OncoTargets and Therapy

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REVIEW

Advances and Prospects of Vasculogenic Mimicry in Glioma: A Potential New Therapeutic Target?

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Vasculogenic mimicry (VM) is the formation of a "vessel-like" structure without endothelial cells. VM exists in vascular-dependent solid tumors and is a special blood supply source involved in the highly invasive tumor progression. VM is observed in a variety of human malignant tumors and is closely related to tumor proliferation, invasion, and recurrence. Here, we review the mechanism, related signaling pathways, and molecular regulation of VM in glioma and discuss current research problems and the potential future applications of VM in glioma treatment. This review may provide a new viewpoint for glioma therapy.

Keywords: glioma, vasculogenic mimicry, glioma stem cells, hypoxia, drug delivery systems, noncoding RNAs

Introduction

Gliomas are among the most common central nervous system tumors. At present, comprehensive high-grade gliomas treatment involves surgical intervention combined with postoperative radiotherapy and chemotherapy. However, the median survival time for patients with glioblastoma is less than 14 months, as the tumors are prone to recurrence and the patient mortality rate is very high.[1] High-grade gliomas are the typical vascular-dependent solid tumor,[2] rich in tumor angiogenesis, and difficulty restricting tumor blood supply is one reason why clinical treatment is problematic.[3]

Antiangiogenic therapy has been an adjuvant therapy for high-grade gliomas for the past decade. The angiogenesis inhibitor bevacizumab has been used in the treatment of glioma. However, neuro-oncologists have found that angiogenic inhibitors have not achieved the desired therapeutic effect in clinical practice.[4–6] It appears that glioma cells (GCs) exhibit "therapy resistance", suggesting the presence of a blood supply source in gliomas that differs from traditional angiogenesis.

Discovery of Vasculogenic Mimicry (VM)

VM was first discovered by Maniotis et al in highly invasive malignant melanoma.[7] VM is a matrix-rich conduit without endothelial cells (ECs), and an EC-independent tumor microcirculation model. Specifically, VM refers to a channel formed by a series of changes, including self-deformation and matrix remodeling of tumor cells to undergo "phenotypic transformation into ECs".[7] The tumor cells that comprise this channel structure show a variety of phenotypic transformations, such as dedifferentiation, where cells show the dual phenotypic characteristics of ECs and tumor cells.

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http://doi.org/10.2147/OTT.S247855

Maniotis et al[7] first found a grid-like structure formed by interconnections between the stroma in malignant melanoma tissue sections. Using transmission electron microscopy, they observed that the grid structure in the tumor tissue was composed of a special kind of channel. This channel contained hemoglobin and plasma components that pass through it. They further used iodate Schiff staining and found that some of the ducts were strongly positive, suggesting that they were rich in matrix components. However, there was no expression of CD34, an EC marker, in the ducts. This finding suggested that there were no vascular ECs present in these structures.

Furthermore, Maniotis et al[7] found that the channels were rich in laminin, collagen IV, collagen VI, and heparan sulfate proteoglycan. Phenotypic analysis of tumor cells suggested that they had undergone a phenotypic transformation into ECs. Hemoglobin, red blood cells, platelets, and other blood components were observed in the duct, indicating that this channel was involved in the microcirculation supplied by the tumor vessels.[7,8]

This kind of tumor cell, with an "EC phenotype", forms the structure of the channels through complex processes of cell deformation, proliferation, migration, and matrix remodeling, to provide the blood supply required for invasive tumor growth. This is also one of the reasons why there is a lack of necrosis in malignant melanoma tissue sections.

Since its initial discovery, VM has been found in other solid tumors, including hepatocellular carcinoma,[9–12] Ewing's sarcoma,[12,13] acute leukemia,[14] ovarian carcinoma,[15,16] cervical cancer,[17] prostate adenocarcinoma,[18] nasopharyngeal carcinoma,[19] non-small cell lung cancer,[20] lung adenocarcinoma,[21] osteosarcoma,[22] gastric cancer,[23,24] breast cancer,[25,26] and renal clear cell carcinoma.[27]

The in vitro detection of VM involves Periodic Acid-Schiff (PAS)-CD34 double immunohistochemical staining to observe the structure of the lumen in the section. If the endothelial marker CD34 (or CD31) is present, PAS-positive staining indicates tumor vessels. If the endothelial marker CD34 (or CD31) is absent, PAS-positive staining indicates VM. Another detection method has been developed based on the Matrigel three-dimensional (3D) culture model of tumor cells in vitro. Arrangement of tumor cells in a 3D reticular structure suggests that the tumor cells have undergone phenotypic transformation into ECs. Additionally, the glycoprotein-rich VM channel was also observed in 3D in an in vitro tumor cell culture model by using X-ray tomography for 3D reconstruction.[28] Through time-lapse dynamic magnetic resonance angiography combined with electron microscopy and immunohistochemistry, this VM structure has been confirmed to be involved in tumor microcirculation.[29]

VM Formation in Glioma

VM was discovered and reported in glioma by Yue and Chen[30] in 2005. They collected 45 cases of WHO II–IV grade astrocytoma tissues and found PAS (+)/CD34 (-) channels in two high-grade astrocytoma tissues. These channels connected to the CD34 positive glioma microvessels and formed part of the microcirculation, which confirmed the existence of VM in gliomas.[30] In a subsequent study of 101 glioma tissue samples, VM was found in glioma tissue sections from 13 samples. The positive rate of VM positively correlated with the degree of malignancy in these samples, indicating that patients with VM often have a poor prognosis and short survival time.[31] The positive rate of VM in highly malignant adult glioblastoma specimens was higher than that in lower-grade glioma tissues.[32,33] CD105 (a vascular EC marker) and CD133 double-positive GCs were also found in high-grade gliomas in children, suggesting that VM is not unique to adult high-grade glioma.[34,35] VM formation in glioma is shown in Figure 1.

Differentiation of Glioma Stem Cells (GSCs)

Using gene chip technology, researchers analyzed and the expression of specific genes in GCs with VM. Their findings suggest that GCs undergoing VM may regain pluripotent characteristics, exhibit an embryonic phenotype, and undergo "transdifferentiation".[36] However, VM has been detected in some malignant tumors with bidirectional differentiation. Taken together, these studies have shown that to form VM, GCs must show "transdifferentiation" characteristics and be able to differentiate.[37] Recently, Mei et al[38] collected 64 glioblastoma tissue samples. Live-cell imaging confirmed that malignant GSCs could differentiate into ECs and produce VM. Among them, CD133 (+) GSCs were considered to have a stronger ability to induce VM formation than CD133 (-) GSCs.[39] Wu et al[40] found that bevacizumab could induce autophagy in GSCs and activate the vascular endothelial growth factor/vascular endothelial growth factor receptor-2 (VEGF/VEGFR-2) signaling pathway, which also promotes VM. This mechanism may, in part, explain the poor clinical efficacy

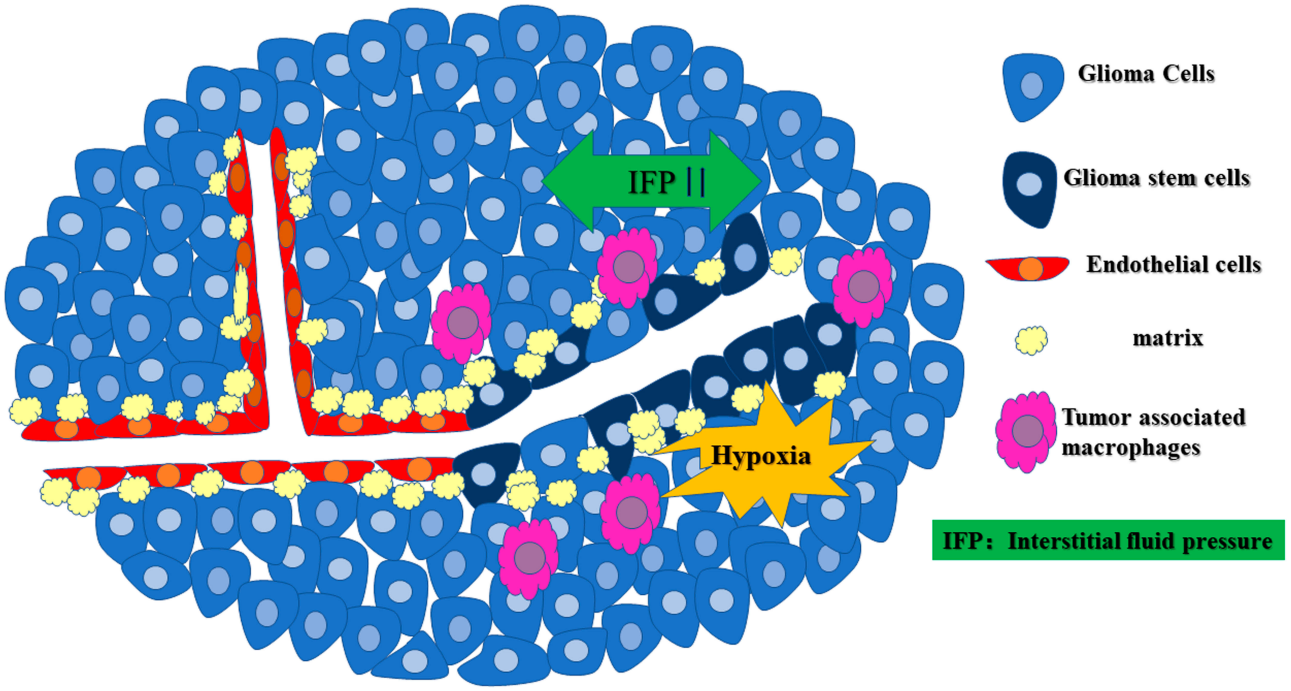

Figure 1 The occurrence of VM in gliomas. Rapid glioma cell proliferation and disordered perfusion in the glioma microcirculation can lead to elevated high interstitial fluid pressure (IFP), the formation of a hypoxic environment in the center of the glioma, M2 tumor-associated macrophage (Pink) infiltration, formation of a duct structure by GSCs with an "EC phenotype" through the complex process of cell deformation, proliferation, migration, and matrix remodeling (yellow), which provides the blood supply required for invasive tumor growth.

of bevacizumab in the treatment of glioma. An increasing number of studies have shown that GSCs play a vital role in the development of VM in glioma.[41] However, Ke et al[42] found that non-stem-like cells of glioma were more prone to gain VM-related gene expression and phenotype than were stem-like cells of the same origin.

Based on the critical role of GSCs in glioma VM, the researchers developed a variety of drug delivery systems (Table 1), hoping to produce the dual effects of inhibiting glioma stem cell growth and glioma VM at the same time. Some receptors, such as VEGFR-2, neuropilin 1 (NRP1), ephrin A, and epidermal growth factor receptor (EGFR), are highly expressed on GSCs within the VM. Multifunctional targeted drug delivery is feasible when these receptors are efficiently targeted. Liposomes or micelles possess a high binding capacity for receptors and demonstrate superiority in tumor-homing imaging.[43–57] This type of treatment is expected to become a new direction for the treatment of glioma.[58]

Formation of Glioma VM in Hypoxic Environments

The rapid proliferation of GCs causes a relative lag in tumor angiogenesis, which then leads to the formation of a hypoxic microenvironment in localized tumor regions. In this hypoxic microenvironment, GCs are arranged autonomously into channels. These GC-arranged VM channels are the key to maintaining the malignant biological characteristics of tumors and have some EC functions and phenotypes.[59,60] The hypoxic microenvironment also activates some related signaling pathways, molecules, and the prolyl hydroxylase activity decreases, allowing the hypoxia-inducible factor (HIF) subunit alpha subunit to escape von Hippel-Lindau degradation. HIF alpha subunits accumulate in the cytoplasm, where they combine with HIF beta to form heterodimers and then translocate to the nucleus to activate target gene transcription.[61] Additionally, hypoxia inhibits HIF degradation, allowing HIF-1α or HIF-2α to be in the nucleus and bind to the hypoxia response element of the target gene. Activation of VEGF, cytokines, stem cell characteristic maintenance-related genes, and epithelial-mesenchymal transition (EMT) inducers could also lead to VM.[62,63]

Rapid cell proliferation and unorganized perfusion in glioma microcirculation can cause an increase in interstitial fluid pressure, inducing ECs to cross the blood-tumor barrier and form a hypoxic environment in the center of

Table 1 Targeting Drug Delivery Systems for Circumventing VM Formation

No	Drug Carrier	Types of Drugs	Name of Drug	Special Conjugate	Other Conjugate	The Transport and Identification Mechanism	The Aim of Treatment	Ref
1	Liposomes	Single	Combretastatin A4	Peptide containing the Asn-Gly-Arg	NA	Endocytosis, CPP	Anti-VM	43
2	Liposomes	Single	PTX	Multifunctional tandem peptide R8-c(RGD)	NA	Endocytosis, CPP	Anti-VM and anti-BCSCs	44
3	Liposomes	single	DOX	Hyaluronic acid ion-pairing nanoparticle	NA	Endocytosis, CPP	Anti-VM and anti-BCSCs	45
4	Liposomes	single	PTX	Tandem peptide R8-dGR	Integrin αvβ3 and NRP1 receptors recognizing peptide	Endocytosis, CPP	Anti-VM and anti-BCSCs	46
5	Liposomes	Dual	PTX; artemether	Mannose-vitamin E derivative; dequalinium-lipid derivative	NA	Glucose transporters; adsorptive-mediated endocytosis	Anti-VM; induction of apoptosis in brain cancer cells and BCSCs	47
6	Liposomes	Single	PTX	TR peptide	Integrin αvβ3-specific vector	Endocytosis, CPP	Anti-VM and anti-BCSCs	48
7	Liposomes	Single	PTX	SHH targeting peptide; VEGFR 2 targeting peptide	CK peptide; GYG linker	PEG-PLA	Anti-VM and anti-BCSCs	49
8	Liposomes	Single	DOX	d-peptide of nicotine acetylcholine receptors	VEGFR 2 and NRP1 recognizing peptide	Endocytosis, CPP	anti-VM	50
9	Micelles	Single	PTX	Tumor-homing peptides	GRP78	Endocytosis, CPP	Anti-VM and anti-BCSCs	51
10	Micelles	Single	PTX	EGFR/EGFRvIII Dual-Targeting Peptide	NA	Endocytosis, CPP	Anti-VM and anti-BCSCs	52
11	Liposomes	Dual	Lycobetaine, OCT	nRGD	NA	Endocytosis, CPP	Anti-VM, anti-BCSCs and anti-tumor-associated macrophages	53
12	Micelles	Single	PTX	Peptide ligand RAP12 of LRP1	NA	PEG-PLA	Anti-VM and anti-BCSCs	54
13	Liposomes	Single	DOX	Myristic Acid-Modified DA7R Peptide	NA	Endocytosis, CPP	Anti-VM and anti-BCSCs	55

(*Continued*)

Table 1 (Continued).

No	Drug Carrier	Types of Drugs	Name of Drug	Special Conjugate	Other Conjugate	The Transport and Identification Mechanism	The Aim of Treatment	Ref
14	hMSCs	Single	Bispecific immunotoxins	VEGF165; ephrin A	PE38KDEL	Injection of engineered hMSCs	Anti-VM and inhibiting tumor growth	56
15	Liposomes	Single	DOX	Heptapeptide A7R	VEGFR 2 and NRP1 recognizing peptide	Endocytosis, CPP	Anti-VM and anti-BCSCs	57

Abbreviations: VM, vasculogenic mimicry; PTX, paclitaxel; DOX, doxorubicin; CTT, octreotide; hMSCs, human mesenchymal stem cells; BCSCs, brain cancer stem cells; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; NRP1, neuropilin-1; RGD, arginine-glycine-aspartic acid; SHH, human sonic hedgehog targeting peptide; LRP1, LDL receptor related protein 1;PEG-PLA, poly(ethylene oxide)- poly(lactic acid); CPP, cell penetrating peptides. NA, not applicable.

the glioma.[61,64] This hypoxia causes GCs with "stem cell characteristics" to form VM channels, which are then connected to endothelial-dependent blood vessels to form early VM structures.[65] This structure is a mixed structure in which glioma microvessels and VM coexist. The spatial and temporal correlations between the VM networks and GCs with "stem cell characteristics" suggest that these cells are the early driving forces of VM.[64]

Matrix Remodeling Is a Critical Step in VM

In the identification of VM, the PAS-positive matrix layer was found to cover the inner surface of the VM structure. At present, the known matrix components include laminin, collagen, mucopolysaccharide, and F tissue factor and its inhibitors. The first several components are also components of the vascular basement membrane, which promotes connection and penetration between the VM structure and glioma microvessels. The balance between F tissue factor and its inhibitors is the key regulatory mechanism controlling anticoagulant function and maintaining VM blood flow.[66]

Immune Cell Infiltration

GCs can recruit tumor-associated immune cells, especially M2 tumor-associated macrophages (TAMs) that express CD68 and CD206.[67] GCs secrete IL-4 to activate TAMs and upregulate the expression of CD68, Arg-1, and CD204. Activated TAMs are widely recruited to, and infiltrate, VM-positive areas where they activate and upregulate cyclooxygenase-2. This further activate prostaglandin E and prostaglandin E receptor 1 through the protein kinase C pathway, and promotes VM in glioma.[68,69]

Regulation of VM in Glioma

Many molecules and signaling pathways are involved in the regulation and development of VM in glioma.

Hypoxia-Related Signaling Pathways

Hypoxia can induce VM. Under hypoxic conditions, leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1) inhibit the EGFR mediated phosphoinositol 3-kinase (PI3K)/AKT pathway and repress the EMT.[70] The inhibition of hypoxia-induced VM in gliomas has been studied.[70] Under hypoxia, the rapamycin target protein is involved in VM formation in glioma through HIF-1α.[63] In the in vitro hypoxia glioma model, B-cell lymphoma 2 (Bcl-2) inhibits VM formation in gliomas by inhibiting the activation of the HIF-1α-MMP-2-MMP-14 signaling pathway.[71] Silencing Beclin-1 can also significantly reduce hypoxia-induced VM formation.[72] Additionally, under hypoxia, some GSCs express vascular endothelial (VE)-cadherin; VE-cadherin and HIF-2α directly interact to contribute to GSC VM formation.[73]

The VEGF family is a group of regulatory molecules critical for angiogenesis in glioma, and it is also involved in VM regulation in gliomas.[41] For example, GSCs express VEGFR-2, which is activated by VEGF and promotes tubule formation. During autophagy in GSCs, phosphorylation of VEGFR-2 is activated by the PI3K-AKT pathway, which promotes the formation of VM in GSCs.[40] The role of VEGF in VM in gliomas was also detected by the dynamic 3D culture model.[74]

VE-cadherin, a member of the cadherin superfamily, is closely related to hypoxia-related signaling molecules. Under hypoxic conditions, VE-cadherin is upregulated in a HIF-1α- and HIF-2α-dependent manner and contributes to hypoxia-induced VM.[73] Abnormal expression of VE-cadherin specifically by ECs was also found in VM glioma-like stem cells, suggesting that VE-cadherin is involved in VM.[75,76]

Matrix Metalloproteinases (MMPs)

MMPs play an essential role in VM formation and are essential protein targets and effectors in the VM regulatory network. It has been reported that both MMP-14 and MMP-2 degrade the gamma 2 laminin subunit into gamma 2′ and gamma 2x fragments and then stimulate glioma cell invasion and VM.[77] In malignant glioma, MMP-14 expression and activation transform MMP-2 precursors into active MMP-2 and affect matrix remodeling, which affects VM formation in glioma.[78] Histone deacetylase activates MMP proteins through the PI3K-ERK signaling pathway and promotes VM formation by regulating the expression of laminin subunit gamma 2 (LAMC2), a mimicry-related molecule in gliomas.[77]

Cytokine Family

Epidermal growth factor (EGF) is increased in GCs, and binding to EGFR activates its downstream pathways, including PI3K-AKT, ultimately activating LAMC2 and cyclooxygenase-2 and promoting VM.[31] The inhibitory effect of LRIG1 on VM in glioma is also mediated by the EGFR signaling pathway.[70] EMT plays an important role in glioma progression.[79,80] Transforming growth factor beta (TGF-β) induces the development of VM,[81] while the TGF-β1 inhibitor galunisertib inhibits astrocyte-induced VM in glioma.[82] Additionally, the expression of insulin-like growth factor-binding protein 2 (IGFBP2) is positively correlated with VM in patients with glioma. IGFBP2 interacts with the integrin alpha5beta1 subunits and enhances CD144 expression in a FAK-ERK pathway-dependent manner, IGFBP2 can also activate CD144 and MMP2 through transcription factor SP1 activation, enhancing VM in gliomas.[83] Aquaporin-1 may play a role in VM in glioblastoma, and it can be used as a new diagnostic biomarker and a potential therapeutic target.[84] In oligodendroglioma, downregulation of *galectin-1* gene expression, a significant decrease in brain expressed X-linked 2 expression, and inhibition of VM may present new therapeutic strategies for reducing chemotherapy resistance.[85] A histone deacetylase inhibitor has also been identified as a promising candidate for VM inhibition in glioblastoma.[77,86] Finally, suppression of Axin1[87] and curA[88] have also been shown to affect VM.

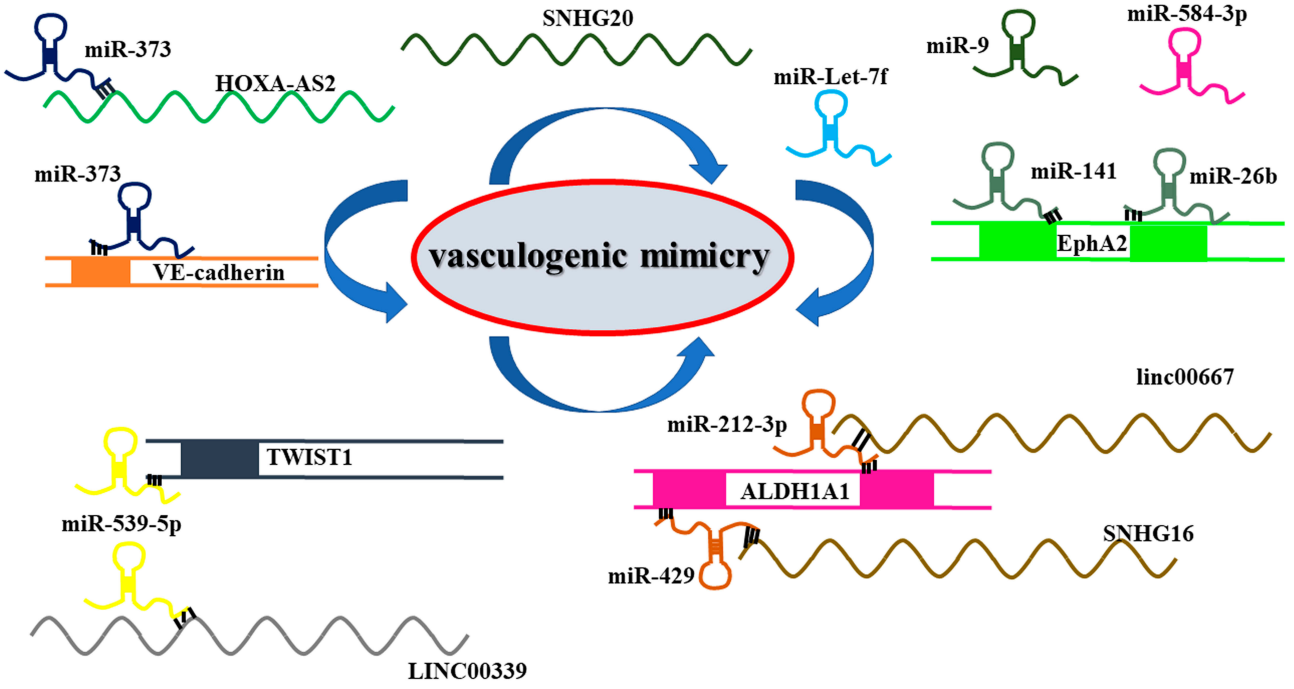

Figure 2 Noncoding RNAs are important regulatory molecules for VM formation in gliomas. The lncRNA-miRNA network played an essential role in regulating VM formation in glioma.

Table 2 The Roles of Major Noncoding RNAs in VM Formation in Glioma

No.	The Types of Noncoding RNAs	The Name of Noncoding RNAs	Function	The Target Molecules	Ref
1	lncRNA	HOXA-AS2	Promotion	Inhibit VE-cadherin expression, and inhibit the expression and activity of MMP-2 and MMP-9, PI3K-AKT signaling pathway	78
2	miRNA	miR-373	Inhibition	Inhibit VE-cadherin expression, and inhibit the expression and activity of MMP-2 and MMP-9, PI3K-AKT signaling pathway	78
3	lncRNA	LINC00339	Promotion	Increase in the expression of TWIST1. TWIST1 upregulates the promoter activities of MMP-2 and MMP-14, and increases the expression and activity of MMP-2 and MMP-14	89
4	miRNA	miR-539-5p	Inhibition	Increase in the expression of TWIST1. TWIST1 upregulates the promoter activities of MMP-2 and MMP-14, and increases the expression and activity	89
5	lncRNA	SNHG16	Promotion	Increase the expression of ALDH1A1	90
6	lncRNA	linc00667	Promotion	Increase the expression of ALDH1A1	90
7	miRNA	miR-212-3p	Inhibition	Inhibit the expression of ALDH1A1	90
8	miRNA	miR-429	Inhibition	Inhibit the expression of ALDH1A1	90
12	lncRNA	SNHG20	Promotion	Upgradation of FOXK1 mRNA by SMD pathway	91
9	miRNA	miR-Let-7f	Inhibition	Disturbing periostin induced migration	92
10	miRNA	miR-141	Inhibition	Controlling EphA2 expression	93
11	miRNA	miR-584-3p	Inhibition	Disturbing hypoxia-induced stress fiber formation and migration of glioma cells	94
13	miRNA	miR-9	Inhibition	Controlling STMN1 expression	95
14	miRNA	microRNA-26b	Inhibition	Controlling EphA2 expression	96

Abbreviations: lncRNA, long noncoding RNA; miRNA, microRNA; TWIST1, transcription factor twist family bHLH transcription factor 1; VE-cadherin, vascular endothelial-cadherin; HOXA-AS2, HOXA cluster antisense RNA 2; ALDH1A1, aldehyde dehydrogenase 1 family member A1; SMD, Staufen1-mediated mRNA decay; EphA2, EPH receptor A2; STMN1, stathmin 1.

Noncoding RNAs

In recent years, the regulatory roles of noncoding RNAs (ncRNAs) in glioma occurrence, metastasis, invasive growth, and angiogenesis have become the focus of glioma research. ncRNAs include long ncRNAs (lncRNAs), microRNAs (miRNAs), and PIWI-interacting RNAs.

lncRNAs are a newly discovered class of ncRNAs with lengths of more than 200 nucleotides. lncRNAHOXA-AS2 is upregulated in glioma tissues and is positively correlated with the positive rate of VM.[78] *HOXA-AS2* knockout attenuates the GC viability and represses VM, which may occur through VE-cadherin inhibition. Moreover, *HOXA-AS2* knockout inhibits the activity of MMP-2 and MMP-9.[78] In addition, LINC00339 expression in glioma positively correlates with VM formation. LINC00339 inhibits miR-539-5p expression, resulting in increased expression of twist family bHLH transcription factor 1 (TWIST1). TWIST1 upregulates *MMP-2* and *MMP-14* promoter activities and expression.[89] The USF1 transcription factor promotes VM in glioma by regulating lincRNA-SNHG16 and linc00667. Silencing of USF1 can inhibit VM occurrence, which may be regulated by a competitive endogenous RNA mechanism.[90] lncRNA SNHG20 also plays a vital role in regulating the formation of VM in glioma.[91]

miRNAs are also essential regulators of VM in glioma. Xue et al[92] found that miR-Let-7f reduces the occurrence of VM in gliomas by inhibiting periostin-induced GC migration. Li et al[93] confirmed that miR-141 expression in primary gliomas is downregulated. miR-141 regulates GC proliferation, migration, and invasion by controlling EphA2 expression, which then affects VM in gliomas. miR-584-3p plays a role in glioma inhibition by inhibiting

VM formation in GCs by antagonizing hypoxia-induced ROCK1-dependent stress fiber formation.[94] miR-9[95] and miR-26b[96] can also be used as potential anti-VM molecules in GCs.

These results suggest that ncRNAs are critical VM regulatory molecules in glioma. Looking for a noncoding RNA molecule may be a potential target for glioma therapy (Figure 2 and Table 2).

Conclusion

The in-depth study of VM in gliomas has shown that VM can be used as a new entry point for the basic research of gliomas, and as a new direction in glioma growth inhibition. Moreover, VM has become the focus of many researchers to solve antiangiogenesis-targeted drug resistance in the treatment of gliomas.

The main issues remaining to be addressed in VM research in glioma are: (1) the glioma microenvironment and its complexity, in which the relationships among various regulatory factors, specific regulatory mechanisms, and glioma VM are not clear; (2) the relationship between GSCs and VM in glioma is not clear; and (3) at present, glioma VM research is mainly supplemental to glioma angiogenesis research, and the relationship between VM and angiogenesis and their interaction with the malignant progression of glioma have not been reported. Nevertheless, the study of the role of VM in gliomas may still provide a new direction for glioma treatment.

Abbreviations

VM, vasculogenic mimicry; ECs, endothelial cells; GCs, glioma cells; PAS, Periodic Acid-Schiff; 3D, three-dimensional; GSCs, glioma stem cells; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2; NRP1, neuropilin 1; EGFR, epidermal growth factor receptor; HIF, hypoxia-inducible factor; EMT, epithelial-mesenchymal transition; TAMs, tumor-associated macrophages; LRIG1, leucine-rich repeat sequences and immunoglobulin-like domain 1; PI3K, phosphoinositol 3-kinase; Bcl-2, B-cell lymphoma; MMPs, matrix metalloproteinases; VE-cadherin, vascular endothelial-cadherin; LAMC2, laminin subunit gamma 2; TGF-β, Transforming growth factor beta; IGFBP2, insulin-like growth factor-binding protein 2; ncRNAs, noncoding RNAs; lncRNAs, long noncoding RNAs; miRNAs, microRNAs; TWIST1, transcription factor twist family bHLH transcription factor 1; IFP, interstitial fluid pressure.

Acknowledgments

This work is supported by grants from the National Natural Science Foundation of China (81702488), China Postdoctoral Science Foundation (2018M641745), Doctoral Start-up Foundation of Liaoning Province (No. 20170520020), Shenyang Science and Technology Bureau (No. 19-112-4-044), and 345 Talent Project fund of Shengjing Hospital of China Medical University.

Disclosure

The authors report no conflicts of interest in this work.

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