Molecular Therapy
Nucleic Acids
Review

Targeting Long Noncoding RNA in Glioma: A Pathway Perspective

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Long noncoding RNAs (lncRNAs) participate extensively in biological processes of various cancers. The majority of these transcripts are uniquely expressed in differentiated tissues or specific cancer types. lncRNAs are aberrantly expressed in gliomas and exert diverse functions. In this article, we provided an overview of how lncRNAs regulate cellular processes in glioma, enumerated the lncRNAs that may act as glioma biomarkers, and showed their potential clinical implications.

Glioma is one of the most common primary intracranial tumors. According to the cellular origin, gliomas are now classified into histological subtypes, including diffuse astrocytic and oligodendroglial tumors, other astrocytic tumors (e.g., pilocytic astrocytoma and pleomorphic xanthoastrocytoma), ependymal tumors, and other gliomas (e.g., angiocentric glioma).[1] To evaluate the degree of malignancy, gliomas are categorized into grades I–IV within each histological subtype.[1] The World Health Organization (WHO) grade IV astrocytoma, glioblastoma multiform (GBM), is one of the most malignant gliomas in adults. Despite the advantage of current therapy combining surgery, antineoplastics, radiation, and tumor-treating fields (TT Fields), the prognosis of GBM patients remain poor, with a median survival of less than 2 years only.[2,3] The 2016 WHO Classification of Tumors of the Central Nervous System[1] presented a major change that molecular parameters are used to establish brain tumor diagnoses, indicating that intensive investigations of glioma at cellular and molecular levels are urgently needed.

The noncoding genome accounts for more than 98% of all sequences, and it regulates a wide variety of cellular processes and pathways in the developmental and pathological contexts.[4] Noncoding RNAs longer than 200 nt are cataloged as long noncoding RNAs (lncRNAs). In the human genome, more than 28,000 distinct lncRNAs have been estimated by the Encyclopedia of DNA Elements (ENCODE) Project Consortium.[5] The mechanisms of lncRNAs regulating gene expression are diverse and not yet fully understood.[6]

On the basis of genomic localization, lncRNAs can be classified into intronic lncRNAs, intergenic lncRNAs (lincRNAs), enhancer lncRNAs (elncRNAs), bidirectional lncRNAs, sense-overlapping lncRNAs, and antisense lncRNAs.[7] The genomic localization of lncRNAs may indicate their potential targets or provide clues of their action modes. As well, the cellular localization of lncRNAs may determine their molecular mechanisms of regulating cellular processes. lncRNAs in the nucleus may interact with chromatin and affect transcriptional regulation and RNA processing,[8,9] while lncRNAs in the cytoplasm can modulate mRNA stability and translation, interact with protein synthesis, and influence cellular signaling cascades.[9] Wang and Chang[6] distilled the action modes of lncRNAs into four archetypes, as signals, decoys, guides, and scaffolds, providing a useful framework to understand the complex functions of lncRNAs. New lncRNAs are being discovered, and how they function as regulators is becoming diversified and more complex.

lncRNAs are aberrantly expressed in cancers and closely interact with tumorigenesis, metastasis, and tumor stage.[8,10] Cancer-associated lncRNAs can be organizationally classified and annotated based on the phenotypes of proliferation, growth suppression, motility, immortality, angiogenesis, and viability, which are proposed as the six hallmarks of cancer.[11] Individual lncRNA may play multiple roles in different cancer phenotypes, while each of the six hallmarks of cancer is modulated by the activity of multiple lncRNAs.[8] lncRNAs are widely expressed in various cancers in a range of different patterns. Some of them exist in many cancers and some are cancer specific, some of them are detectable and correlate with prognostic features of cancers, and some of them act as oncogenes to promote tumorigenesis whereas others act as tumor suppressors.[7] Given the great abundance and functional diversity in cellular processes, lncRNAs may provide a new foundation for developing diagnostic biomarkers and therapeutic targets for cancers.[12–14] In addition, targeting lncRNAs, such as hox transcript antisense intergenic RNA (HOTAIR),[15] HOXA distal transcript antisense RNA (HOTTIP),[16] metastasis-associated lung adenocarcinoma transcript 1 (MALAT1),[17] colorectal neoplasia differentially expressed (CRNDE),[18] and so on, can attenuate chemoresistance and improve the therapeutic efficacy of antineoplastic agents.

In this article, we examine the characteristics of lncRNAs expressed in glioma, highlight the examples of lncRNAs regulating glioma phenotypes, and discuss the lncRNAs that may become glioma biomarkers.

lncRNAs in Glioma

lncRNAs regulate cellular signaling networks in a wide range in glioma. Herein we listed the lncRNAs that have been implicated in

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glioma research and described their functions. In Table 1, we give the details of how lncRNAs and their molecular partners or genomic targets participate in glioma phenotypes of proliferation, growth suppression, motility, viability, and angiogenesis.

MALAT1

MALAT1 is one of the first identified cancer-associated lncRNAs, which was initially demonstrated to be upregulated in lung cancer as a potential prognostic indicator for patients with non-small-cell lung cancer (NSCLC).[19] Vassallo et al.[20] found that WIF1 can inhibit glioma cell migration through attenuation of non-canonical WNT signaling by downregulating MALAT1. Knockdown of MALAT1 was shown to inhibit cell migration, but not proliferation, in glioblastoma cell lines LN-229, LN-18, and LN-428.[20] However, Han et al.[21] reported the different results in human glioma cell lines U87 and U251 that knockdown of MALAT1 promotes cell proliferation and invasion, whereas overexpression of MALAT1 induces reductions in cell proliferation and invasion *in vitro* and tumorigenicity in both subcutaneous and intracranial human glioma xenograft models. They demonstrated that the tumor-suppressive effect of MALAT1 on glioma is associated with extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK)-mediated growth and matrix metalloproteinase 2 (MMP2)-mediated invasiveness.[21] In human glioma cell lines U87 and SHG139, MALAT1 was found to suppress glioma by inhibiting miR-155 expression and activating FBXW7 function.[22] On the contrary, MALAT1 was also found to benefit glioma growth.[23–25] MALAT1 promotes proliferation, suppresses apoptosis, and activates autophagy of glioma cells by sponging miR-101 and upregulating STMN1, RAB5A, and ATG4D expression,[23,24] and it facilitates glioma tumorigenesis by targeting the miR-129/SOX2 axis *in vitro* and *in vivo*.[25] In addition, MALAT1 was found to increase GBM chemoresistance to temozolomide by suppressing miR-203 and promoting thymidylate synthase and ZEB1 expression.[17,26] It seems that MALAT1 exerts both oncogenic and anti-oncogenic functions. We suggest that the effects of MALAT1 on glioma depend on its downstream targets; thus, the whole signaling pathway context should be considered in targeting MALAT1 for glioma treatment.

HOTAIR

HOTAIR has been considered as a negative prognostic factor in liver, colon, and laryngeal squamous cancer patients, and recently it was identified as a critical biomarker for tumor grade, molecular subtype, diagnosis, and prognosis in glioma.[27–29] HOTAIR was reported to promote GBM cell cycle by regulating a predominant PRC2 complex component EZH2.[30] Knockdown of HOTAIR was found to exert a glioma-suppressive function by regulating the miR-326/FGF1-signaling pathway *in vitro* and *in vivo*, indicating the HOTAIR-miR-326-FGF1 axis as a potential therapeutic strategy for glioma treatment.[31] Knockdown of HOTAIR can also increase permeability of the blood-tumor barrier (BTB) by reducing tight junction-related proteins in glioma microvascular endothelial cells via the miR-148b-3p/USF1 pathway, facilitating the delivery of antineoplastic drugs.[32] In addition, HOTAIR is a direct target of bromodomain and extraterminal (BET) domain proteins in GBM.[33] BET proteins are functional requisites for GBM cell growth and malignancy;[34] thus, targeting HOTAIR may block BET protein-induced malignancy of GBM and overcome resistance of GBM to BET bromodomain inhibitors (BBIs), which show broad anticancer effects.

FOXM1-AS

A demethylase of the mRNA modification N6-methyladenosine, ALKBH5, has been reported to affect glioblastoma stem-like cells (GSCs) by modulating pre-mRNA stability and expression of the FOXM1 gene.[35] In this study, the authors showed that the antisense lncRNA of FOXM1, FOXM1-AS, facilitates nuclear interaction of ALKBH5 and FOXM1 pre-mRNA and that FOXM1-AS is critical for GSC tumorigenesis through the FOXM1 axis *in vitro* and in a mouse intracranial xenograft model.[35] The effects of FOXM1-AS on ALKBH5 and FOXM1 revealed an antisense transcript-mediated interaction of pre-mRNA and m^6A enzymes.

HOTTIP

HOTTIP is an antisense lncRNA located at the distal end of the HOXA gene cluster. Expression of HOTTIP is decreased in high-grade glioma tissue samples and GBM cell lines.[36] Overexpression of HOTTIP can inhibit GBM cell proliferation and cell cycle progression, and it promotes apoptosis by downregulating the expression of brain and reproductive expression gene (BRE). By mouse subcutaneous xenograft model, HOTTIP has also been demonstrated to suppress GBM tumorigenesis *in vivo*.[36] Another study revealed that, in glioma cells treated by hypoxia, HOTTIP is significantly upregulated and associated with miR-101-induced ZEB1 expression and epithelial-mesenchymal transition (EMT) process.[37] The authors demonstrated HOTTIP as a key factor in the HIF-1α/HOTTIP/miR-101/ZEB1 axis, which plays essential role in hypoxia-induced EMT and metastasis of glioma.[37]

HOXA11-AS

HOXA11-AS is another antisense transcript located at the HOXA gene cluster. Wang et al.[38] first identified HOXA11-AS as a cell cycle-associated lncRNA and a prognostic factor for glioma patient survival. They found that HOXA11-AS can promote cell proliferation by the regulation of cell cycle progression *in vitro* and *in vivo*.[38] Thereafter, miR-140-5p was found to be a direct target of HOXA11-AS. HOXA11-AS promotes the glioma tumorigenesis by sponging miR-140-5p.[39] Then, miR-214-3p and miR-124-3p were also reported to interact with HOXA11-AS-induced glioma growth and malignancy.[40,41]

ECONEXIN

ECONEXIN (LINC00461) is a novel intergenic lncRNA that was identified by using a combined approach consisting of searching lncRNAs by evolutionary conservation and validating their expression in a MADM glioma mouse model.[42] In glioma cell lines, the inhibition of ECONEXIN induces the upregulation of miR-411-5p and the downregulation of its target, topoisomerase 2 alpha (TOP2A), resulting in decreased cell proliferation. Thus, ECONEXIN

Table 1. Examples of lncRNAs Participating in Glioma Phenotypes

Phenotype	lncRNA	Activity	Mechanism	Reference
Proliferation	MALAT1	promote cell proliferation	sponge miR-101	23,24
		promote GSC tumorigenesis	suppress miR-129 and facilitate SOX2 expression	25
	HOTAIR	promote cell growth	bind to EZH2	27,30
			interact with miR-326/FGF1 pathway	31
	FOXM1-AS	promote GSC tumorigenesis	facilitate nuclear interaction of ALKBH5 and FOXM1 pre-mRNA	35
	HOXA11-AS	affect cell cycle progression	regulate cell cycle proteins	38
		promote tumorigenesis	sponge miR-140-5p	39
			interact with miR-214-3p/EZH2 axis	40
			sponge miR-124-3p	41
	ECONEXIN	promote cell proliferation	interact with miR-411-5p/ TOP2A axis	42
	H19	promote cell proliferation	interact with miR-675/CDK6 axis	49
			interact with miR-140/iASPP axis	52
			reduce miR-152	53
	XIST	promote cell proliferation	interact with miR-152	55
			interact with miR-137/Rac1 axis	57
			sponge miR-429	58
	CRNDE	promote cell growth	interact with P70S6K-mediated mTOR signaling	61
		promote GSC proliferation	negatively regulate miR-186	62
		promote cell proliferation	attenuate miR-384/PIWIL4/STAT3 axis	63
			negatively regulate miR-136-5p	64
	NEAT1	promote cell growth	interact with EGFR/NEAT1/EZH2/β-catenin	69
			interact with miR-449b-5p/c-Met axis	70
		promote GSC proliferation	interact with microRNA let-7e	71
		promote cell proliferation	interact with miR-132/SOX2 axis	73
	HCP5	promote cell proliferation	interact with HCP5-miR-139-RUNX1 feedback loop	78
	HIF1A-AS2	promote GSC growth	interact with IGF2BP2 and DHX9	83
	linc-POU3F3	promote cell proliferation	regulate POU3F3 expression	87
	CASC2c	promote cell proliferation	interact with miR-101	92
	HMMR-AS1	promote cell proliferation	regulate HMMR expression	93
Growth suppression	MALAT1	inhibit cell proliferation	inactivate ERK/MAPK signaling	21
		suppress tumor growth	suppress miR-155 expression and activate FBXW7 function	22
	HOTTIP	inhibit cell proliferation	downregulate BRE	36
	GAS5	inhibit cell proliferation	reduce miR-222 and increase bmf and Plexin C1	43
		inhibit GSC proliferation	interact with miR-196a-5p/FOXO1 feedback loop	44
		inhibit cell proliferation	repress miR-18a-5p	45
	RAMP2-AS1	suppress tumor growth	interact with NOTCH3	84
	CASC2a	inhibit cell proliferation	interact with miR-21	91

(*Continued on next page*)

Table 1. *Continued*

Phenotype	lncRNA	Activity	Mechanism	Reference
Motility	MALAT1	promote cell migration	interact with non-canonical WNT signaling	[20]
Motility	MALAT1	inhibit cell invasion	downregulate MMP2	[21]
Motility	HOXA11-AS	promote cell migration and invasion	interact with miR-214-3p/EZH2 axis	[40]
Motility	HOXA11-AS	promote cell migration and invasion	sponge miR-124-3p	[41]
Motility	GAS5	inhibit cell migration and invasion	reduce miR-222 and increase bmf and Plexin C1	[43]
Motility	GAS5	inhibit GSC migration and invasion	interact with miR-196a-5p/FOXO1 feedback loop	[44]
Motility	GAS5	inhibit cell migration and invasion	repress miR-18a-5p	[45]
Motility	H19	promote cell migration and invasion	derive miR-675	[49,50]
Motility	H19	promote cell migration and invasion	interact with miR-140/iASPP axis	[52]
Motility	H19	promote cell migration and invasion	reduce miR-152	[53]
Motility	XIST	promote cell migration and invasion	interact with miR-152	[55]
Motility	CRNDE	promote cell migration and invasion	interact with P70S6K-mediated mTOR signaling	[61]
Motility	CRNDE	promote GSC migration and invasion	negatively regulate miR-186	[62]
Motility	CRNDE	promote cell migration and invasion	attenuate miR-384/PIWIL4/STAT3 axis	[63]
Motility	CRNDE	promote cell migration and invasion	negatively regulate miR-136-5p	[64]
Motility	NEAT1	promote cell invasion	interact with EGFR/NEAT1/EZH2/β-catenin	[69]
Motility	NEAT1	promote cell invasion	interact with miR-449b-5p/c-Met axis	[70]
Motility	NEAT1	promote GSC migration and invasion	interact with microRNA let-7e	[71]
Motility	NEAT1	promote cell migration and invasion	interact with miR-132/SOX2 axis	[73]
Motility	HCP5	promote cell migration and invasion	interact with HCP5/miR-139/RUNX1 feedback loop	[78]
Motility	CASC2a	inhibit cell migration and invasion	interact with miR-21	[91]
Motility	CASC2c	promote cell migration and invasion	interact with miR-101	[92]
Motility	HMMR-AS1	promote cell migration and invasion	regulate HMMR and mesenchymal phenotypes	[93]
Viability	MALAT1	inhibit apoptosis	sponge miR-101	[23]
Viability	HOTAIR	inhibit apoptosis	interact with miR-326/FGF1 pathway	[31]
Viability	HOTTIP	promote apoptosis	downregulate BRE	[36]
Viability	HOXA11-AS	inhibit apoptosis	sponge miR-140-5p	[39]
Viability	HOXA11-AS	inhibit apoptosis	sponge miR-124-3p	[41]
Viability	GAS5	promote apoptosis	reduce miR-222 and increase bmf and Plexin C1	[43]
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Viability	NEAT1	inhibit GSC apoptosis	interact with microRNA let-7e	[71]
Viability	HCP5	inhibit apoptosis	interact with HCP5/miR-139/RUNX1 feedback loop	[78]
Viability	CASC2a	promote apoptosis	interact with miR-21	[91]
Angiogenesis	H19	promote glioma angiogenesis	interact with miR-29a/VASH2 axis	[51]
Angiogenesis	XIST	promote glioma angiogenesis	interact with miR-137/FOXC1/CXCR7 axis	[56]
Angiogenesis	XIST	promote glioma angiogenesis	sponge miR-429	[58]
Angiogenesis	linc-POU3F3	promote angiogenesis	regulate bFGF, VEGFA, bFGFR, and Angio	[88]

bFGF, basic fibroblast growth factor; bFGFR, bFGF receptor; VEGFA, vascular endothelial growth factor A.

was considered as a potential oncogene that regulates TOP2A by sponging miR-411-5p in glioma.[42]

GAS5

The lncRNA GAS5 is encoded by a small nucleolar RNA (snoRNA) host gene, Growth Arrest-Specific 5 (*GAS5*), exerting tumor-suppressive functions.[43,44] GAS5 increases the expression of tumor suppressor Bcl-2-modifying factor (bmf) and Plexin C1, and it plays the anti-oncogenic role in glioma cells by directly targeting miR-222.[43] Gas5 combined with miR-222 knockdown suppresses glioma growth and prolongs the survival of tumor-bearing nude mice *in vivo*.[43] miR-196a-5p is another target of GAS5 that can stimulate GSC proliferation, migration, and invasion by reducing forkhead box protein O1 (FOXO1). It was shown that GAS5 can suppress the malignancy of GSCs via a miR-196a-5p/FOXO1 feedback loop[44] and inhibit glioma cell proliferation, migration, and invasion by repressing miR-18a-5p.[45] Shen et al.[28] analyzed the level of lncRNA GAS5 in serum samples from 106 patients with primary glioblastoma and its association with outcomes. They found that high levels of GAS5 were associated with decreased likelihood of death, recurrence, and progression in GBM patients, and they concluded that GAS5 level could serve as a reciprocal prognostic predictor of survival and disease progression in GBM patients.[28]

H19

Barsyte-Lovejoy et al.[46] first demonstrated that, as a target of c-Myc, H19 can be directly induced by allele-specific binding to potentiate tumorigenesis. H19 is upregulated in GBM tissues and associated with GBM patient survival. Overexpression of H19 promotes invasion, angiogenesis, and stemness of GBM cells *in vitro*, and it is associated with increased tumor growth in the murine xenograft model.[47,48] As a microRNA derived by the first exon of H19, miR-675 has been reported to regulate glioma cell proliferation and migration through CDK6 and promote glioma cell invasion by targeting Cadherin 13.[49,50] Several other microRNAs, such as miR-29a,[51] miR-140,[52] and miR-152,[53] were also shown to participate in H19-induced glioma tumorigenesis. Moreover, H19 was found to be upregulated in temozolomide (TMZ)-resistant glioma cells. Targeting H19 may overcome TMZ resistance in glioma by suppressing the EMT via the Wnt/β-catenin pathway.[54]

XIST

The lncRNA XIST (X-inactive specific transcript) is a product of the *XIST* gene, playing key roles in cell differentiation and proliferation and genome maintenance.[55] XIST has been identified to be upregulated in glioma tissues and GSCs.[55] Knockdown of XIST exerts a glioma-suppressive function by inhibiting cell proliferation, migration, and invasion and tumor angiogenesis and inducing apoptosis; the *in vivo* studies also showed that knockdown of XIST suppresses tumor growth and prolongs the survival of tumor-bearing nude mice.[55–58] MicroRNA targets, such as miR-152,[55] miR-137,[56,57] miR-429,[58] and miR-29c,[59] have been reported to mediate the oncogenetic effects of XIST on glioma. The inhibition of XIST can also increase blood-tumor barrier permeability, facilitating the delivery of antitumor drugs to a brain tumor.[56] In addition, the XIST/miR-29c axis was shown to regulate DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) and transcription factor specificity protein 1 (SP1), participating in conferring TMZ resistance of glioma.[59]

CRNDE

The gene *CRNDE* was first identified to be upregulated in colorectal cancer, the transcripts of which were categorized as lncRNAs.[60,61] In the validated four *CRNDE* transcripts from the NCBI database, transcript variant 1 (TV-1), the full-length one, has been identified to promote glioma cell proliferation, migration, and invasion via P70S6K-mediated mTOR signaling.[61] Thereafter, miR-186,[62] miR-384,[63] and miR-136-5p[64] were identified as targets of CRNDE. In GSCs, CRNDE decreases the expression levels of XIAP and PAK7 by binding and negatively regulating miR-186, and it promoted the malignant biological characteristics of cells.[62] CRNDE induces the malignant progression of glioma by attenuating the miR-384/PIWIL4/STAT3-signaling pathway.[63] In the *in vivo* studies, knockdown of CRNDE was demonstrated to delay the tumor formation[62] and lead to tumor regression in tumor-bearing nude mice.[63] CRNDE may also function as a competing endogenous RNA (ceRNA) negatively regulating miR-136-5p, and it may promote glioma malignancy by preventing miR-136-5p-mediated repression of Bcl-2 and Wnt2.[64]

NEAT1

NEAT1 (nuclear enriched abundant transcript 1) is an intranuclear lncRNA participating in precursor RNA splicing as a core component of the paraspeckle.[65] NEAT1 is an oncogene that promotes cell proliferation, migration, and invasion in various cancers, including glioma.[66–69] MicroRNA targets, such as miR-449b-5p,[70] let-7e,[71] miR-107,[72] and miR-132,[73] have been found to interact with NEAT1-induced glioma malignancy. miR-181d-5p has been demonstrated to mediate NEAT1-regulated permeability of the blood-tumor barrier by affecting the expression of tight junction proteins ZO-1, Occludin, and Claudin-5.[74] Chen et al.[69] found that the epidermal growth factor receptor (EGFR pathway can regulate NEAT1 and then promote GBM cell growth and invasion by binding to EZH2 and increasing β-catenin. Thus, the EGFR/NEAT1/EZH2/β-catenin axis is a critical effector of tumorigenesis and progression in GBM.[69]

HCP5

The lncRNA histocompatibility leukocyte antigen (HLA) complex P5 (HCP5) is expressed primarily in immune system cells, and it plays a potential role in autoimmunity.[75] The expression of HCP5 in different cancers is various. It is downregulated in ovarian cancer[76] but upregulated in follicular thyroid carcinoma[77] and glioma.[78] Teng et al.[78] found that HCP5 promotes the malignant behavior of glioma cells by binding to microRNA-139, which directly regulates runt-related transcription factor 1 (RUNX1). RUNX1 can also increase the promoter activities and expression of *HCP5*, showing a positive feedback loop of HCP5-miR-139-RUNX1, which plays

a key role in regulating glioma malignancy.[78] In addition, in a subcutaneous xenograft mouse model, the *in vivo* study showed that tumors with knockdown of HCP5 and overexpression of miR-139 had the lowest volume and weight and the corresponding tumor-bearing mice had the longest survival time.[78]

HIF1A-AS2

The lncRNA hypoxia-inducible factor 1 alpha-antisense RNA 2 (HIF1A-AS2) has been found to interact with insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) and ATP-dependent RNA helicase A (DHX9), regulating HIF2A expression and molecular responses to hypoxic stress. HIF1A-AS2 is associated with the malignancy of gastric cancer,[79] strengthens tumor growth and confers chemoresistance in triple-negative breast cancer,[80] plays oncogenic roles in bladder cancer,[81] and promotes the progression and EMT formation of colorectal cancer.[82] In glioma, HIF1A-AS2 acts as a subtype-specific hypoxia-inducible lncRNA upregulated in mesenchymal GSCs.[83] HIF1A-AS2 controls cellular fate and the molecular landscape of mesenchymal GSCs, maintains the function of mesenchymal GSCs in tumorigenicity, and contributes to GSCs' speciation and adaptation to hypoxic stress.[83]

RAMP2-AS1

RAMP2-AS1 was recently identified as a downregulated lncRNA in GBM tissues, interacting with tumor promoter NOTCH3.[84] Overexpression of RAMP2-AS1 was found to suppress GBM growth via the DHC10/NOTCH3/HES1-signaling pathway in GBM cells. The *in vivo* study in a subcutaneous xenograft mouse model also showed that overexpression of RAMP2-AS1 significantly suppresses tumor growth.[84]

linc-POU3F3

Long intergenic noncoding RNA POU3F3 (linc-POU3F3) has been identified as an upregulated lncRNA in esophageal squamous cell carcinoma (ESCC) to promote cancer development.[85,86] Recently, overexpression of linc-POU3F3 was found in glioma to promote cell viability and proliferation by altering the expression level of POU3F3.[87] Glioma cells can induce angiogenesis by secreting exosomes enriched in linc-POU3F3, which then may interactively support glioma tumorigenesis.[88]

CASC2

Cancer susceptibility candidate 2 (CASC2) was identified at first as a tumor suppressor in human endometrial cancer.[89] However, CASC2 generates three alternative transcripts, CASC2a, CASC2b, and CASC2c,[89] and actually it is the lncRNA CASC2a that acts as a tumor suppressor in cancers,[90] including glioma.[91] On the contrary, lncRNA CASC2c is upregulated in glioma and promotes tumorigenesis.[92] Although both CASC2a and CASC2c generate from CASC2, they only share the first three exons but contain different downstream exons.[92] Thus, it is reasonable that CASC2a suppresses glioma growth whereas CASC2c acts as an onco-RNA. It was shown that CASC2a-mediated inhibition of glioma growth, migration, and invasion and promotion of cell apoptosis are associated with the negative regulation of miR-21.[91] CASC2c promotes astrocytoma tumorigenesis by acting as a decoy miR-101 sponge.[92]

HMMR-AS1

We recently reported an HMMR antisense lncRNA, HMMR-AS1, which is upregulated in GBM cell lines and stabilizes HMMR mRNA.[93] Knockdown of HMMR-AS1 suppresses GBM growth *in vitro* and *in vivo*; inhibits cell migration, invasion, and mesenchymal phenotypes; and radiosensitizes GBM by reducing DNA repair proteins.[93] We further found that overexpression of HMMR-AS1 elevates the expression of c-Myc in GBM cells (unpublished data), indicating that HMMR-AS1 may exert an oncogenetic function via MYC-associated pathways. Study of the mechanisms is being performed.

lncRNAs as Potential Glioma Biomarkers

lncRNAs for Glioma Diagnosis

Zhang et al.[27] found that HOTAIR expression is significantly higher in high-grade glioma than in low-grade glioma and that HOTAIR is significantly associated with tumor grade, by analyzing Chinese Glioma Genome Atlas cohort 1 (CGGA1), Repository of Molecular Brain Neoplasia Data (REMBRANDT), and GEO: GSE4290 datasets. The authors also applied three different classification systems to the aforesaid datasets, and they found significant difference in HOTAIR expression between glioma subtypes.[27] In another study, Tan et al.[29] performed qRT-PCR to evaluate HOTAIR level in serum from glioma patients, and they found that HOTAIR in glioma serum is higher than in normal control serum. The authors compared serum HOTAIR levels from 43 GBM patients and 40 controls, and they found that serum HOTAIR could be a diagnostic biomarker for GBM, with an area under the curve (AUC) of 0.913 at the cutoff value of 10.8 (the sensitivity and specificity of HOTAIR are 86.1% and 87.5%).[29]

The lncRNA HOTTIP is a tumor suppressor. Xu et al.[36] analyzed the expression of HOTTIP in 85 glioma tissues and 15 normal brain tissues by using qRT-PCR, and they found that HOTTIP is decreased in glioma and HOTTIP level in high-grade glioma is significantly lower than that in low-grade glioma.

From whole-genome gene profiling of the CGGA cohort, HOXA11-AS expression was found to be significantly higher in high-grade glioma samples (WHO grade III/IV) than in low-grade gliomas (WHO grade I/II).[38] A significant difference in HOXA11-AS expression was also found among the four GBM subtypes in the CGGA mRNA microarray datasets.[38] Then, Cui et al.[39] analyzed the expression of HOXA11-AS in 43 paired glioma tissues and normal brain tissues (NBTs), and they confirmed that HOXA11-AS level is higher in high-grade gliomas.

GAS5 plays the suppressive role in glioma. Zhao et al.[43] investigated GAS5 expression in 5 NBTs and 25 glioma tissues of different grades, and they found that GAS5 level is significantly lower in in high-grade glioma tissues ($p < 0.01$).

The expression of XIST in 69 paired glioma tissues and peritumoral brain edema (PTBE) tissues has been analyzed by qRT-PCR.[59] It was shown that XIST level is higher in patients with malignant glioma (WHO grade III/IV, $p < 0.001$).[59]

Li et al.[64] determined CRNDE expression on 47 glioma specimens and 9 normal brain samples by qRT-PCR, and they found that CRNDE expression is upregulated in gliomas and significantly higher in high-grade (WHO grade III/IV) gliomas than in low-grade (WHO grade I/II) gliomas.

HIF1A-AS2 was demonstrated to be upregulated in GSCs forming mesenchymal GBM, a specific subtype of GBM, and drive growth of mesenchymal GSC tumors and GBM progression in a hypoxic environment.[83]

The expression of linc-POU3F3 was analyzed in 82 glioma specimens, and it was demonstrated to be significantly higher in WHO grade III/IV gliomas than in WHO grade I/II gliomas.[87]

Wang et al.[91] detected the expression of CASC2a, one transcript from the CASC2 gene, in 6 non-tumor brain tissues, 12 grade I/II gliomas, and 12 grade III/IV gliomas, and they found that CASC2a is decreased in gliomas and significantly lower in high-grade gliomas than in low-grade gliomas. On the contrary, by analyzing 80 astrocytoma specimens, Liu et al.[92] demonstrated that the expression of CASC2c, another transcript from the CASC2 gene, is significantly higher in high-grade (WHO grade III/IV) tumors than in low-grade (WHO grade I/II) ones.

lncRNAs for Glioma Prognosis

Based on the datasets of CGGA1, CGGA cohort 2 (CGGA2), and REMBRANDT, Zhang et al.[27] investigated the correlation between HOTAIR expression and overall survival, using Kaplan-Meier survival curve analysis with a log-rank comparison, and they found that overexpression of HOTAIR correlates with a significantly worse survival outcome. In addition, the authors performed univariate Cox regression analysis for 89 GBM patients from the CGGA1 data, and they found that a high level of HOTAIR is associated with overall survival.[27] Then, by using a multivariate Cox proportional hazard model, they found that HOTAIR level correlates independently with overall survival (hazard ratio [HR] = 2.933).[27] A recent study by Shen et al.[28] analyzing HOTAIR level in serum samples from 106 GBM patients showed that a high level of HOTAIR in patient's serum is associated with increased likelihood of death (adjusted HR = 2.04, 95% confidence interval [CI] = 1.08–9.76), recurrence, and progression (adjusted HR = 1.82, 95% CI = 1.04–6.17). Thus, HOTAIR level either in tumor or serum sample can be used as a prognostic indicator for glioma patients.

Wang et al.[38] reported another lncRNA, HOXA11-AS, may indicate poor prognosis of glioma patients. Based on the CGGA database, they performed the Kaplan-Meier survival curve analysis with a log-rank comparison to investigate correlation between HOXA11-AS expression and overall survival, and they found that HOXA11-AS level is inversely correlated with overall survival in grade III glioma (p = 0.0359) and GBM (p = 0.0198).[38] Moreover, they investigated the clinical and genetic variables of 89 GBM patients from the CGGA cohort. After univariate Cox regression analysis, they found that a high expression of HOXA11-AS is statistically associated with overall survival; by using a multivariate Cox proportional hazard model, they found that HOXA11-AS expression correlates independently with overall survival (HR = 1.140).[38] Thereafter, Cui et al.[39] analyzed the expression of HOXA11-AS in 43 paired glioma tissues and NBTs, and they confirmed that HOXA11-AS level is higher in gliomas than in NBTs. The authors performed Kaplan-Meier analysis, and they found that HOXA11-AS overexpression is associated with poor prognosis of glioma patients (p = 0.0179).[39]

Jiang et al.[47] investigated the expression of H19 in 30 samples of GBM and 30 samples of non-tumor brain tissues, and they found that H19 level is significantly higher in GBM tissues compared with non-tumor brain tissues from the same patients ($p < 0.0001$). Then, the authors used the Kaplan-Meier method to analyze progression-free survival for patients in the high-expression and low-expression groups, and they found that a high level of H19 is significantly associated with a poor progression-free survival rate (p = 0.022).[47]

Du et al.[59] detected the expression of XIST in 69 paired glioma tissues and PTBE tissues by using qRT-PCR, and they found that XIST is upregulated in glioma samples. The Kaplan-Meier overall survival curves showed that the survival time of glioma patients with high XIST levels is shorter than that in patients with low XIST levels (p = 0.0007). By using a multivariate Cox proportional hazard model, they found that high XIST expression is of high risk (HR = 2.037, 95% CI = 1.083–3.831).[59]

Liu et al.[92] examined CASC2c level in 80 paraffin-embedded astrocytoma tissue samples by *in situ* hybridization, and they found that the higher expression of CASC2c is markedly correlated with the death of patients (p = 0.001). Then, they did the Kaplan-Meier analysis for overall survival in 80 astrocytomas. By univariate Cox regression analysis, they found that the overall survival rate is significantly lower in patients with CASC2c high expression (p = 0.008); by multivariate Cox proportional hazard regression analysis, they found that a high expression of CASC2c in astrocytoma is an independent prognostic factor of overall survival (HR = 1.98, 95% CI = 1.94–2.26).[92]

Besides HOTAIR, Shen et al.[28] also analyzed GAS5 level in serum samples from 106 GBM patients. They showed that a high level of GAS5 is associated with decreased likelihood of death (adjusted HR = 0.44, 95% CI = 0.18–0.99), recurrence, and progression (adjusted HR = 0.46, 95% CI = 0.16–0.98).[28]

lncRNA Indicating TMZ Resistance

TMZ treatment after surgical resection is one of the most commonly used therapeutic strategies for GBM. However, a large proportion of GBM patients showed no response to TMZ treatment. Chen et al.[17]

Table 2. lncRNAs as Potential Glioma Biomarkers

lncRNA	Clinical Implication	Reference
MALAT1	TMZ resistance	17
HOTAIR	poor prognosis	27,28
	molecular subtype	27
	tumor grade	
HOTTIP	tumor grade	36
HOXA11-AS	poor prognosis	38,39
	tumor grade	
	molecular subtype	38
GAS5	favorable prognosis	28
	tumor grade	43
H19	poor prognosis	47
XIST	tumor grade	59
	poor prognosis	
CRNDE	tumor grade	64
HIF1A-AS2	molecular subtype	83
linc-POU3F3	tumor grade	87
CASC2a	tumor grade	91
CASC2c	poor prognosis	92
	tumor grade	

analyzed 180 GBM tissue samples from 90 paired patients showing response or no response to TMZ by qRT-PCR, and they found that MALAT1 level is significantly higher in GBM patients showing non-response to TMZ ($p < 0.01$), indicating that MALAT1 may become an indicator for TMZ-resistant GBM. Then, MALAT1 level was validated by qRT-PCR assay in another group of 140 serum samples from 70 paired GBM patients showing response or no response to TMZ. The results showed that serum MALAT1 level is higher in GBM patients showing non-response to TMZ ($p < 0.01$); the receiver operator characteristic (ROC) curve was drawn, and the AUC was calculated as 0.764, with the diagnostic sensitivity of 77.1% and specificity of 65.7%; the Kaplan-Meier survival analysis showed that a high expression of serum MALAT1 is correlated with poor overall survival and recurrence-free survival; and the Cox regression univariate and multivariate analysis identified that the level of serum MALAT1 is an independent indicator for overall survival of GBM patients who received TMZ treatment (univariate analysis: HR = 2.318, 95% CI = 1.203–4.875, p = 0.009; multivariate analysis: HR = 2.553, 95% CI = 1.223–5.201, p = 0.008).[17]

Conclusions

lncRNAs participate extensively in cellular regulatory networks in various types of cancer, including glioma. Intracellular signaling networks are modulated in cancer to sustain proliferation, impair cytostatic and differentiation signals, enhance viability, and promote motility.[8] As the examples of lncRNAs participating in glioma phenotypes indicate in Table 1, oncogenic lncRNAs HOTAIR, FOXM1-AS, HOXA11-AS, ECONEXIN, H19, XIST, CRNDE, NEAT1, HCP5, HIF1A-AS2, linc-POU3F3, CASC2c, and HMMR-AS1 are shown to promote glioma growth, whereas HOTTIP, GAS5, RAMP2-AS1, and CASC2a exert tumor-suppressive functions to inhibit cell proliferation. However, the effects of MALAT1 on glioma depend on its downstream targets, although it has been considered as an oncogenic lncRNA in other cancers.[94] By sponging miR-101, MALAT1 promotes glioma growth;[23,24] on the contrary, MALAT1 suppresses glioma by inactivation of ERK/MAPK signaling[21] or suppressing miR-155 expression and activating FBXW7 function.[22] Oncogenic lncRNAs HOXA11-AS, H19, XIST, CRNDE, NEAT1, HCP5, CASC2c, and HMMR-AS1 promote glioma cell motility; GAS5 and CASC2a, as tumor suppressors, inhibit cell migration and invasion. MALAT1 promotes GBM cell migration via non-canonical WNT signaling,[20] but it inhibits glioma cell invasion by the downregulation of MMP2.[21] In the phenotype of viability, MALAT1, HOTAIR, HOXA11-AS, XIST, CRNDE, NEAT1, and HCP5 are shown to inhibit cell apoptosis, whereas GAS5, HOTTIP, and CASC2a are found to promote apoptosis. H19, XIST, and linc-POU3F3 are found to promote angiogenesis, which is crucial for glioma tumorigenesis and survival.

Many lncRNAs are detectable and tumor specific and some of them can indicate tumor severity. In Table 2, we enumerated lncRNAs that may act as glioma biomarkers and showed their potential clinical implications. HOTAIR, HOXA11-AS, and HIF1A-AS2 can be used to distinguish specific glioma subtypes and contribute to the molecular classification of glioma; the expression level of HOTAIR, HOXA11-AS, XIST, CRNDE, linc-POU3F3, or CASC2c is positively correlated with the status of malignant progression of glioma; and the expression of HOTTIP, GAS5, or CASC2a is negatively correlated with the malignancy of glioma. GAS5 is a tumor suppressor indicating favorable prognosis, whereas HOTAIR, HOXA11-AS, H19, XIST, and CASC2c may function as onco-RNAs indicating poor prognosis of glioma patients. MALAT1 can indicate the TMZ resistance of GBM patients and be used as a prognostic factor for GBM patients receiving TMZ treatment.

Although it is promising to discover novel diagnostics and therapeutics for glioma from lncRNAs, to date the characteristics of most lncRNAs remain indefinable. It is improper to apply lncRNAs to diagnostics or therapeutics without a clear picture of the functions of lncRNAs. Thus, in the future, one important challenge is to characterize each lncRNA in detail.

GBM is characterized by intratumoral cellular heterogeneity, with cells from the same tumor exhibiting a distinct phenotypic or epigenetic state or harboring different mutations.[95] Such intratumoral heterogeneity poses a great challenge to GBM diagnosis or treatment.[95] Recently, the landscape of the lncRNA dynamics for an individual cell in GBM was displayed, and the intratumoral expression heterogeneity of lncRNA was systematically characterized by using single-cell RNA sequencing analysis.[96,97] In future studies, we should pay more attention to distinguishing cell-to-cell heterogeneity of lncRNA in glioma, advancing our understanding of the latent

roles of lncRNAs and developing more efficient biomarkers and therapeutic targets.

AUTHOR CONTRIBUTIONS

All authors contributed to designing the study, interpreting the results, and preparing the paper. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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