



Non-Coding RNAs in Glioma Microenvironment and Angiogenesis

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Glioma, especially glioblastoma, is the most common and lethal brain tumor. In line with the complicated vascularization processes and the strong intratumoral heterogeneity, tumor-associated blood vessels in glioma are regulated by multiple types of cells through a variety of molecular mechanisms. Components of the tumor microenvironment, including tumor cells and tumor-associated stromata, produce various types of molecular mediators to regulate glioma angiogenesis. As critical regulatory molecules, non-coding RNAs (ncRNAs) inside cells or secreted to the tumor microenvironment play essential roles in glioma angiogenesis. In this review, we briefly summarize recent studies about the production, delivery, and functions of ncRNAs in the tumor microenvironment, as well as the molecular mechanisms underlying the regulation of angiogenesis by ncRNAs. We also discuss the ncRNA-based therapeutic strategies in the anti-angiogenic therapy for glioma treatment.

Keywords: non-coding RNAs, glioblastoma, tumor microenvironment, tumor vascularization, anti-angiogenic therapy

INTRODUCTION

As early as 1971, Folkman proposed that the growth of solid tumors would be inhibited in the absence of angiogenesis and that both tumor growth and metastasis depended on the formation of new blood vessels. He pointed out that inhibition of angiogenesis was of great significance in tumor therapy (Folkman, 1974). Hanahan and Weinberg (2011) reported tumor angiogenesis as one of the top 10 characteristics of tumors, affirming that angiogenesis played a crucial role in tumor proliferation, invasion, and metastasis (Plate et al., 2012). Generally, neovascularization is essential for the growth of tumors with a diameter of more than 1–2 mm by providing nutrition and oxygen and eliminating metabolic wastes (Cao, 2009). So far, six patterns of angiogenesis in solid tumors have been recognized: sprouting angiogenesis, vasculogenesis, vascular co-selection, intussusceptive vascular growth, vasculogenic mimicry, and tumor stem cell transdifferentiation (Jain and Carmeliet, 2012).

Glioma is the most common and aggressive intracranial central nervous system tumor. As a highly vascularized tumor, the growth, invasion, and recurrence of glioma are all dependent on angiogenesis, resulting in a correlation between vascular density and the degree of malignancy and prognosis (Hanahan and Weinberg, 2011). In particular, glioblastoma (GBM), the most malignant glioma, has a large number of dysplastic new vessels and is the most vascularized brain tumor in humans (Dubois et al., 2014; Giusti et al., 2016; Quezada et al., 2018). Glioma is also featured by the heterogeneity of the tumor tissue. Within the tumor microenvironment composed of tumor cells, stromal cells, and non-cellular components, glioma angiogenesis is a complex process with diverse patterns that are regulated by multiple factors. As a category of critical regulatory molecules in the tumor microenvironment, ncRNAs are indispensable for the communication between diverse cell components and the strict regulation of the expression and secretion of angiogenic factors and cytokines during tumor angiogenesis.

TYPES OF ncRNAs REGULATING ANGIOGENESIS IN THE GLIOMA MICROENVIRONMENT

With the development of high through-put sequencing methodology, the majority of DNA sequence in the human genome has been elucidated. The ENCODE (Encyclopedia of DNA Elements) project revealed that less than 2% of the mammalian genome encode messenger RNA, but at least 70% of the genome are able to produce transcripts of different sizes, mostly ncRNAs (Feingold et al., 2004). ncRNAs play important roles in regulating life activities such as DNA replication, transcription, RNA processing, translation, and protein functions. Functionally, ncRNAs can be grossly divided into two categories: housekeeping and regulatory ncRNAs (Hirayama and Shinozaki, 2010). The housekeeping ncRNAs are parts of the critical molecular machinery required for basic life activities, including transport RNA carrying amino acids, small nucleolar RNA guiding RNA modification and processing, and ribosomal RNA involved in protein synthesis. The regulatory ncRNAs, such as microRNA, long noncoding RNA (lncRNA), and circular RNA (circRNA), participate in multiple processes including tumor angiogenesis (Morris and Mattick, 2014).

microRNAs

miRNAs are important small ncRNAs with a length of 20–22 nucleotides. Classically, miRNAs bind to Ago2 protein to form an RNA-induced silencing complex, which then recognizes and binds to the target mRNA by complementary base pairing, leading to the degradation of the target mRNA (Yang F. et al., 2017). Numerous studies have indicated the critical roles of miRNAs in glioma angiogenesis. For example, in gliomas relative to normal brains, miR-296 is elevated in endothelial cells and directly targets hepatocyte growth factor-regulated tyrosine kinase substrate (HGS). Because HGS mediates the degradation of VEGFR2 and PDGFR β , miR-296 upregulates VEGFR2 and PDGFR β to promote angiogenesis (Wuerdinger et al., 2008).

Aside from miR-296, other miRNAs including miR-93 and miR-675-5p have been reported to promote glioma angiogenesis (Fang et al., 2011; Tchaicha et al., 2011; Lo Dico et al., 2016). In contrast, some miRNAs such as miR-124-3p, miRNA-205, and miR-128 may play inhibitory roles in regulating vascularization (Shi et al., 2012; Yue et al., 2012; Adlakha and Saini, 2014; Zhang et al., 2018). The miRNAs that have been reported to regulate angiogenesis in glioma are summarized in **Table 1**.

lncRNAs

lncRNAs are transcripts longer than 200 nucleotides without open reading frames (Zhao W. et al., 2019). The abnormal expression of functional lncRNAs in gliomas suggests the involvement of lncRNAs in the occurrence, development, and other malignant phenotypes of gliomas (Peng et al., 2018). lncRNAs may function through the following four main mechanisms. First, lncRNAs bind to and regulate the modification, stability, localization, and interaction of target proteins. The NF- κ B-interacting lncRNA NKILA is significantly upregulated in gliomas, and higher NKILA levels are correlated with poorer patient prognosis. NKILA functions by upregulating HIF-1 α expression and the activity of the hypoxia pathway to enhance the Warburg effect and glioma angiogenesis (Chen et al., 2020). Second, lncRNAs bind to long-stranded RNA molecules, including mRNAs, lncRNAs, pre-mRNAs, and pre-miRNAs, to regulate the stability and translation of bound RNAs. For example, ANKHD1 and LINC00346 are elevated, whereas ZNF655 is reduced in glioma-associated endothelial cells. ANKHD1 binds to and enhances the stability of LINC00346, which in turn promotes the degradation of ZNF655 mRNA. ZNF655 functions to target the promoter of ANKHD1. Thus the ANKHD1/LINC00346/ZNF655 feedback loop regulates glioma angiogenesis (Yang et al., 2020). Third, lncRNAs bind to miRNAs and relieve their inhibitory effects on downstream target genes. lncRNA H19 plays an important role in GBM by up-regulating the expression of the angiogenic factor VASH2 through inhibition of miR-29a (Jia et al., 2016; Jiang et al., 2016). In addition, H19 promotes angiogenesis through the miR-342/Wnt5a/ β -catenin axis and the miR-138/HIF-1 α axis (Liu Z. Z. et al., 2020; Zhou et al., 2020). Finally, lncRNAs bind to genomic DNAs to regulate gene transcription. For instance, SLC26A4-AS1 recruits NFKB1 to promote NPTX1 transcription, which exerts anti-angiogenic effects on glioma cells (Li et al., 2021). Whereas many studies have shown the promotion of angiogenesis by several lncRNAs (NEAT, HULC, SNHG16, linc00667, SNHG15, PVT1, etc.) through various downstream pathways (Jia et al., 2016; Zhu et al., 2016; Ma et al., 2017a,b; Zhang et al., 2018; Wang C. et al., 2019; Wang D. et al., 2019; Xu H. et al., 2019; Chen et al., 2020; Liu Z. Z. et al., 2020; Yang et al., 2020; Zhou et al., 2020), lncRNAs may negatively regulate angiogenesis. For example, lncRNA SLC26A4-AS1 suppresses angiogenesis by upregulating NPTX1 *via* NFKB1 transcriptional factor (Li et al., 2021), while LINC00320 inhibits angiogenesis by downregulating NFKB1-mediated AQP9. (Chang et al., 2020). **Table 2** summarizes the lncRNAs participating in the regulation of glioma angiogenesis through different mechanisms.

TABLE 1 | miRNAs involved in the regulation of glioma angiogenesis.

miRNA	Mechanism of action	Effect on angiogenesis	References
miR-296	Target the hepatocyte growth factor-regulated tyrosine kinase substrate (HGS) mRNA, leading to decreased levels of HGS and thereby reducing HGS-mediated degradation of the growth factor receptors VEGFR2 and PDGFR beta.	Promote	Wuerdinger et al. (2008)
miR-93	Promote angiogenesis by suppressing, at least in part, integrin-beta 8 expression.	Promote	Fang et al. (2011) and Tchaicha et al. (2011)
miR-675-5p	Interact with HIF-1 alpha mRNA and the RNA Binding Protein HuR in hypoxia-induced responses.	Promote	Lo Dico et al. (2016)
miR-124-3p	miR-124-3p/NRP-1/GIPC1 pathway.	Inhibit	Zhang et al. (2018)
miRNA-205	Suppress expression of VEGF-A by directly interacting with the putative miRNA-205 binding site at the 3'-UTR.	Inhibit	Yue et al. (2012)
miR-128	Suppress p70S6K1 and its downstream signaling molecules such as HIF-1 and VEGF expression.	Inhibit	Shi et al. (2012) and Adlakha and Saini (2014)

TABLE 2 | lncRNAs involved in the regulation of glioma angiogenesis.

lncRNA	Mechanism of action	Effect on angiogenesis	References
lncRNA NKILA	Increase the expression level of HIF-1 alpha and activate the hypoxia pathway.	Promote	Chen et al. (2020)
lncRNA HULC	Regulate ESM-1 via the PI3K/Akt/mTOR signaling pathway.	Promote	Zhu et al. (2016)
lncRNA PAXIP1-AS1	Recruit transcription factor ETS1 to upregulate KIF14 expression.	Promote	Zhang et al. (2018) and Xu H. et al. (2019)
LINC00346	ANKHD1/LINC00346/ZNF655 feedback loop	Promote	Yang et al. (2020)
lncRNA H19	Bind to miR-29a that targets the 3'-UTR region of vasohibin 2 (VASH2).	Promote	Jia et al. (2016)
	Regulate Wnt5a/beta-Catenin pathway via targeting miR-342.	Promote	Liu Z. Z. et al. (2020) and Zhou et al. (2020)
	Regulate the miR-138/HIF-1 alpha/VEGF axis.	Promote	Liu Z. Z. et al. (2020) and Zhou et al. (2020)
lncRNA NEAT1	Inhibit the angiogenic Akt- FGF-2/TGF-beta/VEGF signaling through ceRNA effect of miR-194-5p and lncRNA NEAT1.	Promote	Wang C. et al. (2019)
SNHG16 and linc00667	USF1/SNHG16/miR-212-3p/ALDH1A1 and USF1/linc00667/miR-429/ALDH1A1 axis regulates the VM of glioma cells.	Promote	Wang D. et al. (2019)
lncRNA SNHG15	Regulate VEGFA and Cdc42 expression via miR-153.	Promote	Ma et al. (2017b)
lncRNA PVT1	Regulate Atg7 and Beclin1 expression via miR-186.	Promote	Ma et al. (2017a)
lncRNA SLC26A4-AS1	Promote NPTX1 transcriptional activity by recruiting NFKB1.	Inhibit	Li et al. (2021)
LINC00320	Downregulate NFKB1-mediated AQP9.	Inhibit	Chang et al. (2020)

circRNAs

CircRNAs are a new family of ncRNAs found in all eukaryotic cells. CircRNA covalently forms a closed loop structure with neither poly (A) tail nor polarity of 5'-3'. Because the structure of circRNA occludes endogenous biomolecules, circRNA is resistant against exonuclease Rnase R digestion and miRNA-mediated non-classical degradation. The biogenesis of circRNAs is regulated by specific cis-acting elements and trans-acting factors, resulting in a tissue-specific and cell-specific expression pattern (Kristensen et al., 2019). Classically, circRNAs specifically bind to and adsorb miRNAs, thereby relieving the inhibitory effects of miRNAs on downstream target genes. For example, down-regulation of circ_002136 expression significantly inhibits the survival, migration, and tube formation of glioma endothelial cells.

Circ_002136 functionally targets miR-138-5p to upregulate SOX13, which as a target gene of miR-138-5p directly associates with and activates SPON2 to promote angiogenesis (He Z. et al., 2019). **Table 3** summarizes the circRNAs (cZNF292, cir-DICER1, circ-SHKBP1, and circSCAF11) involved in the regulation of angiogenesis in the glioma microenvironment (Yang et al., 2016; He et al., 2018; He Q. et al., 2019; Meng et al., 2019). Of note, so far the studies about circRNAs in glioma angiogenesis mainly focus on the classical regulation of miRNAs. However, circRNAs have the capacity to directly bind to proteins and affect their functions. In addition, circRNAs may be associated with pre-mRNA cleavage and ribosomal RNA maturation. Future studies may reveal the involvement of circRNAs in angiogenesis through these non-classical mechanisms.

TABLE 3 | circRNAs involved in the regulation of angiogenesis in glioma.

circRNA	Mechanism of action	Effect on angiogenesis	References
cZNF292	Regulate the Wnt/beta-catenin signaling pathway	Promote	Yang et al. (2016)
circ_002136	FUS/circ_002136/miR-138-5p/SOX13 feedback loop	Promote	He Z. et al. (2019)
circ-DICER1	MOV10/circ-DICER1 / miR-103a-3p (miR-382-5p) / ZIC4 pathway	Promote	He Q. et al. (2019)
circ-SHKBP1	Regulate miR-544a/FOXP1 and miR-379/FOXP2 pathways	Promote	He et al. (2018)
circSCAF11	Regulate the miR-421/SP1/VEGFA axis	Promote	Meng et al. (2019)

ncRNA-RELATED INTERCELLULAR COMMUNICATIONS THAT REGULATE GLIOMA ANGIOGENESIS

Cells and non-cellular components in the glioma microenvironment have complex communications that often favor tumor angiogenesis (Broekman et al., 2018). ncRNAs in the glioma microenvironment utilize multiple communication approaches to execute their functions as key regulators of angiogenesis (Figure 1).

Soluble Factors

Numerous studies have emphasized the pivotal functions of soluble factors in angiogenesis, including the common proangiogenic factors VEGF, angiopoietin, and FGF, and the common angiogenic inhibitors arresten, endostatin, angiostatin, and MMP. Soluble factors are critical mediators of the functions of ncRNAs in regulating angiogenesis. For instance, the lncRNA PVT1 is able to bind and downregulate miR-26b and promote the expression of the soluble factors CTGF and ANGPT2 to boost vascularization (Zheng et al., 2018). CTGF is a member of the CCN family and other CCN proteins such as Cyr61 and NOV have similar functions in glioma (Le Mercier et al., 2008; Sin et al., 2008; Goodwin et al., 2010). Future studies may discover more ncRNAs for regulation of the CCN family. The most common proangiogenic factor VEGFA has been reported to be regulated by multiple ncRNAs including LINC01116, lncRNA CCAT2, and lncRNA TUG1 (Cai et al., 2017; Sun et al., 2020; Ye et al., 2020). It is reasonable that ncRNAs may regulate much more soluble factors to deliberately control angiogenesis (Yu et al., 2017; Yang et al., 2018). Table 4 summarizes the ncRNAs and their target soluble factors that regulate angiogenesis in the glioma microenvironment.

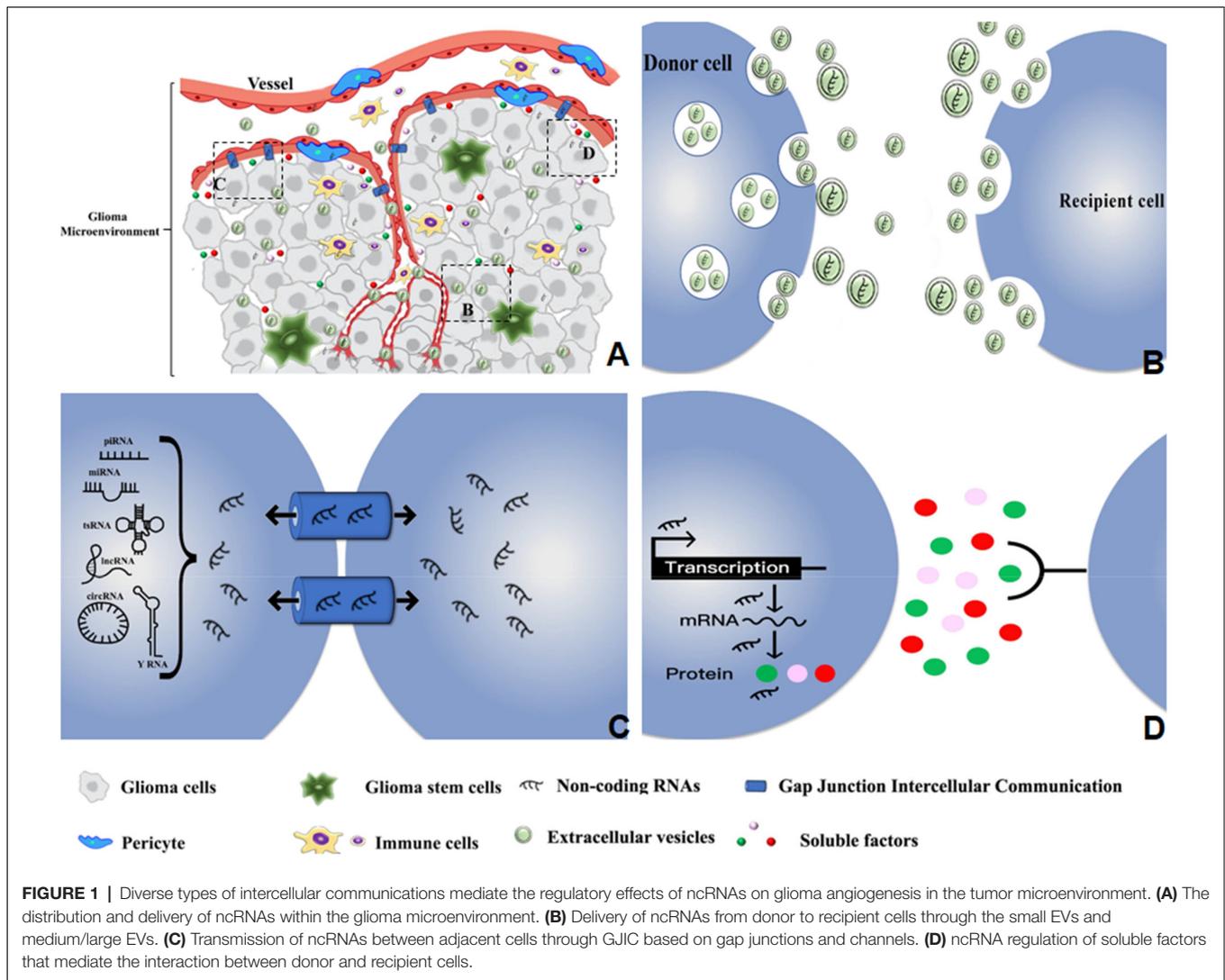
The Gap Junction Intercellular Communication (GJIC)

During glioma invasion and progression, GJIC is an important intercellular communication process based on gap junctions and channels between two adjacent cells that connect the cytoplasm of cells (Katakowski et al., 2010; Hong et al., 2015). Briefly, six connexin (Cx) proteins assemble on one cell to form hemichannels (linkers) that pair with homotypic/heterotypic hemichannels of adjacent cells to mediate GJIC (Laird, 2006). miRNAs can cross gap junction channels to establish intercellular communication and directly affect gene expression in recipient cells (Lim et al., 2011). Cx43 is the most abundant connexin isoform in astrocytes, and down-regulation of Cx43 impairs

tumor cell motility and invasiveness probably through disrupting the GJIC between astrocytes and tumor cells (Bates et al., 2007). GJIC also plays a role in functional miRNA transfer between GBM cells and human microvascular endothelial cells (HMEC; Thuringer et al., 2016). It has been demonstrated that miR-145-5p expressed in HMEC and miR-5096 derived from GBM cells can transfer between the two types of cells through GJIC. MiR-5096 may promote GBM invasiveness and angiogenesis after transferring into HMEC, while miR-145-5p acts as a tumor suppressor after moving into GBM cells (Thuringer et al., 2017). Direct cell-to-cell communication *via* GJIC is superior to indirect communication in terms of specificity and efficiency. *in vivo* delivery of therapeutic miRNAs through GJIC may be more effective but of a shorter duration than other delivery approaches (Lemcke et al., 2015).

Extracellular Vesicles

Due to the lack of specific molecular markers, in 2018 the International Society for Extracellular Vesicles (ISEV) recommended stratifying extracellular vesicles (EV) into small vesicles (<200 nm) and medium/large vesicles (>200 nm) according to their sizes (Thery et al., 2018). Several types of cells can secrete multiple types of EVs including exosomes (30–150 nm in diameter) derived from the inner vesicles, and microvesicles (100–1,000 nm in diameter) formed by outward budding of the cell membrane (Skog et al., 2008; Raposo and Stoorvogel, 2013). EVs play an important role in cell communication events such as direct cell-cell contact, plasma membrane fusion, and receptor-mediated endocytosis. Through transmitting the bioactive components of donor cells into recipient cells, EVs regulate the behaviors of recipient cells and affect the tumor microenvironment (Skog et al., 2008; Balaj et al., 2011; Montecalvo et al., 2012). The biomolecules as cargos of EVs include genomic DNA, cDNA, various RNAs, and proteins (cytoplasmic and membrane-bound), but ncRNAs are the most common and abundant contents of EVs that are transferred between cells with the strongest activity in regulating angiogenesis in the tumor microenvironment (Valadi et al., 2007; Van Der Vos et al., 2011; Rooj et al., 2016). A single GBM cell is able to secrete approximately 10,000 EVs in 48 h (Whitehead et al., 2020). Glioma cells express high levels of lnc-HOTAIR that can be loaded into exosomes and transmitted to endothelial cells, which upregulates the pro-angiogenic factor VEGFA in vascular endothelial cells and ultimately enhances angiogenesis (Ma X. et al., 2017). Table 5 summarizes the ncRNAs enriched in EVs that regulate angiogenesis in the glioma microenvironment.



CELLS IN THE GLIOMA MICROENVIRONMENT INVOLVED IN ncRNA-REGULATED ANGIOGENESIS

Glioma Cells and Glioma Stem Cells (GSCs)

ncRNAs may come from multiple cellular origins in the heterogeneous glioma microenvironment as summarized in **Table 5**. Among glioma cells, GSCs or glioma initiating cells are a small proportion of stem-like tumor cells with self-renewal and multi-lineage differentiation capacity. GSCs are enriched in perivascular niches and function as key regulatory cells to promote angiogenesis (Calabrese et al., 2007; Cheng et al., 2020). GSC-derived exosomes have a central role in angiogenesis and contain plenty ncRNAs in addition to pro-angiogenic factors (VEGF, TGF- β 1, and CXCR4, etc.; Treps et al., 2017; Quezada et al., 2018). Skog et al. (2008) firstly reported that miRNAs loaded in EVs can be taken up by cultured endothelial cells to promote angiogenesis in GBMs. Recently, Lucero et al. (2020)

performed RNA-seq on human brain endothelial cells exposed to GSC-derived EVs along with in silico analysis of epigenetic profiles of GBMs in the TCGA database, and they found that GSC-derived EVs activated transcription of multiple genes in endothelial cells that are highly correlated to angiogenesis. Of note, whereas some reports specifically studied the GSC-derived ncRNAs such as miR-26 and miR-21 in promoting angiogenesis (Sun et al., 2017; Abels et al., 2019; Wang Z.-F. et al., 2019), most studies did not emphasize the hierarchy of glioma cells when it comes to the cellular origin of ncRNAs (Boccaccio and Comoglio, 2013; Gao et al., 2013; Lang et al., 2017; Lucero et al., 2020; Wang et al., 2020). It remains an open question whether the expressions of proangiogenic ncRNAs are under the control, at least in part, of the signaling pathways specifically activated in GSCs.

Mesenchymal Stem Cells

Glioma-associated mesenchymal stem cells (gbMSCs) are stromal cells associated with the malignant development of

gliomas. gbMSCs consist of CD90^{high} and CD90^{low} subgroups with different roles in glioma progression. In particular, CD90^{high} gbMSCs function to increase proliferation and migration of glioma cells, while CD90^{low} gbMSCs have the capacity to transform into pericytes and alter miRNA expression profiles of vascular endothelial cells to promote angiogenesis (Yi et al., 2018). Intracranial xenografts derived from GSCs co-cultured with gbMSCs showed increased CD31 expression, suggesting that gbMSCs enhanced microvascular density (Kong et al., 2013). Because of the functional importance of MSCs in glioma angiogenesis, they may be both origins and targets of ncRNAs for the regulation of angiogenesis. So far there are very limited studies concerning ncRNAs in MSCs (Liu L. et al., 2020). Future studies about the ncRNAs in regulation of MSC phenotypes or the impact of MSC-derived ncRNAs on other components in tumor vasculature will certainly inspire the development of new anti-angiogenic strategies for glioma treatment.

Immune Cells

The glioma tissues contain multiple types of immune cells, and tumor-associated macrophage (TAM) and microglia as the major glioma-infiltrating immune cells account for more than 30% of the GBM bulk cell population (Hambardzumyan et al., 2016). TAM is thought to be closer to macrophages of the M2 type and contributes to the resistance against anti-VEGF therapy through promoting angiogenesis and upregulating Treg cells (Zhu et al., 2017; Powell et al., 2018; Long et al., 2020). ncRNAs delivered by EVs and received by immune cells may be involved in angiogenesis. For example, miR-21 as a cargo of EV is delivered to and ingested by microglia, resulting in regulation of specific downstream mRNA targets and thus promoting angiogenesis (Abels et al., 2019). Future studies may discover more functions of glioma-infiltrating immune cells as the source cells and recipient cells of ncRNAs to regulate angiogenesis in the tumor microenvironment.

ANTI-ANGIOGENIC THERAPY BY TARGETING ncRNAs IN THE GLIOMA MICROENVIRONMENT

Anti-angiogenic therapy has shown promising advances in treating many malignant tumors, but the current strategies are less optimistic in the treatment of gliomas (Carmeliet and Jain, 2011; Gilbert et al., 2014). Accumulating evidence has demonstrated that ncRNAs as key regulatory molecules are involved in the control of diverse target genes and multiple signaling pathways, thus participating in the dynamic and complex angiogenic process. Targeting ncRNAs in the glioma microenvironment will shed light on new strategies for the development of anti-angiogenic therapy.

The Types of ncRNAs Utilized in RNA Therapy

RNA therapy refers to RNA-based targeted therapy either aiming at a specific RNA sequence or utilizing RNA-based molecules as drugs. RNA-based drugs can be grossly divided

into siRNA/shRNA, miRNA, antisense oligonucleotide (ASO), and aptamer in terms of molecular structures. Relative to traditional small molecular chemical drugs and large molecular biopharmaceuticals, RNA therapy is more quantitative, dynamic, and flexible.

The majority of siRNA, miRNAs, and ASOs function by promoting the degradation or blocking the translation of target mRNAs. siRNA, or small interfering RNA, is a class of double-stranded RNA with a length of 20–25 base pairs. By intraperitoneal injection of plasmids encoding siRNAs, Gondi et al. (2004, 2007) showed that siRNAs against uPA, the uPA receptor, and MMP-9 led to a significant reduction in glioma angiogenesis and tumor growth in preclinical mouse models. Likewise, Niola et al. (2006) showed that VEGF-targeted siRNA decreased GBM angiogenesis in a xenograft mouse model. Alternatively, Kargiotis et al. (2008) used adenovirus to deliver siRNA against MMP-2, resulting in decreased invasiveness and inhibition of angiogenesis. In addition to siRNAs, miRNAs and ASOs are being developed for cancer treatment. Both miRNA antagonists and miRNA mimics can work as miRNA-based drugs. As to glioma treatment, the miR-296 antagonist reduces angiogenesis in tumor xenografts *in vivo* (Wuerdinger et al., 2008). ASOs are small-sized single-stranded nucleic acids that form RNA-DNA hybrids with complementary RNA targets to promote RNase-H-mediated degradation of target genes. ASO had been used to target lncRNA TUG1 and inhibit the self-renewal of GSC (Katsushima et al., 2016).

Distinct from other types of RNA molecular drugs, aptamers are oligonucleotide or peptide molecules that bind to specific target molecules, also known as “chemical antibodies”. They are functionally comparable to traditional antibodies but have several advantages including small physical size, flexible structure, multifunctional chemical modification, high stability, and lack of immunogenicity. In addition, aptamers can be internalized after binding to certain receptors and self-cleaved in the presence of ribozyme and target molecules, making them useful as targeted delivery agents. Pegaptanib, approved by the FDA in 2004, is an RNA aptamer that selectively binds VEGF165 to prevent the interaction between VEGF165 and its receptors (VEGF-R1, VEGF-R2, Npn-1) and block VEGF165-mediated signaling, thereby inhibiting choroidal neovascularization and vascular leakage (Gragoudas et al., 2004; Stein and Castanotto, 2017).

Besides the aforementioned RNA-based drugs, targeting the physiological interaction between lncRNAs and miRNAs may provide new approaches for anti-angiogenic therapies (Zhao J. et al., 2019; Teppan et al., 2020). A large number of preclinical and clinical studies have demonstrated a bright future of RNA therapy with a broad spectrum of potential targets in tumor angiogenesis.

EVs as Delivery Tools for RNA Therapy

EVs, especially exosomes, can work as privileged tools for the delivery of RNA cargos in the tumor microenvironment for angiogenic therapy of gliomas (Spinelli et al., 2019; Yekula et al., 2020). Compared with liposomal, metal, and polymeric nanomaterials, exosomes have better bioavailability but less

TABLE 4 | ncRNAs and their target soluble factors involved in the regulation of angiogenesis in glioma.

ncRNA	Mechanism of action	Soluble factor	References
LINC01116	Compete with VEGFA for binding to miR-31-5p	VEGFA	Ye et al. (2020)
lncRNA CCAT2	Activate VEGFA signaling by sponging miR-424	VEGFA	Sun et al. (2020)
lncRNA TUG1	Directly bind to miR-299 to form an RNA-induced silencing complex	VEGFA	Cai et al. (2017)
lncRNA PVT1	Target miR-26b to activate CTGF/ANGPT2	CTGF/ANGPT2	Zheng et al. (2018)
lncRNA SBF2-AS1	Bind to miR-338-3p to regulate EGFL7 expression	EGFL7	Yu et al. (2017)
lncRNA MCM3AP-AS1	MCM3AP-AS1/miR211/KLF5/AGGF1 axis	AGGF1	Yang et al. (2018)

TABLE 5 | ncRNAs in EVs from different cellular origins that regulate angiogenesis in glioma.

ncRNA	Cellular origins	Mechanism of action	References
miR-26	GSC	Activate the PI3K/Akt signaling pathway by targeting PTEN.	Wang Z.-F. et al. (2019)
miR-21	GSC	Stimulate miR-21/VEGF/VEGFR2 signal pathway in ECs	Sun et al. (2017) and Abels et al. (2019)
miR-9-5p	Glioma cell	Target RGS5, SOX7, and ABCB1	Lucero et al. (2020)
lnc-POU3F3	Glioma cell	Upregulate bFGF, bFGFR, VEGFA, and Angio in HBMECs	Lang et al. (2017)
miR-148a-3p	Glioma cell	Activate the EGFR/MAPK signaling pathway via inhibiting ERRF1	Wang et al. (2020)
miR-1	Glioma cell	Inhibit JNK and Met	Boccaccio and Comoglio (2013)
	Glioma cell	Inhibit ANXA2	Gao et al. (2013)
lnc-HOTAIR	Glioma cell	Induction of VEGFA	Ma X. et al. (2017)
lncRNA-FTX	MSCs	Sponge miR-186 that binds to the 3'-UTR of c-Met	Liu L. et al. (2020)

cytotoxicity and immunogenicity. The membrane structure of EVs provides a stable and appropriate environment for the cargo molecules, and the signaling molecules on the surface of EV membranes may guide precise delivery to specific target cells. The ability of EVs to cross the blood-brain barrier is especially important for the treatment of brain cancers. Because of these advantages, EVs have strong potentials to be transformed into effective ncRNA delivery systems. A recent study showed that implantation of the miR-302-367-expressing donor cells to produce EVs containing miR-302-367 in the tumor microenvironment efficiently suppressed GBM development in mouse brain (Fareh et al., 2017; Nair et al., 2018). In addition, the EV donor cells may be genetically engineered to produce EVs with modified surfaces that could lead to more effective delivery to target cells. For example, the donor cells were engineered to express EGFR binding peptides on EV surface, and the modified EVs efficiently delivered let-7a specifically to EGFR-expressing tumor tissues (Ohno et al., 2013). Therefore, EVs may work as effective delivery tools for RNA therapy to express tumor-suppressive RNAs in the tumor microenvironment or specific tumor cells.

Despite the abovementioned advantages, the utilization of EVs in RNA therapy has been obstructed by several problems. There is no universally accepted standard for the isolation, purification, and preservation of exosomes. The mechanisms regulating the sorting and uptake of EVs in the tumor microenvironment remain unclear. Studies from different labs are somewhat incomparable because of the heterogeneity of EVs and the lack of a standardized quantification method. The application of EVs in RNA therapy requires a consensus on the methodology.

THE EMERGING FUTURE OF ncRNAs IN ANGIOGENESIS

The rapidly developing RNA biology is unveiling the critical role of ncRNAs in angiogenesis from multiple unprecedented aspects. Not only new functions but also new categories of ncRNAs have been discovered in the past decade, which certainly will deepen our understanding of ncRNAs in the context of the glioma microenvironment.

RNA Modification

More than one hundred RNA modifications have been reported so far. A well-known case is the N 6-methyladenosine (m6A) modification that refers to the reversible addition of a methyl group to the N element at position 6 of the A base in RNAs, which is the most abundant and well-characterized internal modification in mRNAs. Such RNA modifications occur also in regulatory ncRNAs, which may affect the protein-binding of lncRNAs, maturation of miRNAs, and translation of circRNAs to regulate their biogenesis and functions. The dynamic modifications may endow the ncRNAs with the flexibility to adapt to the constantly changing microenvironment and promote tumor progression.

Many research groups have observed the m6A modification in lncRNAs during the study of the polyA-enriched RNAs (Dominissini et al., 2012; Meyer et al., 2012). The m6A modification may affect the interaction between lncRNAs and their partner proteins. The lncRNA MALAT1 has m6A hypermethylation modification on multiple sites. Two of these m6A residues prevent the formation of the secondary structure of MALAT1 through the “m6A switch” mechanism and enhance the recognition and binding of hnRNP to U5 channels in the

MALAT1 hairpin (Dominissini et al., 2012; Liu et al., 2013, 2015). Interestingly, lncRNAs may also function as an m6A regulator. FOXM1-AS, a lncRNA antisense to FOXM1, promotes the interaction between the m6A demethylase ALKBH5 and the FOXM1 nascent transcripts, leading to the removal of m6A from FOXM1 transcripts to enhance FOXM1 expression in glioblastoma (Zhang et al., 2017).

The m6A modification participates in miRNA maturation. miRNA primary transcripts (pri-miRNA) transcribed from DNA undergo a series of cleavages to get into hairpin miRNA precursor (pre-miRNA) and finally mature miRNAs. However, the canonical m6A motif GGAC is abundant on pri-miRNAs but rarely seen on pre-miRNAs and mature miRNAs. The m6A writer METTL3 binds to pri-miRNAs to execute m6A modification. The m6A-bearing pri-RNAs are then recognized by hnRNP A2B1, which in turn interacts with the microRNA Microprocessor complex protein DGCR8 to promote pri-RNA processing. Therefore, alteration of METTL3 expression may impact the overall m6A levels and the expression of mature miRNAs (Alarcon et al., 2015a,b).

The m6A modification is also prevalent in circRNAs and its read-write mechanisms are similar to those in mRNAs. However, the functions of m6A modification in circRNAs may be different from those in mRNAs. The m6A reader YTHDF2 sequesters methylated circRNA to prevent the activation of the RNA pattern recognition receptor RIG-I, which is essential for the suppression of innate immunity (Zhou et al., 2017; Chen et al., 2019). Meanwhile, the m6A modifications in circRNAs seem to promote the translation initiation from circRNAs through YTHDF3 and the initiation factor eIF4G2 (Yang Y. et al., 2017).

Previous studies have shown that the m6A RNA methylase METTL3 promotes glioma progression by stabilizing the expression of SOX2, suggesting an important role of m6A modifications in glioma (Somasundaram, 2018; Visvanathan et al., 2018). To date, most studies have been focusing on the identification of m6A-modified mRNAs, while little is known about the m6A modification on ncRNAs. Future investigations about the impact of m6A modifications on the production, cellular location, target selection, and other features of ncRNAs will certainly inspire more explorations about the regulation of angiogenesis by ncRNAs in the glioma microenvironment.

RNA-Binding Proteins

RNA-binding proteins (RBP) are a class of proteins that bind to RNAs, including mRNAs and ncRNAs, to regulate their biogenesis and expression levels (Xia et al., 2012; Xu Y. et al., 2019). The READDB¹ database contains the information of 1,344 RBPs and the related diseases (Hashemikhabir et al., 2015). In addition, the catRAPID² and the starBase v2.0³ databases provide useful tools to predict the interactions between RBPs and ncRNAs (Agostini et al., 2013; Li et al., 2014). The binding of RBP to ncRNAs participates in the regulation of target mRNAs from multiple aspects, including mRNA processing, maturation,

transport, localization, and translation (Gerstberger et al., 2014; Janakiraman et al., 2018). In the meantime, the interaction between RBP and ncRNAs affects the expression levels of RBP and/or ncRNAs. Consequently, RBP-ncRNA interaction is involved in the development of neurodegenerative diseases, metabolic diseases, and various cancers (Kim et al., 2017).

RBP regulates not only the generation of miRNAs but also their functions. RBP may have antagonistic or facilitatory effects on miRNAs to synergistically regulate the translation of target genes (Van Kouwenhove et al., 2011; Ho and Marsden, 2014). RBP also affects the stability of lncRNAs. For example, the RBP IGF2BP1 binds to and destabilizes the lncRNA HULC in human hepatocellular carcinoma (Haemmerle et al., 2013). During the biosynthesis of circRNA, RBPs bind to introns near splicing sites and contribute to the production of circRNAs through the RBP-driven cyclization mechanism (Conn et al., 2015; Lyu and Huang, 2017). In addition, RBPs interact with circRNAs to regulate circRNA splicing, processing, folding, stabilization, and localization (Dudekulay et al., 2016). The roles of RBPs as upstream regulators of ncRNAs in glioma microenvironment and angiogenesis are largely unknown.

The Diverse Types of ncRNAs

So far there is no available literature about ncRNAs other than miRNAs, lncRNAs, and circRNAs that have a role in glioma angiogenesis. However, accumulating reports emphasize the biological importance of the diverse types of ncRNAs, which may be star molecules for future studies on the glioma microenvironment.

piRNA

RNAs interacting with the PIWI protein, named as piRNAs (PIWI-interacting RNAs), are a class of 26–31 nt single-stranded small RNAs with a strong uridine monophosphate propensity at the 5' end and methylation modification at the 3' end, which are mainly present in mammalian germ cells and stem cells (Girard et al., 2006). piRNAs were first found in germ cells, functioning to repress transposons and maintain genome stability. Later studies about piRNAs in somatic and tumor cells highlight the diversity and importance of piRNAs. Human PIWI protein is abnormally expressed in breast, pancreatic, and liver cancers (Lee et al., 2006), and the Piwi-like family proteins are overexpressed in GBM (Huang et al., 2021). But little is known about the piRNAs in tumors. Based on the studies of piRNAs in the reproductive system, it is suggested that piRNAs may have similar functions as miRNAs and participate in tumor progression by regulating mRNA targets at the post-transcriptional level (Liu et al., 2019).

YRNA

YRNAs are a class of small RNAs with unique roles as signaling molecules in physiological and biochemical processes such as tumors and cardiovascular diseases, but the exact molecular functions of YRNAs remain elusive. YRNAs account for a relatively large proportion in tumor-derived exosomes, mainly distributed at 29–33 nt. There are four conserved types of YRNA transcripts: YRNA1 (hY1), YRNA3 (hY3), YRNA4 (hY4), and YRNA5 (hY5). In humans, the four YRNAs form a cluster at a single chromosomal locus on chromosome 7q36, which is

¹<http://darwin.soic.iupui.edu/>

²<http://s.tartagialab.com/catrapid/omics>

³<http://starbase.sysu.edu.cn/>

transcribed by the RNA polymerase III. YRNAs consist of a stem-loop structure, an internal loop, and a polyuridine tail. The nucleotide sequences of the internal loop vary greatly, but the upper and lower domains are highly conserved among YRNAs. The loop domain is the least conserved element that regulates chromatin binding. Studies have shown that YRNAs function to initiate chromosomal DNA replication, which is related to cell proliferation (Gulia et al., 2020). Christov et al. (2008) found that the expression of all the four YRNAs was dramatically higher in solid tumors relative to corresponding normal tissues. Down-regulation of YRNA1 and YRNA3 resulted in significant inhibition of cell proliferation, suggesting that YRNA may be a new tumor biomarker and a therapeutic target. In gliomas, YRNA exists as a fragment of approximately 32 nt in length, and hY1, hY4, and hY5 are mainly found in exosomes or free RNP complexes (Wei et al., 2017).

tsRNA

The tRNA-derived small RNAs are collectively referred to as tsRNAs including tRNA-derived RNA fragment (tRF) and tRNA halves (tiRNA). TsRNAs have tissue- and cell-specific expression and are involved in a variety of biological functions, such as stress response, protein translation, ribosome biogenesis, intergenerational transmission of acquired epigenetic information, cell proliferation, apoptosis, and tumorigenesis (Tan et al., 2019). The levels of four tsRNAs (tRNA-ValTAC-3, tRNA-GlyTCC-5, tRNA-ValAAC-5, and tRNA-GluCTC-5) in plasma exosomes were significantly higher in HCC patients (Zhu et al., 2019). Serum tsRNA-ValTAC-41 and tsRNA-MetCAT-37 were used for the diagnosis of pancreatic ductal adenocarcinoma with high accuracy (Xue et al., 2021). The role of tsRNAs in glioma angiogenesis requires further exploration.

DISCUSSION

The ever-changing tumor microenvironment dominates angiogenesis from multiple aspects. ncRNAs are produced by a variety of donor cells to regulate multiple pathways in a series

of different recipient cells in the tumor microenvironment to affect glioma angiogenesis. The complexity of the ncRNA regulatory network is both a chance and a challenge for the development of RNA therapy against angiogenesis. On one hand, ncRNA therapeutics can function on multiple target cells and multiple signaling pathways with high freedom to suppress angiogenesis. On the other hand, people should be super cautious to avoid unwanted off-target effects when utilizing ncRNAs. As for the drug delivery in ncRNA therapy, EVs may work as safe and effective tools to transport ncRNAs in the tumor microenvironment. However, the utilization of EVs requires a widely accepted standard system for the quality control of EVs. Of note, the naturally produced EVs as tumor supportive molecules may be important clinical targets for anti-angiogenic therapy. Taken together, ncRNAs as critical regulatory molecules in the tumor microenvironment are deeply involved in glioma angiogenesis. Future studies would certainly guarantee the anti-angiogenic therapy based on ncRNAs.

AUTHOR CONTRIBUTIONS

DL and WZ: conceptualization. WZ and CN: validation. DL and ZZ: writing—original draft preparation. WZ: writing—review and editing. CX and CN: supervision. DL, CN, and WZ: funding acquisition. All authors contributed to the article and approved the submitted version.

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