothelial-derived vasoactive factors to regulate vascular tone and coagulation. Third, VECs have receptors that interact with various biological factors and are involved in the regulation of angiogenesis and immune responses[15]. Finally, VECs participate in some diseases[39], such as atherosclerosis and malignant tumors.

Barrier and regulation of permeability

VECs are closely arranged on the inner surface of blood vessels and not only provide a smooth surface for healthy blood circulation, but also serve as a selective barrier that is conducive to the exchange of nutrients, wastes, and various signaling molecules to

maintain the dynamic balance of tissues, organs, and the circulatory system throughout the body[40]. Therefore, VECs regulate the permeability of vessels. In different physiological and pathological states, a variety of factors interact with VECs and change the morphology of VECs and the intercellular spaces, leading to changes in the vascular endothelial permeability. In addition to inflammatory mediators such as histamine, bradykinin, thrombin, and platelet-activating factor, vascular endothelial growth factor (VEGF) is also involved in the regulation of endothelial permeability [41]. VEGF is an important signaling molecule synthesized and secreted by VECs and other cells, including smooth muscle cells, fibroblasts, and immune cells. VEGF can interact with VECs to regulate vascular permeability. VEGF binds to VEGF receptor 2 (VEGFR2), activates an intracellular tyrosine kinase activity, regulates downstream signals, and increases vascular penetration[40].

Blood pressure

The regulation of blood pressure is a complex process, and VECs function greatly in it. VECs regulate blood pressure *via* the synthesis and secretion of paracrine signaling molecules and act on smooth muscle cells, whose contraction and relaxation control vascular tension and thus regulate blood pressure[15]. Molecular regulatory networks are one of the research hotspots at home and abroad. Endothelin and NO have attracted wide attention due to their important roles in blood pressure regulation among various molecules.

Endothelin, which is produced by VECs, is an important factor for the promotion of vasoconstriction. Three isoforms of endothelin have been reported, among which, endothelin-1 is the most effective and long-lasting for vasoconstriction. When blood pressure needs to rise, VECs secrete endothelin for vasoconstriction. Endothelin couples with endothelin receptor A, which is located in vascular smooth muscle cells. Endothelin receptor A mainly induces smooth muscle contraction and constricts blood vessels, thus raising blood pressure[42].

Vasodilation is mainly regulated by NO that is synthesized by endothelial NO synthase in VECs. NO functions as a vasodilative factor partly in two ways. First, NO counteracts the contractile effect of acetylcholine on vascular smooth muscle[43]. Second, NO is able to stimulate increased concentration of cyclic guanosine monophosphate and relax vascular smooth muscle[44].

Together, all of these signaling molecules regulate the dynamic stability of blood pressure. They provide the possibility for VECs to be targeted in blood pressure regulation.

Angiogenesis

VECs have significant influence on angiogenesis. New vessels stem from the established vessels with VECs protruding into filopodia[13]. During new blood vessel formation, VECs differentiate into different phenotypes, including so-called tip cells and stalk cells. Tip cells explore signaling molecules and sense the environment, while stalk cells grow to ensure that new blood vessels continue to elongate. When new vessels meet, a vascular anastomosis occurs[45].

VECs have binding sites for a variety of cytokines and are regulated by these cytokines to promote angiogenesis. VEGF is a key proangiogenic factor. It binds to three receptors: VEGFR1, VEGFR2, and VEGFR3. The former two receptors have a great influence on angiogenesis, especially VEGFR2, which promotes the migration and proliferation of VECs by activating phospholipase C- α and phosphatidylinositol-3 kinase and binding to TYR951[46]. In the angiogenic environment, the formation and secretion of the powerful proangiogenic molecule VEGF are increased. VEGF can regulate the proliferation and migration of VECs. Pulkkinen *et al*[47] found that as a specific endothelial target of VEGF, bone morphogenetic proteins (BMPs) 2/4/6 have a significant impact on the regulation of angiogenesis. The Hippo signaling effector TAZ is the key for BMPs to control VEGF signaling *via* the regulation of VEGFR2 expression. In this way, TAZ can regulate VEC survival and proliferation. In addition, other signaling molecules such as heat shock protein A12b, store-operated calcium entry-associated regulatory factor, and orai1 have also been found to be involved in the regulation of VECs and contribute to the progression of angiogenesis.

Hypoxia is an important promoter of angiogenesis especially in a tumor microenvironment. Hypoxia can upregulate hypoxia-inducible factor-1, a factor that activates the transcription of proangiogenic factors including VEGF[48], fibroblast growth factors (FGFs), and placental growth factor (PLGF). PLGF binds to the tyrosinase receptor of VECs to regulate VECs, and FGFs regulate the migration of VECs, both of which can promote the angiogenic process of VECs[13]. It is reported that hypoxia also activates hypoxia-inducible-factor- α -independent proangiogenic pathways including

the mechanistic target of rapamycin and unfolded protein response[49]. Tumoral angiogenesis induces an unharmonious angiogenic profile.

Endothelial-mesenchymal transition

Endothelial-mesenchymal transition (EMT) describes a state in which VECs have lost the characteristic phenotype and functions of endothelial cells and gained the morphological and functional characteristics of mesenchymal stem cells[50]. This transition is important for the maturation of blood vessels and heart valves[51], which may be considered a part of angiogenesis. Many factors, including oxidative stress, fatty acid oxidation, hyperglycemia, and shear stress forces, can be initiators for EMT. However, sometimes EMT might lead to pathological changes and the onset of many diseases, such as MI, atherosclerosis, and hypertension. Therefore, it is important to understand the change and regulation mechanism of EMT of VECs. In the past decade or so, scholars have pursued in-depth exploration of the EMT mechanism and its influence on the body's condition. The transforming growth factor (TGF)- α signaling pathway has been generally regarded as the main regulatory factors for EMT[52]. The TGF- α signaling pathway promotes inhibition of the endothelial gene that encodes connectin and activation of Smad-independent pathways. Then cell adhesion is loosened and EMT occurs.

Activation of some other pathways such as the BMP signaling pathway, Notch signaling pathway, Wnt signaling pathway, and the inflammatory process can also regulate EMT[51].

Atherosclerosis development

As a chronic inflammatory vascular disease, atherosclerosis in the early stage is characterized by the deposition of lipids and complex polysaccharides in the vascular endothelium[46]. Dysfunction and inflammation of VECs have an impact on the early progression of atherosclerosis[53]. NO signaling and reactive oxygen species (ROS) signaling are responsible for regulating VEC activation. NO mainly inhibits the secretion of proinflammatory factors and the migration of immune cells to maintain VECs in a quiescent state. In contrast, ROS is critical to the regulation of inflammation, resulting in VEC activation. Under inflammatory conditions, the nuclear factor kappa-light-chain enhancer of activated B cells signaling pathway (NF- κ B) is induced by ROS. NF- κ B acts as a promoter for monocyte recruitment and alteration of permeability[54]. This process contributes to atherosclerosis. VEC dysfunction promotes the occurrence of atherosclerosis by damaging the integrity of VECs, changing the role of VECs in the control of blood pressure, blood flow, and coagulation, and promoting the deposition of lipids and thrombi on the surface of VECs. The molecular mechanism of VECs in the mediation of atherosclerosis has been explored. Huang *et al*[55] found that the scavenger receptor B-1 in VECs serves as a mediator to promote atherosclerosis by mediating and accumulating low-density lipoprotein. This study demonstrates the mediating role of VECs in atherosclerosis.

Atherosclerotic plaques are a feature of atherosclerosis and contain many mesenchymal cells. Some of these mesenchymal cells originate from EMT of VECs[56]. The accumulation of mesenchymal cells is crucial in atherosclerosis. Mesenchymal cells can secrete proinflammatory molecules and synthesize extracellular matrix proteins and metalloproteases to promote plaque formation. However, the specific role of VEC-derived mesenchymal cells in atherosclerotic plaques has not yet been elucidated.

Immunoregulation

VECs are not only an integral part of the cardiovascular system, but also act as an immune organ throughout the body that is involved in immunoregulation. VECs function in both innate and adaptive immune responses. When carrying out innate immune functions, VECs are involved in many immune functions that macrophages perform[57]. VECs possess danger-associated molecular patterns that recognize harmful endogenous and exogenous components. They are also equipped with some immune receptors, including Toll-like receptors, that induce a series of proinflammatory cellular responses. VECs exert their immune effects in several ways[58-62]. First, VECs act as a barrier against invasive damage and maintain a balance of hemostasis or coagulation. Second, VECs deliver and recruit migrated immune cells [63]. Finally, equipped with the function of primary paracrine secretion, VECs can secrete chemokines, interleukins, interferons, and growth factors. Although VECs are not classical immune cells, they have an important effect on the immune process *via* the mechanisms described above[64,65].

Endothelial glycocalyx is also of importance in the immunomodulatory function of VECs. The endothelial glycocalyx tends to be damaged by sepsis[66]. Endothelial permeability changes as the endothelial glycocalyx is destroyed. Without the protective layer, VECs are directly exposed to the blood and come into contact with various inflammatory cells and cytokines that promote VEC damage. Fluid extravasation and edema coincide with VEC dysfunction. Therefore, the integrity of endothelial glycocalyx is essential for the immune function and other physiological functions of VECs.

Tumor development

Angiogenesis is vital in tumor formation and development. Tumor blood vessels transport oxygen, nutrients, and signaling molecules, and assist in the removal of waste for tumor growth, invasion, and metastasis. The formation of tumor blood vessels mainly occurs through two methods: Sprouting angiogenesis and intussusceptive angiogenesis[45]. Sprouting angiogenesis[13] is the synergism of tip cells and stalk cells regulated by VEGF and Notch signaling, which leads to the formation and continuous elongation of blood vessel buds and promotes the formation of blood vessels. This is a common form of tumor angiogenesis. In intussusceptive angiogenesis, VECs first form an endodermal tube[67]. Then, a base-degraded collagen bundle is attached to the lateral side of the VEC tube and surrounds the lumen. Finally, myofibroblasts promote the maturation of the connective tissue of the blood vessel. The newly formed blood vessel then gives off branches.

It has been reported that VEGF receptors modulate the formation of blood vessels in tumors and are involved in the progression of tumor development. Krebs *et al*[68] investigated the relationship between VEGFR2 and prostate cancer. VEGFR2, as one of the main therapeutic targets of tyrosine kinase inhibitors (TKIs), was upregulated in high-risk prostate cancer. Although TKI-based regimens do not achieve promising result for unselected prostate cancer patients at first sight, they can be beneficial for different patient subgroups. This study uncovered the roles of VEGF receptors in angiogenesis and indicated that VEGF receptors can be taken into consideration in tumor treatment.

CLINICAL PROSPECTS

The role of VECs in blood pressure regulation, angiogenesis, inflammatory processes, tumor development, and atherosclerosis has provided new insights into many medical issues, including tissue engineering and refractory diseases. The application of VECs in these contexts has been widely studied.

Tissue engineering

Tissue engineering has been a topic of interest in recent years. It aims to solve problems involving tissue repair and reconstruction. However, there are still many obstacles for vascularization in traditional stem cell medicine, especially in large tissues, which often die due to insufficient blood supply[69]. Because of their excellent angiogenic ability, VECs have attractive prospects in stem cell medicine. This research direction is mainly focused on coculture with other cells and endothelial-cell-derived extracellular vesicles.

Coculture with stem cells is the most commonly used method for VECs in tissue engineering and researchers have made lasting advances in this realm. Niemistö *et al* were the first to coculture VECs and fibroblasts to promote angiogenesis *in vitro*[70]. Recently, Piard *et al*[71] cocultured HUVECs and human mesenchymal stem cells to promote vascularization and bone regeneration. The level of angiogenesis positively correlated with the total number of HUVECs. These two studies highlight the potential of VECs in angiogenesis. Coculturing VECs with other cells not only promotes vascular regeneration, but also exerts an important effect on tissue regeneration through the interactions caused by contact with other cells. Mutschall *et al*[72] cocultured HUVECs and adipose-derived stem cells for bone regeneration. They found that mineralized substrates and alkaline phosphatase activity were increased, as was the expression of angiogenic marker genes. This study demonstrates that VECs not only promote angiogenesis through coculture but also promote tissue regeneration *via* cell contact. It provides a new direction that VECs can be cocultured with other cells to function *via* cell contact, and more should be explored about this contact.

VECs have also been used to build disease models *in vitro*, which provide a foundation for the development of treatments for various diseases. Campisi *et al*[73] used human induced pluripotent stem cell-derived VECs, brain pericytes, and astrocytes to construct a microvascular network *in vitro* in order to simulate the complex microenvironment of the blood-brain barrier. The establishment of this model represents a new avenue for the study of complex physiological states, which is beneficial for the development of new drugs and therapeutic methods. More study can be conducted for distinct models.

Extensive study of extracellular vesicles has occurred in recent years, and VEC-derived extracellular vesicles have been an area of particular interest. Venkat *et al*[74] found that the use of VEC-derived extracellular vesicles in mice with cerebral ischemia could promote angiogenesis in the brain and increase the density of axons and myelin sheath and polarization of M2 macrophages. The use of VEC-derived extracellular vesicles can effectively avoid many immune problems compared with using VECs directly. This research opens up a new door for the application of VECs.

Refractory diseases

Cardiovascular diseases: VECs are found on the inner surface of cardiovascular vessels, and affect both physiological functions and pathological processes of the cardiovascular system. Therefore, VECs have the potential to serve as seed cells or therapeutic targets. VEC-derived exosomes may have additional potential in the treatment of many cardiovascular diseases, including MI, atherosclerosis, and hypertension.

MI is a serious cardiovascular disease, which is caused by continuous ischemia and hypoxia of the coronary artery. In those experiencing MI, it is difficult to restore the blood supply to the pathological myocardium. After continuous exploration for MI treatments, researchers have focused on regeneration of the coronary vessels. Some have applied tissue engineering methods to implant cells and scaffolds into damaged areas. VECs are considered to be suitable as seed cells because of their critical role in angiogenesis. Ye *et al*[75] used VECs for the treatment of MI in pigs. Their results showed that this strategy could effectively control the development of the disease and improve myocardial function. Rabbani *et al*[76] extracted autogenous VECs from sheep saphenous veins and then injected the cells into the area of MI. They found that autogenous VECs promoted angiogenesis and functional recovery in MI areas. These studies demonstrate the potential of VEC transplantation in the reconstruction of blood supply and functional recovery in MI. However, the transplantation of VECs still coincides with issues such as potentially low cell survival rate and strong immunogenicity of allogeneic VECs. Therefore, some researchers have turned their attention to exosomes derived from VECs. Ong *et al*[77] used VEC-derived exosomes as a vehicle to deliver miRNA-210 and miRNA-126 to cardiac progenitor cells. The results showed that the treatment increased the ejection fraction and improved heart function. This study demonstrates that VEC-derived exosomes can act as a delivery agent in the treatment of MI. This suggests that VEC-derived exosomes can also play a role of transmission in other diseases, which has great clinical value and needs to be confirmed by more studies.

Aside from cell and exosome transplantation, VECs could also be a potential target for the treatment of MI. Myocardial fibrosis is a consequence of heart attack and eventually leads to heart failure. EMT is essential for myocardial fibrosis. Therefore, the process of myocardial fibrosis can be controlled by the regulation of EMT. Chen *et al*[78] found that NUR77, an orphan nuclear receptor, inhibits EMT and thus regulates myocardial fibrosis. Yin *et al*[79] found that Tongxinluo, a common drug used to treat cardiovascular disease, enhanced the expression of endothelial markers in VECs and inhibited EMT. As a result, it inhibits myocardial fibrosis and facilitates the recovery of the blood supply. These studies have demonstrated that the control of EMT can reduce the occurrence of myocardial fibrosis and thus improve recovery of the myocardial blood supply. Researchers have attempted to identify the target molecules of VECs. Li *et al*[16] observed the changes in VECs in mouse models of MI and studied the effect of plasmalemma vesicle-associated protein on the proliferation of VECs *in vitro*. They demonstrated that plasmalemma vesicle-associated protein, a VEC-specific marker, directly regulates the proliferation of VECs. This protein may be an emerging potential therapeutic target. Although it is believed that VECs can be used as a target in the treatment of MI, the precise mechanism and methods of treatment require further exploration, and more work should be done in different animal models.

Apoptosis, dysfunction, and coagulation of VECs are all triggers for atherosclerosis, and represent the early manifestations of the disease. VECs have potential to function in the treatment of atherosclerosis. Studies have also shown that exosomes derived

from VECs can be effective in the development of atherosclerosis. Inflammatory hyperplasia of the arterial wall is a hallmark of atherosclerosis. Control of arterial wall hyperplasia is a promising direction for the treatment of atherosclerosis. Li *et al*[80] modulated the molecular expression of VEC-derived exosomes and used these exosomes for *in vivo* studies. The results showed that the formation of new intima was reduced and the phenotype of vascular smooth muscle cells was altered when VEC-derived exosomes mediated by CD137 signaling were injected. This study showed that VEC-derived exosomes are promising targets for the treatment of atherosclerosis.

Owing to the important role that VECs plays in the progression of atherosclerosis, the control of VECs *via* various mechanisms has been considered a promising direction for atherosclerosis treatment. Therefore, VECs can be used as a target for atherosclerosis therapy. It has been found that low shear stress can induce VEC apoptosis. Some researchers have developed enhanced external counterpulsation, which is a form of noninvasive treatment[81,82]. Enhanced external counterpulsation treats atherosclerosis by increasing the shear stress acting on VECs to inhibit VEC apoptosis. This method is able to reduce the causes of atherosclerosis and is effective for atherosclerosis control. This study demonstrated that enhanced external counterpulsation can be effective as a treatment for atherosclerosis. It also illustrates that more new methods for atherosclerosis treatment may be developed with VECs as the target.

Covered on the surface of VECs, extracellular glycocalyx lesions make contributions to VEC dysfunction and the early development of atherosclerosis. On the contrary, restoring the integrity of the extracellular glycocalyx is beneficial to reverse the dysfunction of VECs and facilitate early treatment of atherosclerosis. Mitra *et al*[83] published a detailed review on this possibility and the corresponding methods for targeting the extracellular glycocalyx in atherosclerosis treatment.

Hypertension is an important and harmful cardiovascular disease, and its development leads to organic changes in blood vessels. VECs are important managers of vascular tension and the occurrence of hypertension is closely related to VEC dysfunction. Although there are currently some treatment methods for hypertension, they hardly address the recovery of dysfunctional VECs. Some researchers have explored VECs as a target for the treatment of hypertension and found that targeted regulation of VECs can be a potential approach. Guo *et al*[84] found that endothelial sirtuin 6 (SIRT6), a highly conserved nicotinamide adenine dinucleotide-dependent histone deacetylase[85], can enhance the function of VECs, inhibit their aging and apoptosis, and facilitate vasodilation of NO. As a result, VEC target regulation *via* modulating SIRT6 has potential in the treatment of hypertension. BMP receptor (BMPR)-2, which is specifically expressed in VECs, regulates angiogenesis by controlling the expression of VECs. It has been reported that the absence of BMPR-2 in VECs can lead to pulmonary hypertension[86]. Therefore, modulation of BMPR-2 has also been considered as a method to treat pulmonary hypertension. Spiekerkoetter *et al* [87] treated pulmonary hypertension with FK506, a drug that alleviates pulmonary artery endothelial cells by inducing BMPR-2. They found that low-dose FK506 is capable of promoting recovery of dysfunctional VECs, which finally reverses pulmonary hypertension. These studies suggest that rescuing VEC dysfunction can be a potential therapeutic method for the treatment of pulmonary hypertension.

The EMT of VECs also contributes to the development of hypertension. Wang *et al* [12] found that promotion of EMT facilitated the development of pulmonary hypertension. Therefore, some researchers have considered treating hypertension by targeting EMT. Yu *et al*[88] downregulated EMT *via* application of paeoniflorin to alleviate pulmonary hypertension. Tsutsumi *et al*[89] also identified that pulmonary hypertension could be treated by inhibiting EMT with TKI nintedanib. Zhang *et al*[90] found that hydrogen solubility inhibited EMT in pulmonary artery hypertension. These studies all highlight the therapeutic potential of EMT in hypertension, although the specific drugs and the methods by which they are administered require further study.

Neurological diseases: In addition to their application in cardiovascular disease, VECs have also been used in the treatment of neurological disease. Zhou *et al*[91] discovered that in the process of nerve injury, brain microvessels function as phagocytes to engulf myelin debris. During this process, VECs are also involved in angiogenesis associated with demyelinating lesions. This study suggested that the role of VECs in demyelinating lesions may lead to new therapeutic approaches for neurological diseases *via* control of the phagocytic process.

Extracellular vesicles from VECs are also helpful in nervous system impairment. Yue *et al*[92] cocultured HUVECs with neurons and found that HUVEC-derived exosomes prevented neuronal injury. Venkat *et al*[74] found that exosomes derived

from brain VECs can promote neurological recovery in diabetic stroke mice. These studies demonstrated that VEC-derived extracellular vesicles may be used as a drug directly or as a carrier of other drugs. However, the method and effectiveness of the treatment need to be further studied.

Diabetes: Diabetes mellitus is a chronic metabolic disease that is difficult to cure and is accompanied by a variety of complications. Beta cell dysfunction in the pancreas is the main cause of insulin-dependent diabetes mellitus, and the main approach for treatment involves increasing the source of insulin. Pancreatic transplantation may be a promising treatment for the promotion of insulin production. Yue *et al* cocultured HUVECs and beta cells and constructed a bioartificial pancreas encapsulation device [92]. They found that coculture with HUVECs enhanced secretion of islet beta cells. Barba-Gutierrez *et al* [93] covered isolated islets with VECs and found that VECs could enhance the vascularization of pancreatic islets, promote insulin secretion, and improve the success rate of transplantation. Lazzari *et al* [20] cultured human skin fibroblasts and HUVECs in pancreatic acellular scaffolds and found that HUVECs significantly increased the vasculature of the scaffolds. These studies confirmed the role of VECs in promoting vascularization and enhancing islet function in pancreas and islet transplantation.

When exposed to high blood glucose concentration for an extended period of time, VECs may experience pathological changes, including the overexpression of ROS, which is an essential promoter of VEC dysfunction. VEC dysfunction further brings about vascular disease in multiple organs of the body and is the basis of various complications. Therefore, treatment of VEC dysfunction has become one of the methods to prevent and treat diabetic complications. Studies have found that metformin, the first-line antidiabetic agent, is a good regulator for the control of VEC dysfunction in diabetic patients, in addition to its main target for the control of blood glucose by respiratory chain complex 1. Ouslimani *et al* [94] found that metformin can reduce ROS and inhibit the occurrence of VEC dysfunction. Targosz-Korecka *et al* [95] found that metformin can promote recovery of endothelial glycocalyx dysfunction, which is conducive to the recovery of VEC dysfunction. In addition, other approaches to treat diabetic VEC dysfunction are being explored. Wang *et al* [96] found that 12(S)-hydroxyeicosatetraenoic acid [12(S)-HETE], an arachidonic acid metabolite, is able to damage VECs and alter VEC permeability by changing the phosphorylation levels of adherens junctions. Otto *et al* [97] conducted a study in a mouse model of diabetes to identify the function of 12(S)-HETE. They found that 12(S)-HETE is capable of activating intracellular cation channel transient receptor potential vanilloid 1. VEC dysfunction is promoted through the process above. Conversely, inhibition of VEC dysfunction prevents the progression of diabetes. These findings suggest that the regulation of 12(S)-HETE to rescue VEC dysfunction could be a new therapeutic approach for diabetes. These studies validate the importance and mechanisms of VECs in the development of diabetes and, more importantly, shed new light on the potential of targeting VECs for the treatment of diabetes. The mechanism of treatment and additional drugs and treatment methods need to be further investigated.

Malignant tumors: Malignant tumors are life-threatening and remain difficult to cure. Excessive angiogenesis is a characteristic of many malignant tumors. Therefore, many researchers have begun to explore whether VECs can be used for malignant tumor therapy. The therapeutic application of VECs in malignant tumors mainly occurs in two ways: (1) Serving as a target for clinical treatment; and (2) Participating in the construction of *in vitro* malignant tumor models. Early antiangiogenic drugs failed to identify malignant tumor VECs from normal VECs, leading to damage of healthy VECs during treatment. Recently, it was found that under the influence of the tumor microenvironment, tumor VECs are heterogeneous and express different phenotypes from normal VECs [98,99], which provides opportunities for successful VEC-targeted treatment of malignant tumors. However, anticancer mechanisms and new drugs targeting VECs should be developed more widely.

To explore clinical treatment methods, malignant tumor models have been comprehensively studied. Lazzari *et al* [20] cocultured pancreatic malignant tumor cells, fibroblasts, and HUVECs to construct a pancreatic malignant tumor model *in vitro* and this model is helpful in advance of preclinical drug trials. Swaminathan *et al* [100] established a model of breast cancer *in vitro* by coculturing mammary epithelial cells and VECs on alginate scaffolds. Furlan *et al* [101] established several different coculture models of VECs and cancer cells to study the related mechanisms of angiogenesis in breast cancer. These models can be used for the development of new anticancer drugs and treatments.

Inflammation: VECs also have potential in the treatment of inflammation, especially in coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[102], a virus that has had significant impact on the world since 2019. Pathogenic mechanisms and treatment methods of COVID-19 have attracted worldwide attention and extensive research on SARS-CoV-2 has been carried out. It has been widely reported that SARS-CoV-2 binds to angiotensin-converting enzyme 2 in VECs[103], affecting the balance between angiotensin-converting enzyme 2, angiotensin-converting enzyme 1, and angiotensin II, which leads to inflammation and damage of VECs and organs. Therefore, promotion of VEC recovery represents a new way to enhance therapeutic effects and improve the prognosis of COVID-19. In addition, the endothelial glycocalyx is also damaged by COVID-19[104]. Studies have found that there is an increase in endothelial glycocalyx fragments in patients with COVID-19. This finding not only indicates that endothelial glycocalyx fragments can be used to evaluate the extent of endothelial injury, but also reflects the extent of damage to the body by COVID-19. It demonstrates that the recovery of endothelial glycocalyx injury to reactivate the function of VECs may be another method to treat COVID-19.

In addition, thrombus formation is a serious complication in COVID-19 patients and VECs are also targeted by SARS-CoV-2. Khan *et al*[105] found that large thrombi in COVID-19 patients entered the heart and were life-threatening. Other studies have found that the occurrence of thromboembolism is related to the severity of disease progression and mortality[106,107]. Anticoagulation is also regulated by VECs to some extent. Therefore, anticoagulation and restoration of normal functions of VECs are crucial in the treatment of patients with COVID-19. However, much effort still needs to be made toward finding effective treatments.

Problems and solutions of VECs application

In the application of VECs, there are still some problems that should be addressed. First, cell sources and culture methods need to be carefully considered. Tissue-derived VECs are more reliable than human-induced VECs. For example, the aorta and the human umbilical vein are common sources[23,35,36]. Second, how to obtain a large number of VECs for medical applications and how to make VECs function in the most efficient way are still worth further exploration. HUVECs are the most frequent choice due to their excellent proliferation and amplification ability[72,92]. In terms of culture methods, emerging research in recent years has broken out of the limitation of 2D culture and developed new culture methods, including 3D culture and microgravity culture for VECs[35,71]. These new culture methods also improved the quality and amplification efficiency of VECs. Third, in the process of cultivating VECs, it is necessary to prevent not only the contamination of microorganisms, but also the contamination of other cells. Crouch *et al*[34] have described in detail the steps taken to isolate and purify VECs in adult mouse brain microregions *via* fluorescent-activated cell sorting with anti-CD31 antibodies. This recent study has provided a good method for the purification of VECs. The application of VECs will inevitably encounter immunogenic obstacles, and the application of autologous cells[76] and extracellular vesicles[74,80] is a good solution. However, this is usually limited in the clinic (Table 1).

CONCLUSION

VECs have been widely used in stem cell medicine because of their important roles in angiogenesis and tissue regeneration. However, the application of VECs is subject to many restrictions, including limited sources of VECs, invasive acquisition processes, and immune-rejection due to the immunogenicity of heterogenous and allogeneic VECs. Although induced pluripotent stem cells represent a new source of VECs, their phenotypes are different from those of tissue-derived VECs and there is some uncertainty about their application. If VEC transplantation is to be used in clinical treatment, there are still ethical concerns as well as a lack of relevant application norms at present. The application of VECs in stem cell medicine is mostly allotransplantation, and the problem of immunogenicity arising from it remains to be solved. Many studies have shown that VECs have potential to function as therapeutic targets for a variety of diseases such as atherosclerosis, MI, hypertension, malignant tumors, and COVID-19. However, many treatment methods and mechanisms are still in the verification stage and lack sufficient clinical evidence, especially the role of VEGFRs in development and treatment of malignant tumors.

Table 1 Summary of roles of vascular endothelial cells as checkpoint for immunological patrolling

Role of VECs	Molecule type	Suggested mechanisms	Ref
Express pattern recognition receptors	TLRs (TLR1-TLR10)	Contribute to early stages of the immune response against various microbial agents	Sturtzel <i>et al</i> [15]
	NLRs	Sense intracellular microbial invaders and danger molecules produced under stress	Fleissner <i>et al</i> [58]
	RLRs	Involved in antiviral immune response and contribute to chronic inflammatory disease	Asdonk <i>et al</i> [59]
	AIM2-like receptors	Form an inflammasome with the ligand and ASC to activate caspase-1	Hornung <i>et al</i> [60]
	C-type lectin receptors	Regulate signal cascades in response to distinct pathogen- or self-derived components	Kim <i>et al</i> [61]
Express proangiogenic molecules	FGFs	Anneal adherens junctions and promote VEC migration	Potente <i>et al</i> [13]
	NEU1	Restrains VEC migration	Cross <i>et al</i> [62]
	VEGF	Induces VEC phenotype changes and regulates proliferation and migration of VECs	Potente <i>et al</i> [13]
	IL-8	Induces VEC proliferation	Sturtzel <i>et al</i> [15]
Express adhesion molecules	P-selectin	Recruits leukocytes	Sturtzel <i>et al</i> [15]
	E-selectin	Attaches monocytes	Sturtzel <i>et al</i> [15]
	ICAM-1; VCAM-1	Function as VEC activation markers	Sturtzel <i>et al</i> [15]
Express MHC	MHC I	Leads to recruitment of antigen-specific; naïve CD8+ T cells	Mai <i>et al</i> [63]
	MHC II	Presents endothelial antigens to immune cells	Mai <i>et al</i> [63]
Express immune checkpoints	PD-L1/2	Inhibits T cell activation	Rodig <i>et al</i> [64]
	ENO-1	A major glycolytic enzyme, over-expressed in various cancer tissues	Zheng <i>et al</i> [65]
Express pro-inflammatory cytokines	IL-10, IL-6, and IL-8	Function as a complementary mechanism for the detrimental effects of viruses on atherosclerosis	Asdonk <i>et al</i> [59]

TLRs: Toll-like receptors; NLRs: Nucleotide-binding oligomerization-domain (NOD)-like receptors; RLRs: Retinoic acid inducible gene-I (RIG-I) like receptors; AIM2: Absent in melanoma 2; NEU1: Epidermal growth factor like domain 7; IL: Interleukin; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell-adhesion molecule; MHC: Major histocompatibility complex; PD-L1/2: Programmed death-ligand 1/2; ENO-1: Enolase 1; FGFs: Fibroblast growth factors; VEC: Vascular endothelial cell; VEGF: Vascular endothelial growth factor.

Despite the numerous challenges, the important role played by VECs and their exosomes in many physiological and pathological processes has prompted a new direction for the treatment of many diseases and represents a broad prospect in the development of stem cell medicine.

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