Roles of endothelial cell specific molecule-1 in tumor angiogenesis (Review)

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Abstract. Angiogenesis plays a crucial role in tumor growth and metastasis, and is heavily influenced by the tumor microenvironment (TME). Endothelial cell dysfunction is a key factor in tumor angiogenesis and is characterized by the aberrant expression of pro-angiogenic factors. Endothelial cell specific molecule-1 (ESM1), also known as endocan, is a marker of endothelial cell dysfunction. Although ESM1 is primarily expressed in normal endothelial cells, dysregulated ESM1 expression has been observed in human tumors and animal tumor models, and implicated in tumor growth, metastasis and angiogenesis. The precise role of ESM1 in tumor angiogenesis and its potential regulatory mechanisms are not yet conclusively defined. However, the aim of the present review was to explore the involvement of ESM1 in the process of tumor angiogenesis in the TME and the characteristics of neovascularization. In addition, the present review discusses the interaction between ESM1 and angiogenic factors, as well as the mechanisms through which ESM1 contributes to tumor angiogenesis. Furthermore, the reciprocal regulation between ESM1 and the TME is explored. Finally, the potential of targeting ESM1 as a therapeutic strategy for tumor angiogenesis is presented.

Contents

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1. Introduction

Tumors pose a serious threat to human health, and their occurrence, progression and metastasis are influenced by several factors. These include angiogenesis, which plays a crucial role in tumor growth. The formation of new blood vessels leads to the supply oxygen and nutrients to the tumor, contributing to its growth and metastasis (1). Consequently, inhibition of angiogenesis has emerged as a promising approach for cancer treatment. At present, a number of anti-angiogenic drugs, including bevacizumab and sorafenib are available for clinical use (2). However, the limited effectiveness and development of resistance in certain patients have restricted the application of these drugs (2). Therefore, novel targets are being sought to identify an alternative strategy for the development of more effective anti-angiogenic drugs.

Endothelial cell-specific molecule-1 (ESM1), also known as endocan, is a proteoglycan that is released from cells and circulates in the bloodstream (3). Under normal physiological conditions, ESM1 is primarily expressed in the bronchial epithelium, as well as in vascular endothelial cells in the lung and kidneys (4). However, under pathological conditions, ESM1 is aberrantly expressed and interacts with its substrate proteins to promote abnormal cell adhesion, proliferation and angiogenesis (5). During tumor development, ESM1 is sporadically expressed in tumor cells and upregulated in tumor vascular endothelial cells, thereby modulating angiogenesis (6-10).

The present study is a comprehensive review of the importance of ESM1 in tumor angiogenesis, which aims to summarize the underlying mechanisms. By elucidating the role of ESM1 in tumor angiogenesis, it is hoped that valuable ideas and directions will be provided for the future development of more effective anti-angiogenic therapies.

2. Structure and expression of ESM1

Structure of ESM1. ESM1 was initially isolated from a human umbilical vein endothelial cell (HUVEC) cDNA library constructed by Lassalle *et al* (11) in 1996. It is a secreted proteoglycan composed of an 165-amino-acid polypeptide covalently linked to a sulfated dermal polysaccharide chain (11,12). The gene encoding human ESM1 is located on chromosome 5 at the q11.2 gene locus (13). This gene consists of three exons, exons 1-3. Exon 1 encodes an N-terminal cysteine-rich region

that contains an epidermal growth factor (EGF)-like domain, while exon 2 encodes a phenylalanine-rich region that is considered to be involved in ESM1 function. Exon 3 encodes a cysteine-free C-terminal region of 33 amino acids, including a unique O-glycosylation site at serine 137 (13,14). The protein structure of ESM1 is illustrated in Fig. 1. The ESM1 protein detected in human serum and HUVEC supernatants has a molecular weight of 50 kDa. However, purified mature ESM1 obtained from the 293-ESM1 cell line is a 165-amino-acid protein with a predicted molecular weight of only 20 kDa, which indicates that post-translational modifications occur when ESM1 is secreted (15). The modification site has been identified to be serine 137, where a single dermatan sulfate polysaccharide chain is bound (15).

Expression and regulation of ESM1. ESM1 is physiologically expressed in various tissues with proliferative activity in the human body, including gastrointestinal glandular, bronchial, pulmonary capillary, glomerular and renal tubular tissues. Conversely, it is not expressed in tissues without proliferative properties, including large blood vessels and the spleen (5). However, expression and secretion of ESM1 can become abnormal under pathological conditions. In diseases associated with the endothelium, such as pneumonia, hypertension and coronary heart disease, the serum levels of ESM1 can be dysregulated; hence, ESM1 has been established as a potential marker for endothelial dysfunction (4,16,17). Furthermore, studies have revealed an association between aberrant ESM1 expression and the development of various tumors. For example, clinical investigations have observed increased ESM1 levels in secretions or serum from patients with nasopharyngeal, endometrial and ovarian carcinoma (18,19). In addition, elevated ESM1 expression has been observed in cancer cells, including cervical cancer, squamous cell cancer of the head and neck, esophageal cancer and hepatocellular cancer cells (6,8,20,21). Notably, ESM1 expression has been demonstrated to be increased in the vascular endothelial cells of prolactinoma and gastric cancer, indicating its involvement in tumor angiogenesis (22,23).

The expression of ESM1 is regulated by multiple factors. Inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and lipopolysaccharide (LPS), as well as hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), high glucose, high salt and lead, can upregulate ESM1 (24-26). By contrast, interferon-g, platelet-derived growth factor, angiotensin 2, endothelin 1 and insulin have inhibitory effects on ESM1 expression (27,28).

3. Processes of tumor angiogenesis

Regulation and major processes of tumor angiogenesis. Angiogenesis in tumors is regulated by a balance of pro- and anti-angiogenic factors. Neovascularization occurs when the levels of pro-angiogenic factors exceed those of anti-angiogenic factors (29).

Among pro-angiogenic factors, the VEGF family and its receptors have been extensively studied. The VEGF family includes VEGF subtypes A-E and placental growth factor, among which VEGF-A plays a major role in the regulation of angiogenesis (30). VEGF-A interacts with its receptors, primarily VEGF receptors 1 and 2 (VEGFR1/2), with a stronger affinity for VEGFR1 (31). However, the binding of VEGF-A to VEGFR-2 promotes mitosis and the permeability of vascular endothelial cells, leading to angiogenesis, and serves as the principal regulatory mechanism in angiogenesis (31). In the context of tumors, endothelial cells have been found to exhibit autocrine production of VEGF-A, while tumor cells exhibit paracrine secretion of VEGF-A (32). VEGF-A has been identified to be one of the most influential factors in tumor angiogenesis (32).

In addition to the VEGF/VEGFR-2 pathway, angiopoietin-2 (Ang2) and its receptor, which is known as Ang1 receptor or tyrosine-protein kinase receptor TEK, are also involved in tumor angiogenesis. Ang2 expression is normally low in dormant endothelial cells but can be upregulated by hypoxia, endothelial cell activation and VEGF-A (33). The upregulation of Ang2 expression in tumor endothelial cells increases vascular endothelial cell permeability, leading to tissue hypoxia and the subsequent upregulation of VEGF-A, thereby promoting angiogenesis (33).

Furthermore, tumor cells have been shown to secrete fibroblast growth factor (FGF) to stimulate endothelial cell proliferation (34). In addition, tumor-associated macrophages and fibroblasts secrete matrix metalloproteinases (MMPs) that degrade the extracellular matrix (ECM) and thereby facilitate tumor angiogenesis (35). These factors collectively contribute to the complex regulation of angiogenesis in tumors.

There are four main steps in the formation of tumor vessels. First, angiogenesis is initiated in response to stimulation from hypoxia, inflammation and reactive oxygen species in the tumor microenvironment (TME). Tumor cells release factors such as VEGF and FGF to induce angiogenesis through paracrine signaling (32). Endothelial cells, in turn, respond by autocrine signaling with increased VEGF production and Ang2 upregulation (33). Inflammatory, endothelial and stromal cells, among others, secrete MMPs, specifically MMP-2, -9 and -14 (36).

Secondly, vascular sprouting occurs as MMPs degrade the basement membrane (BM) and ECM. This weakens the connections between pericytes and endothelial cells, allowing endothelial cells in dormant vessels to sense angiogenic signals (36). In response, the endothelial cells at the leading edge of capillary growth are converted into tip cells, which are highly proliferative and can migrate towards the angiogenic signals (36,37).

Thirdly, vascular lumen formation occurs. Stalk cells, located behind the tip cells, proliferate and modify their morphology to establish adherent and tight junctions with neighboring endothelial cells. This process results in the formation of the vascular lumen (38,39).

Finally, vascular maturation occurs. Once the vascular lumen is formed, neovascularization occurs through a series of signaling events that recruit pericytes and facilitate the deposition of BMs. These processes contribute to the maturation of the newly formed vasculature. The various processes by which angiogenesis occurs in the TME are shown in Fig. 2.

Characteristics of tumor neovascularization. The distribution, morphology, structure and function of neovascularization in tumor tissues differ significantly from those of normal

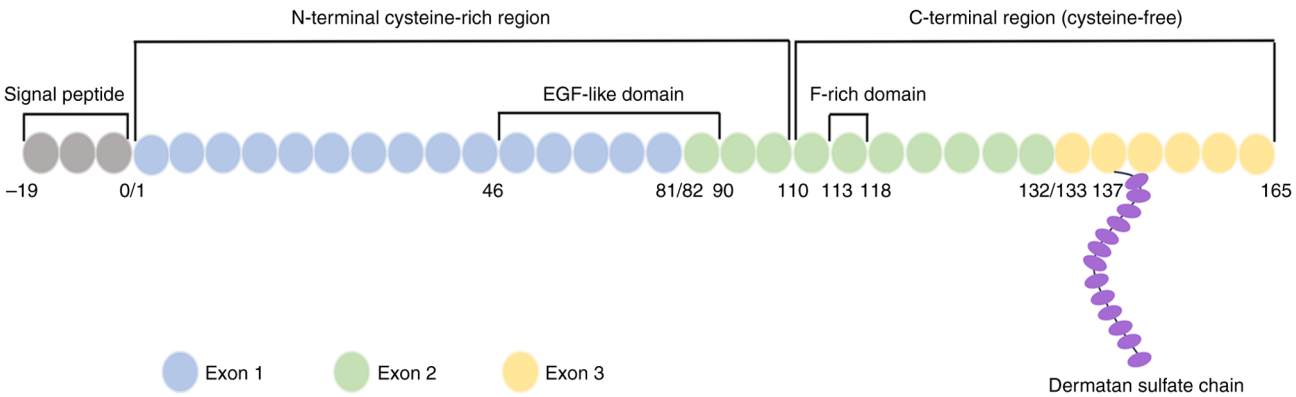

Figure 1. Protein structure of ESM1. In terms of protein structure, ESM1 consists of three domains: i) Signal peptide, which is removed when the protein matures; ii) N-terminal cysteine-rich region, and iii) C-terminal region (cysteine-free). There is an EGF-like domain in the N-terminal cysteine-rich region. The C-terminal region contains an F-rich domain and a dermatan sulfate chain bound to serine 137. ESM1, endothelial cell specific molecule-1; EGF, epidermal growth factor; F, phenylalanine.

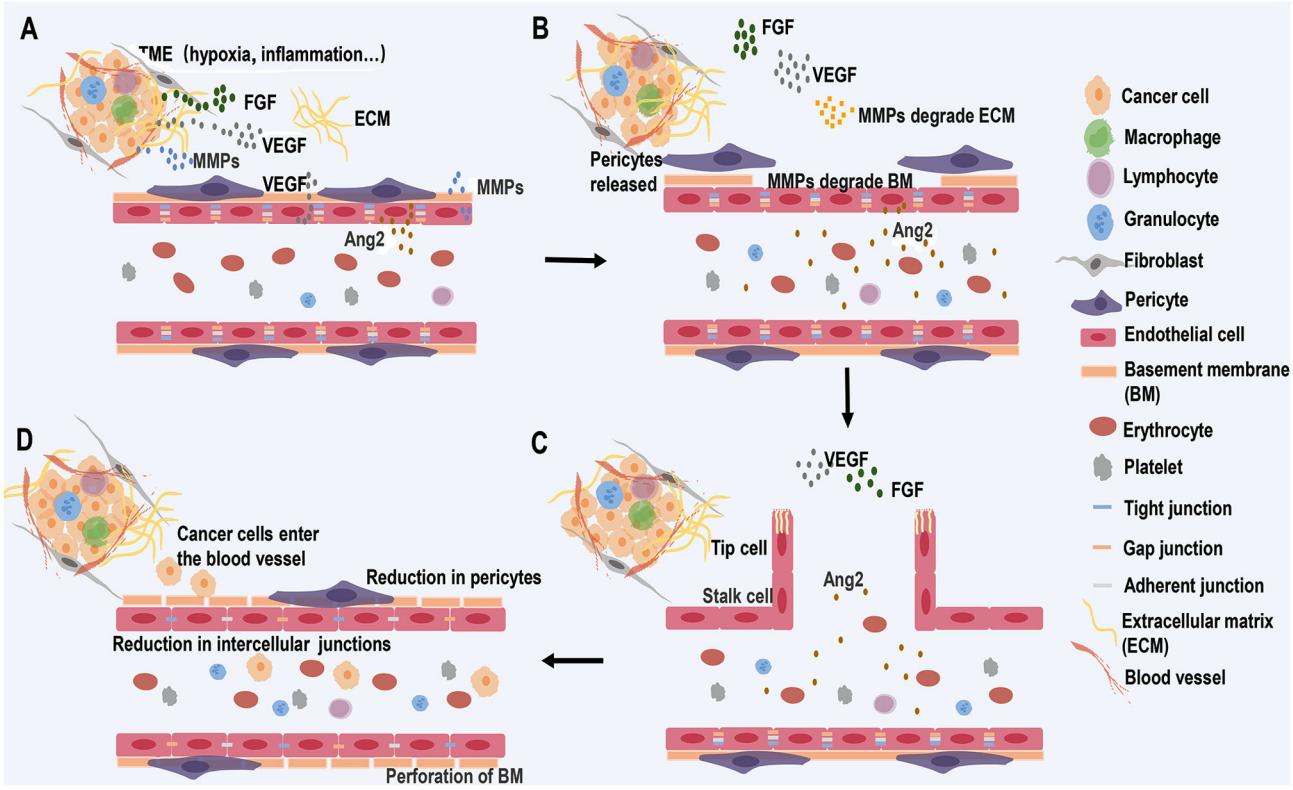

Figure 2. Process of tumor angiogenesis. (A) In the TME, angiogenesis is initiated by the release of VEGF and FGF from tumor cells, the increased production of VEGF and Ang2 by endothelial cells, as well as the secretion of MMPs by inflammatory, endothelial, stromal and other types of cells. (B) MMPs degrade the BM and ECM. This degradation weakens the connections between pericytes and endothelial cells, allowing endothelial cells in dormant vessels to sense angiogenic signals. (C) Endothelial cells in the leading edge of capillary growth are converted into tip cells. Stalk cells, located behind the tip cells, proliferate and modify their morphology to establish adherent and tight junctions with neighboring endothelial cells. This process results in the formation of the vessel lumen. (D) Vascular maturation occurs. The permeability of the new blood vessels is increased, due to a reduction in pericytes, disruptions in intercellular adherent and tight junctions, and abnormalities in BM structure. The increased permeability provides favorable conditions for tumor metastasis. TME, tumor microenvironment; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; Ang2, angiotensin 2; MMPs, matrix metalloproteinases; BM, basement membrane; ECM, extracellular matrix.

physiological blood vessels. In tumors, the distribution of blood vessels is not uniform, as a higher micro-vessel density is generally observed in the central region compared with the surrounding and normal tissues outside the tumor (40). However, certain studies have indicated that the blood vessel density within the tumor is lower than that in the surrounding tissue due to the production of anti-angiogenic factors by tumor cells and excessive matrix deposition, leading to hypoxia (40,41).

In addition to being unevenly distributed within the tumor, tumor blood vessels have distinct characteristics. They often exhibit a curved morphology, disorganized vascular networks

and increased vascular permeability. This increased permeability is attributed to a reduction in pericytes, disruptions in intercellular adherent junctions and tight junctions, and abnormalities in BM structure, including uneven thicknesses and perforations (42-45). These features provide favorable conditions for tumor metastasis, as shown in Fig. 2.

4. Regulation of ESM1 in tumor angiogenesis

Interaction of ESM1 with tumor angiogenesis factors. The role of ESM1 in angiogenesis has been established in various studies. For example, it has been revealed that ESM1 is specifically expressed in retinal endothelial tip cells during mouse development (46). In experiments with ESM1 knockout mice, it was observed that these cells had fewer filopodia and reduced phosphorylation of extracellular signal-regulated protein kinase (ERK) compared with those in wild-type mice, leading to delayed vascular development (46). Furthermore, ESM1 expression was found to be upregulated in mouse models of hypoxia-induced retinal vascular neovascularization and laser-induced choroidal vascular neovascularization (47). In addition, the administration of an intravitreal injection of ESM1 neutralizing antibody to the mice resulted in the significant downregulation of several vascular neovascularization-associated factors, including VEGFR1, VEGFR2, placental growth factor and MMP-2 (47).

The role of ESM1 in tumor angiogenesis has been confirmed through *in vivo* and *in vitro* experiments. For instance, a study showed that lung adenocarcinoma tumors subcutaneous transplanted in ESM1 knockout mice exhibited reduced neovascularization compared with those in wild-type mice (46). Similarly, the volume of subcutaneously transplanted tumors formed by ESM1 knockout ovarian cancer A2780 cells was smaller compared with these formed by control A2780 cells (48). In *in vitro* experiments, the tube formation ability of HUVECs was observed to decrease when they were incubated with supernatants from ESM1 knockdown A2780 cells (48). These findings suggested that ESM1 promotes angiogenesis *in vivo* and *in vitro*.

Further investigations into the mechanism of action of ESM1 have shown its involvement in the regulation of several angiogenic factors and receptors. For example, the knockdown of ESM1 in GH3 and MMQ rat prolactinoma cell lines led to the reduced expression of genes associated with angiogenesis, such as VEGFR2, von Willebrand factor and EGF receptor (EGFR) (22). Similar results were obtained when ESM1 was silenced in AN3CA and RL95-2 endometrial cancer cells, which resulted in the downregulation of the angiogenic factor receptors VEGFR1, VEGFR2 and EGFR, ultimately leading to reduced angiogenesis, while ESM1 overexpression had the opposite effects (49). ESM1 has been shown to influence the major angiogenic factor VEGF, as the knockdown of ESM1 decreased VEGF expression in human cervical cancer squamous cell carcinoma cells (50). Conversely, VEGF is able to regulate ESM1; *in vivo* experiments with VEGF-A knockout mice or mice injected with VEGFR2 blockers showed a reduction in the ESM1 expression of the mice (47). Studies have revealed that the binding of VEGF-A to VEGFR2 leads to the phosphorylation of VEGFR2 and the subsequent activation of downstream signaling pathways that regulate ESM1 expression (47,51). The interactions of ESM1 with factors associated with tumor angiogenesis are shown in Table I and Fig. 3.

In summary, ESM1 promotes angiogenesis via the regulation of angiogenic factors, and there is a reciprocal relationship between ESM1 and angiogenic factors, which form a positive feedback loop.

Role of ESM1 in the signaling pathway of tumor angiogenesis. Limited research has been conducted on the specific signaling pathways by which ESM1 regulates tumor angiogenesis. However, existing studies suggest the involvement of several signaling pathways, including the phosphoinositide 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK), Notch and nuclear factor-κB (NF-κB) pathways.

PI3K/AKT signaling pathway. PI3K and AKT play a critical role in various processes, including tumor growth, metabolism and angiogenesis (52). ESM1 has been found to act through the PI3K/AKT pathway during angiogenesis. For example, it was found that when HUVECs were cultured with the supernatants of SW480 and SW620 colorectal cancer cells transfected with ESM1 mimic, their tube-forming ability was increased (53). Further experiments demonstrated that the transfection of these cancer cells with ESM1 mimic upregulated the expression of MMP-2, MMP-3, MMP-9, VEGF, cyclooxygenase-2 and HIF-1α through the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway (53). Considering that ESM1 increases the binding of VEGF to VEGFR2 (46), and PI3K/AKT/mTOR is downstream of the VEGF/VEGFR2 pathway (54), this suggests that ESM1 activates the PI3K/AKT/mTOR pathway via the phosphorylation of VEGFR2, consequently upregulating the aforementioned angiogenesis-related factors. In a study of non-small cell lung cancer cells, it was observed that recombinant ESM1 directly bound to EGFR and facilitated the binding of EGF to EGFR, leading to activation of the EGFR signaling pathway (55). The activated EGFR, in turn, was indicated to upregulate ESM1 via Janus kinase/signal transducer and activator of transcription 3 signaling and ERK/ETS-like kinase, thereby establishing a regulatory loop between ESM1 and EGFR (55). In addition, another study revealed that the activated EGFR pathway sustains angiogenesis in solid tumors through the downstream PI3K/AKT/mTOR signaling pathway (56). Summaries of the mechanism by which ESM1 regulates tumor angiogenesis via the PI3K/AKT signaling pathway are shown in Table I and Fig. 3.

MAPK signaling pathway. The MAPK pathway, which includes the ERK, c-Jun N-terminal kinase (JNK) and p38 signaling pathways, plays a crucial role in a number of cellular processes, including cell proliferation, differentiation and apoptosis, angiogenesis and tumor metastasis (57). *In vivo* and *in vitro* experiments have confirmed that ESM1 regulates angiogenesis through the MAPK pathway. For example, *in vivo* experiments conducted using ESM1 knockout mice revealed a reduction in phosphorylated ERK in the retina, which led to delayed vascular development (46). In addition, *in vitro* experiments involving the stimulation of human retinal endothelial cells and HUVECs with recombinant ESM1 demonstrated the activation of MAPK (ERK, JNK and p38) signaling pathways associated

Table I. Tumor angiogenesis factors and signaling pathways regulated by ESM1.

First author/s, year	*In vivo* or *in vitro*	ESM1 expression	Biological importance	ESM1-regulated genes/proteins/pathway	(Refs.)
Cai *et al*, 2016	*In vitro*	Down	Inhibits the viability of GH3 and MMQ rat prolactinoma cell lines	VEGFR2; VWF	(22)
Rocha *et al*, 2014	*In vivo* and *in vitro*	Down	Inhibits retinal vascular outgrowth	VEGF; ERK	(46)
Su *et al*, 2018	*In vitro*	Up	Promotes retinal neovascularization	VEGFR1, VEGFR2, PIGF, MMP-2; ERK; P38	(47)
Li *et al*, 2023	*In vivo* and *in vitro*	Down	Inhibits ovarian cancer angiogenesis	VEGF; PI3K/Akt/mTOR	(48)
He *et al*, 2022	*In vitro*	Up	Promotes endometrial cancer angiogenesis	VEGFR1, VEGFR2, EGFR	(49)
Li, 2023	*In vitro*	Down	Inhibits proliferation, invasion and apoptosis of SiHa and ME-180 cervical squamous cell carcinoma cell lines	VEGF	(50)
Yang *et al*, 2023	*In vivo* and *in vitro*	Up	Promotes colorectal cancer angiogenesis	MMP-2, MMP-3, MMP-9, VEGF, COX-2, HIF-1α; PI3K/Akt/mTOR	(53)
Yang *et al*, 2020	*In vitro* and *in vivo*	Up	Promotes non-small cell lung cancer growth	EGF; EGFR; JAK/STAT3; ERK/ELK	(55)
Lee *et al*, 2014	*In vitro* and *in vivo*	Up	Promotes vascular cell permeability	VEGFR1, VEGFR2, MAPK (ERK, JNK, P38)	(58)
Kang *et al*, 2022	*In vivo* and *n vitro*	Up/down	Promotes/inhibits breast cancer angiogenesis	VEGF; DLL4	(63)
Huang *et al*, 2021	*In vitro*	Down	Inhibits SW13 human adrenocortical carcinoma cell line growth	DLL4	(64)
Kumar and Mani, 2021	*In vitro*	Up	Promotes NO and ROS in endothelial cells	NF-κB	(68)

ESM1, endothelial cell specific molecule-1; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; VWF, von Willebrand factor; PIGF, placental growth factor; MMP, matrix metalloproteinase; ERK, extracellular signal-regulated protein kinase; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; EGF, epidermal growth factor; EGFR, EGF receptor; COX-2, cyclooxygenase 2; HIF-1α, hypoxia-inducible factor-1α; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; ELK, ERK/ETS-like-1 kinase; MAPK, mitogen-activated protein kinase; DLL4, d-like ligand 4; NO, nitric oxide; ROS, reactive oxygen species; NF-κB, nuclear factor-κB.

with angiogenesis (47,58), which further confirms the relationship between ESM1 and the MAPK signaling pathway. Phosphorylated ERK, JNK and p38 can translocate into the nucleus and induce VEGF production, thereby regulating angiogenesis (57,59,60). Furthermore, since ESM1 maintains tumor angiogenesis through regulation of the EGFR signaling pathway, and rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/ERK and PI3K/AKT are the main signaling pathways downstream of EGFR (55,61), ESM1 can also regulate these pathways. Summaries of how ESM1 regulates tumor angiogenesis through the MAPK signaling pathway are shown in Table I and Fig. 3.

Notch signaling pathway. The Notch signaling pathway plays a critical role in normal cell differentiation, proliferation, apoptosis and angiogenesis under physiological conditions (62). In pathological conditions, it also regulates angiogenesis. For instance, ESM1 overexpression in the MDA-MB-231 human breast cancer cell line and mice enhances angiogenesis via the upregulation of VEGF and d-like ligand 4 (DLL4, a ligand of Notch1 in the Notch signaling) (63). In addition, ESM1 activates the DLL4/Notch signaling pathway in adrenocortical carcinoma cells (64) (Table I and Fig. 3). It is worth noting that activation of the DLL4/Notch pathway inhibits VEGF-induced neovascularization (65). This may appear contradictory to the angiogenic role of ESM1; however, it has been suggested that

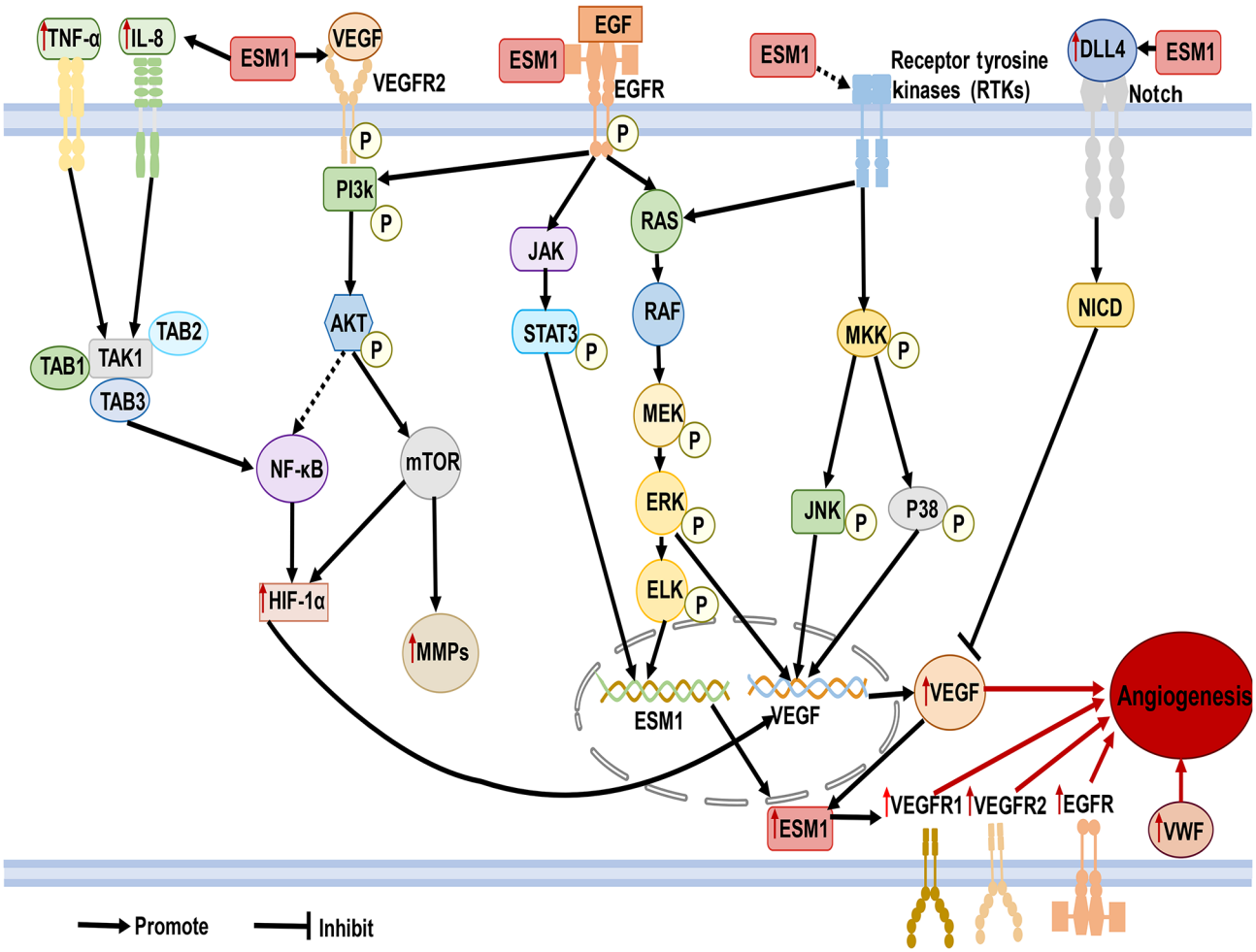

Figure 3. Roles and mechanisms of ESM1 in tumor angiogenesis. Solid lines indicate demonstrated mechanisms and dashed lines indicate possible mechanisms. ESM1 activates the NF-κB pathway in two ways: Via the upregulation of TNF-α and IL-8, and via promotion of binding between VEGF and VEGFR2. The activated NF-κB upregulates VEGF via the transcription factor HIF-1α, thereby promoting angiogenesis. ESM1 also activates the PI3K/AKT/mTOR pathway to upregulate MMPs, VEGF and HIF-1α by facilitating the binding of VEGF with VEGFR2. Regarding EGF and its receptor EGFR, ESM1 not only directly binds to EGFR but also facilitates the binding of EGF to EGFR, leading to activation of the EGFR signaling pathway. The activated EGFR, in turn, increases ESM1 expression through the JAK/STAT3 and ERK/ELK pathways, establishing a regulatory loop between ESM1 and EGFR. Increased ESM1 also upregulates angiogenesis-related factors such as VEGFR1, VEGFR2, EGFR and VWF, thereby promoting angiogenesis. In addition, activated EGFR can upregulate HIF-1α and MMPs through the PI3K/AKT/mTOR pathway. In the MAPK pathway, ESM1 increases the expression of VEGF through ERK, JNK and p38. As for the Notch pathway, the ligand DLL4 is upregulated by ESM1, thereby inhibiting VEGF expression. ESM1, endothelial cell specific molecule-1; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; IL-8, interleukin-8; VEGF, vascular endothelial growth factor; VEGFR1/2, VEGF receptor 1/2; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; MMPs, matrix metalloproteinases; HIF-1α, hypoxia-inducible factor-1α; EGF, epidermal growth factor; EGFR, EGF receptor; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; ERK, extracellular signal-regulated kinase; ELK, ETS-like kinase; JNK, c-Jun N-terminal kinase; VWF, von Willebrand factor; DLL4, d-like ligand 4; P, phosphorylated; TAB1-3, TAK1-binding protein 1-3; TAK1, transforming growth factor-b-activated kinase 1; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK/MKK, mitogen-activated protein kinase kinase; NICD, Notch intracellular domain.

activation of the DLL4/Notch pathway contributes to vessel sprouting (66). Since the number of studies investigating the regulatory mechanisms of ESM1 in the DLL4/Notch pathway is limited, the precise role of the DLL4/Notch pathway in ESM1-mediated angiogenesis regulation remains unclear, emphasizing that further research is necessary.

NF-κB signaling pathway. The NF-κB pathway is crucial in tumor angiogenesis (67). ESM1 has been shown to regulate tumor angiogenesis through the NF-κB pathway. Recombinant ESM1 has been shown to activate NF-κB in HUVECs (68), and it is known that NF-κB is downstream of PI3K/AKT (69). Therefore, it is speculated that ESM1 activates NF-κB through the PI3K/AKT pathway. Furthermore, ESM1 upregulates inflammatory factors such as TNF-α and IL-8, both of which can activate NF-κB (58,70,71). Furthermore, NF-κB upregulates VEGF via HIF-1α, leading to angiogenesis (72). The regulation of tumor angiogenesis by ESM1 through the NF-κB signaling pathway is summarized in Table I and Fig. 3.

5. Interaction of ESM1 with the TME

Mutual reinforcement between hypoxia and ESM1. In addition to tumor cells, the TME comprises various components, including fibroblasts, endothelial cells, immune cells and ECM (73). Rapid and uncontrolled tumor growth, coupled with inadequate blood supply, leads to the TME typically being hypoxic (74). Hypoxia is mainly characterized by the production of HIF (75). Among the HIF family, HIF-1α is

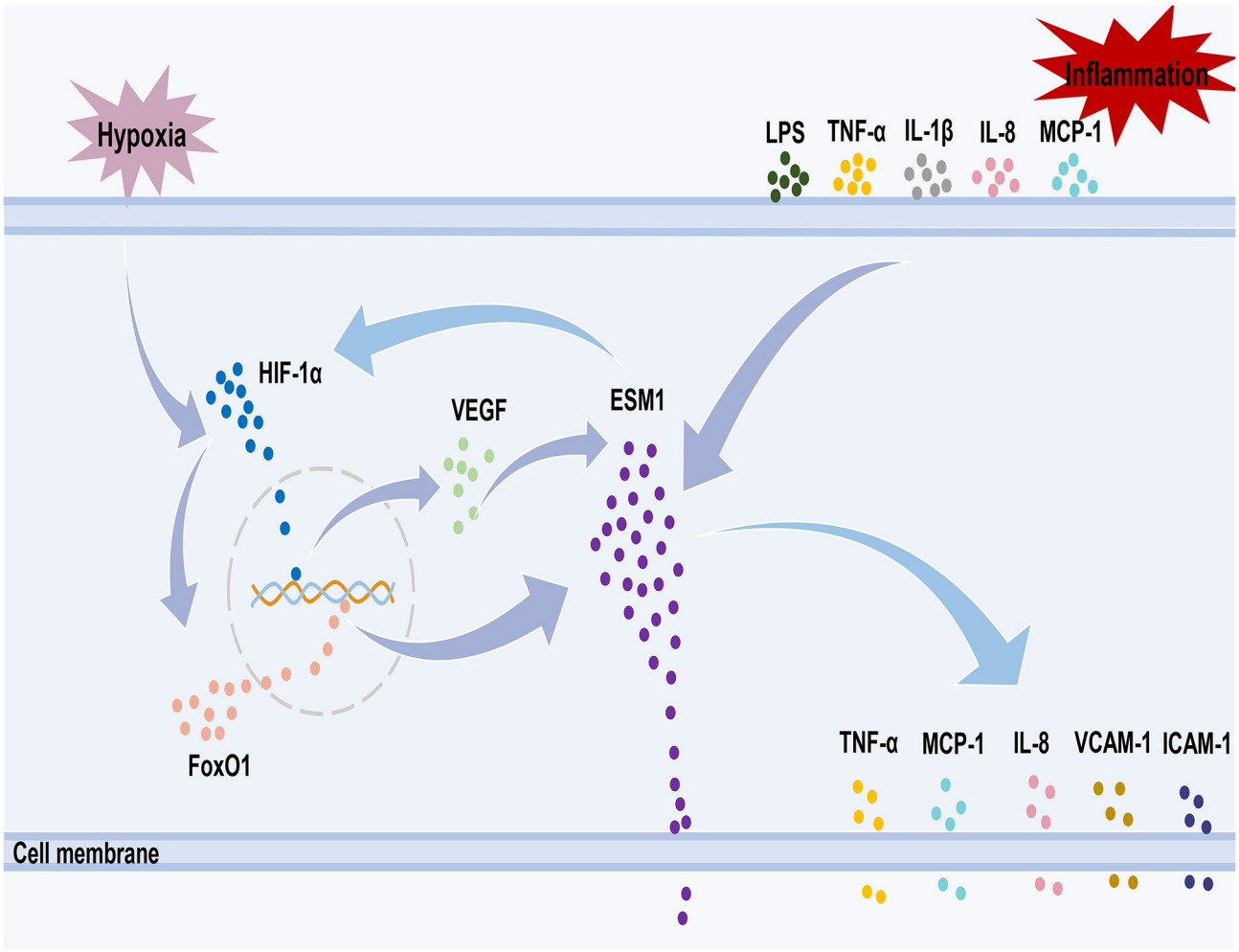

Figure 4. Interaction of ESM1 with hypoxia and inflammation in the tumor microenvironment. Under hypoxia, HIF-1α upregulates ESM1 by promoting VEGF expression and facilitating the entry of the transcription factor FoxO1 into the nucleus; Notably, ESM1 can also accelerate hypoxia via the upregulation of HIF-1α. Similarly, following stimulation by inflammatory factors, such as LPS, TNF-α, IL-1β, IL-8 and MCP-1, the level of ESM1 is increased. ESM1 also increases the expression of TNF-α, IL-8, MCP-1, VCAM-1 and ICAM-1. ESM1, endothelial cell specific molecule-1; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; FoxO1, Forkhead box O1; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; IL, interleukin; MCP-1, monocyte chemotactic protein-1; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular cell adhesion molecule-1.

the primary transcription factor associated with hypoxia (76). Studies have confirmed the existence of a regulatory relationship between HIF-1α and ESM1. For example, when HUVECs were exposed to intermittent hypoxia, ESM1 expression was significantly increased in a time-dependent manner. However, the knockdown of HIF-1α expression led to a reduction in ESM1 levels under these conditions (77). The regulation of ESM1 expression by HIF-1α was shown to be mediated VEGF (77), as shown in Fig. 4. In addition, in human umbilical artery endothelial cells, HIF was found to facilitate the translocation of the transcription factor Forkhead box O1 (FoxO1) from the cytoplasm to the nucleus in response to hypoxia, thereby upregulating ESM1 levels (78), as shown in Fig. 4. These findings indicate that HIF-1α indirectly regulates ESM1 through VEGF and FoxO1. Moreover, ESM1 has been found to regulate HIF-1α. *In vitro* experiments demonstrated that ESM1 promoted drug resistance, proliferation, migration, invasion and epithelial-mesenchymal transition through HIF-1α in A549 and PC-9 non-small cell lung cancer cells following intermittent hypoxia (79). Similar results were observed in a mouse model of lung cancer in which the mice were exposed to chronic intermittent hypoxia and a small interfering RNA targeting ESM1 was delivered using a lentivirus (79), as shown in Fig. 4. It is evident that HIF-1α and ESM1 mutually regulate each other, forming a positive feedback loop. In summary, hypoxia induces the expression of ESM1 in the TME, and the elevation of ESM1 further exacerbates tissue hypoxia, ultimately promoting angiogenesis.

Mutual reinforcement between inflammation and ESM1. Inflammation is a prominent feature of the TME. Within the TME, inflammatory cells play a pivotal role in tumor development, growth and metastasis through the secretion of chemokines, inflammatory factors and growth factors (80,81). A link between ESM1 and inflammation has been shown in several studies. Clinical investigations have identified that ESM1 levels are elevated in the plasma or tissue of patients afflicted with various inflammatory diseases, including acute respiratory distress syndrome, sepsis and rheumatoid arthritis (82-84). In addition, experimental research has substantiated the association between high ESM1 levels and inflammatory responses, since *in vitro*

assays using HUVECs and *in vivo* experiments using mice revealed increased levels of ESM1 following treatment with LPS (58).

ESM1 levels have also been found to increase in HUVECs following stimulation with IL-8, monocyte chemotactic protein-1 (MCP-1) and TNF-α (58), as depicted in Fig. 4. As aforementioned and illustrated in Fig. 3, ESM1 activates HUVECs through the MAPK pathways, namely ERK, JNK and p38, and the NF-κB pathway (58). Furthermore, the treatment of HUVECs with IL-1β results in the induction of ESM1 expression (11), as shown in Fig. 4. It has also been shown that ESM1 can influence the expression of inflammatory factors, chemokines and adhesion molecules. Upon stimulation with LPS and IL-1β, HUVECs and trophoblast cells exhibited significantly increased expression of IL-6, IL-8 and MCP-1, but when ESM1 was knocked down using small interfering RNA, the stimulatory effect of IL-6, IL-8 and MCP-1 expression was diminished in both cell types (85), as depicted in Fig. 4.

In another study, the culture of HUVECs with ESM1 for 3 h led to the upregulation of IL-8, MCP-1 and TNF-α expression (58). Furthermore, ESM1 also upregulated vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) (58), as shown in Fig. 4. Conversely, ESM1 knockdown reduced VCAM-1 and ICAM-1 protein expression in mouse aortic vascular smooth muscle cells (26). These findings indicate that a reciprocal regulatory relationship exists between specific inflammatory factors and ESM1; inflammatory factors upregulate ESM1 expression, while ESM1 induces the expression of factors associated with inflammation, thereby exacerbating inflammation within the TME and promoting angiogenesis.

6. Value of ESM1 as a future therapeutic target for cancer

Current research progress of ESM1. As a novel marker of cancer, ESM1 has been studied extensively. Research has shown that ESM1 is involved in the process of tumor development in two ways: Firstly, it is abnormally expressed in cancer cells and participates in tumor cell proliferation, migration and invasion (6,8,20,21); secondly, its expression is increased in vascular endothelial cells, which is associated with the promotion of cancer angiogenesis (22,23). Most of these findings have been obtained from experiments using cells or animals. However, only the abnormal expression of ESM1 in tumor tissues has been confirmed in clinical trials (18,19). Although ESM1 has been shown to be closely associated with tumorigenesis, no interventional agents targeting ESM1 are currently being used in the clinic.

Based on the association between ESM1 and tumors, and the lack of clarity regarding the mechanism of ESM1 in the development of cancer, it is necessary to further clarify its mechanism through various studies in the future, particularly in clinical research. Following this, the development of novel antitumor drugs that target ESM1 may be possible.

Value of ESM1 as a prognostic and predictive indicator of cancer. The relationship of ESM1 with tumor growth, metastasis and patient prognosis has garnered significant attention within the medical community. Clinical investigations have consistently confirmed the abnormal expression of ESM1 in the blood or tumor tissues of patients with diverse cancers. Notably, elevated ESM1 levels have been observed in the circulatory systems of patients diagnosed with endometrial, cervical, renal, breast and lung cancer, multiple myeloma and hepatocellular carcinoma (19,86-90). Furthermore, upregulated ESM1 expression has been detected in tumor samples collected from patients with pancreatic neuroendocrine tumors and glioblastoma (91,92).

A meta-analysis exploring the association between ESM1 expression and the prognosis of patients with cancer has unveiled a significant negative association between ESM1 levels and patient survival rate (93). Consequently, ESM1 has emerged as a promising novel tumor marker for the evaluation of treatment efficacy, monitoring of disease progression and assessment of prognosis in patients with cancer. The practicality of using ESM1 in clinical settings is bolstered by its status as a secreted protein readily detectable in blood samples. In fact, commercial enzyme-linked immunosorbent assay kits designed for the detection of ESM1 have already entered the market, which further substantiates the feasibility of using ESM1 as a cancer marker in future clinical practice.

Therapeutic strategies and drug development for ESM1. Given the pivotal role of ESM1 in tumor development and metastasis, it has emerged as a promising therapeutic target for cancer. Future therapeutic strategies for ESM1 may include the following: i) Inhibiting the synthesis and secretion of ESM1; ii) neutralizing the already-produced ESM1, and iii) blocking the downstream signaling pathways activated by ESM1.

Research has clearly shown that factors such as inflammation and hypoxia can stimulate the expression and release of ESM1 (58,77). Consequently, the use of anti-inflammatory drugs and inhibitors targeting HIF-1α is a viable approach for impeding the synthesis and secretion of ESM1. Monoclonal antibodies designed for the neutralization of ESM1 have not yet been developed; however, the search for ESM1-neutralizing antibodies is a promising direction for future drug development efforts. Furthermore, ESM1 has been shown to activate downstream signaling pathways, including the PI3K/AKT, MAPK and NF-κB pathways (53,58,68). Inhibitors targeting these pathways may serve as an additional means for blocking the downstream effects mediated by ESM1.

7. Conclusions and prospects

The present review reveals the multifaceted roles of ESM1 and the underlying mechanisms by which ESM1 promotes tumor angiogenesis. It also comprehensively summarizes the regulatory mechanisms governing ESM1 within the TME. In summary, it describes how ESM1 expression is increased in response to hypoxic and inflammatory conditions within the TME. This heightened ESM1 expression, in turn, orchestrates the expression of pro-angiogenic factors through the PI3K/AKT, MAPK, NF-κB and Notch signaling pathways, thereby inducing angiogenesis.

Furthermore, the review introduces the concept that ESM1 actively engages with the TME. ESM1 expression is increased within the TME and, notably, ESM1 reciprocally promotes the progression and maintenance of the TME via the regulation of inflammatory factors, thereby establishing a positive feedback loop between ESM1 and the TME.

As an emerging tumor marker, ESM1 plays a pivotal role in tumor growth, metastasis, invasion and angiogenesis. Consequently, it is a promising biomarker for disease monitoring and a potential therapeutic target for clinical practice in the future. However, it is worth noting that the research on the role of ESM1 in angiogenesis remains limited, and the precise mechanisms by which ESM1 regulates angiogenesis require further exploration in future studies.

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JZ and PZ were responsible for drafting and revising the manuscript, and creating the figures. JW and JS revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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