



Review Article

Relationship between LncRNA-MEG3 and Vascular Endothelial Cell Function

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Abstract | Maternally expressed gene 3(MEG3) is a highly conserved long non-coding RNA (lncRNA) with anticancer effects in mammals. It is associated with the occurrence and development of various diseases. Vascular endothelial cells (VECs) are important parts of the blood vessel wall, and the integrity of their structure and function is crucial for maintaining normal vascular function. Studies have shown that MEG3 plays an important role in the regulation of VECs function, including the proliferation, migration, apoptosis, angiogenesis, and inflammatory response of VECs. This paper will review the effect of MEG3 on the function of VECs and its potential molecular mechanism, aiming to provide a conceptual basis for the potential of using MEG3 as a clinical diagnostic, prognostic, and targeted therapeutic approach for vascular-related diseases.

Received | May 05, 2024; **Accepted** | September 24, 2024; **Published** | November 22, 2024

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Citation | Huadan, M., S.Z. Safi, H. Junjie, W. Hua, G. Xingrong and I.S.B. Ismail. 2024. Relationship between LncRNA-MEG3 and vascular endothelial cell function. *Sarhad Journal of Agriculture*, 40(4): 1451-1462.

DOI | <https://dx.doi.org/10.17582/journal.sja/2024/40.4.1451.1462>

Keywords | lncRNA-MEG3, vascular endothelial cells, p53; Akt; miRNA, inflammation



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Introduction

Blood vessels are an important part of the circulatory system, carrying oxygen and nutrients to tissues and organs, as well as carbon dioxide and metabolic waste to the lungs and kidneys for elimination. Blood vessels are composed of a variety of cells and substrates such as VECs, basement membrane, smooth muscle cells, and outer membrane, among

which VECs are the innermost layer of the blood vessel wall, direct contact with blood, and play a major role in regulating the biological function of blood vessels (Kruger-Genge *et al.*, 2019). Under normal conditions, VECs maintain certain homeostasis and maintain the integrity and function of blood vessels. When stimulated by hypoxia, trauma, inflammation, or tumor, VECs will undergo a series of changes, including proliferation, migration, apoptosis secretion,

etc., thus regulating the formation or remodeling of blood vessels (Lee *et al.*, 2021).

Angiogenesis refers to the process of forming new blood vessel branches through the proliferation, migration, and differentiation of VECs based on existing blood vessels (Lee *et al.*, 2022). Angiogenesis is an important physiological phenomenon, which is necessary for embryonic development, tissue repair, reproduction, and other processes. However, excessive or insufficient angiogenesis can also lead to the occurrence and development of a variety of diseases, such as ischemic heart disease, cerebrovascular disease, rheumatoid arthritis, and tumors (Dal Canto *et al.*, 2019). Apoptosis is the most common programmed death mode. Apoptosis of VECs is affected by a variety of factors, such as oxidative stress, inflammatory factors, apoptosis genes, apoptosis suppressor genes, *etc.*, which is an important cell homeostasis regulation mechanism and a disease-related pathological process. Such as atherosclerosis, diabetes, ischemia reperfusion injury, *etc.* (Watson *et al.*, 2017). Inflammation in VECs is an important immune response process and a pathological mechanism related to chronic diseases such as atherosclerosis, hypertension, and obesity. After infection or injury, VECs express and release a variety of inflammatory mediators, such as adhesion molecules, chemokines, and cytokines, thus inducing leukocytes to cross the endothelial cell layer from the blood to the tissue. It plays a role in immune defense and repair (Pober and Sessa, 2007). Therefore, it is of great significance to explore the molecular mechanism affecting the function of VECs and seek effective regulatory targets for the prevention and treatment of related diseases.

In recent years, with the development of high-throughput sequencing technology, it has been found that only about 2% of the sequences in the human genome encode proteins, while most of the sequences are transcribed as non-coding RNA. Including small non-coding RNAs and lncRNAs (Ahmed *et al.*, 2016; Mattick *et al.*, 2023). lncRNAs have a variety of structures and functions, and can participate in the regulation of gene expression and influence cell function by interacting with DNA, RNA or protein (Dhanoa *et al.*, 2018). Thousands of lncRNAs have been found to play an important role in various physiological and pathological processes, such as cell proliferation, differentiation, migration, apoptosis, epigenetic regulation, chromosome stability, stress

response, *etc.* (Dhanoa *et al.*, 2018; Jain, 2020). Some of these lncRNAs are also associated with angiogenesis, known as angiogenic-associated lncRNAs (Angio-lncRNAs) (Yu and Wang, 2018). MEG3 is one of the common Angio-lncRNAs, which can interact with p53 and act as a sponge for microRNA-9 (miRNA-9, miR-9). It regulates the expression of various angiogenesis factors, including vascular endothelial growth factor (VEGF), thereby inhibiting the proliferation, survival, and angiogenesis of vascular endothelial cells (Yu and Wang, 2018).

Since MEG3 was discovered in 2000, researchers have long focused on its relationship with cancer. In recent years, the role of MEG3 in the development of diabetic vascular complications and cardiovascular diseases has gradually gained attention. The regulatory effect of MEG3 on the function of VECs outside of tumor tissues is also becoming clearer. However, to date, no comprehensive review has been conducted on the relationship between MEG3 and VEC function. Therefore, this paper aims to review and summarize the research progress in this field, which is of significant importance for understanding the molecular mechanisms underlying diseases related to vascular dysfunction, such as cancer and ischemic stroke, and for developing new therapeutic strategies.

Search method

Literature search using the PubMed database with the keywords("maternally expressed gene 3" or "MEG3" or "lncRNA-MEG3") AND ("endothelial cell" or "endothelium"). Search cutoff date: April 16, 2023, Focus on citing literature from the past 8 years.

Overview of MEG3: MEG3, transcribed from the maternal genome, is located in an imprinted gene cluster on human chromosome 14 and mouse chromosome 12, sharing a common promoter with multiple other lncRNAs and miRNAs (Ghafouri-Fard and Taheri, 2019; Sommerkamp *et al.*, 2019). MEG3 is considered to be a tumor suppressor gene due to its activity in inhibiting cell proliferation and promoting cell apoptosis, and its expression is reduced or absent in a variety of human tumors and tumor cell lines (Ghafouri-Fard and Taheri, 2019). MEG3 can regulate multiple signaling pathways and gene expression such as p53 by interacting with DNA, RNA or protein. In addition to playing an important role in the occurrence and development of tumors, MEG3 is also associated with a variety of other diseases, such

as cardiovascular diseases (Bai *et al.*, 2019), neurodegenerative diseases (Huang *et al.*, 2021), osteoporosis (Zhu *et al.*, 2021), *etc.* In recent years, more and more studies have shown that MEG3 is closely related to the function of VECs. MEG3 can affect the proliferation, migration, apoptosis, tube formation, inflammatory response and other functions of VECs through different molecular mechanisms (Yu and Wang, 2018), thus regulating the biological functions of blood vessels.

Molecular mechanism of MEG3 regulating VECs function

MEG3 regulates the function of VECs through the p53 signaling pathway: p53 is a well-known tumor suppressor protein that plays a key role in maintaining genomic stability and preventing tumorigenesis (Marei *et al.*, 2021). p53 can be activated by a variety of stress signals, such as DNA damage, hypoxia, oxidative stress and oncogene activation, *etc.*, thus regulating the expression of target genes and inducing cell cycle arrest, apoptosis or senescence (Marei *et al.*, 2021). p53 is essential for maintaining the function of VECs and preventing vascular disease (Chan *et al.*, 2022).

Studies have shown that MEG3 expression can increase the level of cell tumor antigen p53 and selectively activate the expression of p53 target gene, indicating that MEG3 exerts its biological functions through p53 (Huang *et al.*, 2011; Lu *et al.*, 2013). As for how MEG3 activates p53, it was previously thought that MEG3 activates p53 by disrupting the interaction between p53 and mouse double minute 2 homolog (MDM2) (Huang *et al.*, 2011). In recent years, based on improved research methods, more evidence supports MEG3 regulating p53 independently of its interaction with MDM2 (Bauer *et al.*, 2021). Polypyrimidine tract-binding protein 3 (PTBP3) is a splicing factor that binds to the polypyrimidine region of precursor mRNA and regulates its selective splicing. The combination of PTBP3 and the 3' untranslated region (3' UTR) affects the stability of mRNA and translation efficiency (Hu *et al.*, 2018). PTBP3 not only mediates tumor growth and metastasis, but also regulates the expression of multiple genes related to cell cycle, apoptosis, aging, and protein modification (Chen *et al.*, 2022). When combined with PTBP3, MEG3 can inhibit the splicing regulation of PTBP3 on cyclin-dependent kinase inhibitor 1 (CDKN1A) and BCL2 associated X (BAX), which are the down-

stream genes of p53, thus promoting the expression of CDKN1A and BAX (Shang *et al.*, 2013). CDKN1A and BAX are two proteins that promote apoptosis and inhibit cell cycle progression (Al-Khalaf *et al.*, 2017). Therefore, MEG3 activates p53 signaling pathway, inhibits VECs proliferation and promotes apoptosis through interaction with PTBP3.

MEG3 regulates the function of VECs through the Akt signaling pathway: Akt, also known as protein kinase B (PKB), is an antiapoptotic serine/threonine protein kinase. Activated Akt mediates the inhibitory or stimulating phosphorylation of various downstream targets. Widely involved in the regulation of cell growth, proliferation, apoptosis and other processes (Yang *et al.*, 2019). Activation of the Akt pathway promotes cell proliferation and migration (Mu *et al.*, 2022) and inhibits apoptosis (Jia *et al.*, 2021). Studies have shown that MEG3 negatively regulates the Akt signaling pathway. MEG3 expression was down-regulated in breast cancer tissues and cell lines, and overexpression of MEG3 reduced the proliferation and invasion of VECs and inhibited the formation of capillaries, accompanied by the down-regulation of Akt signal. This suggests that MEG3 may inhibit tumor growth and angiogenesis by regulating the Akt signaling pathway (Zhang *et al.*, 2017). Endothelial to mesenchymal transition (EMT) refers to the process in which endothelial cells lose their original features and transform into mesenchymal cells (myofibroblasts and smooth muscle cells) under the action of various stimulation factors. EMT is one of the mechanisms for the formation of retinal neovascularization and fibrous vascular membranes (Sanchez-Duffhues *et al.*, 2016), and plays an important role in the pathogenesis of diabetic retinopathy (Abu *et al.*, 2015; He *et al.*, 2021). It was suggested that overexpression of MEG3 in DR Rats and cell models shows inhibition of PI3K/Akt/mTOR signaling pathway, thereby inhibiting EMT (He *et al.*, 2021). Although the inhibitory effect of MEG3 on tumors seems to have become a consensus, some scholars have pointed out that lung adenocarcinoma patients with higher MEG3 levels have lower survival rates, in lung adenocarcinoma tissues, overexpression of MEG3 can stimulate the Akt signaling pathway and promote the proliferation and invasion of lung adenocarcinoma cells (Li *et al.*, 2019). In conclusion, with in-depth studies on the biological functions of MEG3, more and more evidence shows that the regulation of Akt signaling pathway is one of the main

mechanisms for MEG3 to regulate the function of VECs.

MEG3 adjusts the function of VECs through miRNA: MiRNAs are a class of small molecular RNAs with a length of about 22 nucleotides, which can regulate gene expression by complementation binding with the 3'UTR of target gene mRNA, resulting in degradation of target gene mRNA or translation inhibition (Lee *et al.*, 2014). MiRNAs are involved in a variety of biological processes and physiological functions, such as apoptosis, autophagy, oxidative stress, and cellular inflammation (Zhu *et al.*, 2023). At the same time, miRNAs can act as oncogenes or tumor suppressor genes by regulating the expression and function of genes associated with tumor occurrence, development, and metastasis (Zhang *et al.*, 2021).

The interaction between MEG3 and miRNAs is considered to be one of the main mechanisms for MEG3 to regulate the function of VECs. MEG3 can serve as a competing endogenous RNA (ceRNA) of miRNAs. It can compete with miRNAs to bind the 3'UTR of target gene mRNA, releasing the suppression effect of target gene mRNA and thus increasing the expression of target gene mRNA. For example, MEG3 is significantly down-regulated in human ovarian carcinoma-derived microvascular endothelial cells (ODMECs) compared to normal ovarian endothelial cells, overexpression of MEG3 leads to decreased angiogenesis of ODMECs (Li *et al.*, 2023). The MS2 hairpin assay showed that MEG3 acts as a platform for sponge miR-376a, RASp21 protein activator 1 (RASA1) is a key inhibitor of angiogenesis and is directly targeted by miR-376a, studies showed that MEG3 inhibits angiogenesis through miR-376a/RASA1 axis in ODMECs (Li *et al.*, 2023). In addition, MEG3 has been observed as an endogenous sponge in human Aortic Endothelial Cells (AECs), inhibiting the function of miR-223 through sequence complementarity and increasing the expression of Nod-like receptor pyrin domain3 (NLRP3), thereby enhancing pyroptosis (Zhang *et al.*, 2018). It has also been reported that MEG3 can interact with miR-21 and inhibit the function of miR-21, phosphatase and tensin homolog (PTEN) and ras homolog gene family, member B (RhoB) are the target genes of miR-21, High expression of PTEN and RhoB inhibit the proliferation of VECs in coronary artery disease (CAD) tissues (Wu *et al.*, 2017).

Impact of MEG3 on VECs functions

MEG3 and angiogenesis: VECs proliferation is the basis of angiogenesis and one of the important characteristics of vascular diseases. VECs migration is a key step of angiogenesis and an important process of vascular repair. MEG3 can regulate VECs proliferation and migration in a variety of ways, thus affecting angiogenesis. It was believed that the promotion of advanced glycation end products (AGEs) in diabetic vascular disease is related to the high expression of MEG3, MEG3 was up-regulated in human umbilical vein endothelial cells (HUVECs) treated with AGEs, inhibition of MEG3 expression restores AGE-induced inhibition of cell viability and proliferation (Ju *et al.*, 2019). He *et al.* (2017) pointed out that MEG3 negatively regulates the proliferation and angiogenesis of VECs, and MEG3 overexpression significantly inhibits the proliferation and *in vitro* angiogenesis of VECs, while MEG3 knockdown has the opposite effect. It has been reported that MEG3 expression is significantly reduced in the brain tissue of ischemic stroke rat models, further studies have found that overexpression of MEG3 inhibits functional recovery and decreases capillary density after ischemic stroke, while downregulation of MEG3 improves brain injury and increases angiogenesis after ischemic stroke (Liu *et al.*, 2017). Similarly, Dai *et al.* (2023) found that overexpression of MEG3 inhibits migration and angiogenesis of VECs by blocking the expression of decorin (DCN), while inhibition of MEG3 by siRNA leads to increased expression of DCN and promotes proliferation and migration of VECs, thus enhancing angiogenesis. One of the main pathological features of atherosclerosis is the formation of plaque in the intima of the great or middle artery. A large number of neovascularization in plaques leads to bleeding and blood vessel thrombosis, which is easy to induce cardiovascular diseases (Xu *et al.*, 2020). Interestingly, MEG3 has an anti-atherosclerosis effect by inhibiting the growth, migration, and angiogenesis of human microvascular endothelial cells (HMEC-1) (Xu *et al.*, 2020). It can be seen that MEG3 mainly negatively regulates the proliferation, migration and angiogenesis of VECs, and its high expression is conducive to improving the prognosis of tumor and DR Patients. However, for patients with ischemic stroke, MEG3 often suggests poor prognosis.

The molecular mechanism of MEG3 regulating angiogenesis is mainly related to its regulation of miRNA. For example, MEG3 inhibits the proliferation of

VECs by inhibiting the expression of miR-21, which plays an important regulatory role in the progression of coronary atherosclerosis (Wu *et al.*, 2017). MEG3, acting as a molecular sponge, has been observed to inhibit miR-6720-5p and up-regulate the expression of cytochrome b5 reductase 2 (CYB5R2) in human retinal microvascular endothelial cells (hRMECs) of DR Patients, thereby inhibiting the formation of DR neo vascularization (J. Chen *et al.*, 2021). In the oxygen-glucose deprivation (OGD) VECs model of stroke, MEG3 is playing the role of ceRNA, decreased angiogenesis in human brain microvascular endothelial cells (HBMECs) by targeting miR-122-5p/NDRG3 (Luo *et al.*, 2022). It can be seen that miRNAs interacting with MEG3 are not the same in different tissue cells and under different pathophysiological conditions. Other miRNAs involved in MEG3-mediated regulation of VECs function include miR-9 (He *et al.*, 2017), miR-421 (Ye *et al.*, 2019), miR-93 (Ju *et al.*, 2019), miR-147 (Xu *et al.*, 2020), etc. p53 is a tumor suppressor protein widely expressed in various tissues, the p53 signaling pathway is also involved in the regulation of angiogenesis. PTBP3 is a binding protein of MEG3, and the interaction between the two activates the p53 signaling pathway and plays a role in inhibiting angiogenesis (Shihabudeen *et al.*, 2019). In addition, it has been suggested that MEG3 inhibits angiogenesis in VECs is correlated with its effect on Notch signaling pathway (Liu *et al.*, 2017) and Akt signaling pathway (Ye *et al.*, 2018; Zhang *et al.*, 2017).

MEG3 has become an important tumor suppressor gene due to its inhibitory effect on the proliferation, migration and angiogenesis of VECs. However, MEG3 plays a completely opposite role in vascular diseases related to chronic wounds and stroke. Therefore, it is necessary to fully understand the biological functions of MEG3. It is particularly important to intervene in the expression of MEG3 in different pathophysiological processes.

Programmed death of VECs and MEG3: The dysfunction of VECs can be manifested as blocked proliferation and migration, decreased tube forming ability, and increased programmed death including apoptosis, pyroptosis and ferroptosis. Apoptosis is a typical Caspase-dependent programmed cell death. Caspase-3, Bax and p53 are stimulators of apoptosis, while Bcl-2 is the suppressor. Studies indicated that MEG3 can regulate apoptosis by up-regulating

Caspase-3, Bax and p53 and down-regulating Bcl-2 (Wang *et al.*, 2018). It has been reported that increased activity of apoptosis protein Caspase-3 was observed in human pulmonary microvascular endothelial cells (HPMECs) induced by cigarette smoke extract, along with increased MEG3 levels. MEG3 transfection led to the upregulation of MEG3, which led to more apoptosis of HPMECs, while MEG3 knockout reduced apoptosis, suggesting that MEG3 was involved in the regulation of apoptosis of HPMECs (Bi *et al.*, 2020). Li *et al.* (2021) reported that apoptosis of Brain Microvascular Endothelial Cells (BMECs) after intracerebral hemorrhage was associated with MEG3's regulation of miR-1930-5p/Ml1 axis, MEG3 has been demonstrated to act as a molecular sponge for miR-1930-5p, while Ml1 is the downstream target of miR-1930-5p, MEG3 competitively binds to miR-1930-5p to regulate Ml1, and overexpression of Ml1 promotes apoptosis of HBMECs. In addition, Xu *et al.* (2020) reported that MEG3 can induce HMEC-1 apoptosis and speculated that MEG3 is one of the main mechanisms of anti-atherosclerosis. Pyroptosis and ferroptosis are newly discovered programmed death modes, which are also found to be regulated by MEG3. For example, MEG3 mediates ferroptosis of cerebral microvascular endothelial cells in rat models of ischemic brain injury caused by OGD combined with hyperglycemia (C. Chen *et al.*, 2021). In mouse models of atherosclerosis, pyroptosis related proteins in AECs and MEG3 are simultaneously elevated, further studies have confirmed that, MEG3 promotes the pyroptosis of AECs by inhibiting the function of miR-223 (Zhang *et al.*, 2018).

It can be seen that MEG3 is an important regulator of VECs death, and the p53 signaling pathway and miRNA molecular sponging are its main regulatory mechanisms. p53 is an important tumor suppressor and a major coordinator of DNA damage responses, which can induce apoptosis and cell cycle arrest. MEG3 can interact with the RNA-binding protein PTBP3 to inhibit the function of PTBP3, thereby stimulating the expression of VE-cadherin and β -catenin, which are target genes of PTBP3, thus activating the p53 signaling pathway and promoting apoptosis in VECs (Shihabudeen *et al.*, 2019). MEG3 can interact with a variety of miRNAs to form ceRNAs, thereby releasing miRNA target gene expression and regulating VECs apoptosis. Multiple miRNAs have been found to be involved in the regulation of VECs function. For example, miR-147 is involved in medi-

ating MEG3 to promote the apoptosis of HMEC-1 (Xu *et al.*, 2020), and miR-223 is involved in mediating MEG3 to promote the pyroptosis of AECs (Zhang *et al.*, 2018). Competitive binding of miR-135a to MEG3 inhibits AECs damage and apoptosis in chronic intermittent hypoxia mice (Ding *et al.*, 2020).

MEG3 and VECs Inflammation: Inflammation acts as a defense mechanism against stimuli, inflammation is the common pathophysiological basis of infection, injury, poisoning and other diseases. VECs are extensively involved in inflammatory response, and promote leukocyte adhesion and migration through the expression of adhesion molecules and chemokines, and exogenous clotting pathway can be initiated to promote local thrombosis by expressing cytokines. It was reported that MEG3 was significantly down-regulated in HUVECs stimulated by hyperglycemia, and MEG3 knockdown aggravated inflammatory damage in HUVECs (Wang *et al.*, 2018), suggesting that MEG3 was an inhibitor of inflammation in HUVECs. An increase in miR-19b and a decrease in suppressor of cytokine signaling 6 (SOCS6) were observed in high-glucose (HG) induced hRMECs, further research confirmed that MEG3 regulate the miR-19b/SOCS6 axis through the JAK2/STAT3 signaling pathway, thereby inhibiting HG induced apoptosis and inflammation (Xiao *et al.*, 2020). Qiu *et al.* (2016) found that MEG3 expression significantly lowered in both the retina of diabetic mice induced by streptozotocin (STZ) and the VECs exposed to HG and oxidative stress, MEG3 knockdown exacerbated retinal vascular dysfunction *in vivo*, manifested by severe capillary degeneration, microvascular leakage and increased inflammation, which further verifies the inhibitory effect of MEG3 on VECs inflammation. Pyroptosis is a newly discovered programmed cell death mode. NLRP3, the upstream molecule of pyroptosis pathway, activates Caspase-1, which further cleavage pyroptosis executive protein Gasdermin D (GSDMD), resulting in cell perforation, and lyse precursors of IL-1 β and IL-18 to form mature IL-1 β and IL-18, thus triggering inflammatory response (Yu *et al.*, 2021). Melatonin has significant anti-inflammatory properties. In atherosclerotic ApoE^{-/-} mouse models treated with a high-fat diet, researchers found that melatonin reduced the pyroptosis of AECs and inhibited the expression of inflammatory factors (Zhang *et al.*, 2018). Further *in vitro* studies showed that MEG3 acted as a molecular sponge in AECs

treated with oxidized low density lipoprotein (Ox-LDL), inhibiting miR-223 function and increasing NLRP3 expression via sequence complementarity, then the pyroptosis of VECs was enhanced, thereby aggravating endothelial inflammation (Zhang *et al.*, 2018).

The regulatory mechanism of inflammation is complex, involving the regulation of multiple signaling pathways such as nuclear factor kappa-B (NF- κ B) and mitogen-activated protein kinases (MAPKs). At present, studies on the mechanism of MEG3 regulating inflammation in VECs are still very limited, and the mechanism through which MEG3 regulates inflammation in VECs remains unclear, which needs further study.

Diseases closely related to MEG3

Tumors: MEG3 plays an important regulatory role in tumor VECs, and is closely related to tumor angiogenesis and VECs function. Tumor angiogenesis is a key process in tumor growth and metastasis, and MEG3 can inhibit the growth, migration and invasion of tumor cells through a variety of regulatory mechanisms (Jiao and Zhang, 2019), on the contrary, the loss of MEG3 is considered one of the driving factors for tumor migration and invasion (Tu *et al.*, 2023). Currently, the most thoroughly researched regulatory mechanism of MEG3 on tumor angiogenesis is miRNA-mediated translation inhibition, and regulation of the Akt signaling pathway has also been confirmed as one of its mechanisms. For example, Wei *et al.* (2023) found that MEG3 inhibits liver cancer cell migration and angiogenesis induced by M2 macrophage polarization through the miR-145-5p/DAB2 axis, and inhibits tumor growth *in vivo*. Gu *et al.* (2017) pointed out that MEG3's anticancer effect on pancreatic cancer is related to its regulation of the PI3K/AKT/Bcl-2/Bax/Cyclin D1/p53 and PI3K/AKT/MMP-2/MMP-9 signaling pathways. In addition, some studies have indicated that MEG3 can indirectly inhibit the proliferation and lumen formation of tumor VECs by inhibiting the expression of the angiogenesis-related factor VEGF (Dai *et al.*, 2018).

In summary, MEG3 affects tumor growth, invasion, and metastasis by inhibiting tumor angiogenesis. However, further research is needed to elucidate the specific molecular mechanisms and pathways of MEG3 in tumor VECs.

Ischemic stroke: Ischemic stroke is a common neu-

rovascular disease with a complex pathogenesis that includes processes such as ischemia, hypoxia, and cell death. The reestablishment of blood flow to brain tissue is closely related to the prognosis of ischemic stroke. MEG3 can regulate angiogenesis following ischemic stroke by affecting the function of BMECs. In a rat model of ischemic stroke, high expression of MEG3 was observed to promote apoptosis in HBMECs (Wang *et al.*, 2020), while downregulation of MEG3 improved brain injury and increased angiogenesis in ischemic stroke (Liu *et al.*, 2017). *In vitro* studies have also shown that knocking down MEG3 protects rat brain microvascular endothelial cells (RBMVECs) from oxygen-glucose deprivation/reoxygenation (OGD/R)-induced apoptosis, enhances the expression of hypoxia inducible factor-1 α (HIF-1 α) and VEGF, and reduces the production of reactive oxygen species (ROS). Further research indicates that the p53/NOX4 pathway mediates the inhibitory effect of MEG3 on RBMVEC function (Zhan *et al.*, 2017). Similarly, Chen *et al.* (2021) reported that MEG3 promotes ferroptosis in RBMVECs after OGD by regulating the p53/NOX4 pathway. Additionally, MEG3 acts as a competitive endogenous RNA in HBMECs following OGD, modulating their function by targeting miRNAs and downstream pathways (Luo *et al.*, 2022). Given the significant regulatory role of MEG3 in post-stroke angiogenesis, researchers have been focusing on targeted therapy against cerebral infarction by targeting MEG3, which has shown promising results. Shen *et al.* (2018) reported that targeted treatment of a rat cerebral infarction model with MEG3 shRNA plasmids encapsulated in nanopolymers resulted in reduced infarct volume, increased capillary density, and significantly improved function of HBMECs. With further research, targeted therapy focusing on MEG3 is expected to have broad application prospects.

Coronary artery disease: Atherosclerosis is the primary pathological change in coronary artery disease (CAD), and neovascularization within atherosclerotic plaques is a major factor in the progression of atherosclerosis. Therefore, controlling plaque angiogenesis is considered a key preventive measure for atherosclerosis. Research has shown that MEG3 exerts significant anti-atherosclerotic effects by regulating the function of VECs. In the cardiac tissue of CAD patients, downregulation of MEG3 expression was observed, while overexpression of MEG3 inhibited VEC proliferation and reduced the expression of cyclin D1,

ki-67, PCNA, type I collagen, type V collagen, and proteoglycans. Further studies have indicated that the inhibition of miR-21 by MEG3 is one of the mechanisms through which these biological functions are exerted (Wu *et al.*, 2017). *In vitro* studies have shown that MEG3's inhibitory effect on VEC function may be mediated through the sponging of miR-147, which in turn suppresses the expression of intracellular cell adhesion molecule-1 (ICAM-1), known for its role in inducing angiogenesis, thereby exerting anti-atherosclerotic effects (Xu *et al.*, 2020).

Notably, MEG3 expression levels in the peripheral blood of patients with obstructive CAD are significantly higher than in healthy controls. ROC curve analysis suggests that MEG3 could potentially serve as a biomarker for predicting and diagnosing CAD (Saygili *et al.*, 2021). It is evident that MEG3 has multifaceted and complex effects on the development and progression of CAD. Besides influencing VEC proliferation, migration, and angiogenesis, MEG3 can affect VEC pyroptosis (Zhang *et al.*, 2018) and smooth muscle cell apoptosis through various mechanisms (Bai *et al.*, 2019). The complex relationship between MEG3 and CAD warrants further in-depth research to be gradually elucidated.

Diabetic Angiopathy: In recent years, MEG3 has attracted widespread attention in the field of diabetes research. Studies have found that damage to VECs in diabetes is associated with dysregulated MEG3 expression. In high glucose-induced HUVECs, cell proliferation, migration, and angiogenesis are inhibited, and MEG3 expression is elevated. MEG3 can impair VEC function under high glucose conditions through mechanisms such as regulating the PI3K/Akt pathway and targeting miRNA (Ju *et al.*, 2019; Ye *et al.*, 2018). Diabetic retinopathy, one of the most common diabetic vascular complications, is associated with abnormal retinal neovascularization. Research suggests that MEG3 plays a significant protective role in diabetic retinopathy. It has been reported that serum MEG3 levels are reduced in patients with diabetic retinopathy, and MEG3 may delay the progression of diabetic retinopathy by inhibiting the expression of transforming growth factor- β 1 (TGF- β 1) and VEGF (Zhang *et al.*, 2018). Similarly, Qiu *et al.* (2016) reported significant downregulation of MEG3 in the retinas of diabetic mice and high glucose-induced retinal VECs. MEG3 is involved in regulating the proliferation, migration, and angiogenesis of retinal

VECs through the PI3K/Akt signaling pathway, and knocking down MEG3 exacerbated retinal vascular dysfunction.

Interestingly, Wang *et al.* (2018) found that knocking down MEG3 aggravated inflammation damage in high glucose-induced HUVECs while simultaneously stimulating VEC proliferation and inhibiting cell apoptosis, suggesting that MEG3 has a complex regulatory role in VECs under high glucose conditions. The specific mechanisms of MEG3's actions in this context require further in-depth research.

Conclusions and Recommendations

In conclusion, MEG3 can affect the angiogenesis, inflammatory response, programmed death and other functions of VECs by interacting with different signaling pathways and target genes, thus regulating physiological or pathological angiogenesis. These results indicate that MEG3 plays an important role and significance in vascular biology. As research progresses, MEG3 may become a potential diagnostic and prognostic marker for vascular-related diseases, and a therapeutic target for these diseases. In conclusion, MEG3 is an interesting and challenging area of research that requires more experimental data and clinical evidence to support and refine its role and mechanism in VECs function.

Acknowledgments

The authors acknowledge the Baise Scientific Research and Technology Development Plan Project (Baik20224118) for this work.

Novelty Statement

This review provides new insights into how LncRNA-MEG3 influences vascular endothelial cell function, offering a comprehensive analysis of its regulatory mechanisms and potential implications for vascular health. By synthesizing current research, it identifies novel pathways and therapeutic targets for future investigation.

Author's Contribution

All author contributed equally in writing, review and revision of this review article.

Conflict of interest

The authors have declared no conflict of interest.

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