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REVIEW

A promising field: regulating imbalance of EndMT in cardiovascular diseases

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ABSTRACT

Endothelial–mesenchymal transition (EndMT) is widely involved in the occurrence and development of cardiovascular diseases. Although there is no direct evidence, it is very promising as an effective target for the treatment of these diseases. Endothelial cells need to respond to the complex cardiovascular environment through EndMT, but sustained stimuli will cause the imbalance of EndMT. Blocking the signal transduction promoting EndMT is an effective method to control the imbalance of EndMT. In particular, we also discussed the potential role of endothelial cell apoptosis and autophagy in regulating the imbalance of EndMT. In addition, promoting mesenchymal-endothelial transformation (MEndT) is also a method to control the imbalance of EndMT. However, targeting EndMT to treat cardiovascular disease still faces many challenges. By reviewing the research progress of EndMT, we have put forward some insights and translated them into challenges and opportunities for new treatment strategies for cardiovascular diseases.

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1. Endothelial–mesenchymal transition in the cardiovascular diseases

Endothelial–mesenchymal transition (EndMT), a subtype of epithelial–mesenchymal transition (EMT), is that endothelial cells (ECs) lose endothelial characteristics and acquire characteristics of mesenchymal cells. Cardiovascular System always accompanies EndMT: EndMT plays a key role in heart development; EndMT is a reversible and homeostasis process, which can be disrupted by post-developmental EndMT resulting in deterioration of vascular function and plaque formation observed in atherosclerosis [1,2]. EndMT is required for normal heart valve development, and EndMT occurs in endocardial cells activated by the transforming growth factor-β (TGF-β) and other ligands, triggering their migration to the endocardial cushion and forming the heart valve stroma [3]. Endothelial fatty acid oxidation (FAO), a key regulator of EndMT, works through changes in intracellular acetyl-CoA levels, Xiong J et al. Found, and deletion of endothelial carnitine palmitoyl transferase II (Cpt2E-KO) disruping FAO increases the size of the embryo's EndMT, leading to thickening of the heart valve [4]. Studies have shown that endothelial cells transform to mesenchymal cells under hypoxic conditions, invade cardiac tissue to promote myocardial fibrosis, and release TGFβ-1 to induce myocardial cell apoptosis, leading to the development of heart failure in vivo [5]. Though many studies show percentage of mesenchymal cells (derived from endothelial cells) rate is relatively low it is the mesenchymal cells (derived from endothelial cells) disturb the barrier function of the endothelium thus enable enhanced crosstalk of the endothelium and cardiomyocytes. These indicate that EndMT contributes to the accumulation of cardiac fibroblasts and loss of cardiomyocytes, which promotes myocardial fibrosis. In addition, endothelial-derived mesenchymal cells also promote diabetic myocardial fibrosis [6], and chronic pulmonary hypertension [7].

EndMT is widely involved in the occurrence and development of atherosclerosis. In addition to the aforementioned we mentioned that EndMT is involved in the formation of atherosclerotic plaques. The earliest stage of atherosclerotic lesions occurs in endothelial cells [8]. Previous studies have shown that oscillatory-

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shear (OSS) [9] and low-shear [10] stress-induced EndMT is a potential pathogenesis of early atherosclerosis, and the anti-inflammatory and anticoagulant effects of uniform laminar flow shear stress (LSS) on endothelial cells are anti-atherosclerotic [11]. Moonen JR's group demonstrated that EndMT is involved in fibroproliferative vascular disease, and it promotes neointimal hyperplasia and atherosclerotic differentiation of endothelial cells. Importantly, they found that EndMT was regulated by shear stress in an ERK5-dependent manner, and showed that this is a new atherosclerotic protection mechanism for uniform layer shear stress, which explains to some extent focal vascular disease [12]. What is important is the development of atherosclerosis, such as the formation of plaques, which will cause changes in local blood flow to form low shear stress and oscillating shear stress to promote EndMT and accelerate the process of atherosclerosis to form a vicious circle [13]. A rise in Reactive Oxygen Species (ROS) beyond a "normal" or "physiological" threshold level results in a process called "oxidative stress", which can also promote EndMT [14]. In addition to oxidative stress EndMT mediated endothelial fibrosis are closely connected to the inflammatory conditions, and the key regulator of inflammation NF-κB has been reported to promote the development of EndMT, causing endothelial cells to differentiate into fibroblasts and impair function [15]. There is also evidence supporting osteogenic cells derived from the vascular endothelium contributing vascular calcification [16]. The enhanced BMP signaling results in EndMT was an essential step [16]. Moreover sex determining region Y-box 2 mediates activation of specific serine proteases which is essential for initiating EndMT [17]. Furthermore fibrodysplasia ossificans progressiva (FOP) is also a vascular disease based on EndMT induces a stem cell-like phenotype [18]. Proteomics analysis of non-dilated ascending aorta by Maleki S et al. found that EndMT activity was increased in patients with bicuspid aortic valve (BAV), and speculated that the induction of EndMT/EMT in BAV ascending aorta may be related to the aorta's constant exposure to non-physiological hemodynamics and/Or embryo developmental defects [19]. EndMT leads to instability of endothelial cell connections and enhanced vascular permeability of the ascending aorta, which may lay the foundation for increased susceptibility to aneurysms [20]. Inhibiting EndMT only reduces the possibility of aneurysm, and cannot reverse the deterioration of the aortic valve wall.

There is also evidence supporting EndMT is involved in angiogenesis [21] which is a complex, multi-step process including a series of continuous events that begin with the proliferation and survival of ECs, then they migrate and finally differentiate into capillary-like networks. One of the characteristics of advanced proliferative diabetic retinopathy is the formation of abnormal new blood vessels on the surface of the retina [22]. Based on previous research reports that high glucose can induce endothelial cells to undergo EndMT, Feng L et al. further investigated the role of RKIP, a Raf kinase inhibitor protein (RKIP), in the glucose-induced EndMT in capillary endothelial cells in Diabetic retinopathy (DR), and the result showed that it negatively regulates EndMT [23]. The beneficial angiogenesis benefits from the regulation of EndMT dynamic balance. However, in most cases, EndMT cannot be well regulated and breaks the vascular homeostasis, leading to malignant results such as vascular remodeling. Therefore, whether angiogenesis can be beneficially developed has yet to be further studied. Maintaining the balance of EndMT may be a good choice. In aggregate, the imbalance of EndMT is closely related to myocardial fibrosis of the cardiovascular system, atherosclerosis, vascular calcification, aneurysms and angiogenesis.

2. Recent advances in regulating imbalance of EndMT

2.1 Block signaling pathways of promoting EndMT

The most direct strategy to inhibit endothelial mesenchymal transformation is to interfere with the signaling pathway that activates EndMT. The TGF-β superfamily are the most prominent participants in EndMT, and the pleiotropic effect of TGF-β on endothelial cells has been reported in detail [24]. TGFβ signaling through Smad-dependent and independent pathways direct

regulates EndMT [24]. In TGF-β/Smad1 signal transduction, TGF-β1 binds to transforming growth factor-βRII, recruits and phosphorylates TGF-βRI, and activates Smad2/3/4 consisting of phosphorylated Smad2/3 and Smad4/3 and Smad4 complex [25]. And then the complexs are shifted into the nucleus to induce RELM-β transcription [25]. SB432542, a SMAD inhibitor, could reduce the protein levels of Resistin-like molecule-β (RELM-β), p-SMAD2, p-SMAD3, and SMAD4 which could ameliorate TGF-β1-induced EndMT in HUVECs and HPAECs [25]. It has been reported that TGF-β silenced sirtuin 1 (SIRT1) expression via promoter hypermethylation and histone modification [26]. However, as a class III histone deacetylase, its activation inhibits TGF-β-induced EndMT in HUVEC cell lines with Smad4 deacetylation [27]. Another study showed that upregulation of SIRT1 deacetylase activity attenuated TGF-β-induced the expression of extracelluar matrix proteins through inhibiting Smad3 in murine mesangial cell line cells [7]. In addition, the activation of SIRT1 also suppressed that of TGF-βR1 expression and inhibited the nuclear translocation of Smad2/3 in TGF-β1-treated H5V cells [28]. In TGF-β signaling through Smad-independent pathway, SIRT1 reportedly inhibited Akt signaling pathways in cardiac fibrosis [29]. However, Sirt1 may promote TGF-β/Smad-dependent transcription in fibroblasts, due to Sirt1 negatively regulates the expression of Smad7, an endogenous inhibitor of canonical Smad signaling in fibroblasts [27,30]. The progress of EndMT through TGF-β/Smad and Akt/mTOR/p70S6K signaling pathways plays an important role in renal allograft recipients with renal interstitial fibrosis and chronic allograft dysfunction [31], according to Wang Z et al., and in their further research they found that hepatocyte growth factor (HGF) inhibits TGF-β1-induced EndMT of HUVEC and HRGECs by reducing the levels of phosphorylated Akt, mTOR, p70S6K, Smad2, and Smad3 [32].

Aside from TGF-β, the canonical Wnt signaling has also been reported to regulate EndMT. The natural regulation of the Wnt pathway occurs mainly at the level of inhibitors secreted extracellularly. In the study by Blyszczuk P et al. TGF-β-dependent myofibroblast differentiation is mediated by secreted WNTs, myocardial fibrosis depends on the bioavailability of extracellular WNTs, and TAK1-dependent Wnt protein secretion represents TGF-β-mediated human and mouse Myocarditis is a new downstream key mechanism of myocardial fibrosis and remodeling, and their data also suggest that inhibition of Wnt signaling can improve cardiac function [33]. Dickkopf-1 (DKK-1) a powerful antagonist of wnt/β-catenin signaling, which can mediate endothelial cell activation via inhibiting the Wnt /β-catenin pathway. DKK-1 stimulation increased the expression of EndMT markers such as N-cadherin, Twist, and vimentin, while reducing the expression of endothelial cell marker VE-cadherin and promoted EndMT. Interestingly, it enhances angiogenesis in HUVEC cells by upregulating VEGFR2 mRNA expression independent of Wnt signaling pathway [34]. In addition, the standardized Wnt signal is an important component of aortic valve and vascular calcification. Cheng SL et al. found that MSX2 and WNT7 family members stabilized the bovine AoEC phenotype, while Dkk1 promoted EndMT in cultured bovine aortic endothelial cells (AoECs). The animal experiments demonstrate that Cdh5-Cre; Wnt7b(fl/fl); LDLR$^{-/-}$ mice exhibited more significant aortic fibrosis, collagen accumulation, and calcium deposition after challenge with atherogenic high-fat diets [35]. Dickkopf-3 in abnormal endothelial cell secretions is a possible ligand of the Wnt/bcatenin pathway, which not only antagonizes the role of the known Wnt pathway inhibitor Dkk1 in the process of fibroblasts to myofibroblasts, but also induces EndMT [36].

There are also reports that the Notch signaling pathway is involved in the EndMT process. In one study, one of the possible mechanisms by which Relaxin inhibits cardiac fibrosis is the inhibition of EndMT in fibrotic hearts, and the Notch pathway may mediate this process [37]. According to Lin QQ et al., activation of Notch signaling pathway can induce the progression of EndMT and promote the development of atherosclerotic lesions [38]. In the study by Zhang J et al., they found that miR-29a/b negatively regulate Notch2 expression and inhibit high glucose-induced EndMT in human retinal microvascular endothelial cells, which can be reversed by overexpression of

Notch2 [39]. Numb has been shown to be a negative regulator of EndMT, which negatively regulates Notch signaling pathway in EndMT of Diabetic nephropathy (DN) [40]. In addition, Scutellarin prevents isoprenaline-induced myocardial fibrosis via inhibition of cardiac EndMT potentially, which is also associated with the Notch pathway [41].

In addition to the above signaling factors, EndMT induced by TGF-β can be inhibited by fibroblast growth factor (FGF) by modulating let-7 miRNA [42]. Vascular endothelial growth factor (VEGF) inhibits EndMT through VEGF-R2, but through VEGF-R1 promotes EndMT by reducing the bioavailability of VEGF [43,44]. From the current research, FGF and VEGF play an anti-EndMT role also by blocking TGF-β signaling pathway. These signal pathways crisscross and regulate the process of EndMT, which are effective targets for controlling EndMT imbalance. What is important is that the signal regulation network of EndMT and the apoptosis signal regulation network have an intersection. With reference to the relationship between EMT and apoptosis, we will discuss the feasibility of apoptosis in controlling EndMT imbalance. What's more, we will also discuss the flexible application of autophagy strategies to inhibit EndMT.

2.2 Reasonable application of apoptosis

Apoptotic cells produce more substances which regulates EndMT, thus inhibit endothelial apoptosis helps controling EndMT. EMT is a mechanism that deceives cell death [45], which is well interpreted in survival and metastasis of cancer cells. Similarly, EndMT becomes a buffer zone for endothelial cells to escape apoptosis. These indicate that there is a deep correlation between the regulation of EndMT and the regulation of apoptosis. Nicotinamide, the precursor of nicotinamide adenine dinucleotide (NAD), effectively inhibited TGF-β-1-induced corneal EndMT and decreased the levels of EndMT regulators snail and slug [46]. Furthermore NAD^+ precursors can effectively prevent the apoptosis of the corneal endothelium through reactivating AKT signaling [47]. Vaccarin protects HUVECs from ox-LDL-induced EndMT and apoptosis by inhibiting ROS/p38MAPK signaling pathway [48]. Naringin and vaccarin have similar endothelial protective effects, which is naringin modulated ox-LDL-induced apoptosis, EndMT, and inflammation in vitro, via the YAP pathway [49]. Although researchers have regarded EndMT and apoptosis as important factors of endothelial damage, few people have studied the potential link between apoptosis and EndMT. It has been reported that vascular endothelial cell apoptosis is involved in various stages of atherosclerosis [50]. It may be the continuous influence of these apoptotic factors that the dynamic balance of EndMT is broken and endothelial cells undergo EndMT to obtain an invasion ability, migrate into the middle layer of blood vessels and transdifferentiate into smooth muscle cells in the process of atherosclerosis [51]. Compared with EndMT, the damage of endothelial cell apoptosis to blood vessels is greater, more rapid, and the consequences are more serious. In addition, the factors that induce EndMT are also partially the same as those that induce endothelial cell apoptosis, such as oxidative stress and low shear stress [52]. TGF-β is thought to activate apoptosis [53]. ECs apoptosis induced the production of TGF-β1 in both apoptotic and neighboring viable cells, Exacerbating EndMT imbalance, but it can be relieved by Blocking Smad3, PI3k/Akt, and MAPK/ERK signaling pathway [54]. It shows that although endothelial cell apoptosis contributes to more endothelial cells undergoing EndMT, after breaking the downstream signal of TGF-β EndMT imbalance is relieved. Based on their research, it can be concluded that the ultimate goal of the stimulus is to cause the death of endothelial cells, EndMT delays this death process, and then the stimulus is removed, and there is no threat of death, EndMT is no longer activated.

When myocardial infarction occurs milk fat globule-epidermal growth factor 8-mediated myofibroblasts engulfment of apoptotic cells, myofibroblasts acquires antiinflammatory properties [55]. Therefore, myofibroblasts controls the infarct area effectively, but myocardial fibrosis is relieved by promoting the apoptosis of myofibroblasts. CCN5 reverses cardiac fibrosis established in HF mouse models via inhibiting the trans differentiation of EndMT and fibroblasts into myofibroblasts, and in particular by increasing the

apoptosis of myofibroblasts [56]. Although the molecular mechanism is not fully understood, CCN5 exerts these effects at least in part by inhibiting the TGF-β signaling pathway [56]. So reasonable application of apoptosis is also a Strategy to cope with EndMT.

2.3 Autophagy targeted therapy strategy

Targeted autophagy therapy, whether it is targeted at autophagy defects or enhanced autophagy, is very promising in regulating EndMT. With the continuous development of research on autophagy in cardiovascular disease, researchers combine autophagy-targeted therapeutic strategy with regulating EndMT [57], although the precise role of Autophagy in EndMT has not been fully elucidated yet. The mechanism weakening EndMT by enhanced autophagy has been explored preliminarily. Myofibroblast-like cells (MFLCs) promote human pulmonary microvascular endothelial cells to undergo EndMT by inhibiting autophagy, moreover rapamycin reversed the phenotypic alterations and the gene expression changes in ECs co-cultured with MFLCs [58]. Hypoxia triggered EndMT and autophagic flux increased in human cardiac microvascular endothelial cells (HCMECs) [59]. In addition, improving the level of autophagy partially inhibited EndMT while blocking autophagy promoted EndMT [59]. Autophagy attenuated EndMT induced by hypoxia via p62-dependent degradation of intracellular Snail (the key transcription factor in the downstream of TGF-β signaling pathway to trigger EndMT [60]) and Twist (a key transcription factor that maintains the invasive mesenchymal phenotype [59,61,62]. MiR-204 suppressed autophagy by targeting 3′UTR of ATG7 mRNA, down-regulation of miR-204 enhanced autophagy, thereby impacting p62-dependent degradation of Snail and Twist [62]. When rat pulmonary artery intima and human pulmonary artery endothelial cells were hypoxic, miR-204 was down-regulated and its further down-regulation by using miR-204 inhibitor suppressed hypoxia-induced EndMT [62]. The lack of autophagy exacerbates EndMT. Marchi S's data point to the key role of autophagy defects which is highly correlated with EndMT in the pathogenesis of cerebral cavernous deformity [63,64]. According to reports, deletion of the essential autophagy gene ATG7 in endothelial cells leads to impaired autophagic energy flux of endothelial cells, and endothelial cells acquire a phenotype consistent with EndMT [65]. Hammoutene A et al. found Hepatic endothelial cell autophagy defects lead to endothelial cell inflammation, EndMT, and endothelial cell apoptosis [66]. It is interesting that autophagy defect-induced EndMT is dependent on IL6 in human microvascular endothelial cells and Il6-neutralizing antibody rescued metabolic defects and organ fibrosis in HFD-fed Atg5 Endo [67].

However, some studies have shown that autophagy promotes EndMT. Liu C et al. suggested that hypoxia challenge activated the level of autophagic flux and resulting in obviously upregulated the expressions of collagen I and connective tissue growth factor (CTGF) at the protein level in systemic sclerosis fibroblasts, as well as the expressions of vimentin and α-SMA in HUVECs, while the expressions of VE-cadherin and CD31 were decreased compared with the normoxic treatment [68]. What's more, blockade of autophagic flux inhibited collagen synthesis and EndMT [69]. Autophagy mediated by monocyte chemotactic protein-induced protein 1(MCPIP1) promoted the SiO_2-induced loss of an endothelial phenotype by human umbilical vein endothelial cells [70]. Autophagy induction of early endothelial progenitor cells can increase or decrease mesenchymal properties of renal endothelial cells [71]. These illustrate the nature of the double-edged sword of autophagy to some extent. Actually controversies exist regarding the role of autophagy on EndMT [72]. Autophagy is indeed involved in the regulation of EndMT homeostasis. When responding to environmental pressure, Autophagy and EndMT should work together to combat external stimuli. If autophagy can fully cope with it, EndMT becomes a burden and is inhibited, such as the degradation of related transcription factors mentioned above. But when autophagy cannot control the deterioration of the situation, EndMT cannot avoid the occurrence of which includes the secretion of several pro-inflammatory cytokines related to autophagy [72] (especially the cytokines involved in promoting EndMT). When autophagy for EndMT regulation turns counterproductive,

targeted autophagy inhibition is also an indispensable study.

Macroscopically speaking, autophagy is involved in regulating the balance of EndMT. When endothelial cells are induced to undergo phenotypic transformation, autophagy is activated to combat EndMT. However, the continuous activation of autophagy will become an independent stimulating factor for endothelial cells, which will have to initiate EndMT to combat the adverse consequences of autophagy such as apoptosis.

Figure. Endothelial cell autophagy and apoptosis have a deep relationship with EndMT. Endothelial cells can consume apoptosis "signals" through EndMT to avoid the worse effects caused by apoptosis. However, the intersection of EndMT and apoptosis is worth digging. From the intersection of autophagy and apoptosis, the dual effects of autophagy on EndMT can also be mapped. Autophagy can degrade the key transcription factors Snail and Twist that induce EndMT to inhibit EndMT. However, the complex relationship between autophagy and the secretion of pro-inflammatory cytokines, as well as some of the unknown complex regulatory networks of autophagy promote EndMT. Endothelial cell autophagy maintains EndMT homeostasis.

2.4 Promote mesenchymal–endothelial transition

Promoting mesenchymal-endothelial transformation (MEndT) is a strategy that inhibits EndMT that has not attracted attention or is easily overlooked. The plasticity of endothelial cells changes their phenotype from endothelial cells to mesenchymal cells, and vice versa, which are considered to be EndMT and MEndT [73]. EndMT is a dynamic process, including endogenous expression of endothelial cells related proteins that maintain endothelial cell phenotype and acquired expression of mesenchymal cell-related proteins. In general, researchers ignore the self-sustaining ability of endothelial cells, that is, the glow of promoting MEndT is masked by inhibiting EndMT. The process of EndMT has not been divided into stages, and some researchers have proposed the concept of "Partial EndMT"[74]. Corresponding to this is "Full EndMT", which is the main reason for the dynamic imbalance of EndMT, because fully transformed endothelial cells are difficult to return to endothelial cells. EndMT is an instinctive activity of endothelial cells in response to stimulation. When the dynamic balance is broken, endothelial cells will become fibroblasts after undergoing EndMT and participate in the related progress of fibrotic diseases. MEndT refers to the transformation of stromal cells into endothelial cells, which is very similar to the reversal process of EndMT. This should arouse people's attention. The most significant part of promoting MEndT should be to protect endothelial cells from the occurrence of "Full EndMT". Certainly, if the fibroblasts transformed from endothelial cells can regain the endothelial phenotype and then restore the endothelial cell function, it is of great significance for fibrotic diseases.

At present, the research on MEndT has not introduced the inhibition of EndMT, but the connectivity between the two is worth exploring in depth. Cardiac fibroblasts are considered sentinel cells in the myocardium and actively respond to environmental stressors, including differentiation into a myofibroblast phenotype in response to ischemic and mechanical injury. Also, cardiac fibroblasts can undergo differentiation into endothelial-like cells. Studies have shown that cardiac fibroblasts undergo MEndT into neo-endothelial cells in damaged hearts, and have shown can be enhanced to promote heart repair, and the transcription factor p53 regulates such a switch in cardiac fibroblast fate [75]. It is interesting that the MEndT plays an important role in increasing the number of coronary endothelial cells after myocardial infarction, but genetic lineage tracking shows that myocardial fibroblasts have expanded significantly after injury, but have no effect on new coronary vessels, indicating no contribution of MEndT to the formation of neovascularization, indicating that the mesenchymal-endothelial cells did not contribute any to the neovascularization [76]. This seems to be contradictory, but the focus of our attention is not whether fibroblasts can be transformed into endothelial cells, but the protective effect of MEndT. The complete conversion of fibroblasts into endothelial cells does not play a decisive role in the repair of damage after myocardial

infarction. It is still too early to increase the number of endothelial cells derived from fibroblasts. To some extent, MEndT can replace EndMT in response to environmental pressure and form a barrier to protect endothelial cells.

Perhaps the researchers' expectations of MEndT are too high and the research is not deep enough. We all hope to make the "Full EndMT" completely reversed or the fibroblast "Full MEndT", but this is difficult, and the goal can be to save the EndMT imbalance. Studies have suggested the hope of Full MEndT, which can reprogram adult fibroblasts into functional cardiomyocytes by combining rich lineage transcription factors [77]. In addition, studies have reported that adult fibroblasts can be reprogrammed into functional cardiomyocytes by combining rich lineage transcription factors. Studies have suggested the hope of Full MEndT, which can reprogram adult fibroblasts into functional cardiomyocytes by combining rich lineage transcription factors. In fact, some studies have paid attention to the existence of the MEndT process in the dynamic balance of EndMT. In one study, hydrocortisone (HC) supplementation to the basal medium significantly enhances the barrier properties of human brain microvascular endothelial cells (HBMEC/ciβ), and these effects of HC on HBMEC/ciβ could be summarized as facilitating endothelial differentiation characteristics while concurrently retarding mesenchymal characteristics [78]. Generally speaking, MEndT is considered to be an important process in tumorigenesis and embryonic development and in one study it is proposed for juvenile angiofibromas [79]. In recent studies, Lin F et al. found that miR-133 promotes fibroblast angiogenesis and MEndT, thereby reducing myocardial fibrosis [80], and the research by the Batlle R et al. shows that the kinase p38α via downregulating TGF-β and JNK signals inhibits mesenchymal cell angiogenesis procedures, including the transition to an endothelial-like phenotype [81]. There are few reports on the biological phenomenon of MEndT. It may be too early to use it as a strategy to control the imbalance of EndMT, but its role cannot be ignored.

3. Conclusions and future perspectives

EndMT is an effective target for the treatment of cardiovascular diseases. Endothelial cells adapt to the complex environment of the cardiovascular system through EndMT. Therefore, the signal transduction to promote EndMT is very active, and directly or indirectly blocking these signal pathways is an effective method to control EndMT imbalance. In addition, reasonable application of apoptosis and autophagy can also maintain the balance of EndMT. In fact, EndMT is an inevitable physiological activity. But EndMT imbalance will become the pathological basis of cardiovascular disease, and under the pathological conditions to exacerbate this imbalance to form a vicious circle. Therefore, it is necessary to fully describe the role of EndMT in the pathogenesis of various cardiovascular diseases. At the same time, it is necessary to deepen the research on the mechanism of regulating EndMT, so as to better control EndMT imbalance.

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