Qian *et al. Cell Communication and Signaling* (2025) 23:16
https://doi.org/10.1186/s12964-025-02028-y

Cell Communication and Signaling

REVIEW Open Access

Broadening horizons: molecular mechanisms and disease implications of endothelial-to-mesenchymal transition

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Abstract

Endothelial-mesenchymal transition (EndMT) is defined as an important process of cellular differentiation by which endothelial cells (ECs) are prone to lose their characteristics and transform into mesenchymal cells. During EndMT, reduced expression of endothelial adhesion molecules disrupts intercellular adhesion, triggering cytoskeletal reorganization and mesenchymal transition. Numerous studies have proved that EndMT is a multifaceted biological event driven primarily by cytokines such as TGF-β, TNF-α, and IL-1β, alongside signaling pathways like WNT, Smad, MEK-ERK, and Notch. Nevertheless, the exact roles of EndMT in complicated diseases have not been comprehensively reviewed. In this review, we summarize the predominant molecular regulatory mechanisms and signaling pathways that contribute to the development of EndMT, as well as highlight the contributions of a series of imperative non-coding RNAs in curbing the initiation of EndMT. Furthermore, we discuss the significant impact of EndMT on worsening vasculature-related diseases, including cancer, cardiovascular diseases, atherosclerosis, pulmonary vascular diseases, diabetes-associated fibrotic conditions, and cerebral cavernous malformation, providing the implications that targeting EndMT holds promise as a therapeutic strategy to mitigate disease progression.

Keywords Endothelial-mesenchymal transition, Endothelial cells, Mesenchymal phenotype, Non-coding RNA, TGF-β signaling pathway

Introduction

It has been well accepted that endothelial cells (ECs), which make up the lining of the blood vessels, play a vital role in maintaining homeostasis of the body mainly through safeguarding transport logistics, preserving vascular integrity, and modulating vascular tone [1]. ECs with a classic cobblestone appearance not only serve as a transport corridor for trafficking immune cells and generate a solid mechanical barrier against intruders but also exert indispensable paracrine function via releasing cytokines and growth factors [2]. Moreover, ECs tend to govern the recruitment of immune cells and influence the extravasation of leukocytes at inflammatory regions

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through regulating the expression levels of an array of adhesion molecules and chemokines [3, 4]. In contrast to ECs, mesenchymal cells are recognized as a group of stellate or spindle-shaped stromal cells with decreased expression levels of belt-like adherens and tight junctions. They are capable of transmigrating across the extracellular matrix and further producing the connective tissues that support the functions of organs [5].

Endothelial-mesenchymal transition (EndMT) refers to a well-known biological process in which ECs tend to experience a plethora of molecular events that result in alterations in phenotypes toward mesenchymal cells (e.g., myofibroblasts, smooth muscle cells) [6]. In the process of EndMT, ECs are prone to delaminate from the polarized cell layer, lose their intercellular junctions, obtain potent migratory capability, and penetrate the underlying tissues [7]. Indeed, this process bears a resemblance to epithelial-to-mesenchymal transition (EMT), which is a well-investigated biological event frequently occurring during the process of embryonic development and cancer progression. It has been accepted that EndMT described above is classified as type II EMT and is featured with loss of endothelial junctions and attenuated expression levels of endothelial markers, including CD31 and CD34 [8]. Despite the fact that EndMT shares rather similar phenotypes to EMT, there do exist a variety of certain pathophysiological differences between these two events. The predominant discrepancy is situated at the alterations in expression levels of different cellular markers in the process of the transitioning event [9].

It has been increasingly recognized that non-coding RNAs (ncRNAs), mainly including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs, play pivotal roles in regulating the progression of EndMT in multiple pathological conditions. miRNAs are thought to be small fragments of RNA (typically 20–25 nucleotides), which can bind to the complementary sequences within target mRNAs and subsequently tend to degrade the mRNA by virtue of cleavage or destabilization or suppress the translation of mRNAs into proteins [10]. Of note, ncRNAs are categorized as lncRNAs when they harbor more than 200 nucleotides. Their mechanisms of action vary not only between divergent lncRNAs but also under the circumstance that one specific lncRNA is capable of functioning through distinct mechanisms [11]. To this end, lncRNAs and miRNAs, described separately in this review, therefore emerge as promising therapeutic targets with the purpose of modulating EndMT.

Given that EndMT has been validated to be involved in regulating embryonic development as well as playing pivotal roles in orchestrating the pathogenesis of multiple genetically determined and acquired human diseases, gaining insight into the underlying mechanisms and treatment regimens of EndMT has been receiving increasing attention. In this review, we mainly summarize the molecular and regulatory mechanisms of EndMT occurrence, in particular highlighting the functions of ncRNAs in curbing the development of EndMT. Furthermore, we outline the mechanisms underlying EndMT, which has profound consequences on aggravating various vasculature-related diseases, providing the implications that targeting EndMT may be an effective and efficient approach to retarding the progression of these diseases.

Regulatory mechanisms of EndMT

It has been widely held that EndMT represents a process that myofibroblastic characteristics are obtained for ECs by virtue of a unique form of EMT, during which the expression levels of a series of endothelial markers, including VE-cadherin, CD31, von Willebrand factor (vWF), and TEK tyrosine kinase (TIE1/2), are decreased [12], but the expression levels of mesenchymal markers, such as α-smooth muscle actin (α-SMA), N-cadherin, Vimentin, and SM22α, are increased [13] (Fig. 1). Indeed, EndMT is thought to be characterized by disruption of intercellular contacts and cell polarity, alterations of cell morphology to spindle shape, as well as acquisition of migratory and invasive properties. Moreover, EndMT has been increasingly recognized as a preponderant biological process curbing development as well as various types of diseases, including cancer [14], cardiovascular diseases [9], and pulmonary hypertension [15]. To this end, understanding the molecular regulatory mechanisms of the progression of EndMT is essential for unveiling the therapeutic strategies for a variety of EndMT-associated diseases.

Cytokines for triggering EndMT

An increasing number of studies have demonstrated that numerous growth factors and pro-inflammatory factors are able to participate in giving rise to the induction of EndMT, with transforming growth factor-β (TGF-β) family members playing crucial roles [16]. TGF-β is regarded as a multifunctional regulator that is capable of influencing an array of biological behaviors of multiple types of cells, such as proliferation, differentiation, apoptosis, adhesion, and migration [17]. EndMT, like EMT, is susceptible to being substantially triggered in the presence of secreted cytokine TGF-β by virtue of strengthening the expression levels of EndMT transcription factors. It has been highly appreciated that numerous types of cancer tend to express high levels of TGF-β, which induces the initiation of EndMT that results in the production of cancer-associated fibroblasts (CAFs). In fact, TGF-β and bone morphogenetic protein (BMP) are inclined to compose an important signaling cascade to serve as critical modulators to affect vascular remodeling and

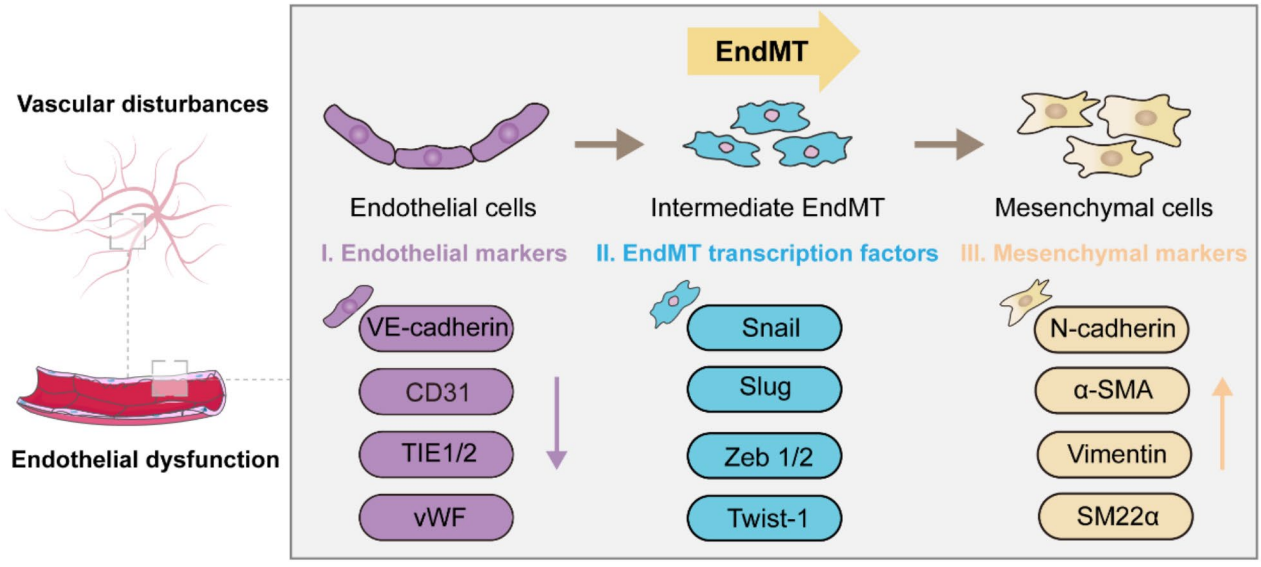

Fig. 1 ECs undergo EndMT, which is thought to be the source of CAFs and myofibroblasts. This schematic diagram demonstrates the morphological profiles (cell elongation) as well as the increased migration and invasion capabilities of mesenchymal cells. The observed phenotypic changes are accompanied by altered expression levels of a series of critical genes, as validated by the decreased expression of endothelial markers (VE-cadherin, CD31, TIE1/2, and vWF) and increased expression of mesenchymal markers (N-cadherin, α-SMA, Vimentin, and SM22α)

development, as well as play an irreplaceable role in probing the functions of ECs to propel the progression of multiple diseases [18]. In ECs, TGF-β is able to arrest the cell cycle in the G1 phase to further inhibit proliferation, stimulate differentiation, and potentially enhance apoptosis [19]. Indeed, TGF-β family members tend to mediate their downstream effects through binding to heteromeric receptors mainly comprised of type I and type II receptors. More specifically, TGF-β binds to its receptors to promote the phosphorylation of receptor-mediated Smad [18]. It has been documented that TGF-β is capable of exerting a striking effect on regulating myofibroblastogenesis through conferring the induction of EndMT both in vitro and in vivo [20]. Additionally, TGF-β1 has been demonstrated to provoke the initiation of EndMT in various types of ECs, including aortic ECs [21]. Furthermore, TGF-β2 is prone to result in the induction of EndMT via modulating a series of signaling cascades, including Smad, MEK, PI3K, and p38 mitogen-activated protein kinase (MAPK) signaling pathways, whereas the silence of Snail is able to block TGF-β2-mediated initiation of EndMT [22]. Notably, it has been recognized that numerous mediators tend to trigger EndMT by participating in the activation of the TGF-β signaling pathway. For instance, the Kras mutation has been reported to yield the induction of EndMT by virtue of modulating the TGF-β/BMP-Smad4 signaling pathway [23].

It has been envisioned that numerous inflammatory mediators play vital roles in driving the initiation of EndMT, owing to the fact that pro-inflammatory cytokines and leukocyte-mediated signals are inclined to lead to the activation of ECs and subsequently give rise to their morphological alteration [24]. A plethora of studies have illustrated that the critical regulators, including tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), and endotoxin, are able to activate ECs and transform them into mesenchymal-like cells [24, 25]. Of note, TNF-α, as a cytokine predominantly released by macrophages, has been reported to be involved in the regulation of the immune response, and it has been shown that TNF-α induces EndMT via binding to its receptor TNF receptor (TNF-R) and promotes the translocation of nuclear factor κ B (NF-κB) into the nucleus [24], as well as downregulates BMP receptor 2 (BMPR2) to facilitate vascular calcification [26]. Moreover, TNF-α induces the expression of H19, thereby activating the TGF-β signaling pathway and, in turn, triggering the occurrence of EndMT via a ten-eleven translocation 1 (TET1)-dependent epigenetic mechanism [27]. It has also been elucidated that TNF-α-mediated EndMT can be reversible and works at least partially through regulating TIE1 [28]. Nevertheless, the mechanisms underlying TNF-α participating in TGF-β-mediated EndMT have not been fully demonstrated. In 2020, Yoshimatsu et al. revealed that TNF-α could drive TGF-β-dependent EndMT initiation, which further exacerbated the progression of tumors [29]. In fact, multiple types of ECs undergo EndMT under the stimulation of TGF-β and TNF-α, accompanied by elevated and diminished expression levels of mesenchymal and endothelial markers, respectively, as well as persistent

activation of the Smad2/3 signaling pathway. Intriguingly, it has also been shown that TNF-α tends to strengthen TGF-β2-mediated EndMT in human lymphatic ECs and that both cytokines are capable of triggering the production of Activin A and further lowering the expression of its inhibitory molecule Folistatin, thereby facilitating the progression of EndMT [30].

It has been increasingly recognized that IL-1β, as one of the most important IL-1 family members, has been reported to be involved in regulating the progression of acute and chronic inflammation in a complex network of signaling molecules. More importantly, IL-1β is closely related to endothelial dysfunction and is able to trigger the initiation of EndMT [31]. The activation of IL-1β in ECs can be induced upon BMP/Smad and non-Smad BMP signaling cascades, and it has been unveiled that gemigliptin is capable of preventing the development of IL-1β-mediated EndMT, as reflected by upregulating the expression of endothelial markers and downregulating the levels of mesenchymal markers [32]. More interestingly, the in vitro studies demonstrated that co-stimulation of TNF-α and IL-1β was inclined to significantly trigger the occurrence of EndMT and further boost the expression of histone deacetylase 3 [33], as well as diminish the expression of Sirtuin 6 (SIRT6) in ECs [34]. Of note, epigenetic regulation of transgelin expression by enhancer of zeste homolog-2 (EZH2) tends to serve as an epigenetic integrator of IL-1β and TGF-β2 signaling, addressing the critical cellular signaling cascades that are associated with EndMT at the level of epigenetic regulation [35]. In fact, it has been shown that the combined treatment of IL-1β, TGF-β, and TNF-α is prone to propelling the progression of EndMT in pulmonary artery ECs and subsequently giving rise to morphological changes in EndMT-derived cells, as well as resulting in alterations in the expression levels of endothelial and mesenchymal markers [31].

EndMT-related signaling pathways

Presently, many EndMT-related signaling pathways have been proven, such as TGF-β, WNT, MAPK, and Notch signaling pathways (Fig. 2). It has been highly appreciated that the TGF-β signaling pathway can be delivered by Smad or non-Smad signaling cascade-associated proteins. Indeed, the TGF-β/Smad signaling cascade acts as a ternary signaling complex, which further generates a serine/threonine kinase complex upon the effects of additional pivotal factors that can bind to the TGF-β receptor (TGFβR). When TGF-β binds to TGFβR2, it further phosphorylates TGFβR2, as well as results in the recruitment and activation of TGFβR1, which in turn gives rise to the striking activation of the Smad signaling cascade [36]. Intriguingly, vactosertib, as a highly potent TGFβR1 small molecule inhibitor with a well-tolerated and acceptable safety profile, has demonstrated prominent efficacy in various types of cancers [37]. It has been widely held that Smad proteins harbor at least three known functional groups: R-Smads, including Smad1, 2, 3, 5, and 8; the common mediator Smad (Co-Smad), as exemplified by Smad4; and the inhibitory Smads (I-Smads), in particular Smad6/7 [38]. In the cytoplasm, the activated receptor-regulated Smads (R-Smads) generate heterodimeric complexes with Smad4 and subsequently translocate into the nucleus to synergistically regulate gene expression in conjunction with transcription factors and enhancers [18]. On one hand, activated TGFβR is prone to enhancing the phosphorylation levels of Smad2/3 as well as alternative Smad proteins [39]. On the other hand, Smad7 emerges as an effective antagonist of the TGF-β/Smad1 signaling cascade by interactions downstream of the TGFβR that result in reduced activation of Smad2/3 [40]. Relying on the proteins linked to the ligand-receptor interactions, TGF-β binding to its receptor is capable of leading to the activation of a non-canonical TGF-β signaling cascade through modulating a wealth of kinases, including ERK, p38, JNK, PI3K/PKB, and ROCK [41, 42]. In normal epithelial cells, TGF-β acts as a potent cell growth suppressor. Conversely, the TGF-β signaling pathway has been found to be out of control or mutated in cancer cells, and TGF-β fails to modulate cell proliferation [43].

It has been increasingly recognized that phosphorylation of TGFβR1 driven by the increased Ser/Thr kinase activity of TGFβR2 tends to produce a docking site in the Gly/Ser-rich domain of TGFβR1, which results in the recruitment of the key transcription factors, including Smad2/3 [44, 45]. Smads are frequently phosphorylated at Ser residues in their C-terminal domain, propelling the production of a complex with coactivator Smad4 [46]. R-Smads and Smad4 consist of conserved MH1 and C-terminal MH2 domains, which have impacts on their capability to generate complexes and further bind to the minor groove of DNA [47]. In addition, phosphorylation of MH2 domains upon the activation of TGFβR1 is essential for oligomerization of Smad2/3 with Smad4, as well as allowing the nuclear translocation of the R-Smad/Smad4 complex via responding to the signals of nuclear localization. The signals enable the binding of importins β1, 7, and 8 to the complex and promote the subsequent translocation into the nucleus [48–50]. Moreover, Lys-rich sequences in the MH1 domain of R-Smads pave the way for nuclear translocation of Smad1 and Smad3 [51]. In addition to contributing to the activation of Smads, TGF-β signaling is also able to govern the activation of inhibitory Smad proteins (e.g., Smad6 and Smad7), which can bind to TGFβR1 and subsequently hamper the recruitment of effector Smads [52]. This system introduces strict mechanisms to hinder the abnormal

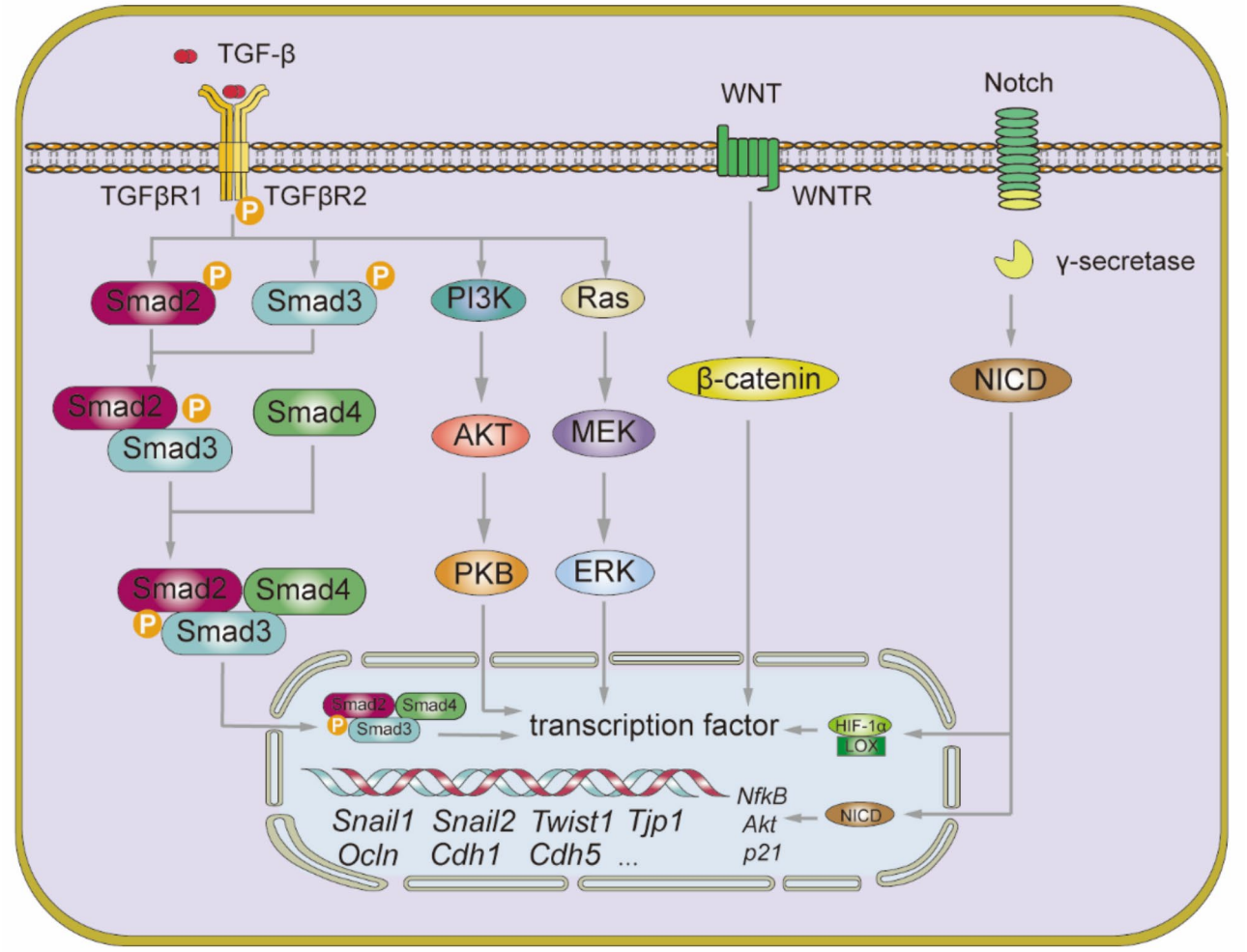

Fig. 2 Schematic diagram of the underlying mechanisms of the EndMT phenomenon. EndMT is initiated by crucial transcription factors. These signals include TGF-β/TGFβR, WNT, MAPK, and Notch signaling pathways

activation of this signaling pathway. Further, in BMP signaling, the basic signaling cascade remains the same, but BMP receptors take advantage of phosphorylated Smad1/5/8 in place of the Smad2/3 complex [53]. Once entered in the nucleus, the Smad complex binds to the critical regulatory elements and subsequently triggers the transcription of key genes that are related to EndMT. The complex of R-Smads is inclined to directly bind to the promoter of *Snail* to initiate its transcription and further form a complex with Snail to repress the expression levels of genes encoding E-cadherin and occludin [54].

In fact, TGF-β has been deemed to be a striking activator of multiple kinase signaling pathways, including ERK, JNK, and p38 MAPK. These signaling pathways have been illustrated to be both independent of Smad signaling and through regulating the Smad complex. Of note, the MEK-ERK signaling cascade has been implicated to exert striking effects on curbing the crosstalk with the canonical Smad signaling pathway and on the activation of EndMT. A growing body of evidence has suggested that the MAPK signaling pathway may be involved in TGF-β signaling pathway-mediated transcription [55], and that the activation of Smads signaling pathways upon TGFβR1 appears not to be necessary for the activation of p38 MAPK [56]. The oncogenic guanosine triphosphatase Ras tends to result in the activation of ERK signaling [57], which is in agreement with the findings that activation of EndMT-associated transcription factors, such as *Twist1*. This indicates that EndMT requires a concomitant Ras signaling cascade to visualize the phenotypic alterations [58]. Activation of TGFβR results in the phosphorylation of adaptor protein Src homology 2 domain-containing transforming protein at Tyr residues, allowing the complex of growth factor receptor-bound 2-son of sevenless homolog 1 to dock and further to contribute to the activation of Ras and its downstream ERK signaling pathway [59].

The WNT signaling pathway plays a critical role in regulating tissue formation and differentiation, processes essential for early development [60]. Notably, activation

of the WNT signaling cascade has been shown to promote EndMT in ECs, whereas inhibition of this pathway can effectively mitigate EndMT progression. Increasing evidence highlights the pivotal role of WNT signaling in mediating TGF-β-induced EndMT. In vitro studies with human aortic ECs have demonstrated that TGF-β stimulation significantly enhances the mRNA and protein expression levels of key WNT ligands, including WNT2, WNT4, WNT10B, and WNT11 [61, 62]. A short hairpin RNA (shRNA) screening analysis illustrated that *WNT2* is also needed for TGF-β-mediated downstream consequences [62], depicting the indispensable role of the WNT signaling pathway in regulating myocardial fibrosis as well as EMT/EndMT in mice with myocarditis [63].

The Notch receptor consists of extracellular and intracellular domains. The latter contains the motifs that are crucial for nuclear translocation. Upon interactions with ligands on the surface of neighboring cells, the Notch intracellular domain (NICD) is cleaved by γ-secretase, enabling its translocation into the nucleus [64, 65]. Once inside the nucleus, NICD binds to the DNA-bound CSL transcription repressor complex, thereby activating the transcription of genes involved in tumor progression, such as NF-κB, AKT, and p21 [66–68]. Notably, the Notch signaling pathway is intricately linked to TGF-β signaling. Activation of the TGF-β/Smad3 pathway facilitates the binding of Notch1 to its ligand Jagged-1, leading to the expression of mesenchymal markers in endothelial cells [69]. Notch signaling can regulate Snail1 expression both directly [70, 71] and indirectly via inducing the expression of hypoxia-inducible factor 1a (HIF-1α), which binds to the promoter of encoding lysyloxidase (LOX), enhancing its transcription. LOX subsequently stabilizes Snail1, thereby driving the progression of EndMT [72]. Additionally, various factors, including blood flow shear stress, relaxin, and rapamycin, have been reported to activate the Notch signaling pathway, thereby influencing EndMT progression [73–75]. In addition to the direct consequences mediated by its intracellular domain, Notch can also indirectly induce EndMT by virtue of regulating multiple signaling pathways, such as NF-κB and β-catenin signaling pathways [76].

Methods of inducing EndMT

The EndMT process in vitro is accomplished by the alterations of cellular phenotypes, and usually, ECs tend to experience EndMT in response to chemical or physical stimuli. TGF-β has been shown to be the predominant EndMT trigger, and EndMT can normally be induced following 8–12 h stimulation of TGF-β [77]. EndMT is also prone to being triggered upon TGF-β together with additional stimuli, including IL-1β [78] or H_2O_2 [79]. Each of these in vitro models can provide an effective tool for studying molecular mechanisms of EndMT. Oxidative stress has been accepted as another element to promote EndMT, and it has been uncovered that oxidative stress could potentially aggravate EndMT under the conditions of atherosclerosis and renal fibrosis [80]. In the in vitro context, H_2O_2, as the classical inducer of oxidative stress, is inclined to propel the occurrence of EndMT [79]. H_2O_2 in combination with TGF-β, as well as inhibition of reactive oxygen species (ROS), can prevent oxidative stress-mediated EndMT [79]. EndMT is also boosted upon the proinhibition of nitric oxide synthase, which decreases nitric oxide bioavailability and augments oxidative stress [81]. Indeed, the role of oxidative stress in regulating EndMT requires further exploration. Pulmonary microvascular ECs grown under hypoxic conditions displayed a prominent reduction in terms of CD31 expression, accompanied by remarkable elevations in the expression levels of αSMA and two alternative mesenchymal markers, including collagen (COL) 1A1 and COL3A1. Moreover, hypoxia is able to enhance the proliferation and migration of αSMAexpressing mesenchymallike cells, which implies that hypoxia gives rise to EndMT [82]. In fact, EndMT serves as a hallmark of diabetes-related vascular complications. By virtue of examination of intermittent high glucose (12 h of 25 mM glucose followed by 12 h of 5.5 mM glucose in three continuous cycles totaling 72 h), transient high glucose (24 h of 25 mM glucose followed by 48 h of 5.5 mM glucose), and constant high glucose (72 h of 25 mM high glucose) on the acquisition of mesenchymal features, it has been revealed that intermittent high glucose maximally triggers various mesenchymal-like traits in EC as validated by the increased expression of α-SMA and Slug [83]. The in vitro model established by Pessolano and colleagues could also facilitate the progression of EndMT. In their model, the binding of annexin A1 and formyl-peptide receptors boosts the secretion of vascular endothelial growth factor A (VEGF-A) that interacts with VEGFR2 and further activates the signaling pathway to augment cell motility in an autocrine manner, as displayed by the phenotypes of EndMT [84].

The in vivo induction of EndMT is normally conducted in mice, which are subsequently examined for the expression levels of EndMT markers on specific mouse tissues. When tumors are present in mice, EndMT spontaneously takes place within the tumors. The in vivo-induced phenotypes of EndMT can also be observed by virtue of the endothelial-specific Cre-lox lineage tracking system, which fluorescently labels ECs and activates Cre-recombinase, which serves as a specific enzyme that emits fluorescent signals [85]. It has been demonstrated that the endothelial marker CD31 is significantly downregulated but co-localized with the mesenchymal marker α-SMA in the intimal layer of small pulmonary arteries in rats subjected to chronic hypoxia [82]. These data imply the

potential function of hypoxia in triggering the occurrence of EndMT in vivo [82]. Immunofluorescence staining is a powerful method to visualize TGF-β-induced EndMT by assessing the expression, localization, and morphological changes of specific endothelial and mesenchymal markers, thereby serving as indicators of EndMT progression. The TGF-β2-mediated EndMT process has also been investigated using mouse pancreatic microvascular endothelial cells as a model. Notably, Snail has been identified as a key transcription factor driving TGF-β2-induced EndMT in the MS-1 cells [86]. Additionally, RNA sequencing, an efficient and comprehensive tool for transcriptome analysis, can effectively evaluate the extent of EndMT by profiling the expression patterns of endothelial and mesenchymal markers.

Epigenetic regulation of EndMT

Epigenetic refers to the heritable regulation of gene expression that occurs without altering the underlying DNA sequence. An increasing number of studies have highlighted that EC epigenetic modifications, including DNA methylation and histone modifications, as well as ncRNAs, play significant roles in propelling EndMT progression [87, 88].

Table 1 The effects of ncRNAs on EndMT

ncRNAs		Function	Target gene	Disease
miRNAs	miR-9	Promote EndMT	TNF-α, NF-κB, TGF-β, DKK1	Inflammation, lung cancer
	miR-200c	Inhibit EndMT	ZEB1, ZEB2	Lung cancer, kidney diseases
	miR-155	Promote EndMT	SHIP-1	Pulmonary fibrosis
	miR-29a-5p	Inhibit EndMT	DHRS4	Colorectal cancer
	miR-483	Inhibit EndMT	CTGF	Kawasaki diseases
	miR-125b	Promote EndMT	Apelin	Cardiac fibrosis
	miR-21	Promote EndMT	PTEN	Cardiac fibrosis
	miR-145	Inhibit EndMT	Smad3	Pulmonary fibrosis
lncRNAs	MALAT1	Promote EndMT	miR-205-5p	Atherosclerosis
	PVT1	Promote EndMT	Twist1	Prostatic cancer
	ZFAS1	Promote EndMT	miR-150-5p	Atherosclerosis
	H19	Inhibit EndMT	TET1	Renal fibrosis
	MEG3	Inhibit EndMT	DNMT1	Diabetic retinopathy
	SNHG7	Inhibit EndMT	miR-34a-5p	Diabetic retinopathy

DNA methylation and histone modification

Epigenetic regulation tends to take place at the DNA level, where DNA methylation results in the silence of gene expression or is inclined to be reversed in the presence of DNA demethylases. During the EndMT process, accompanied by alterations in terms of gene expression, epigenetics serves as the determinant that influences cellular dichotomization during the cancer progression. In ECs, DNA methylation or histone modification plays an important role in governing the expression levels of endothelial-specific genes and upstream modulators. For instance, DNA methylation inhibits the expression of Klf2 and Klf4 [89], known to be two flow-inducible transcription factors, which are essential for strengthening endothelial function and are reported to participate in regulating EndMT [90]. Global histone methylation on lysine residues is closely related to the occurrence of EndMT. For instance, transcriptional inhibition of methylation on histone H3 lysine upon the treatment of histone methyltransferase EZH2 prevents IL-1β- and TGF-β2-mediated EndMT, which is correlated to the reduction of repressive components in the promoters of mesenchymal genes [35]. Indeed, TGF-β1 augments DNA methylation in the promoter of the RAS inhibitor RASAL1, thereby elevating the expression levels of Snail1, Snail2, and Twist and thus driving EndMT both in vitro and in vivo. Notably, BMP7 can reverse the promoter methylation of RASAL1 mediated by TGF-β1 and subsequent silenced gene expression by inducing the expression of DNA demethylation enzyme TET3 [89]. Furthermore, ncRNAs have also been validated to be indispensable epigenetic modulators of EndMT. lncRNAs are inclined to leverage EndMT via interfering with histone modifications, among which GATA6-AS has been found to reinforce EndMT via regulating the expression of LOXL2 [91].

ncRNAs regulate EndMT

ncRNAs play a critical role in influencing cell fate determination. Recent studies have uncovered the essential roles of ncRNAs in modulating EndMT (see Table 1). While ncRNAs, such as miRNAs and lncRNAs, may not have a pronounced impact on the process of encoding proteins [92]. They play crucial roles in regulating multiple cellular processes, including proliferation, differentiation, and apoptosis of cells [93]. miRNAs and lncRNAs are also able to be employed as reliable biomarkers to predict the prognosis of patients with lung cancer [94]. Notably, lncRNAs and miRNAs have been revealed to modulate the TGF-β signaling cascade [95]. Additionally, a wealth of lncRNAs can interact with miRNAs to influence TGF-β-mediated EMT [96]. Herein, we summarized the molecular mechanisms by which miRNA and lncRNA regulate EndMT (Fig. 3).

miRNAs regulate EndMT

miRNAs are deemed to be small non-coding RNAs that can modulate gene expression at the post-transcriptional level through repressing mRNA translation or increasing mRNA degradation [97]. miRNAs are prone to reshaping EndMT through changing the activities of signaling intermediates, contributing to alterations in signal amplitude and output. The consequences of multiple physiological and pathological processes, such as cancer, cardiovascular, and metabolic diseases, highly rely on the functions of miRNAs. Nonetheless, uncovering the exact roles of unique miRNAs in the pathophysiological conditions is challenging, resulting from the extreme complexity of their effects. Indeed, the action of miRNAs can be modulated through an array of underlying mechanisms, such as genetic polymorphisms, methylation of miRNA promoters, asymmetric selection of miRNA chains, interaction with RNA-binding proteins, or alternative coding/non-coding RNAs [98]. Gaining insight into how the above events influence the functions of miRNAs to govern stress responses in cells and organs, or during the progression of specific pathologies, including metabolic diseases or cancer, not only deepens our knowledge on the molecular mechanisms of complicated diseases but also facilitates the development of new therapeutic strategies on the basis of miRNA targeting.

miR-9 has been validated to be a small RNA that exerts striking effects on influencing a variety of biological processes, such as proliferation, migration, differentiation, and apoptosis of cells. It has been shown that miR-9 can be modulated by the mediators of TNF-α signaling [99]. It has also been revealed that miR-9 not only ameliorates the expression of NF-κB and further regulates TGF-β and inflammatory responses but also strengthens tube formation [99, 100]. Moreover, miR-9 is also able to result in the activation of the WNT/β-catenin signaling pathway via targeting the negative modulator DKK1 [101]. More interestingly, miR-9 is capable of modulating the expression levels of various transcription factors that participate in regulating the development of EndMT, including *Snail* and *Slug* [102, 103]. All these transcription factors exert important effects in modulating EndMT by influencing the expression levels of regulators involved

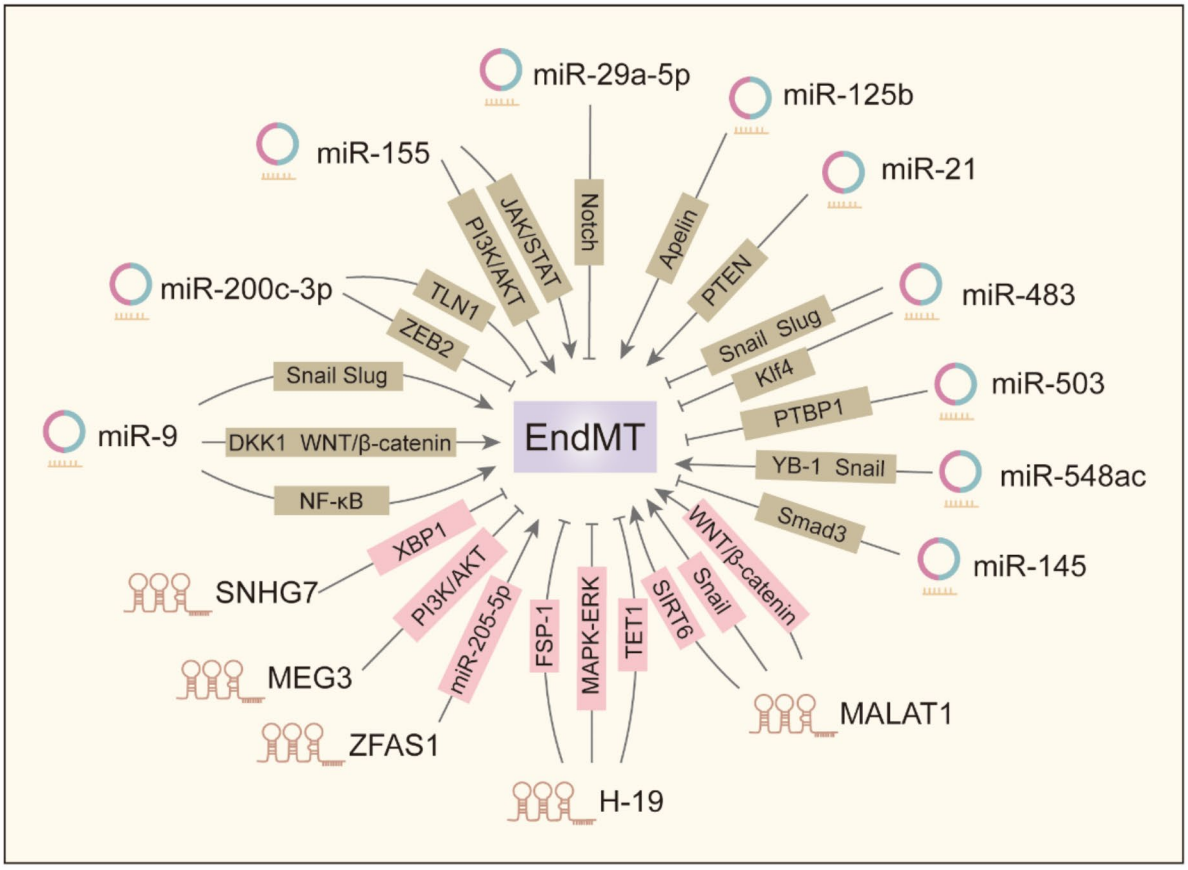

Fig. 3 Roles of ncRNAs in affecting the progression of EndMT. Examples of how ncRNAs interfere with the critical signal molecules in the process of EndMT

in various processes, such as genes encoding ECM, cell adhesion molecules, and cytoskeletal proteins.

The miR-200 family has been reported to be related to drug-resistant tumors [104]. miR-200c-3p processed from the 3-terminal arm has been elucidated to participate in the development of multiple types of kidney diseases [105]. Indeed, miR-200c-3p antagonizes the proliferation and migration of renal artery ECs through directly targeting ZEB2 [106], and it allows modulating integrin activation and cell adhesion via targeting TLN1 [107]. Silencing of FERMT2 reverses the inhibitory effect of miR-200c-3p on EndMT, which instructs the progression of EndMT in the arterial bypass graft vessels [108].

miR-155 has been recognized as a pro-inflammatory factor [109]. Inhibition of miR-155 has been shown to reduce cell proliferation and downregulate mesenchymal markers, suggesting that suppression of miR-155 can effectively hinder the progression of EndMT [110, 111]. Of note, endothelial miR-155 exerts an essential effect on the lung fibrosis by virtue of EndMT [111]. Further, SHIP-1 has been verified to be a target of miR-155 that influences the EC response in lung fibrosis through regulating PI3K/AKT, JAK/STAT, and SMAD/STAT signaling cascades [112]. Interestingly, miR-155 is closely associated with the changes of various EC functions. For example, miR-155 triggers EC apoptosis and inflammatory response, ameliorates aortic diastolic function, and propels the development of atherosclerosis via targeting Bmal1 [113]. Moreover, miR-155 is robustly expressed in Klf5-overexpressing vascular smooth muscle cells (VSMCs), which are then transferred to ECs through exosomes. It regulates the expression of endothelial tight junction-associated proteins and serves as an important modulator of endothelial barrier function [114]. Of note, exosomal miR-155 derived from M1 macrophages augments EndMT and attenuates mitochondrial function through leading to the activation of the NF-κB signaling pathway in ECs following traumatic spinal cord injury [115].

It has also been reported that miR-29a-5p plays a pivotal role in controlling the progression of various types of diseases [116, 117]. Overexpression of miR-29a-5p counteracts parathyroid hormone-induced EndMT. More specifically, miR-29a-5p mimics, GSAP siRNA, and γ-secretase inhibitors antagonize parathyroidin-mediated activation of γ-secretase, thereby braking the activation of the Notch1 signaling pathway and thus retarding EndMT [118].

Admittedly, aberrant expression of miR-483 has been demonstrated to be related to the development of a variety of pathological conditions, such as cancer, diabetes, and cardiovascular diseases [119]. There are multiple studies showing that miR-483 is capable of modulating EndMT in various types of cells, such as peritoneal mesothelial cells and prostate cancer cells, which indicates that miR-483 could potentially exert striking effects on the pathogenesis of diseases that are related to EndMT [120]. It has been shown that miR-483 curtails oscillatory flow-triggered EndMT via impairing the expression levels of Snail, Slug, Twist, and Tagln [121]. Meanwhile, ECs expressing miR-483 mitigate the expression levels of serum-mediated mesenchymal markers and enhance the expression levels of endothelial markers in Kawasaki patients. At a mechanistic level, miR-483 can be activated in the presence of Klf4 and subsequently targets the 3'UTR of CTGF mRNA to initiate the occurrence of EndMT [120].

In fact, other miRNAs have also been documented to be involved in the development of EndMT. For instance, miR-125b has been exhibited to yield the development of EndMT by targeting Apelin [122]. Furthermore, miR-21 has been found to target PTEN and participate in TGF-β-induced EndMT through the phosphatase and tensin homolog/Akt pathway [123]. Additionally, the depletion of miR-503 tends to drive the progression of EndMT, and the overexpression of miR-503 hinders the development of EndMT. The functions of miR-503 in impinging EndMT may be in part mediated through PTBP1 [124]. Moreover, miR-548ac suppresses the expression level of YB-1 via binding to the 3'UTR of its mRNA. YB-1 is observed to promote the translation of Snail, which is a critical modulator of EndMT, thereby producing a miR-548ac/YB-1/Snail mutual feedback loop that triggers the EndMT in an acidic microenvironment [125]. Of interest, miR-145 is known to reverse TGF/Smad-mediated EndMT via directly targeting Smad3, thereby regulating the progression of pulmonary fibrosis [126].

lncRNAs regulate EndMT

It has been highly appreciated that lncRNAs are regarded as a group of ncRNAs longer than 200 nucleotides. In the cytoplasm, lncRNAs are able to leverage the translation of mRNAs, as well as elevate or diminish the stability of mRNAs [127]. In the nucleus, lncRNAs are able to change the chromatin structure via interfering with PRC2, increase or decrease gene transcription through contributing to the recruitment of transcription factors, and exert profound consequences on miRNA processing [128]. Thus, it can be inferred that lncRNAs are tightly associated with the progression of multiple human diseases.

It has been increasingly recognized that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) serves as an important lncRNA that is closely related to tumor metastasis [129]. Furthermore, it has recently been implicated to be a key inducer of EndMT. Indeed, overexpressing MALAT1 boosts the impacts of bovine-LDL on the induction of EndMT as well as on the activation

of the WNT/β-catenin signaling cascade [130]. This suggests that the activation of MALAT1, under the condition of atherosclerosis depending on the WNT/β-catenin signaling cascade, plays a key role in influencing pathological EndMT [130]. The suppression of MALAT1 prevents high-glucose-triggered EndMT and impedes the proliferation, migration, and tube formation of ECs via targeting miR-205-5p [131]. It has also been unveiled that MALAT1 is prone to operate on senescence-mediated EndMT through elevating the expression level of Snail [132]. Furthermore, SIRT6 acts as a NAD-dependent histone deacetylase, and SIRT6 can directly bind to the promoter of MALAT1 to prohibit its expression level [133]. MALAT1 is inclined to competitively bind to miR-145, thereby counteracting the inhibitory function of miR-145 and propelling the progression of EndMT [134]. Alongside MALAT1, several other lncRNAs have also been implicated in promoting the development of EndMT. In prostate cancer, the lncRNA PVT1 is observed to drive tumor invasion and metastasis at least partially through triggering the occurrence of EndMT, and PVT1 can positively modulate the expression of Twist1 to aggravate EndMT [135]. Furthermore, it has been uncovered that lncRNA ZFAS1 strengthens LDL-mediated EndMT through regulating the miR-150-5p/Notch3 signaling axis [136].

Of interest, there are also a plethora of lncRNAs that retard the progression of EndMT. For example, miR-29a has been shown to mediate EndMT, and elevated expression of lncRNA H19 is tightly related to repression of miR-29a level in diabetic mice [137]. Silencing of H19 expression substantially curtails renal fibrosis both in vitro and in vivo, which is owing to the inhibited expression of the EndMT-related gene named FSP-1. All of these suggest that suppression of lncRNA H19 may serve as a novel therapeutic strategy for fighting against diabetic kidney disease [137]. Endothelial activation of the H19/TET1 signaling has been found to play a pivotal role in fueling the development of EndMT, with TNF-α inducing the expression of H19, which subsequently leads to the activation of TGF-β signaling and then the occurrence of EndMT via a TET1-dependent mechanism [27]. Indeed, H19 governs the mRNA and protein levels of TGF-β1 on the basis of the Smad-independent MAPK-ERK1/2 signaling pathway, a mechanism that is independent of the TGF-β1 mRNA and protein levels and interacts with miR-200b [138].

Additionally, overexpression of lncRNA MEG3 is capable of alleviating the progression of EndMT in rats as well as in cellular models of diabetic retinopathy through inhibiting the PI3K/AKT/mTOR signaling pathway [139]. Of note, DNMT1 can drive EndMT in diabetic retinopathy by recruiting methyltransferases to enhance the methylation of MEG3 promoter, consequently repressing the MEG3 expression [139]. In addition, overexpression of SNHG7 is prone to prevent HG-induced EndMT and tube formation via the miR-34a-5p/XBP1 axis in HRMECs [140].

Physiological roles of EndMT

Indeed, EC plasticity and EndMT exert striking effects on curbing normal embryonic development, and maintenance of EC function at the stage of adulthood is important for promoting tissue homeostasis. The occurrence of EndMT was first identified during studies of the endothelial cushion formation in mouse embryos, a process fundamental for understanding the physiological roles of EndMT [141]. Notably, EndMT has been closely associated with the development of cardiac and semilunar valves [142, 143]. In the process of heart development, multiple signaling cascades are able to govern the development of EndMT [144]. In terms of the Hippo signaling pathway, the signaling cascade involving BMP and the ligands and receptors of TGF-β influences the expression levels of endocardial Snai1, Snai2, and Twist [144]. As for the NOTCH signaling pathway, Notch can be expressed on whole endocardial cells before endocardial transplantation. When the ligand binds to the Notch1 receptor, the NICD is released by protease cleavage and translocates into the nucleus, where it serves as a transcriptional cofactor to regulate the expression of Snai1 and Snai2 [145], thereby suppressing the transcription of VE-cadherin and ultimately driving the progression of EndMT [146]. Furthermore, research has revealed that EndMT contributes to angiogenesis in the early postnatal retina, a transition regulated by VEGF signaling [147]. It has been increasingly recognized that EndMT may present specific metabolic profiles, and TGF-β has been observed to result in a prominent reduction in terms of mitochondria-dependent fatty acid oxidation (FAO) when EndMT is triggered in vitro [78]. In fact, activation of the EndMT program is tightly related to changed endothelial metabolism. FAO has been verified to fuel vascular sprouting through stimulating *de novo* nucleotide synthesis of DNA replication as well as proliferation of angiogenic ECs, and the reduction of key metabolic kinases CPT1 and acetyl-CoA in FAO can inhibit the TGF-β-mediated activation of EndMT-associated signaling pathways [148]. In other cell types, the TGF-β signaling cascade has been validated to influence glucose metabolism [149], lipid metabolism [150], as well as mitochondrial function [151]. It has been widely held that ECs lining in the vessel wall are exposed to multiple mechanical stresses [152, 153], inflammatory stimuli [154], and metabolic alterations [155]. The initiation of EndMT can be governed by various molecular mechanisms, but how these underlying mechanisms interact with each other requires clarification. Nevertheless, it is undoubtedly true that EndMT

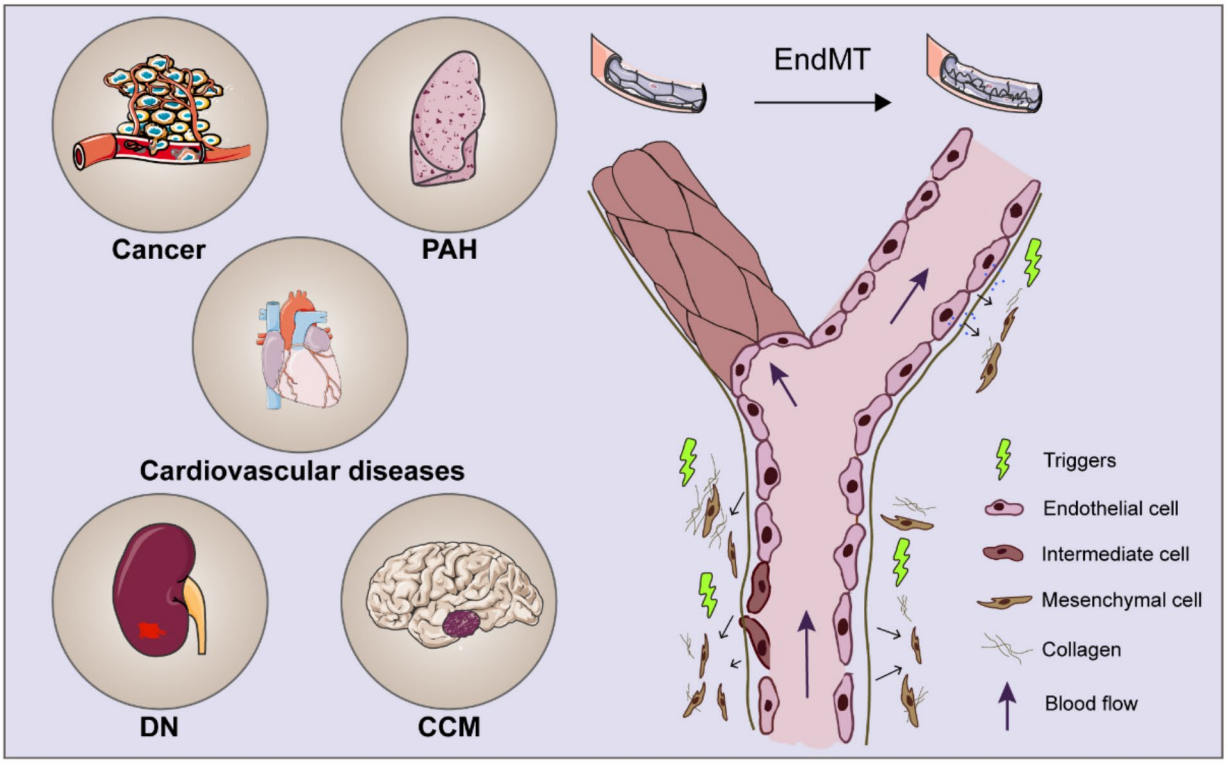

Fig. 4 Roles of EndMT in multiple pathological conditions. Activation of EndMT results in multiple pathological conditions, including cancer, PAH, cardiovascular diseases, DN, and CCM

plays a crucial role in affecting normal physiology and may also be aberrant or exacerbated under the disease conditions.

Roles of EndMT in different diseases

It has been well established that EndMT plays a pivotal role in accelerating various types of pathological conditions. Notably, endothelial dysfunction may tend to be an obvious impact of EndMT and potentially confer the remodeling of pathological tissues, which can exacerbate the development of various types of diseases, including cancer, cardiovascular diseases, pulmonary vascular disease, diabetes-associated fibrotic conditions, and cerebral cavernous malformation (CCM) (Fig. 4) [156–158].

Roles of EndMT in tumor angiogenesis

EndMT and mesenchymal-to-endothelial transition (MEndT) have been well elucidated in tumors as the driving forces of mesenchymal stroma and tumor angiogenesis, respectively [159]. An increasing number of studies on EndMT demonstrate that endothelial disruption resulting from inflammatory stress contributes to pathological angiogenesis that is deemed to be the representative feature of cancer [160]. Indeed, EndMT has been found to be present in a variety of types of tumors and has been illustrated to propel tumor development and aggravate metastasis [161]. This biological behavior can confer the production of new blood vessels in the tumor microenvironment (TME), or namely, angiogenesis, which is essential for tumor progression and survival. Angiogenesis has been thought to be required in controlling tumor development and is triggered upon the sprouting of ECs, which disrupt the apical-stromal polarity and impair the cell-cell interactions. However, MEndT is regarded as the reverse phenotype of EndMT and participates in angiogenesis scenarios [162]. It has been recently shown that this process acts as the source of tumor angiogenesis in the TME [62, 159]. Notably, critical components that initiate the onset of EndMT in ECs include mechanical stimulation, lipid penetration, and oxidative stress [163]. Slug and Snail, as the important EndMT transcription factors, are also observed to be highly expressed in ECs of tumor blood vessels, and the expression of Slug is closely related to angiogenesis and further tumor metastasis [164]. Cancer cells are capable of triggering EndMT via influencing extracellular vesicles correlated to the angiogenic fraction [165]. It has also been elucidated that CCL18 secreted from mast cells activated by non-small-cell lung cancer-tumor-derived microvesicles propels the migration of HUVECs, tube formation, as well as EndMT, thereby enhancing angiogenesis [166].

The TME plays a vital component in accelerating the progression of EndMT. Targeting the components of the TME can possibly retard the development of EndMT and limit cancer progression. Immunotherapy has been deemed to be a promising strategy for cancer treatment. It has been demonstrated that targeting immune checkpoints, including PD-1 and CTLA-4, is capable of improving the immune response against tumor cells as well as preventing the progression of EndMT [167, 168]. In fact, CAFs emerge as a predominant component of TME and result in tumorigenesis by virtue of various ways [161]. CAFs are potentially derived from several types of cells, including resident fibroblasts, epithelial cells, mesenchymal stem cells, and adipocytes, whereas EC-derived myofibroblasts and mesenchymal cells via EndMT are also observed to be a specific source of CAFs in different mouse models [169]. Nevertheless, the precise contribution of EndMT to the generation of CAFs has not been completely clarified.

It has been well accepted that EndMT is able to attain tumor immune evasion due to the fact that mesenchymal cells tend to express low expression levels of immune antigens, enabling them to be less detectable by the immune system [170, 171]. In addition, EndMT is prone to yield treatment resistance through boosting the expression levels of drug efflux pumps, which potentially reduces the effectiveness of chemotherapy and alternative therapies [172]. To this end, EndMT may represent an indispensable target for preventing cancer progression. In fact, EndMT is inclined to give rise to the damage of the endothelial barrier function and may also pave the way for the intravasation and extravasation of tumor cells. Under the circumstance that EndMT is triggered upon the secretions of tumors, the transendothelial migration of tumor cells is significantly elevated [173]. In a mouse model of lung cancer, PLEK2 knockdown inhibits TGF-β-induced human lung microvascular endothelial cell EndMT and the destruction of the vascular endothelial barrier and reduces the spread of lung cancer cells [174]. Therefore, by virtue of increasing transendothelial migration of tumor cells, EndMT can be regarded as a vital biological process for optimal metastatic spreading. Admittedly, EndMT tends to exert substantial effects on promoting tumor progression and metastasis. For example, miR-494 is able to enhance the expression levels of mesenchymal markers by inhibiting the expression of SIRT3 by virtue of regulating the SIRT3/TGF-β/Smad signaling cascade, as well as exert striking effects on modulating the proliferation and migration of hepatocellular carcinoma cells [175].

Roles of EndMT in cardiovascular diseases

There is a growing body of evidence showing that EndMT is tightly related to the occurrence of cardiovascular diseases in adults, including atherosclerosis, pulmonary hypertension, valvular diseases, and fibroelastic hyperplasia [176, 177].

Cardiac fibrosis is deemed to be the detrimental consequence of excessive production of myofibroblasts as well as the scar-generating cells that accumulate following cardiac injury. Fibrotic diseases are featured with activation of fibroblasts or myofibroblasts as well as increased cell number, resulting in excessive deposition of ECM, thereby subsequently resulting in organ dysfunction and further global disease [178]. Indeed, EndMT offers an alternative source of fibroblasts for fibrotic tissues and organs, and fibrotic diseases are severe health issues and contribute to high mortality. Myocardial fibrosis has been illustrated to be related to the development of EndMT since 2007 [9]. EndMT is triggered following myocardial infarction and gives rise to cardiac fibrosis following myocardial infarction with the deposition of excessive ECM in the myocardium as well as perivascular tissues. Interstitial fibrosis is characterized by unbalanced turnover and extensive deposition of diffused collagen in the interstitial regions, frequently under the conditions of pressure or volume overload. Of interest, TGF-β is prone to frequently binding to ALK-1 in ECs, thus promoting the activation of Smad1 and Smad5 and resulting in the modulation of vascular homeostasis, cell proliferation, as well as angiogenesis [179]. On the contrary, under the conditions that TGF-β binds to ALK5, it then gives rise to the activation of Smad2 and Smad3, which prevents the proliferation of cells and facilitates the progression of EndMT [179]. Furthermore, Angpt2 emerges as a potent antagonist for the Angpt1/TIE2 signaling pathway, which plays a pivotal role in enhancing vascular structure and function [180, 181]. Lee and colleagues elucidated that Angpt2 is extensively expressed in the ECs of the marginal area of the infarct regions in the heart following myocardial infarction, accompanying remarkable elevation in the light of FOXO1 expression [182]. The knockout of Angpt2 inhibits the elevated expression of EndMT-associated genes, including Col12a1, Fstl3, and Pcolce [183]. Of interest, MMP14 has been demonstrated to be a critical modulator of latent activation of TGF-β [184]. TGF-β activity can be detected in lipopolysaccharide (LPS)-activated bone marrow-derived macrophages in wild-type mice rather than in macrophage-specific MMP14 knockout mice [185]. The depletion of MMP14 also inhibits the TGF-β/p-Smad2 signaling cascade in cardiac ECs, myofibroblasts, as well as VSMCs following myocardial infarction [47, 186]. Collectively, reduction of MMP14 function in macrophages following myocardial infarction prevents macrophage-induced EndMT and further fibrosis, restricts left ventricle remodeling, and thus maintains cardiac function [185].

In fact, EndMT also plays a vital role in bridging the relationship between endothelial dysfunction and atherosclerosis, and the accumulation of mesenchymal cells (e.g., myofibroblasts, VSMCs, and osteoblasts) appears to be even more critical to the formation of plaque and ultimately atherosclerosis. The excessive exposure gradually contributes to the activation of ECs and further EndMT. A single-cell RNA sequencing (scRNA-seq) study by Zhao and co-workers was performed by virtue of EC-enriched single cells isolated from the heart and aorta of mice following 12 weeks feeding of a standard chow or diabetogenic high-fat diet with cholesterol. They identified eight EC clusters, three of which highly expressed classic mesenchymal markers that serve as indicative of EndMT. Additionally, the metabolic transcriptomic analysis subsequently demonstrated that EndMT-derived fibroblast-like cells are prevalent in atherosclerosis. These cells exhibit decreased FAO and enhanced biological functions, including the modulation of extracellular matrix (ECM) organization and apoptosis [187]. Previous studies have demonstrated the participation of EndMT in driving the progression of atherosclerosis via co-staining of atherosclerotic plaques and porcine vascular endothelial and mesenchymal markers [188]. This study also demonstrated the effects of the ERK5 signaling pathway on limiting the development of EndMT under uniform laminar shear stress [188]. It has also been elucidated that low oscillatory shear stress paves the way for exacerbating EndMT, whereas high shear stress aggravates the occurrence of EndMT [189]. The relationship between EndMT and disorders of blood flow also implies that EndMT may act as the driving force for the development of atherosclerosis. Additionally, endothelial-specific deletion of TGFβR1/2 in mouse models of atherosclerosis has been demonstrated to restrict the progression of EndMT, reduce the inflammatory responses and plaque development, and even confer plaque regression [190]. Thus, these studies offer prominent mechanistic insights into the importance of EndMT in the development of atherosclerosis, suggesting that EndMT emerges as a bridge between inflammatory responses and disturbed shear stress, with tissue remodeling propelling the formation of atherosclerotic plaque. All of these indicate that EndMT can be an effective and efficient therapeutic target for limiting the development of vulnerable plaques in atherosclerosis.

Roles of EndMT in pulmonary vascular diseases

Notably, the roles of EndMT in influencing pulmonary fibrosis [191] as well as vascular remodeling [188] are also gaining increasing attention nowadays. The effects of EndMT on influencing different pulmonary vascular diseases are listed as follows.

Pulmonary arterial hypertension (PAH) is regarded as a rare pathological condition induced by distal pulmonary vasoconstriction, aberrant remodeling of blood vessels, vascular occlusion, and the generation of featured plexiform lesions, with dysfunction in ECs being a classic characteristic of PAH [192]. A classic study illustrating the role of EndMT in PAH was an interventional study with rapamycin, which showed that rapamycin could reverse the expression of EndMT-associated proteins when both endothelial and mesenchymal markers were examined in situ [15]. Solidifying the experimental results for clarifying the role of EndMT in influencing PAH, Good and colleagues illustrated important traits of EndMT in a PAH model mediated through a combined stimulation of VEGFR antagonist Sugen 5416 (SU5416) and chronic hypoxia [193, 194]. Co-localization of vWF and α-SMA was observed in 6% of lung vessels in the mice with Sugen-induced hypoxia compared with 1% of lung vessels in control animals [193], which supports the findings by Qiao et al. [195] and Kurakula et al. [196] to demonstrate the relevance to human diseases. Moreover, co-localization of vWF and α-SMA was observed in 4% of the pulmonary arterioles from patients with systemic sclerosis-associated PAH, whereas it was absent in the non-PAH controls [197]. To explore the role of EndMT in exerting the impacts on phenotypes in PAH, various groups evaluated functional readouts of PAH and demonstrated that PAH-related endothelial dysfunction and reprogramming are associated with EndMT [198]. A growing body of evidence indicates that EndMT triggered by IL-1β, TGF-β, and TNF-α is present in PAH. There has been a study showing that the protein expression of HMGA1 in PAH is tightly related to cells that undergo EndMT. Of interest, the expression of HMGA1 is in turn related to a decreased expression level of BMPR2 [199]. Additionally, it has been unveiled that HIF-2α ameliorates hypoxia through triggering the expression of Snai1/2. Therefore, endothelial-specific knockout of HIF-2α results in the exacerbated PAH [197]. Further, it has been revealed that ginsenoside Rg1 is capable of alleviating the alterations in pulmonary hemodynamic function and vascular remodeling, repressing the pathological conditions, ameliorating hypoxia-mediated inflammation and EndMT, boosting the expression of CCN1, as well as suppressing the NF-κB and TGF-β signaling pathways [200].

An increasing number of studies have uncovered that EndMT plays a critical role in influencing the pathogenesis of pulmonary fibrosis [201]. In fact, in animal models of pulmonary fibrosis, it has been validated that EndMT results in the accumulation of fibrotic tissues [202]. In the tissue samples isolated from the patients with pulmonary fibrosis, it has been shown that endothelial cell-derived MMP19 promotes pulmonary fibrosis

by inducing EndMT [203]. Collectively, there has been a growing body of evidence illustrating that EndMT exerts striking effects on influencing the progression of pulmonary fibrosis, and thus manipulation of the process may serve as a promising therapeutic approach for fighting against pulmonary fibrosis. The roles of ECs in governing pulmonary fibrosis are not supposed to be ignored. An endothelial lineage tracing study elucidated that approximately 16% of fibroblasts were transformed from ECs as well as were involved in modulating the pathological progression of bleomycin-mediated pulmonary fibrosis in mice [204]. Nevertheless, more studies are required to completely highlight the underlying mechanisms of EndMT in pulmonary fibrosis and to develop reliable therapeutic strategies to target this process.

Roles of EndMT in diabetes-associated fibrotic conditions

Diabetes mellitus (DM) has been regarded as one of the most frequently observed chronic diseases globally [205]. A common feature of diabetic complications is tissue fibrosis [206]. Diabetic nephropathy (DN), a leading cause of chronic kidney disease, affects approximately 40% of patients with type 1 or type 2 diabetes [207]. In fact, high concentrations of glucose are prone to lead to the activation of the diacylglycerol-protein kinase C signaling cascade, which is related to dysfunction of ECs, elevated formation of ECM, as well as activated TGF-β [208]. Recent findings indicate that high glucose levels upregulate Bach1 expression in human glomerular endothelial cells, which promotes Snail expression and EndMT [209]. Furthermore, SETD8 counteracts EndMT by interacting with Bach1 to regulate Snail transcription [209]. Elevated sphingosine-1-phosphate receptor 2 (S1PR2) expression has been observed in glomerular endothelial cells of DN mouse models and glucolipid-treated HUVECs. Notably, inhibiting S1PR2 reverses EndMT and restores endothelial barrier integrity [210]. Hyperglycemia also suppresses lysine methyltransferase 5 A (KMT5A) levels and histone H4 lysine 20 methylation, a critical downstream target of KMT5A [211]. KMT5A upregulation has been shown to reduce profilin 2 (PFN2) expression and mitigate EndMT under high-glucose conditions [211]. Additionally, KMT5A regulates enolase1 transcript, thus participating in hyperglycemia-induced EndMT in the glomeruli of DN patients [212]. Pharmacological targeting of the EndMT pathway shows promise as a therapeutic strategy for DN. Empagliflozin, for instance, inhibits EndMT via the VEGF-C/VEGFR3 pathway and alleviates renal interstitial fibrosis [213]. Similarly, rutin mitigates EndMT by suppressing autophagy through the PI3K/AKT/mTOR pathway [214], while lovastatin reduces oxidative stress and downregulates TGF-β signaling to ameliorate EndMT in DN glomeruli [215]. Although existing interventions and glycemic control strategies can delay DN progression [216], further research is necessary to develop precise therapies targeting EndMT.

Roles of EndMT in CCM

It has also been reported that EndMT is capable of attaining the progression of CCM, a type of cerebrovascular disease that commonly contributes to brain hemorrhage, seizure, as well as paralysis [217]. Loss-of-function mutations in CCM1 can be one of the leading causes of the occurrence of CCM. In endothelial-specific CCM1 (also called KRIT1)-deleted mice, ECs in the vascular lesions of brains tend to experience EndMT, as evidenced by the fact that the expression of N-cadherin is boosted to enhance vascular malformations. The knockout of CCM1 in ECs promotes the release of BMP6, subsequently enhancing the response sensitivity to TGF-β and activating BMP signaling to give rise to EndMT [158]. As such, EndMT has been illustrated to be crucial for the initiation and development of CCM. In agreement with these observations, Takada and colleagues elucidated that ECs in either cerebral or orbital CCM were prone to express both the endothelial marker CD31 and the mesenchymal markers, including α-SMA and CD44, which highlighted the onset of EndMT. In quiescent ECs, Klf2 and Klf4 have been shown to partner to modulate a combinatorial mechanism [218]. The depletion of Klf4 disrupts the combinatorial mechanism, thereby leading to the upregulation of Klf2 as an adaptive response. Nonetheless, elevated expression of Klf2 overdrives the depletion of Klf4, yielding an evident EndMT phenotype [219]. By virtue of analyzing a larger number of CCM samples, EndMT cell types of CCM have been identified at the single-cell level, and it has been revealed that a novel set of potential marker genes for EndMT cell annotation are present in CCM. Of interest, the expression level of SPI1 in HUVECs and brain primary ECs of mice has been shown to be tightly associated with classic mesenchymal characteristics, which verifies that the development of EndMT can be triggered in the presence of SPI1. Additionally, the expression levels of various representative immune factors are highly expressed following the overexpression of SPI1, which unveils the immune characteristics in the progression of EndMT [220].

Conclusion and future directions

It has been well accepted that EndMT plays a beneficial role in influencing embryonic development, whereas it tends to be detrimental during the progression of endothelial growth, in particular in tumors, where EndMT is prone to exacerbate the development of tumors. The inducible and plastic ECs exert significant effects on shaping TME. Indeed, EndMT is reported to be involved in excessive angiogenesis and is able to govern the microenvironment of stromal cells as well as vascular

remodeling to support the dissemination and metastasis of tumor cells. Moreover, it results in the resistance to cancer treatment through directly or indirectly regulating the TME. In fact, EndMT is deemed to be an essential biological phenotype that boosts the plasticity of TME as well as the progression of tumor cells. EndMT is capable of modulating different stages of tumor progression, including tumorigenesis, tumor growth, and propagation to treatment response. Collectively, manipulation of EndMT emerges as a promising therapeutic strategy to fight against tumor development, so exploring strategies to retard the progression EndMT is worthy of gaining increasing attention in terms of cancer treatment, and further studies on dissecting the underlying mechanisms of EndMT as well as treatment regimens for EndMT will be of great significance.

Furthermore, TGF-β-induced EndMT has also been observed during the process of cardiac fibrosis [9], as well as being found to be associated with the deposition of collagen matrix and thus the development of disease. The concomitant depletion of functional ECs also potentially results in capillary rarefaction, thereby yielding tissue ischemia that emerges as a striking engine of fibrosis. The role of EndMT in cardiac fibrosis, however, remains controversial, which relies on the profiles of the cardiovascular damage and the degree of the fibrosis [79]. For instance, EndMT maintains a low level of pressure overload or ischemia-reperfusion (I/R) models, where the extent of inflammatory and fibrotic responses is extremely lower than that following acute ischemic injury [221, 222]. Furthermore, the methodologies used for evaluating EndMT contain various limitations. For example, immunofluorescence technology is not sensitive enough to precisely examine and measure the low expression levels of proteins that characterize cells during the process of EndMT. Lineage-tracing approaches are preferable, though the specificity of the driver also represents a caveat [119, 177]. Therefore, more precise and reliable methods are worth applying in EndMT-mediated disease studies in future research.

Taken together, EndMT is closely related to multiple tubular diseases, all of which are the important reasons for morbidity and mortality all over the world, whereas there are still multiple obstacles to address before the complete therapeutic functions of targeting EndMT can be gradually observed. Admittedly, there are alternative unknown hurdles and unforeseen issues to be addressed in addition to these difficulties. Nonetheless, by virtue of collaborative and focused efforts, we believe that great strides can be made in understanding and manipulating EndMT as a promising therapeutic strategy for multiple pathological conditions. It is imperative to highlight that while numerous studies discussed in this review have demonstrated the fundamental roles of EndMT-related molecular mechanisms in vascular diseases such as cancer, PAH, CCM, cardiovascular disease, and DN, their implications extend to other conditions, including age-related macular degeneration and fibrodysplasia ossificans progressiva. These broader associations warrant future efforts to summarize and generalize EndMT's contributions to a wider spectrum of diseases. Insights into EC biology and EndMT provide valuable information on the underlying mechanisms of vascular diseases, paving the way for developing therapeutic approaches targeting EndMT-induced endothelial reprogramming. Investigating the molecular pathways of EndMT is able to uncover novel therapeutic targets and approaches for an array of diseases where EndMT plays a role in their initiation and progression, potentially revolutionizing the therapeutic paradigm for these conditions. Collectively, our understanding of EndMT has dramatically expanded, strengthened by an abundance of experimental data. Emerging conceptual and practical insights into EndMT emphasize opportunities to modulate this process. Both partial and full EndMT are driven by similar cellular activities and transcriptional regulators, indicating the requirement for experimental approaches that track cellular phenotypes and functions. Whether a universal therapeutic strategy can address EndMT-mediated mechanisms across different diseases remains an intriguing field for future investigation.

Abbreviations

α-SMA	α-smooth muscle actin
BMP	bone morphogenetic protein
BMPR2	bone morphogenetic protein receptor 2
CAF	cancer-associated fibroblasts
CCM	cerebral cavernous malformation
COL	collagen
DM	diabetes mellitus
DN	diabetic nephropathy
ECs	endothelial cells
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
EndMT	endothelial-mesenchymal transition
FAO	fatty acid oxidation
EZH2	enhancer of zeste homolog-2
HIF-1α	hypoxia-inducible factor 1α
IL-1β	interleukin-1β
lncRNAs	long non-coding RNAs
LOX	lysyloxidase
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
miRNAs	microRNAs
MALAT1	metastasis-associated lung adenocarcinoma transcript 1
MEndT	mesenchymal-to-endothelial transition
NICD	Notch intracellular domain
ncRNAs	non-coding RNAs
NF-κB	nuclear factor κ B
PHD2	prolyl hydroxylase structural domain protein 2
PAH	pulmonary arterial hypertension
ROS	reactive oxygen species
scRNA-seq	single-cell RNA sequencing
shRNA	short hairpin RNA
SIRT6	sirtuin 6
TIE	TEK tyrosine kinase
TET	ten-eleven translocation

TGF-β	transforming growth factor-β
TGF-βR	transforming growth factor-β receptor
TME	tumor microenvironment
TNF-α	tumor necrosis factor-α
TNF-R	tumor necrosis factor receptor
VEGFR2	vascular endothelial growth factor receptor 2
VSMCs	vascular smooth muscle cells
vWF	von Willebrand factor

Acknowledgements
Not applicable.

Author contributions
C. Q. and G. D. conceptualized and wrote the original draft. C.Y., W. Z. and C. Z. took part in the authoritative discussion. Q.S., Y. L. and Y. Z. contributed with supervision and reviewing the original draft. All authors reviewed the manuscript.

Funding
This work was supported by the projects of National Natural Science Foundation of China (82274233 to Yang Zhao and 82101844 to Qiuhong Shen), Natural Science Foundation of Jiangsu Province (BK20240146 to Yang Zhao) and Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX23_2062 to Guanglu Dong).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors are consent for publication.

Competing interests
The authors declare no competing interests.

Received: 15 October 2024 / Accepted: 3 January 2025
Published online: 09 January 2025

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