# Role of ZEB1 in angiogenesis and therapeutic potential (Review)

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**Abstract.** Zinc finger E-box binding homeobox 1 (ZEB1), a key transcription factor governing epithelial-mesenchymal transition, plays indispensable roles in embryonic development, neural differentiation and a wide range of pathological processes. Emerging evidence has revealed that ZEB1 exerts multifaceted and context-dependent functions in angiogenesis. Under physiological conditions, ZEB1 contributes to the regulation of vascular development and endothelial homeostasis, whereas in pathological settings it promotes aberrant neovascularization through diverse molecular mechanisms. In the present review, the structural characteristics, biological functions and regulatory mechanisms of ZEB1 were systematically summarized, with a particular focus on recent advances regarding its roles in both physiological and pathological angiogenesis. Furthermore, the therapeutic potential of targeting ZEB1 in vascular diseases was discussed and future research directions that may facilitate the development of novel strategies for the prevention and treatment of angiogenesis-related disorders were highlighted.

## Contents

## 1. Introduction

Angiogenesis, the process by which new blood vessels arise from pre-existing vasculature and subsequently undergo structural remodeling, is essential for tissue homeostasis, wound healing and organ regeneration (1). Classical angiogenic processes primarily occur through endothelial sprouting, intussusceptive angiogenesis, and vascular fusion. In addition to these canonical mechanisms, certain pathological conditions enable tissues, particularly tumors, to establish a blood supply through alternative vascularization strategies, such as vessel co-option and vasculogenic mimicry (VM) (2). Under normal physiological conditions, vascular growth is tightly controlled by a dynamic equilibrium between pro-angiogenic and anti-angiogenic factors. Disturbance of this balance can result in excessive or aberrant vascularization, contributing to the development and progression of numerous diseases, including malignant tumors and neovascular retinal disorders (3,4). Given its pivotal role in both physiological and pathological processes, angiogenesis has been the focus of

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*Abbreviations:* ZEB1, Zinc finger E-box binding homeobox 1; EMT, epithelial-mesenchymal transition; VM, vasculogenic mimicry; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; PTMs, post-translational modifications; CtBP, C-terminal binding protein; HDAC, histone deacetylase; hESCs, human embryonic stem cells; VESCs, vascular endothelial stem cells; EndMT, endothelial mesenchymal transition; CoNV, corneal neovascularization; CDKis, cyclin-dependent kinase inhibitors; CAFs, cancer-associated fibroblasts; CSCs, cancer stem cells

*Key words:* ZEB1, angiogenesis, therapeutic, EMT

extensive research for decades. Consequently, elucidating the molecular mechanisms that regulate vascular growth has become a major research priority and has facilitated the development of anti-angiogenic therapies as important treatment strategies for a variety of angiogenesis-associated diseases (5).

Vascular endothelial cells serve as the primary effector cells driving angiogenesis. Emerging evidence has revealed substantial transcriptional and functional heterogeneity among endothelial populations across different organs and tissue microenvironments. This heterogeneity largely determines tissue-specific vascular functions and influences susceptibility to diverse pathological conditions (6,7). Among the molecular networks governing vascular growth, signaling pathways mediated by vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) are recognized as core regulatory axes. These pathways function in a coordinated and complementary manner to regulate distinct stages of angiogenic development (8-10). Nevertheless, angiogenesis is not controlled exclusively by endothelial cells. Multiple cellular components of the tissue microenvironment, including tumor cells, immune cells and fibroblasts, as well as environmental stimuli such as hypoxia and inflammation, can profoundly influence vascular formation by modulating endothelial function (11). Therefore, angiogenesis is orchestrated through dynamic interactions between endothelial cell-intrinsic signaling networks and extrinsic cues derived from the surrounding microenvironment.

Therapeutic strategies targeting angiogenic signaling pathways, including anti-VEGF antibodies and multi-target tyrosine kinase inhibitors, have demonstrated significant clinical efficacy in the treatment of solid tumors and ocular neovascular disorders. These successes have provided strong proof-of-concept for anti-angiogenic therapy as a viable therapeutic approach (12). However, accumulating clinical evidence has highlighted several important limitations of current anti-angiogenic treatments, including variable therapeutic responses, the development of acquired resistance, and compensatory activation of alternative pro-angiogenic pathways resulting from adaptive network reprogramming (13,14). These challenges suggest that pathological angiogenesis cannot be fully explained by the VEGF-, PDGF- and FGF-centered signaling axes alone. Consequently, identifying upstream regulators and alternative molecular networks that coordinate multiple angiogenic pathways has become increasingly important for elucidating the mechanisms underlying persistent neovascularization and therapeutic resistance. Such efforts may facilitate the development of more effective and durable anti-angiogenic strategies.

Zinc finger E-box-binding homeobox 1 (ZEB1) is a member of the zinc finger E-box-binding homeobox (ZEB) family of transcription factors, which comprises two closely related proteins, ZEB1 and ZEB2. Although these factors share considerable structural homology and overlapping functions, they exhibit distinct tissue distributions and biological activities (15). Owing to its prominent roles in epithelial-mesenchymal transition (EMT), cellular plasticity and vascular regulation, ZEB1 has attracted substantially greater attention and therefore serves as the primary focus of the present review.

Initially identified as a transcriptional repressor involved in embryonic development, ZEB1 was subsequently established as a master regulator of EMT (16,17). As a central transcriptional integrator, it coordinates multiple signaling pathways, including TGF-β, Notch and Wnt/β-catenin, thereby influencing cell fate determination, phenotypic plasticity, migration and survival (18). Emerging evidence further indicates that its biological functions extend beyond EMT, encompassing important roles in vascular remodeling and angiogenesis through the regulation of endothelial cell behavior and angiogenic microenvironmental signaling (19-21). In the present review, current knowledge regarding the roles of ZEB1 in both physiological and pathological angiogenesis were summarized, with particular emphasis on the molecular mechanisms through which it regulates endothelial function and orchestrates angiogenic microenvironmental responses. The therapeutic potential of targeting ZEB1 was further discussed and future perspectives for the development of precision therapies aimed at angiogenesis-related diseases were highlighted.

## 2. Structure and post-translational modifications of ZEB1

ZEB1, also known as δEF1 or TCF8, belongs to the ZEB family of transcription factors. Its molecular functions are governed by the coordinated action of distinct structural domains and by multilayered regulation through post-translational modifications (PTMs) (Fig. 1). While its structural domains determine DNA-binding specificity and protein-protein interactions (PPIs), PTMs dynamically modulate ZEB1 activity and stability, thereby fine-tuning its transcriptional regulatory capacity. Through these integrated mechanisms, ZEB1 exerts broad regulatory effects on diverse biological processes, including EMT, cell proliferation and cell migration.

Structurally, ZEB1 contains two clusters of C2H2-type zinc finger domains at its N-terminus (NZF) and C-terminus (CZF), which specifically recognize and bind conserved E-box sequences [5'-CACCT(G)-3'] in target gene promoters, forming the structural basis for DNA binding and transcriptional regulation (22). The central region includes a homeodomain that does not bind DNA directly but mediates PPIs. At the C-terminal end, ZEB1 features a C-terminal binding protein (CtBP) interaction domain with a conserved PXDLS motif (Pro-X-Asp-Leu-Ser) that recruits the corepressor CtBP and assembles histone deacetylase (HDAC) complexes to repress target gene transcription (23). ZEB1 also contains a SMAD-binding domain, which mediates the recruitment of downstream effectors in the TGF-β signaling pathway, and a p300/CAF-binding domain, where lysine acetylation modifications regulate the switch between transcriptional activation and repression (18).

A diverse array of PTMs enables the fine-tuned regulation of ZEB1 activity. Site-specific phosphorylation by different kinases modulates its DNA-binding affinity, the recruitment of corepressor complexes, and protein stability. Phosphorylation by PKC attenuates the DNA-binding capacity of ZEB1, which relieves transcriptional repression and increases target gene expression (24). Under DNA-damage conditions, ATM-mediated phosphorylation stabilizes nuclear ZEB1, thereby promoting the DNA damage response and conferring radio-resistance (25). In addition, activated ERKs

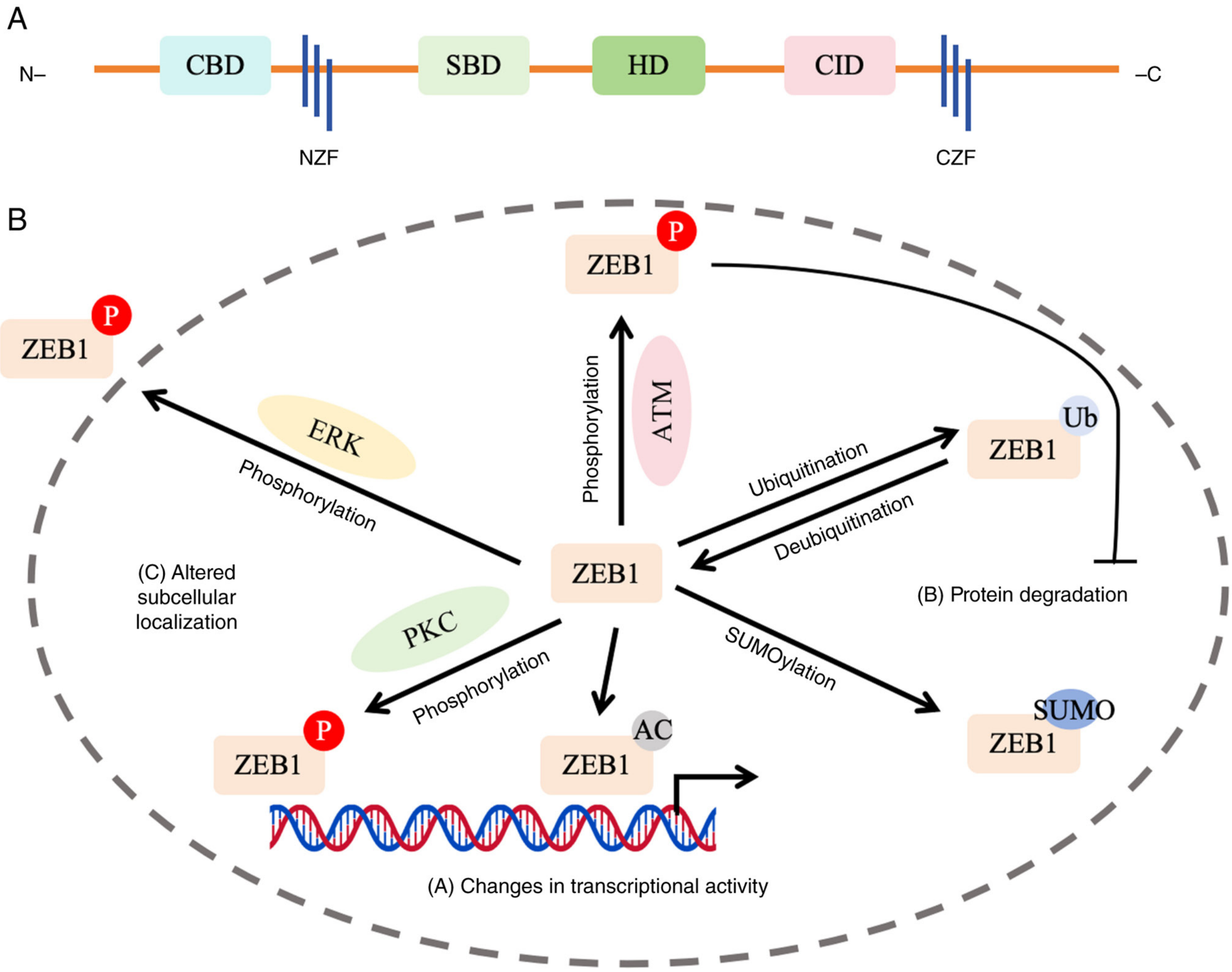

Figure 1. ZEB1 structure and protein post-translational modification schematic. (A) ZEB1 is formed by two DNA-binding zinc finger domains located near the N-terminal (NZF) and C-terminal (CZF) regions. Other domains include CBD, SBD, HD and CID. (B) ZEB1 is regulated by phosphorylation, acetylation, SUMOylation, and ubiquitination/deubiquitination, which together affect its stability, localization, and transcriptional activity. →: promote; -|: inhibit. ZEB1, Zinc finger E-box binding homeobox 1; HD, homeodomain; CID, C-terminal binding protein interaction domain; SBD, SMAD-binding domain; CBD, p300/CAF-binding domain.

phosphorylate ZEB1, thereby promoting its translocation from the nucleus to the cytosol (26). Acetylation further modulates ZEB1 function by altering its interactions with CtBP, HDAC or p300, PCAF, and Tip60 complexes, thereby switching its role between transcriptional repression and activation. This mechanism allows acetylation to influence TGF-β/BMP signaling and downstream processes including EMT, tumor progression and angiogenesis (27,28). SUMOylation has also been shown to regulate ZEB1 stability. In hepatocellular carcinoma (HCC) models, SUMOylation enhances ZEB1 protein stability, thereby promoting EMT and invasive behavior (29,30). Finally, ZEB1 protein levels are tightly governed by the balance between ubiquitination and deubiquitination. The E3 ligase Siah promotes ubiquitin-mediated degradation of ZEB1, suppresses EMT and impedes breast cancer (BC) progression, whereas the deubiquitinases USP51 and USP18 stabilize ZEB1 in BC and esophageal squamous cell carcinoma, respectively, thereby enhancing migratory and invasive potential (31-33). In addition, it has been recently shown that crosstalk among PTMs finely regulates ZEB1 function. Acetylation of lysine 811 (K811) protects ZEB1 from recognition and degradation by the ubiquitin-proteasome system, thereby maintaining its protein stability and transcriptional regulatory activity (34). Similarly, the phosphorylation of serine 585 (S585) mediated by ATM kinase can also inhibit ZEB1 degradation and enhance its transcriptional activity (25).

Thus, the structural domains of ZEB1 provide the molecular framework for its transcriptional regulatory activity, whereas PTMs modulate its stability, subcellular localization, DNA-binding capacity and cofactor recruitment preferences in response to specific signaling contexts. Together, these features enable ZEB1 to adopt distinct functional states under different cellular conditions. They also help explain the context-dependent roles of ZEB1 across diverse cell types and signaling environments, providing a molecular basis for its involvement in vascular homeostasis and pathological vascular remodeling.

## 3. Role of ZEB1 in physiological angiogenesis

The vascular system is one of the earliest functional organ systems to form during embryonic development. It consists of a complex branching network composed of vascular endothelial cells and supporting cells and plays a crucial role in maintaining physiological homeostasis (35). The differentiation of vascular endothelial cells represents a key early event in angiogenesis and the establishment of the vascular network (36). Luo *et al* (19) observed that ZEB1 expression progressively decreases during the directed differentiation of human embryonic stem cells (hESCs) into vascular endothelial cells (19). Their work further demonstrated that ZEB1 directly binds to promoter regions and transcriptionally represses the expression of endothelial-specific genes, including VEGFR2, CD146 and CD144, thereby suppressing their transcriptional activity and ultimately inhibiting endothelial differentiation and angiogenesis. These findings suggest that ZEB1 functions as a gatekeeper during the early stages of endothelial lineage differentiation by repressing endothelial-specific transcriptional programs, thereby ensuring proper temporal control of differentiation.

However, during embryonic development in ZEB1 heterozygous knockout mice, investigators observed a phenotype characterized by impaired angiogenesis. Previous studies have shown that homozygous ZEB1 knockout mice can develop to term but die shortly after birth and feature severe thymic defects and extensive skeletal abnormalities derived from neural crest lineages (37). In Zeb1 knockout mice, perinatal death is accompanied by small hemorrhages and vascular malformations in the head as early as embryonic day 11.5 (E11.5). By E15.5, these phenotypes intensify, presenting as growth retardation, edema, multifocal hemorrhage, and curling of the limbs and tail, along with markedly reduced pulmonary capillary density, delayed vascularization, and impaired cardiomyocyte differentiation (37-39). These findings suggest that ZEB1 gene expression is important for the development of the embryonic vascular system and associated organs. Notably, this model represents systemic gene dosage insufficiency; therefore, the observed vascular abnormalities cannot be simply interpreted as direct consequences of endothelial ZEB1 deficiency. Instead, a systemic reduction in ZEB1 levels may indirectly affect vascular development through non-endothelial cell-mediated mechanisms.

To further elucidate cell-autonomous effects, investigators crossed Tie2-Cre transgenic mice with Zeb1$^{fl/fl}$ mice to generate a constitutive endothelial cell-specific Zeb1 knockout model, termed Zeb1$^{\Delta EC}$. In this model, Tie2-Cre is continuously expressed in endothelial cells from embryonic stages onward and does not require exogenous induction, resulting in stable ZEB1 deletion throughout development and adulthood. In the context of skeletal vascularization, the endothelial-specific deletion of ZEB1 led to a reduction in type H vessel formation in bone. However, the density of CD31$^+$ vessels in non-skeletal tissues, including the heart, liver, kidney and spleen, was comparable between Zeb1$^{\Delta EC}$ mice and littermate controls. Mechanistically, ZEB1 maintains histone acetylation at the promoter regions of Dll4 and Notch1, thereby directly activating their transcription and enhancing Notch signaling to promote type H vessel formation (40). By contrast, Fu *et al* (41) generated an inducible endothelial cell-specific Zeb1 conditional knockout mouse model, termed Zeb1$^{i\Delta EC}$, by crossing Zeb1$^{fl/fl}$ mice with Cdh5-Cre$^{ERT2}$ mice. When ZEB1 inactivation was induced with tamoxifen at 8 weeks of age, the investigators observed no obvious differences in vascular morphology or vascular density between Zeb1$^{i\Delta EC}$ and wild-type mice. To further evaluate the role of endothelial ZEB1 in postnatal physiological angiogenesis, ZEB1 deletion was induced on postnatal days 3 and 6, followed by retinal whole-mount immunofluorescence staining on post-natal day 7. No significant defects in retinal angiogenesis were observed. Together, these findings suggest that during vascular homeostasis and short-term postnatal retinal vascular expansion, ZEB1 deficiency may be compensated by other angiogenic signaling pathways and therefore may not produce overt morphological abnormalities. By contrast, type H vessel formation in bone appears to be more sensitive to ZEB1 loss, suggesting that ZEB1 may primarily exert its vascular functions within specific endothelial cell subpopulations and tissue microenvironments.

In addition to participating in the formation of specific vascular subtypes, ZEB1 may also contribute to the long-term maintenance and regeneration of vascular networks by regulating state transitions in vascular endothelial stem cells (VESCs). During the later stages of organ development and the maintenance of vascular homeostasis, the continuous renewal of the vascular network primarily depends on VESCs, which possess the capacity for self-renewal and the generation of new endothelial cells. Yu *et al* (42) first identified, through *in vivo* lineage tracing, a subpopulation of endothelial cells expressing the protein C receptor (Procr), termed Procr$^+$ endothelial cells. This cell population exhibits long-term self-renewal capacity and can differentiate into mature vascular endothelial cells as well as pericytes. Further studies revealed that Procr$^+$ endothelial cells display certain features associated with endothelial mesenchymal transition (EndMT) and exhibit high levels of ZEB1 expression. Consequently, ZEB1 has been proposed as an important molecular marker of this endothelial subpopulation (41). Subsequent studies have shown that ZEB1 can transcriptionally repress Wif1, thereby preventing excessive activation of the Wnt/β-catenin signaling pathway and promoting the transition of VESCs from a highly proliferative state to a relatively quiescent state. This mechanism suggests that ZEB1 contributes to the maintenance of endothelial stem cell quiescence through the modulation of Wnt/β-catenin signaling, thereby playing a regulatory role in vascular homeostasis and regeneration (42).

Current evidence suggests that ZEB1 may perform stage- and endothelial subpopulation-dependent functions in vascular biology. During the early differentiation of hESCs toward the endothelial lineage, ZEB1 can restrict the initiation of the endothelial fate program. By contrast, within specific tissue vasculatures or endothelial progenitor subpopulations, ZEB1 may contribute to the maintenance of endothelial cell states, angiogenesis and vascular homeostasis. Indeed, molecules exhibiting stage-dependent functions, such as ZEB1, are not uncommon. For example, Notch signaling suppresses excessive endothelial cell migration and proliferation during early embryonic development, whereas during vascular sprouting and remodeling, the Dll4-Notch axis coordinates tip-stalk cell specification, thereby promoting proper vessel wall formation and the establishment of a functional vascular network (43). Therefore, the role of ZEB1 cannot be simply categorized as pro- or antiangiogenic. Instead, it should be interpreted in the context of developmental stage, tissue origin, endothelial cell subtype, and local signaling environment. However, current evidence is largely derived from systemic genetic models, *in vitro* differentiation systems, or a limited number of specialized endothelial cell subpopulations, making it difficult to fully elucidate the endothelial cell-autonomous functions of ZEB1 in endothelial cells. In addition, recent single-cell transcriptomic studies have revealed substantial transcriptional heterogeneity among endothelial cells across different organs and tissue environments (44). Different endothelial cell subpopulations play distinct roles in angiogenesis, vascular homeostasis and tissue-specific functions. However, the expression patterns and functional roles of ZEB1 across these diverse endothelial subtypes remain largely unexplored and require further systematic investigation.

## 4. ZEB1 in pathological angiogenesis

*ZEB1 in vascular endothelial cells.* Vascular endothelial cells are the primary effector cells of angiogenesis, and their proliferation, migration and phenotypic plasticity play critical roles in the formation of abnormal blood vessels. Previous studies suggest that ZEB1 can participate in pathological angiogenesis in endothelial cells by directly regulating key processes such as endothelial proliferation and phenotypic transition (39,45).

Multiple microenvironmental factors, including hypoxia, inflammation and oxidative stress, are recognized as major drivers of pathological angiogenesis. In a corneal neovascularization (CoNV) model induced by alkali burn, local tissue injury leads to a pronounced hypoxic environment, which markedly upregulates the expression of hypoxia-inducible factor-1α in vascular endothelial cells and subsequently promotes the transcriptional upregulation of ZEB1 (46,47). Upregulated ZEB1 can form a transcriptional repression complex with CtBP and directly suppress the transcription and expression of cyclin-dependent kinase inhibitors (CDKis) (39). The downregulation of CDKis relieves inhibitory constraints on endothelial cell cycle progression, thereby promoting endothelial proliferation and contributing to alkali burn-induced CoNV formation. A similar phenomenon has also been observed in diabetic retinopathy (DR). Under ischemic and hypoxic conditions, ZEB1 expression is markedly upregulated in retinal vascular endothelial cells. ZEB1 can bind to the 5'-untranslated regions of the CAVIN3 gene, thereby promoting its transcription. The resulting upregulation of CAVIN3 subsequently activates the ERK/JAG1 signaling pathway, contributing to the progression of DR-associated pathological angiogenesis (48). These studies suggest that, in pathological angiogenic microenvironments, ZEB1 can respond to microenvironmental stimuli such as hypoxia and drive aberrant endothelial cell proliferation and neovascularization through multiple signaling axes. Notably, Jin *et al* (39) reported that ZEB1 heterozygous knockout did not reduce VEGF expression, suggesting that the proangiogenic effects mediated by ZEB1 may not depend on the upregulation of VEGF expression. These findings suggest that ZEB1 may participate in certain forms of VEGF-independent pathological angiogenesis and provide potential mechanistic insights into why some vascular proliferative diseases show incomplete responses or acquired tolerance to anti-VEGF therapy.

EndMT refers to the biological process through which endothelial cells partially or completely lose their endothelial characteristics under specific stimuli and acquire mesenchymal characteristics (49). A recent study suggests that during angiogenesis, a subset of endothelial cells may transiently acquire mesenchymal-like features during the sprouting phase, which enhances their migratory capacity and facilitates new vessel formation, whereas sustained or excessive EndMT can contribute to pathological angiogenesis (50). TGF-β1 is considered one of the key signaling molecules that induces EndMT. Zhang *et al* (51) reported that in human umbilical vein endothelial cells, TGF-β1 upregulates ZEB1 expression through the UCA1/miR-455 signaling pathway, thereby inducing EndMT and increasing endothelial cell viability, proliferation, migration and tube formation capacity. In addition, under high-glucose conditions, the HDAC7/FOXO1 signaling axis can similarly activate ZEB1 expression and induce EndMT, promoting the transition of endothelial cells from a relatively quiescent state to a proliferative state. This process is often accompanied by microvascular pathological changes, including increased vascular permeability, basement membrane thickening, pericyte loss and the formation of acellular capillaries (51). These findings suggest that, under pathological stimuli such as TGF-β and hyperglycemia, ZEB1-mediated EndMT may promote pathological angiogenesis. Notably, ZEB1 does not merely function as a passive downstream effector of TGF-β signaling. Another study revealed that ZEB1 can interact with CBP/p300 and co-occupy the promoter region of the TGF-β gene, thereby promoting its transcriptional activation (45). Thus, TGF-β1 can induce ZEB1 expression and initiate EndMT, whereas upregulated ZEB1 may further increase TGF-β transcription, potentially forming a positive feedback regulatory loop. During pathological angiogenesis, sustained activation of this feedback mechanism may lead to excessive EndMT and ultimately the promotion of aberrant neovascularization.

In summary, under various pathological stimulation conditions, ZEB1 becomes aberrantly activated. On the one hand, it promotes endothelial cell proliferation by transcriptionally regulating downstream target genes and signaling pathways. On the other hand, as a key transcriptional regulator of EndMT, ZEB1 can alter the endothelial cell phenotype, thereby affecting vascular stability and promoting pathological vascular remodeling (Fig. 2). Together, these findings suggest that in pathological contexts, ZEB1 may contribute to abnormal angiogenesis by regulating endothelial cell proliferation and phenotypic plasticity.

*ZEB1 in non-endothelial cells and the angiogenic microenvironment.* In addition to endothelial cell regulation, angiogenesis is also shaped by the local microenvironment. This microenvironment consists of various cellular and non-cellular components, including perivascular cells, fibroblasts, immune cells, tumor cells and cancer stem cells (CSCs). These components promote angiogenesis by secreting growth factors, remodeling the extracellular matrix (ECM), and influencing inflammatory responses. Previous studies suggest that ZEB1 not only functions within endothelial cells but also indirectly influences angiogenesis by regulating the phenotype and secretory functions of non-endothelial cells (52,53).

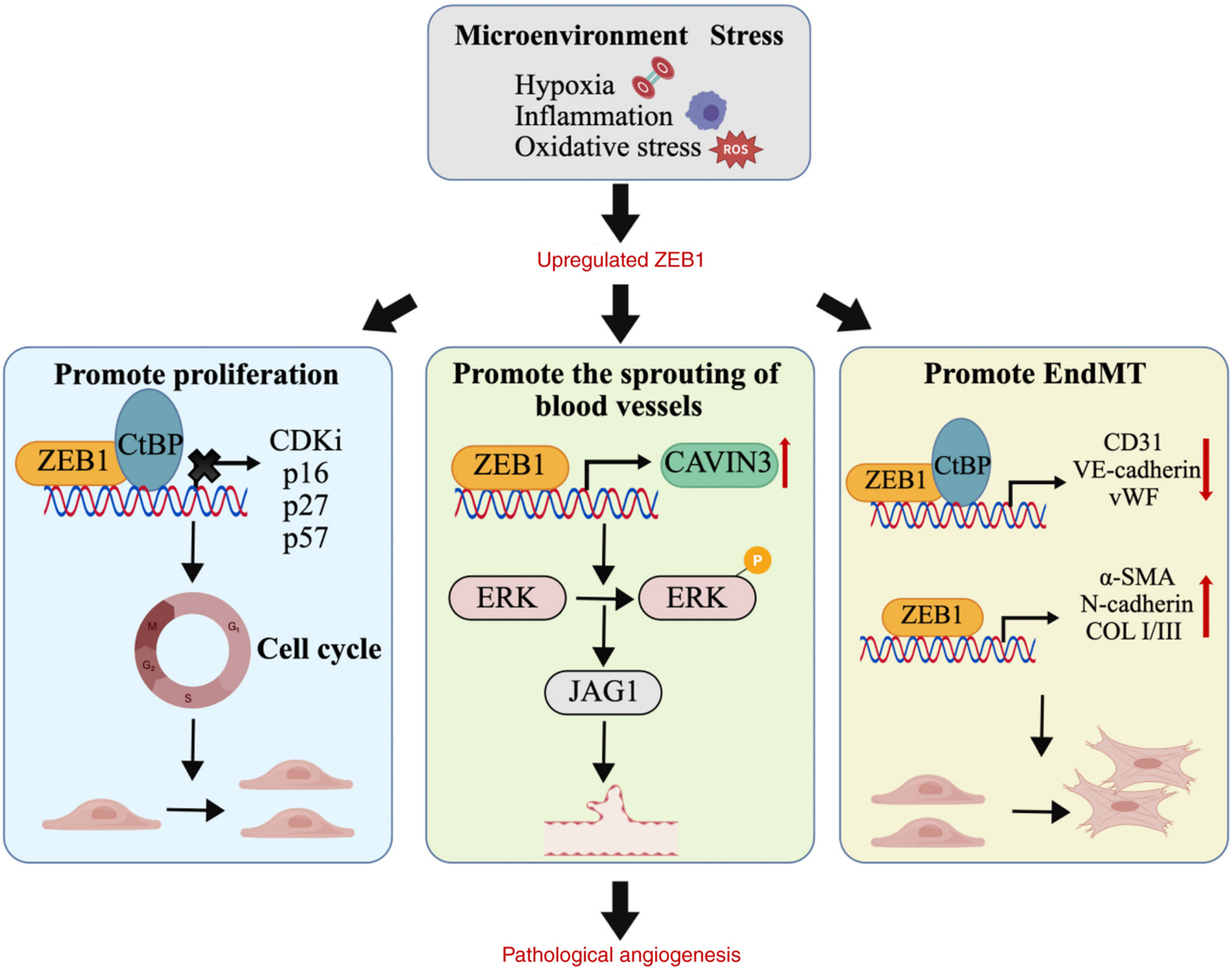

Figure 2. Proposed mechanisms by which ZEB1 promotes pathological angiogenesis. Microenvironmental stimuli, including hypoxia, inflammation and oxidative stress, induce ZEB1 expression and contribute to pathological angiogenesis through multiple mechanisms. First, ZEB1 forms a transcriptional repressor complex with CtBP, suppresses CDKis, relieves cell-cycle arrest, and promotes endothelial cell proliferation. Second, ZEB1 enhances vascular sprouting by transcriptionally activating Cavin3, which subsequently increases JAG1 expression through ERK signaling activation. Third, ZEB1 promotes EndMT by repressing endothelial gene expression while inducing mesenchymal marker expression, thereby facilitating endothelial phenotypic reprogramming and vascular remodeling. →: promote; x: inhibit. Created with BioGDP.com (100). ZEB1, Zinc finger E-box binding homeobox 1; CtBP, C-terminal binding protein; CDKi, cyclin-dependent kinase inhibitor; EndMT, endothelial-to-mesenchymal transition; ROS, reactive oxygen species.

Pericytes are important components of the angiogenic microenvironment and play key roles in maintaining microvascular structural integrity and vascular homeostasis through direct contact with endothelial cells and paracrine signaling interactions (54). At present, studies investigating the role of ZEB1 in pericytes are limited, although several indirect lines of evidence have been reported. During coculture with endothelial cells, mesothelial cells acquire a pericyte-like phenotype, accompanied by upregulation of ZEB1 expression and a shift from a rounded morphology to enlarged, migratory mesenchymal-like cells. These observations suggest that ZEB1 may participate in pericyte differentiation (52). In addition, ZEB1 expression has been detected in pericytes located within neovascular regions of idiopathic pulmonary fibrosis tissues, although its functional role in these cells has not been systematically investigated (55). Therefore, direct functional evidence clarifying the regulatory mechanisms of ZEB1 in pericytes is lacking, and its potential role in pericyte-mediated angiogenesis and vascular stabilization warrants further study.

Fibroblasts represent a central component of the angiogenic microenvironment and primarily regulate angiogenesis through paracrine mechanisms, thereby indirectly promoting vascular formation (56). In BC, ZEB1 is highly expressed in cancer-associated fibroblasts (CAFs) and functions by forming a complex with p53 and recruiting HDAC1/2, which promotes p53 deacetylation and degradation. This process suppresses the transcriptional activity of p53 and subsequently upregulates the expression and secretion of several proangiogenic factors, including FGF2, FGF7, VEGF and IL6, thereby contributing to the establishment of a proangiogenic microenvironment (53). In addition, single-cell transcriptomic analyses have revealed that inflammatory CAFs are markedly enriched in BRCA1-mutant triple-negative BC, where they interact with tumor endothelial cells through the CXCL and VEGF signaling pathways. Notably, tumor endothelial cells with high expression of ACKR1 exhibit upregulated expression of angiogenesis-related genes, including ANGPT2, MMP1 and SELE, and are positively correlated with ZEB1 expression, suggesting that ZEB1 may participate in the regulation of angiogenesis mediated by CAF-endothelial cell interactions (57).

Immune cells are important regulators within the angiogenic microenvironment. Under pathological conditions, infiltrating myeloid immune cells, such as macrophages and neutrophils, can adopt a phenotype that supports angiogenesis and contributes to an inflammatory microenvironment through cytokine secretion and ECM remodeling (58). Under physiological conditions, ZEB1 is expressed at low levels in immune cells from the bone marrow but can be strongly induced by inflammatory stimuli such as lipopolysaccharide. It has been identified that in macrophages, ZEB1 can directly bind to the p62 promoter and promote its transcription, thereby activating autophagy and helping maintain the inflammatory M1 phenotype (59). In addition, in a CoNV model induced by alkali burn injury, ZEB1 expressed in corneal immune cells and fibroblasts can directly bind to the promoter regions of inflammatory genes such as TGF-β1/3 and NF-κB, thereby enhancing their transcription and amplifying inflammatory signaling (60). Further investigations have demonstrated that in myeloid cells (Csf1r$^+$ cells), ZEB1 promotes cell survival under inflammatory conditions by suppressing apoptosis mediated through the Tnf/Tnfr1 signaling pathway, thereby prolonging the retention of these cells at sites of tissue injury and contributing to the development of CoNV (61).

Tumor cells are a major component of the angiogenic microenvironment. Through paracrine signaling, they activate endothelial cells and promote their proliferation and migration, thereby supporting new vessel formation. In BC, ZEB1 has been shown to directly activate VEGFA transcription by recruiting the transcription factor SP1 to the VEGFA promoter, thereby driving tumor angiogenesis through paracrine mechanisms (62). In glioma, ZEB1 can increase VEGFA expression by regulating ARL13B and activating the Hedgehog signaling pathway, which promotes both angiogenesis and tumor invasion (63).

CSCs constitute a highly plastic subpopulation within tumors, and their associated microenvironment also plays an important role in pathological angiogenesis (64,65). It has been revealed that CSCs can promote angiogenesis through paracrine signaling (66). Jiang *et al* (20) further demonstrated that in CSCs, ZEB1 activates the PI3K/p38/MAPK signaling pathway, which enhances the recruitment of the transcription factor SP1 to the VEGFA promoter, thereby increasing VEGFA expression and promoting tumor angiogenesis. In turn, vascular endothelial cells can provide the Notch ligand Jag1 to adjacent CSCs, inducing Notch1-dependent upregulation of ZEB1 and forming a positive feedback loop that further promotes tumor growth and angiogenesis.

Overall, in addition to its effects on endothelial cells, ZEB1 also influences the angiogenic microenvironment through multiple non-endothelial cell types (Fig. 3). Although the downstream signaling pathways activated by ZEB1 in non-endothelial cells may differ, their convergent effects often involve the secretion of multiple proangiogenic factors. These findings suggest ZEB1 may promote angiogenesis across different cellular contexts through relatively conserved transcriptional regulatory programs. In addition, ZEB1 may participate in the formation of multiple intercellular positive feedback loops, thereby continuously amplifying angiogenic signals within the local microenvironment and driving pathological angiogenesis. These findings indicate that future interventions should focus not only on targeting ZEB1 itself but also on ZEB1-mediated intercellular communication and feedback amplification mechanisms. However, direct evidence for a functional role of ZEB1 in pericytes remains limited. With respect to immune cells, the current review has largely focused on myeloid populations, whereas their roles in other immune cell subsets are less well understood. By contrast, ZEB1 has been more extensively studied in fibroblasts, tumor cells and CSCs; however, how these cell types coordinate angiogenesis through intercellular communication remains unclear. An improved understanding of how ZEB1 functions across interacting cell populations within the angiogenic microenvironment is essential for determining its role in pathological angiogenesis.

*ZEB1 in non-classical modes of vascular formation*. Under certain pathological conditions, tumors and other diseased tissues can obtain a blood supply through alternative vascularization mechanisms, including VM, vessel co-option and intussusceptive angiogenesis (11). These processes do not depend on endothelial proliferation and sprouting, but instead involve tumor cell plasticity, cell migration and ECM remodeling. ZEB1, as a regulator of cellular plasticity, has been implicated in these alternative modes of vascular formation.

VM refers to a process in which highly aggressive tumor cells, through cellular plasticity, form vessel-like channel structures that enable blood perfusion in the absence of endothelial cell involvement. This mechanism provides structural and metabolic support for sustained tumor growth, invasion and distant metastasis (67). Previous studies have indicated that ZEB1 plays an important regulatory role in VM formation. Liu *et al* (68) were the first to report that ZEB1 can promote VM formation in colorectal cancer cells by inducing EMT. ZEB1 is also involved in CSC-associated VM formation (69). In prostate cancer, ZEB1 promotes CSC stemness and VM formation through activation of the Src signaling pathway (70). Langer *et al* (71) further demonstrated that ZEB1 regulates autocrine signaling pathways involved in VM by modulating the expression of microRNA (miRNA or miR)-200c, miR-183, miR-96 and miR-182. Vascular endothelial cadherin (VE-cadherin) has been recognized as a key molecule in the regulation of VM (72). Studies have shown that ZEB1 can directly bind to the VE-cadherin promoter and increase its transcription, thereby increasing the ability of tumor cells to form VM structures (68,73). Moreover, in HCC, the deubiquitinase USP22 stabilizes the ZEB1 protein through its deubiquitinating activity, which enhances ZEB1-mediated VEGFA transcription and further promotes VM formation (74). VM is intrinsically dependent on tumor cell plasticity, EMT and ECM remodeling, all of which are core functional domains regulated by ZEB1. By integrating multiple mechanisms, including EMT and cancer stemness, ZEB1 enables tumor cells to acquire an endothelial-like phenotype and the ability to form perfusion-like channel structures. This process may allow tumors to maintain their blood supply when endothelial cell-dependent angiogenesis is insufficient or under the selective pressure of antiangiogenic therapy.

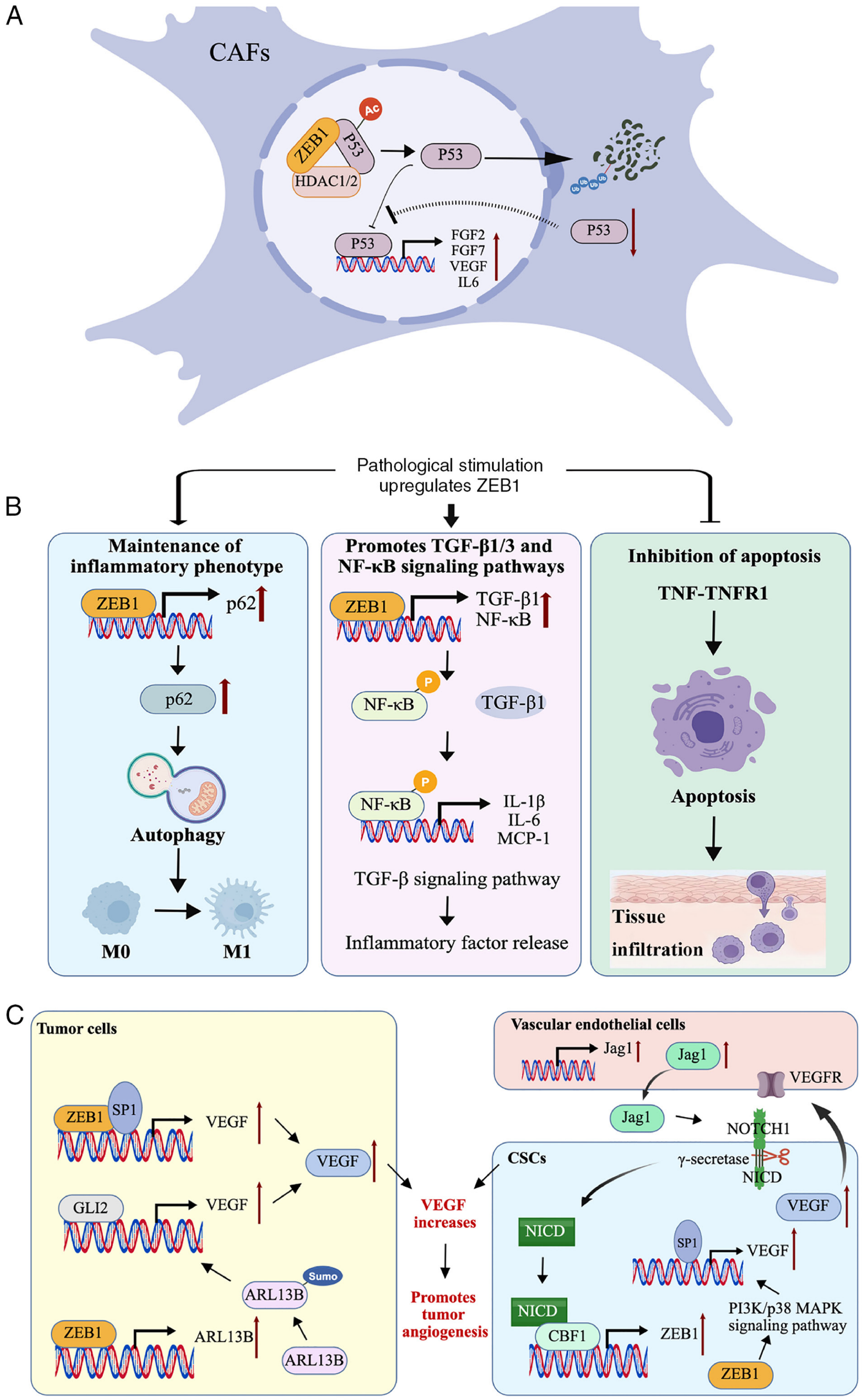

Figure 3. Schematic illustration of the multicellular mechanisms through which ZEB1 reshapes the angiogenic microenvironment. (A) In CAFs, ZEB1 forms a complex with p53 and recruits HDAC1/2, promoting p53 deacetylation and degradation. This relieves p53-mediated transcriptional repression of pro-angiogenic factors, including FGF2, FGF7, VEGF and IL-6, thereby enhancing angiogenic signaling within the tumor microenvironment. (B) In inflammatory cells, pathological stimuli induce ZEB1 expression and sustain inflammatory activation through the p62/NF-κB signaling pathway. ZEB1 promotes the transcription of TGF-β1, TGF-β3 and NF-κB target genes, enhances the production of pro-inflammatory mediators, and suppresses TNF-TNFR1 signaling-mediated apoptosis, thereby facilitating inflammatory cell infiltration and creating a pro-angiogenic inflammatory microenvironment. (C) In tumor cells and CSCs, ZEB1 promotes angiogenesis through multiple signaling pathways. ZEB1 enhances VEGF expression by activating SP1-dependent transcription and the Hedgehog signaling pathway, including through transcriptional upregulation of ARL13B. In CSCs, ZEB1 activates the PI3K/p38 MAPK-SP1 signaling axis to stimulate VEGF secretion. CSC-derived VEGF subsequently activates endothelial cells, inducing Jagged1 expression, which activates NOTCH1 signaling in neighboring CSCs and further increases ZEB1 expression, thereby establishing a positive feedback loop linking endothelial cells and CSCs. →: promote. Created with BioGDP.com (100). ZEB1, Zinc finger E-box binding homeobox 1; CAFs, cancer-associated fibroblasts; HDAC, histone deacetylase; CSCs, cancer stem cells; VEGF, vascular endothelial growth factor.

Vessel co-option describes the direct use of preexisting mature vessels by tumor cells, without the need for new vessel sprouting (75). This process primarily depends on the adhesion of tumor cells to the outer surface of blood vessels and their migration along the vascular wall, and its molecular mechanisms involve integrin, L1CAM and the YAP signaling pathways (76). A previous study suggested a close association between ZEB1 and integrin-related signaling pathways (77). In lung cancer cells, the miR-200 family forms a double-negative feedback loop with ZEB1, whereby downregulation of miR-200 leads to increased ZEB1 expression, thereby alleviating the repression of its downstream target CRKL (78). CRKL, an adaptor protein, activates the FAK/Src signaling pathway via β1 integrin signaling, promoting cellular invasion and metastasis. In addition, cooperation between ZEB1 and YAP has been reported in multiple tumor types. ZEB1 directly interacts with YAP, converting it from a transcriptional repressor to a coactivator, and together they drive target gene expression, promoting tumor cell plasticity and metastasis (79,80). However, direct evidence demonstrating the functional role of ZEB1 in vessel co-option remains limited, and its precise mechanisms require further investigation.

ZEB1 is increasingly linked to alternative modes of tumor vascularization. In VM, it acts as a transcriptional regulator that drives VM formation in tumor cells by promoting EMT and regulating VE-cadherin expression, thereby enabling the formation of endothelium-independent perfusion channels across multiple tumor types. By contrast, the role of ZEB1 in vessel co-option remains less well defined. Existing studies suggest that it is associated with integrin, FAK signaling and the YAP pathway, suggesting its potential involvement in this process. Clarifying how ZEB1 contributes to vessel co-option may provide new insight into the broader regulatory network of tumor vascularization and inform strategies to overcome resistance to antiangiogenic therapies.

## 5. Therapeutic strategies

Although the molecular mechanisms of ZEB1 in pathological angiogenesis are well-established, current strategies targeting ZEB1 for vascular intervention remain confined primarily to cellular models, with few studies advancing to animal or *in vivo* systems (Table I). Current approaches for targeting ZEB1 can be broadly divided into two categories: Small-molecule inhibitors that disrupt the ZEB1-CtBP transcriptional repressor complex, and nucleic acid-based strategies, including small interfering RNAs (siRNAs), short hairpin RNAs and miRNA mimics, that directly reduce ZEB1 expression.

As a CtBP substrate analog, MTOB can functionally attenuate ZEB1-CtBP-mediated transcriptional repression by modulating CtBP activity and its association with transcriptional complexes. By contrast, NSC95397 appears to act primarily by disrupting the PPI between CtBP and ZEB1 (81,82). Both compounds can inhibit the formation of the ZEB1-CtBP complex *in vitro* and reduce cellular proliferative capacity. However, only 10 $\mu$M NSC95397 significantly suppresses endothelial cell migration and tube formation. In a mouse model of alkali burn-induced CoNV, the topical administration of NSC95397 markedly reduced CoNV, providing important evidence that targeting the ZEB1 transcriptional complex may be a viable strategy for treating pathological ocular angiogenesis (39). Although NSC95397 is often considered a potential small-molecule inhibitor of ZEB1, its target specificity remains limited. Previous studies initially identified NSC95397 as an inhibitor of CDC25 phosphatases (83,84). Moreover, because CtBP is broadly involved in multiple transcriptional regulatory processes, this class of compounds may also affect other CtBP-dependent signaling pathways. In addition, the current evidence is largely restricted to local administration and animal models; systematic evaluations of its pharmacokinetics, safety profile and long-term toxicity after systemic administration are still lacking.

Nucleic acid-based interventions can directly reduce ZEB1 expression at the post-transcriptional level, offering relatively high sequence specificity and targeting flexibility. With recent advances in nano-delivery systems, peptide micelle nanoparticles have been explored for the codelivery of ZEB1 siRNA and doxorubicin, thereby suppressing tumor growth while simultaneously interfering with tumor-associated angiogenesis (85). In addition, certain biomaterials have also been used to modulate ZEB1-related signaling pathways. For example, reduced graphene oxide hydrogels can activate the ZEB1/Notch1 signaling pathway, thereby promoting osteogenic-angiogenic coupling and bone regeneration (86). These findings suggest that biomaterial-mediated regulation of ZEB1 may represent a new strategy for modulating angiogenesis-associated tissue repair. Compared with small-molecule inhibitors, nucleic acid-based strategies theoretically provide greater targeting precision. However, their translational application remains constrained by several factors, including delivery efficiency, tissue penetration, *in vivo* stability and immunogenicity. Nanomaterials may help overcome some of these delivery barriers by improving the stability and local enrichment of ZEB1-targeting nucleic acids. Notably, some nanomaterials may also directly regulate ZEB1-related signaling pathways, thereby influencing angiogenesis and tissue repair. Therefore, nanomaterials may have dual value in ZEB1-targeted interventions: They can serve not only as delivery platforms but also as functional materials that modulate ZEB1-associated angiogenic signaling.

Beyond the aforementioned strategies that have been validated in angiogenesis-related models, additional approaches for regulating ZEB1 have also been extensively explored in various disease contexts. For example, nucleic acid-based interventions, such as miR-200 mimics, can suppress pathological processes including tumor growth and tissue fibrosis by reducing ZEB1 expression (18,87-90). Moreover, several pharmacological agents and natural compounds, including metformin, caffeic acid ethyl ester and baicalin, have been reported to modulate ZEB1 expression or function through distinct signaling pathways (91-95). Collectively, these studies provide a broader strategic basis for targeting ZEB1 in pathological angiogenesis.

However, unlike diseases such as fibrosis, pathological angiogenesis usually involves a complex local microenvironment and dynamic interactions among multiple cell types. Therefore, achieving precise, endothelial cell-specific regulation remains a major challenge. At present, several endothelial cell-targeted delivery strategies have shown promise in antiangiogenic research. For instance, drug delivery systems designed

Table I. Therapeutic strategies targeting ZEB1.

| Angiogenesis | | | | | |
|---|---|---|---|---|---|
| Authors, year | Agent | Mechanism | Species | Model | (Refs.) |
| Jin *et al*, 2020 | MTOB | Interferes with CtBP activity, disrupting the binding of the ZEB1-CtBP complex | Mouse | Alkali burn-induced corneal neovascularization | (39) |
| Jin *et al*, 2020 | NSC95397 | Disrupts the ZEB1-CtBP complex, causing CtBP dissociation | Mouse | Alkali burn-induced corneal neovascularization | (39) |
| Fang *et al*, 2014 | ZEB1 siRNA | RNAi-mediated gene silencing | Mouse | Nonsmall cell lung cancer | (85) |
| Zhou *et al*, 2023 | ROS Scavenging Graphene-Based Hydrogel | Activation of the ZEB1/Notch1 pathway | Mouse | Calvarial defect model | (86) |
| Magenta *et al*, 2011 | miR200 mimics | Targets the 3'-UTR of ZEB1 mRNA, inhibiting ZEB1 translation | Mouse | Acute hindlimb ischemia | (90) |
| Others | | | | | |
| Hu *et al*, 2022 | Ethyl caffeate | Inhibits ZEB1 expression | Mouse | Renal fibrosis | (92) |
| Zhao *et al*, 2025 | Baicalein | Downregulates ZEB1 via FTOdependent m6A demethylation | Mouse | Pancreatic cancer | (94) |
| Xie *et al*, 2024 | Jia Wei Qingxin Lotus Seed Drink | JMJD1C/SP1/ZEB1 axis | Mouse | Diabetic kidney disease | (93) |
| Cortés *et al*, 2023;<br>Wang *et al*, 2018 | Metformin | miR200 mimics | Mouse<br>Human | Myeloid cell<br>Colorectal cancer cell lines | (59,95) |

to recognize VEGFR2-positive endothelial cells can induce endothelial cell apoptosis and exert antiangiogenic effects (96). Similarly, the delivery of the antiangiogenic fusion protein htsFLT01 by MiRGD-based nanocomplexes can target the tumor vasculature, thereby suppress angiogenesis and reduce tumor volume (97). These vascular-targeting technologies provide important references for further exploring precise ZEB1-targeted interventions in pathological angiogenesis.

## 6. Conclusions

In summary, accumulating evidence suggests that ZEB1 participates in the regulation of both physiological and pathological angiogenesis in a context-dependent manner. Under physiological conditions, ZEB1 contributes to endothelial homeostasis and vascular integrity through interactions with key developmental signaling pathways, including Wnt and Notch. In pathological settings, stimuli such as hypoxia and inflammation may promote aberrant ZEB1 activation, which has been associated with tumor angiogenesis, ocular neovascularization and the progression of several vascular-related diseases. Collectively, these findings support a role for ZEB1 in angiogenic regulation and highlight its potential relevance as a therapeutic target.

Despite its therapeutic promise, effective strategies for selectively targeting ZEB1 remain limited. Given that its activity is tightly controlled by multiple PTMs, modulation of the upstream regulatory machinery governing ZEB1 stability and function may provide an alternative avenue for therapeutic intervention. Furthermore, although ZEB1 and ZEB2 share substantial structural homology, emerging evidence suggests that they perform distinct and potentially complementary roles in vascular regulation (98,99). However, direct comparative studies within the same cellular and disease contexts remain scarce, and the extent of their functional redundancy or cooperation has yet to be fully elucidated.

Therefore, future investigations should focus on developing endothelial-specific delivery systems, improving the druggability of ZEB1-associated regulatory pathways, and systematically dissecting the unique and overlapping functions of ZEB family members through advanced genetic models and multi-omics approaches. A deeper understanding of these mechanisms will not only refine our knowledge of angiogenic regulation but also facilitate the development of precision therapies for angiogenesis-related diseases.

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## Availability of data and materials

Not applicable.

## Authors' contributions

RR and CY were responsible for the overall conceptualization and writing of the review. XY and LJ contributed to literature collection, data interpretation, and preparation of the figures and table. FC and LZ oversaw the critical review of the manuscript, contributed to the interpretation of the literature, and coordinated the study. LZ conducted project administration. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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