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Review

Endothelial to mesenchymal transition in atherosclerotic vascular remodeling

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ABSTRACT

Endothelial cells are the main components of the heart, blood vessels, and lymphatic vessels, which play an important role in regulating the physiological functions of the cardiovascular system. Endothelial dysfunction is involved in a variety of acute and chronic cardiovascular diseases. As a special type of epithelial-mesenchymal transition (EMT), endothelium to mesenchymal transition (EndMT) regulates the transformation of endothelial cells into mesenchymal cells accompanied by changes in the expression of various transcription factors and cytokines, which is closely related to vascular endothelial injury, vascular remodeling, myocardial fibrosis and valvar disease. Endothelial cells undergoing EndMT lose their endothelial characteristics and undergo a transition toward a more mesenchymal-like phenotype. However, the molecular mechanism of EndMT remains unclear. EndMT, as a type of endothelial dysfunction, can cause vascular remodeling which is a major determinant of atherosclerotic luminal area. Therefore, exploring the important signaling pathways in the process of EndMT may provide novel therapeutic strategies for treating atherosclerotic diseases.

1. Introduction

Atherosclerosis, a chronic complex multifactorial disease, is a major cause of death worldwide. The earliest changes that eventually result in the formation of atherosclerotic lesions occur in the endothelium. Endothelial barrier is integral to regulating the extravasation of cells and cytokines from the blood and to maintaining vascular homeostasis. A significant number of studies [1,2] have highlighted the contribution of endothelial cell dysfunction in human diseases. Loss of endothelial barrier integrity, disordered endothelial proliferation, and enhanced inflammatory cell infiltration are common features of the pathogenesis of vascular diseases [3]. Studies suggest exposure of endothelial cells to chronic stresses and inflammatory factors can promote endothelial cells to undergo a process termed EndMT [4,5]. A number of studies support the capacity of endothelial cells to contribute to vascular smooth muscle cells (SMCs) and cardiac fibroblast populations through the process of EndMT. EndMT is a process that is characterized by the loss of features of endothelial cells and acquisition of specific markers of mesenchymal cells, which plays a key role in regulating endothelial function and development and structural remodeling of myocardium, blood vessels and valves, suggesting that it has important research significance in the field of cardiovascular diseases [6]. Vascular remodeling, a major determinant of atherosclerotic luminal area, is a bottleneck to improve the prognosis of ischemic diseases, which includes vascular wall cells and extracellular matrix structure and morphological changes [7]. EndMT, as a type of endothelial dysfunction, can cause vascular remodeling. Importantly, EndMT may be reversible [8,9]. Thus insights into the mechanisms controlling EndMT are relevant to vascular remodeling and are important to develop the new therapies aimed at reversing vascular remodeling to reduce atherosclerosis. This article reviews the characteristics, functions, and roles of EndMT in atherosclerotic vascular remodeling.

2. Physiology and pathology related to EndMT

The vascular endothelium is a monolayer squamous epithelium lining the luminal surface of the blood vessels and has a strong physiological function. Endothelial dysfunction is involved in the occurrence and development of cardiovascular diseases [10]. One of the consequences of the loss of normality of the endothelium is the

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occurrence of a process called EndMT. EndMT [11], a newly recognized type of cellular transition, is closely related to a better understood process termed epithelial to mesenchymal transition (EMT) which has been demonstrated to participate in biological and pathological process. It is associated with downregulation or loss of typical endothelial cells markers such as vascular endothelial-cadherin (VE-cadherin) and cluster of differentiation 31 (CD31) and acquire mesenchymal markers including alpha smooth muscle actin (α-SMA), fibroblast specific protein 1 (FSP-1), and fibronectin, which manifest migratory, invasive, and proliferative phenotypes, alteration in cytoskeletal composition and organization to induce a striking change in cell morphology that forms elongated, spindle-shaped cells [12,13]. Previous studies showed that EndMT is a critical process of embryonic cardiac development. EndMT was known to be contributing to physiological activities of cardiogenesis, the endocardial cells undergo mesenchymal transition to form the cardiac valves and septa. In addition to regulating cardiac development, EndMT plays a key role in embryonic vascular development. Hall et al. [14] demonstrated that endothelial cells can transform into smooth muscle cells (SMCs) during the formation of human pulmonary artery intima. During coronary artery formation, epicardial EMT may be an important factor in the formation of coronary vascular smooth muscle cells and surrounding cardiomyocytes [15,16]. Emerging evidence in recent years shows that EndMT may participate in a number of diseases, including pulmonary hypertension, atherosclerosis (AS), cardiac fibrosis, neointima formation, tumors and so forth. However, little is known about the signaling mechanisms that cause endothelial cells to transform into mesenchymal cells. Transforming Growth Factor-Beta (TGF-β), Notch, Wnt, microRNAs or other signaling pathways and cytokines could direct or indirectly mediate EndMT [17]. TGF-β superfamily, which include isoforms TGF-β1 and TGF-β2 as well as Bone Morphogenetic Proteins (BMPs) BMP2, BMP4, BMP6, BMP9, and BMP10 [18], regulates EndMT marker gene expression. In endothelial cells, TGFβ ligand binds to TGFβR2 which then recruits and phosphorylates TGFβR1. The activated TGFβR1 phosphorylate Smad2/3 [18]. Subsequently, Smads are translocated to the nucleus, where they regulate EndMT gene expression. Other signaling pathways such as Wnt/β-catenin [19], Notch [20], and various receptor tyrosine kinases have also been shown to activate EndMT. All of these pathways induce expression of transcription factors such as Snail, Slug, Twist, LEF-1, ZEB1, and ZEB2 that cause the repression of endothelial genes and/or expression of mesenchymal genes [21]. Targeting these pathways have the potential for the treatment of EndMT-related diseases.

3. AS and vascular remodeling

Arteries consist of three morphologically distinct layers: intima; media; and adventitia [22]. The intima is bounded on the lumen by a continuous layer of endothelial cells that form a protective barrier between the blood and the artery wall. The media consists entirely of smooth muscle cells, surrounded by connective tissues, including collagen and glycosaminoglycan, as well as elastic fibers. The adventitia contains both smooth muscle cells and fibroblasts together with relatively large amounts of collagen, glycosaminoglycan, and elastic fibers. The changes associated with the lesions of atherosclerosis occur principally within the intima. Atherosclerosis [23] is the formation of lipid deposition, smooth muscle cell proliferation, foam cell formation, fibrous tissue and mucopolysaccharide and other matrix formation in the arterial intima, according to the progress of the disease it can be divided into fatty streaks, fibrous plaques, atheromatous plaques and plaques complex lesion [24].

Arteries have long been considered a “steel” pipeline. The size of the plaque determines the degree of stenosis of the lumen after atherosclerosis. In 1987, Glagov et al. [25] proposed the concept of remodeling for the first time. They found that in the early stage of atherosclerosis, with plaque enlargement, compensatory expansion of angiogenesis. Subsequent studies found that the area of the lumen of the vessel is not related to the size of the atheroma, but is mainly determined by the cross-sectional area of the vessel [26]. In recent years, with the extensive development of percutaneous transluminal coronary angioplasty (PTCA), there is increasing evidence suggesting that the degree of stenosis displayed by coronary angiography has no obvious correlation with the clinical symptoms and the occurrence of acute coronary events. In contrast, coronary artery events are closely related to plaque vulnerability. At the same time, intravascular ultrasound (IVUS) found that blood vessels with normal coronary angiograms had hidden atherosclerotic plaques. The reason for these phenomena is vascular remodeling.

Vascular remodeling is a major determinant of atherosclerotic luminal area, which includes vascular wall cells and extracellular matrix structure and morphological changes. Atherosclerotic vascular remodeling can occur in the intima, media and adventitia of blood vessels [27–29]. The process of vascular remodeling may involve hemodynamic, endothelial function and inflammation, which relate to growth, apoptosis, shift of cells as well as break down, build up and rearrange of extracellular matrix [30]. Vascular remodeling can be divided into two types: compensatory remodeling and decompensated remodeling [31]. Coronary atherosclerosis has compensatory expansion in the early stage. This positive remodeling [32] is an important compensatory mechanism to maintain coronary blood flow and prevent lumen stenosis; The negative remodeling of atherosclerosis is the main mechanism of coronary artery stenosis and restenosis after coronary intervention. Vascular remodeling is considered to be an important issue in atherosclerotic disease [33]. An in-depth understanding of this issue will enable us to understand coronary heart disease and other atherosclerotic diseases from a new perspective and propose new ideas for the prevention and treatment of these diseases.

4. EndMT and vascular remodeling

A large number of studies have implicated EndMT in the of vascular diseases including cerebral cavernous malformations [34], pulmonary hypertension [35], vascular graft remodeling [36] and atherosclerosis [37]. For example, Pulmonary vascular remodeling [38,39] is the main pathological feature of pulmonary hypertension, and its influence can spread to the entire layer of the blood vessel wall. EndMT causes abnormal proliferation of smooth muscle-like cells and expression of large amounts of extracellular matrix proteins, resulting in thickening of the middle layer of blood vessels, which in turn causes blood vessel remodeling (Fig. 1). Vascular remodeling is an adaptive change of blood vessels to blood flow and circumferential stress. In the early stage of atherosclerosis, enlarged atheromatous plaques increase the shear stress on the vessel wall, stimulating endothelium to secrete the vasodilator nitric oxide (NO) [40], which promotes the secretion of metalloproteinases (MMPs) and inhibits vascular smooth muscle cells (VSMC) proliferate and promote apoptosis. This response is endothelium dependent and NO plays the key role in the process. Certain vascular shear stress [41,42] is necessary to maintain the stability of intravascular environment, allowing vascular endothelium to be at rest. Low level shear acts on arterioles, blood vessel bends, and bifurcations, can cause damage to vascular endothelial cells and are involved in cell proliferation, migration, and death, causing negative vascular remodeling and inducing atherosclerosis eventually. One of the causes of negative remodeling after PTCA or atherosclerotic plaque exfoliation is a decrease in perfusion. Britten et al. [43] applied IVUS to patients with coronary heart disease and found that there is positive remodeling of blood vessels in the early stage of atherosclerosis. This positive remodeling is positively correlated with the size of plaque, maintaining a certain coronary basal blood flow. Increasing shear force can promote positive remodeling of coronary arteries; and risk factors such as hypertension and hyperlipidemia can reverse positive remodeling and even lead to negative remodeling, and are associated with coronary heart disease symptoms [31,44].

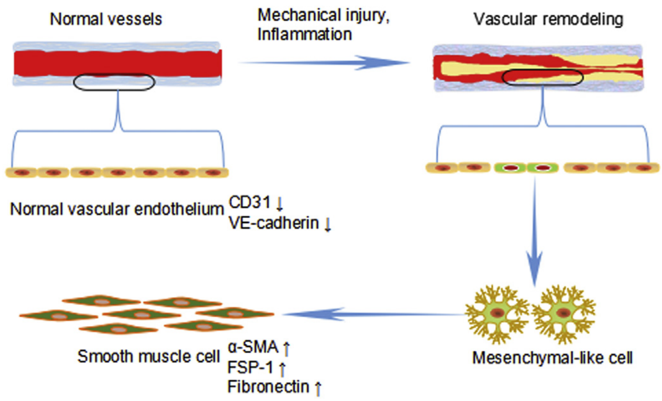

Fig. 1. The Relationship between EndMT and Vascular Remodeling.
Fig. 1-EndMT, associated with downregulation or loss of typical endothelial cells markers such as vascular endothelial-cadherin (VE-cadherin) and cluster of differentiation 31 (CD31) and acquired mesenchymal markers including alpha smooth muscle actin (α-SMA), fibroblast specific protein 1 (FSP-1), and fibronectin, which manifests migratory, invasive, and proliferative phenotypes, alteration in cytoskeletal composition and organization to induce a striking change in cell morphology that forms elongated, spindle-shaped cells,and eventually cause atherosclerotic vascular remodeling

Normal vascular endothelium is critical in the process of vascular remodeling. Lerman et al. [45,46] found that coronary vascular endothelial dysfunction and vascular remodeling occurred simultaneously in the early stage of coronary artery disease in patients with coronary heart disease. Tronc et al. [47] confirmed that NO plays a key role in the increase of blood vessel diameter-mediated by increased blood flow. If the endothelium is unable to effectively sense hemodynamic changes and produce NO, it causes negative vascular remodeling. Simultaneously, endothelial dysfunction was also involved in the process of vascular remodeling. Daniel et al. [48] found that the release of NO from the remodeled vascular endothelium was significantly decreased after ligation of the common carotid artery in mice. Endothelium-dependent relaxation energy after balloon injury is impaired and leads to abnormal vascular remodeling. To some extent, the functional state of vascular endothelium can determine the nature of vascular remodeling, that is, severe endothelial dysfunction predicts the development of vascular remodeling in a negative direction. EndMT as a type of endothelial disorder is closely related to vascular remodeling. Endothelium-protected drugs can inhibit restenosis after atherosclerosis or vascular injury. Lau et al. [49] invaded the rabbit aorta by balloon and intervened with the anti-oxidation and lipid-lowering drug probucol which was found to inhibit intimal thickening and vascular stenosis after balloon injury, and also promote positive vascular remodeling. Its mechanism of action is mainly through the improvement of vascular endothelial function, but has little effect on blood lipids. Therefore, it can be seen that EndMT is closely related to vascular remodeling. However, the mechanism between EndMT and vascular remodeling are still unclear. It has been reported that TGFβ1 is an important factor in promoting the formation of vascular remodeling, and it mainly regulates cell proliferation and differentiation by activating smad-dependent or smad-dependent pathways [36]. TGF-β1 is the most important extracellular matrix regulator. TGF-β1 up-regulates the expression of type I collagen by acting on the proximal promoter of the *COL1A2* gene, affecting the remodeling process of damaged blood vessels. At the same time, we know that TGF-β pathway mediates EndMT is an important mechanism leading to graft vein remodeling [50]. Vascular remodeling usually occurs after traumatic surgery such as angioplasty and vascular grafting, including intimal hyperplasia and adventitial remodeling [51]. Cooley et al. [36] reported that transplantation of mouse veins into the femoral artery to simulate human coronary artery bypass grafting (CABG) surgery. It was found that TGFβ/Smad/Slug-mediated EndMT which plays a key role in venous vascular remodeling. In the process of mini-pig model pulmonary vein ligation and stent implantation, the researchers found that EndMT progression was evident in the early stages of endothelial injury of pulmonary veins, which is represented by the activation of TGF /Smad signaling pathway [52]. In addition to acute vascular injury such as angioplasty and vascular transplantation, EndMT induced by chronic vascular injury also plays a key role in intimal proliferative vascular remodeling. [12]. In the process, various factors to endothelial injury, such as inflammation, low oxygen and mechanical shearing force, to raise TGF beta, FGF, such as cytokines, promote MMPs and serine protease expression, thus reducing the cell - cell or cell - connection matrix, and promote vascular endothelial EndMT, participate in atherosclerotic vascular calcification narrow and after stent [52,53], pulmonary hypertension [12] and other vascular restenosis arteriovenous fistula [54] reconstruction process.

5. TGF-β and angiogenesis

Angiogenesis is a remodeling process that occurs during normal physiological conditions, embryonic development, wound healing, reproductive cycles, and inflammation. A variety of factors that promote angiogenesis, such as VEGF [55,56], have been identified that stimulate the proliferation and migration of vascular endothelial cells to form new blood vessels. TGF-β is recognized as one of the key factors promoting EndMT and can induce the expression of VEGF[56] in endothelial cells and promotes angiogenesis and vascular remodeling. Krishnan et al. [57] also have demonstrated that TGF-β can increase VEGF/PlGF secretion via the ALK-5 pathway and create a pro-angiogenic milieu for the tumor or induce EndMT by decreasing endothelial properties and increasing the mesenchymal signatures for the tumor to become potentially more invasive. Although VEGF can promote angiogenesis, other factors are required to participate. It has been shown in the literature that TGF-β also induces the expression of platelet-derived growth factor (PDGF) and exerts the same proangiogenic effect as VEGF [58]. It has been revealed a role for Lysyl oxidase-like 2 (LOXL2) in the regulation of angiogenesis by modulation of EndMT in endothelial cells [59]. LOXL2 knockdown reduces expression of EndMT markers and inhibits TGF-β-induced EndMT. Thus, in future research, we will further explore the relationship between EndMT and atherosclerosis vascular remodeling.

6. Conclusions and future perspectives

EndMT is a process associated with downregulation or loss of typical endothelial cells markers such as vascular endothelial-cadherin (VE-cadherin) and cluster of differentiation 31 (CD31) and acquire mesenchymal markers including alpha smooth muscle actin (α-SMA), fibroblast specific protein 1 (FSP-1), and fibronectin, which manifest migratory, invasive, and proliferative phenotypes, alteration in cytoskeletal composition and organization to induce a striking change in cell morphology that forms elongated, spindle-shaped cells [12,13]. The vascular endothelium is active in the physiological and pathological state of the cardiovascular system, and its role in the process of vascular remodeling cannot be underestimated. EndMT, as a kind of endothelial dysfunction, participates in and affects the complex pathophysiological process of vascular remodeling. Therefore, EndMT has a good prospect as an intervention point for vascular remodeling. However, due to the lack of understanding of EndMT and vascular remodeling, the relationship between the two may be far more complicated than currently understood, and further research is needed. Current research on vascular remodeling and EndMT still has limitations. For example, although IVUS can observe plaque and vessel wall, atherosclerosis is a diffuse vascular lesion, and both positive and negative remodeling can occur simultaneously in a single vessel. The normal referenced blood vessels selected are often diseased blood vessels. Therefore, the measured positive remodeling and negative remodeling are often inaccurate. If a vessel with dilatant remodeling is actually used as a reference, then normal blood vessels are measured as contractile remodeling. At the same time, most studies of vascular remodeling are using animal models. However, animal models of vascular remodeling after atherosclerosis are different from human models: animal atherosclerosis models are all rapidly formed in a short period of time, and the situation of vascular remodeling is different from that of human beings; the rupture of atherosclerotic vulnerable plaque may be unique to humans, and there is no ideal animal model of vulnerable plaque at present; most animal experiments at present use peripheral blood vessels to study atherosclerotic artery remodeling, which may be different from coronary artery remodeling. There are some difficulties and limitations in the study of atherosclerotic vascular remodeling in humans, and now there is a lack of ideal animal models for this aspect of research. Therefore, we still need to continue to explore the relation between the remodeling of blood vessels and EndMT, thereby to inhibit atherosclerosis.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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