DOI: 10.53469/jcmp.2025.07(01).36

Research Progress on Mechanism of Action of Vascular Endothelial Cells in Autologous Arteriovenous Fistula Stenosis

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Abstract: ***At present, arteriovenous fistula is the preferred vascular access for hemodialysis patients. In clinical practice, arteriovenous fistula is often narrow, in which vascular endothelial cells play an important role. This paper introduces the mechanism of arteriovenous fistula stenosis, the function of endothelial cells, the common injury mechanism, and the relationship between endothelial cells and endometrial hyperplasia, and further discusses the role of vascular endothelial cells in the occurrence and development of arteriovenous fistula stenosis, in order to provide new ideas for improving the prognosis of arteriovenous fistula stenosis by intervening vascular endothelial cells.***

Keywords: Arteriovenous fistula, Vascular endothelial cells, Intimal hyperplasia, Endothelium-mesenchymal transformation, Shear force**.**

1. Introduction

In recent years, with the extension of human life expectancy and the high incidence of many chronic diseases, the number of patients with chronic kidney disease (CKD) and end-stage kidney disease continues to increase. Multiple evidences have shown that the high incidence and mortality of CKD and end-stage kidney disease have become a huge economic burden for families and countries [1, 2]. Maintenance hemodialysis (HD) is an important way to treat end-stage kidney disease, and effective vascular access is a key factor for the survival of hemodialysis patients, which is known as the lifeline to maintain hemodialysis [3]. Arteriovenous fistula has a higher long-term patency rate and a lower incidence of infection and complications, so arteriovenous fistula has become the first choice for vascular access. Mature AVF undergoes outward dilation of the vessel wall and inward remodeling, arterializing the veins and providing adequate blood flow for hemodialysis. However, according to statistics, the annual patency rate of AVF1 is 62.6% [4]. Studies have shown that intimal hyperplasia (IH) during vascular reconstruction is the main histopathological cause of AVF lumen stenosis or maturation failure [5, 6]. The vein wall has three layers: outer membrane, media membrane and inner membrane. The outer membrane layer is composed of extracellular matrix, fibrocytes and immune cells. The fluid in the outer membrane contains nourishing blood vessels surrounding the veins and providing arterial blood to the venous wall. The mesial layer is mainly composed of smooth muscle cells, and vascular endothelial cells (VEC) are the intima closest to blood [7], which play an important role in the development of intima hyperplasia in the process of vascular reconstruction [8]. This article mainly introduces the latest research progress of vascular endothelial cell proliferation and AVF stenosis, analyzes the relationship between the two, and provides a new idea for the prevention and treatment of AVF vascular stenosis in the future.

2. Physiological and Pathological Mechanism of AVF Stenosis

The pathophysiological mechanism of AVF stenosis is complex and the result of multiple factors. Studies have shown that intimal hyperplasia is the main cause of AVF stenosis [9, 10]. Intimal hyperplasia is a complex physiological and pathological process, involving a variety of cell signal changes and cell proliferation. Neointimal hyperplasia refers to the activation, abnormal proliferation and migration of myofibroblasts, fibroblasts and smooth muscle cells in the outer (or media) membrane to the intima region, and the combination with the extracellular matrix to thicken the vascular wall fibromyocytes [9, 11]. Intimal hyperplasia of AVF is mainly related to the following mechanisms: 1) The occurrence of upstream and downstream events. Upstream events are more important in the initial damage to the vascular wall, which mainly include vascular injury, surgical trauma, hemodynamic changes, and the use of bioincompatible grafts. Downstream events are usually caused by a series of reactions induced by upstream vascular injury, characterized by the interaction of pro-inflammatory mediators such as cytokines, chemokines, matrix metalloproteinases, and adhesion molecules [12], 2) Abnormal vascular remodeling: Upstream and downstream events can also cause the activation, proliferation and migration of vascular smooth muscle cells, resulting in abnormal vascular remodeling and thus intimal hyperplasia [9]. 3) Other factors include inflammation, uremia, hypoxia, shear stress and thrombosis [13].

3. Function and Function of Vascular Endothelial Cells

Vascular endothelial cells (VECs) are the innermost lining of arteries, veins, and capillaries that come into direct contact

with blood. Therefore, the most basic function of VEC is defense and barrier function. From the time it was first described in 1865 until the early 1970s, it was assumed that VEC was merely an inert barrier separating blood from surrounding tissues. In fact, ECs are polarized cells: their membranes are not uniform, they differentiate into different regions. The VEC lumen is directly exposed to blood components and circulating cells, while the basolateral surface is separated from the surrounding tissue by a glycoprotein basement membrane, which is secreted by the endothelial cells themselves and anchored to their cell membranes. The shape of the EC varies along the vascular tree, but is usually thinner and slightly longer. VEC lining the vascular lumen is a single flat epithelium, whose long axis is mostly consistent with the direction of blood flow, forming a smooth surface inside, which can greatly reduce the shear stress caused by blood flow and facilitate blood flow [14]. Second, VEC senses hemodynamic changes and blood signals, and responds by releasing vasoactive substances that regulate the contraction and relaxation of blood vessels to maintain the balance of the body's internal environment. In addition, VEC is involved in multiple stages of neovascularization, during which the mobilization of circulating endothelial progenitor cells is not required.

3.1 Heterogeneity of Vascular Endothelial Cells

Endothelial cells (EC) are heterogeneous within and between tissues. The expression of EC is different in different organs and different blood vessels, and important morphological, physiological and phenotypic differences enable endothelial cells to perform specific functions in different sites and between different blood vessels. First, within the same tissue/organ, vascular endothelial cells (VEC) can be divided into arterial, venous, and capillary endothelium. The arterial endothelial cell layer is thicker, with elastic membrane and smooth muscle cells, which can withstand high blood pressure and shear stress. The endothelial cell layer of the wall of the vein is thin, the lumen is large, and the elastic membrane is often absent. Arterial and venous endothelial cells expressed different molecular markers, Ephrin-B4, coup-TF-ii and Nrp2 were the major markers of intravenous endothelial cells. In addition, arterial endothelial cell markers mainly included ephrin-B2, Notch1, Hey1/2, Dll4, Nrp1, Alk1, Depp, etc. [15]. Compared with arterial and venous endothelial cells, capillary endothelial cells are more like a transitional state between arterio-venous zonation, with gradual changes in gene transcription characteristics from veins to arteries, which is very typical in heart and brain vessels [16-18]. From the beginning, arteries need to recruit cells from capillaries and veins to expand, and the cells migrate against the blood flow to join and expand the arterial network. VEGF and Notch signal promote arterial differentiation; Venous differentiation requires reduced VEGF activation and relies on expression of the transcription factor COUP-TFII (also known as NR2F2).

3.2 Sugar Calyx, an Important Substance on the Surface of Endothelial Cells

The apex or intracavity plasma membrane of the EC carries the glycocalyx (GCX), a complex macromolecular network structure [19] with a multilayered structure that selectively regulates the passage of small to very large molecules through the vascular wall. GCX has a variety of features. GCX acts as a barrier by carrying its own negative charge and complex network structure to block macromolecules [20, 21]. The GCX negative charge repels negatively charged cells, such as white blood cells, red blood cells, and platelets, away from GCX. Macromolecules larger than 70 kDa are blocked from the tight network structure of GCX. However, albumin (67 kDa), despite being negatively charged at neutral pH, is tightly bound to GCX [22] due to its amphoric characteristics. Through this binding, the hydraulic conductivity across the vascular barrier is reduced [23].

Glycocalyx acts as a mechanical transducer through its intracellular protein domain, enabling the EC to sense mechanical stress [20, 24]. Conformational changes in glycocalyx and the shedding of particles help to regulate vasomotor tension, thereby regulating oxygen distribution by triggering the release of nitric oxide [25]. Through this rheological mechanism, glycocalyx helps maintain homeostasis in peripheral tissues [26].

3.3 Shear Stress

The VEC is a key sensor of shear stress in the blood flow and is able to sense and respond to different types of shear stress, thereby expressing corresponding genes in different regions. Endothelial cells transmit shear force to multiple mechanical sensor sites through the cytoskeleton, including integrins, membrane glycosylated proteins, endothelial cell linkerins, mechanosensitive ion channels, G-protein-coupled receptors, and membrane phospholipids [27]. When the shear stress is increased, the expression of eNOS gene is up-regulated and the eNOS promoter transcriptional activation is activated rapidly, which can increase the release of NO.

3.4 Regulation of Vasoconstriction and Relaxation

Vecs secrete vasodilator factors such as nitric oxide (NO) and prostacycline (PGI2). NO and PGI2 can be released in large quantities when stimulated by substances such as angiotensin II, acetylcholine, histamine, and arachidonic acid [28]. VEC also produces endothelium-derived hyperpolarization factor (EDHF), which may be the main endothelium-dependent vasodilation pathway when endothelial NOS/NO is lacking [29]. In addition, VEC can also secrete endothelium-derived factors, thereby inducing vasoconstriction. In the vascular system, proendothelin is released from the basal surface of endothelial cells and converted into mature endothelin outside the cells by membrane-bound "endothelin converting enzyme (ECE)" [30].

3.5 Endothelial Cells and Thrombosis

EC secretes various signals and mediators to prevent blood clotting and platelet adhesion and aggregation under normal physiological conditions. Prostacycline (PGI2) and nitric oxide (NO) secreted by EC act as major antiplatelet mediators [31]. The two mediators synergistically increase cAMP content in platelets, thereby preventing them from aggreging [32], thereby inhibiting thrombus formation. EC also hydrolyzes effective platelet aggregators ATP and ADP to AMP and adenosine on the surface of its lumen by extracellular nucleotidase [33], thereby reducing platelet

aggregation [34]. In addition, endothelial cells maintain blood flow by promoting the activity of various anticoagulant pathways [35].

3.6 Endothelial Cells and Neovascularization

In general, the EC is at rest. When tissue is hypoxic or damaged, endothelial cells can germinate through highly coordinated blood vessels and rapidly form new blood vessels [34]. This process is maintained by local EC and does not require the involvement of circulating endothelial progenitor cells [36, 37]. Angiogenesis is a complex process that includes vascular dilation, basement membrane degradation, endothelial cell migration and chemotaxis, increased vascular permeability, and ultimately EC proliferation and angiogenesis. During angiogenesis, the capillary plexus is remodeled into a mature and functional vascular bed through germination, microvascular growth, and fusion [38, 39]. The process of angiogenesis depends on endothelial cells, pericytes [40], inflammatory cells [41], and other neighboring cells associated with the extracellular matrix (ECM) and vascular basement membrane (BM). In contrast to embryonic development, adult angiogenesis is a process closely associated with many physiological and pathological processes, such as pathophysiological conditions (such as inflammatory diseases [42], cancer [43]) or wound healing [44, 45].

4. Mechanism of Action of Vascular Endothelial Cells in AVF Stenosis

First of all, as a powerful receptor effector cell, VEC can release various active substances to maintain the dynamic balance of blood vessels after receiving various physical and chemical stimuli. Uremia itself, anastomosis of internal fistula, hemodynamic changes after internal fistula and repeated puncture cause sustained damage to EC, inducing the increase in the production of various active substances such as chemokines, adhesion factors and cytokines, and then triggering inflammatory response, leading to leukocyte adhesion, platelet activation, proliferation of vascular smooth muscle cells and extracellular matrix deposition [46].

A large number of studies have shown that physiological or pathological mechanical stress affects vascular biological changes mainly through EC. Unlike unidirectional blood flow in physiological conditions, oscillatory blood flow can be formed in the local vascular wall of AVF, and its mechanical stress can activate the EC autocrine proliferation pathway. It leads to upregulation of mitogen-activated protein kinase, nuclear factor-κB (NF-κB) nuclear translocation, downregulation of Kuppel like factor-2 expression, increase of pro-proliferative factors such as IL-8 and MCP-1, decrease of nitric oxide synthase expression, and increase of ET-l and angiotensin II, which impair vascular tone regulation and affect EC permeability. Interferes with cytoskeletal rearrangement, affects the stability of intercellular adhesion connections, and damages the structure and function of EC [47].

VEC can acquire myofibroblast-like properties through a special form of epithelial-mesenchymal transformation (EMT) called endothelial-mesenchymal transformation (EndoMT). During EndMT, the expression of VEC markers such as VE-Cadherin and CD31 decreased, while the expression of mesenchymal markers such as αSMA, N-Cadherin and Calponin appeared [48, 49]. EndMT follows cell-to-cell contact and loss of cell polarity into fusiform, differentiation into migration and invasion phenotypes, and enhances ECM production [50, 51]. In some cases, EndoMT causes VEC-derived mesenchymal cells to stratify and migrate to underlying tissues. EndoMT was first described as a process of angiogenesis and mesenchymal heart pad formation (a precursor to heart valves) during embryonic development. In adulthood, EndoMT is associated with heart, kidney, and dermis fibrosis, blood vessel (re) stenosis, pulmonary hypertension, and cancer. Recently, the contribution of EndoMT to the development of atherosclerosis and intimal hyperplasia of AVF has been demonstrated [52-56].

Zhang et al. [57] demonstrated that BRD4, as a member of the special BET family, controls the EndoMT process by coordinating TGF-β1-induced VEC transcription program, including the production of EndoMT markers such as α-SMA and ZEB1 transcription factors. In vitro, BRD4 (as opposed to BRD2 or BRD3) silencing dominates and sufficiently blocks EndoMT, and this BRD4 effect is dependent on BD2, not BD1. In vivo, BRD4 knockdown or significant negative expression of BD2(BRD4) inhibits neointima formation, which is a key step in the failure of venous transplantation involving EndoMT.

J Pathol et al. [56] confirmed that EndoMT occurs in endometrial hyperplasia and early lesion formation and is partly controlled by micrornA-374B. They found that TGF-β-induced micrornA-374b silences MAPK7 signaling and induces EndoMT in the absence of exogenous TGF-β. In addition, in Mir-374b-expressing VECs, restoration of MAPK7 signaling eliminated pathological effects. Mir-374b levels are elevated in human coronary artery disease and inversely correlated with MAPK7 expression. These data suggest that the TGF-β-Mir-374b-MAPK7 axis plays a detrimental role in EndoMT induction during intimal hyperplasia and early lesion formation.

5. Summary and Outlook

This paper mainly introduces the mechanism of AVF narrowing, the function and effect of VEC, and the relationship between them. In conclusion, AVF stenosis is closely related to endometrial hyperplasia after VEC injury, although the specific mechanism is not fully understood. To gain a deeper understanding of the pathogenesis of AVF stenosis, we must leverage innovations in genetics, cell biology, and imaging, and combine basic and clinical thinking with biological and human models to lay a solid foundation for clinical treatment.

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