# LncRNAs associated with glioblastoma: From transcriptional noise to novel regulators with a promising role in therapeutics

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**Glioblastoma multiforme (GBM) is the most widespread and aggressive subtype of glioma in adult patients. Numerous long non-coding RNAs (lncRNAs) are deregulated or differentially expressed in GBM. These lncRNAs possess unique regulatory functions in GBM cells, ranging from high invasion/migration to recurrence. This review outlines the present status of specific involvement of lncRNAs in GBM pathogenesis, with a focus on their association with key molecular and cellular regulatory mechanisms. Also, we highlighted the potential of different novel RNA-based strategies that may be beneficial for therapeutic purposes.**

## INTRODUCTION

The central dogma of molecular biology postulates the transmission of the genetic information from genomic DNA to messenger RNA (mRNA), then proteins.[1] However, a large portion of genetic information that does not get translated into proteins raises a question about the possible roles of this non-coding portion of the genome in cellular functions. Later studies have highlighted the significance of these untranslated regions previously referred to as unused DNA responsible only for transcriptional noise.[2,3] Most (~80%) of the mammalian genome consists of non-coding RNA (ncRNAs) genes, as annotated by ENCODE (Encyclopedia of DNA Elements) and FANTOM (Functional Annotation of the Mouse/Mammalian Genome). ncRNA falls into two sub-categories, based on the length of the transcripts; small ncRNAs are shorter than 200 nt and include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small interfering RNAs (siRNAs), and microRNAs (miRNAs), whereas long ncRNAs (lncRNAs) are longer than 200 nt. They are structurally similar to mRNAs. lncRNA's genes are transcribed by RNA polymerase II, capped at the 5′ end, polyadenylated at the 3′ end, and contain promoter region that can be spliced.[2] lncRNAs comprise fewer exons (~2.8 exons) than do protein-coding genes and do not have an open reading frame (ORF). lncRNAs usually have a lower expression level but higher tissue-specificity than do most mRNAs.[4,5] lncRNAs serve a dynamic role in modulating the expression of various genes at the transcriptional, post-transcriptional, translational, and epigenetic levels, but information on their specific mechanisms is limited.[6]

In the last few years, 127,802 transcripts from 56,946 lncRNAs genes have been cataloged in LNCipedia (https://lncipedia.org/), the largest lncRNA database. Some of these are aberrantly expressed and could be considered as potential therapeutic targets in clinical oncology and treatment of viral diseases.[7–9]

### lncRNAs

Depending on the genomic location and with respect to neighboring protein-coding genes, lncRNAs can be sense, antisense, intronic, intergenic, and bidirectional. Sense and antisense are transcribed in the same or opposite direction of protein-coding gene strands. Bidirectional lncRNAs are transcribed in the opposite direction of their neighboring protein-coding gene (<1 kb away). Intronic lncRNAs are transcribed completely from the introns of the protein-coding gene, while intergenic lncRNAs are transcribed from different genomic locations.[10] The activity of lncRNAs depends on its subcellular localization, allowing division of lncRNAs into nuclear or cytoplasmic subgroups.[11] A gene transcriptional status can be regulated by transcriptional interference and chromatin remodeling acquired from lncRNA located in the nuclear region.[12,13] In contrast, lncRNAs that are exported to the cytoplasm serve as mediators for RNA processing and can affect mRNA stability or regulate protein function.[14]
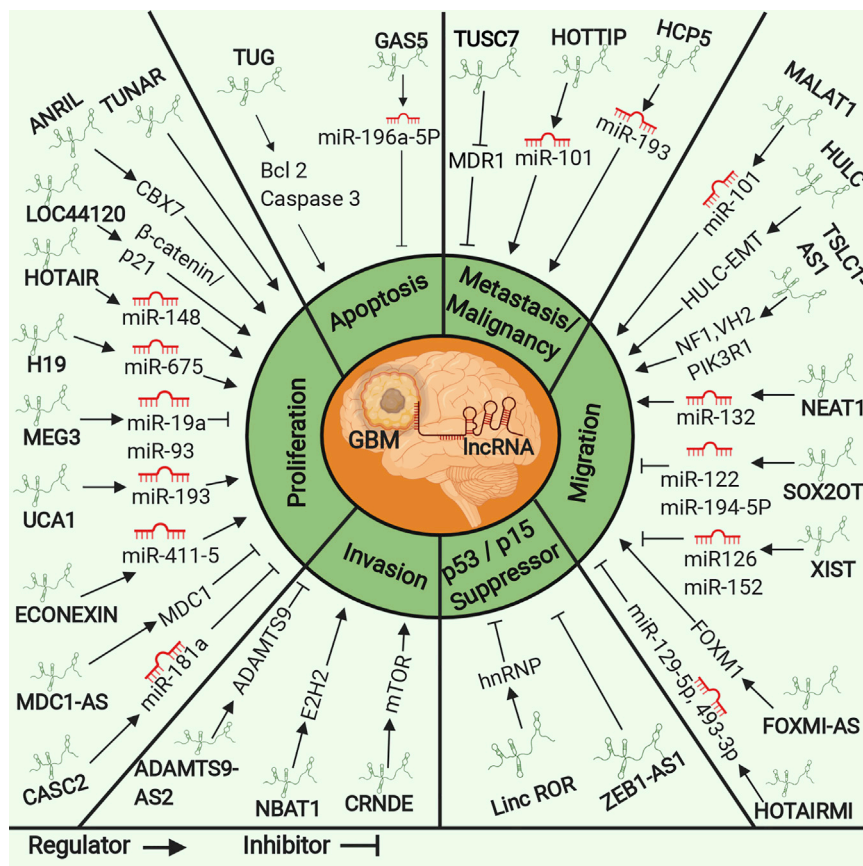
lncRNAs can interact with RNA, proteins, and DNA via different modes of molecular mechanisms such as signaling, decoy, guide, scaffold, and miRNA sponge. lncRNAs can function as a signaling molecule for any biological condition and are capable of regulating the expression of genes concerning a specific response; as a decoy

Figure 1. Representation of specific long non-coding RNAs that are well associated with glioma and function via targeting various miRNAs or genes/proteins and regulate various pathways such as proliferation, invasion, migration, apoptosis, and metastasis by acting as both regulators and inhibitors

response to chemotherapy because of intrinsic and acquired resistance.[17] Unfortunately, these treatments have not been able to significantly improve the survival rate because of complications from the treatment procedures or the inability to eliminate GBM invasiveness.[20] To develop robust treatment options, it is crucial to develop a deep understanding of molecular and cellular aspects of glioma pathogenesis.

## MAIN lncRNAs IN GLIOMAS

Most lncRNAs in glioma are aberrantly expressed and participate in the regulation of critical cellular processes[21]. lncRNAs can be organized based on their capabilities to regulate several characteristics and phenotypes as shown in detail in Figure 1 and Table 1.

### HOX transcript antisense intergenic RNA (HOTAIR)

*HOTAIR* is mapped at chromosome 12q13 and is 2,158 nt long.[22,61] Recent reports suggest that it can impact histone methylation, resulting in the silencing of target genes.[22] *HOTAIR* is highly expressed in GBM and can act as an independent prognostic factor.[61] In gliomas, *HOTAIR* targets miRNA (miR)-148b-3p and miR-326.[23] One study showed that *HOTAIR* is involved in the proliferation and tumorigenic potential of GBM by regulating the cells via the EZH2 and Wnt/β-catenin pathways.[62] Moreover, *HOTAIR* can act as exosomal lncRNAs playing a significant role in the regulation of angiogenesis in glioma. For instance, patients with recurrent GBM showed increased serum levels of *HOTAIR* exosomal lncRNA that were associated with poor response to TMZ and worse prognosis.[63]

### HOTAIR myeloid-specific 1 (HOTAIRM1)

*HOTAIRM1* was first identified as a myeloid-specific regulator of the *HOXA* (homeobox A cluster) gene family and is located between the *HOXA1* and *HOXA2* loci. It regulates the transcription of specific genes during myeloid cell differentiation and maturation via chromosome remodeling.[64] *HOTAIRM1* showed an increased expression level especially in the high-grade astrocytomas and is involved in glioma development.[25] Moreover, reports suggest that *HOTAIRM1* has significant roles in glioma recurrence.[26] A study by Liang et al.[65] in 2019 observed that the overexpression of *HOTAIRM1* was positively related to glioma grade progression. In U87 and LN229 cells,

molecule resulting in binding and sequestering of protein sequences, thereby regulating gene expression; as a guide, it can recruit RNA-binding protein to its target genes, either in *trans* or *cis*; and as a scaffold, lncRNAs function to keep proteins together and form a complex with specialized biological functions.[15]

### lncRNAs in glioblastoma

Glioblastoma multiformes (GBMs) account for almost 80% of all primary brain tumors.[16] In general, patients show a poor prognosis with a median survival of ~1 year.[17] As of the 2016 edition of the World Health Organization classification, gliomas are classified based not only on histopathologic appearance but also on well-established molecular parameters.[18] The incorporation of molecular features has most notably impacted the classification of astrocytic and oligodendroglial tumors, which are now grouped together as diffuse gliomas, based on the growth pattern, behavior, and shared isocitrate dehydrogenase (IDH) genetic status. Methylation profiling, a powerful method to evaluate one aspect of the epigenetic landscape of brain tumors, may be added to histologic and standard genetic approaches to classify brain tumors, possibly refining how brain tumors are classified in the future.[19] The conventional treatment of GBM includes a combination of three different approaches: surgical resection, irradiation, or temozolomide (TMZ) chemotherapy.[20] Most patients with glioma have a poor

**Table 1. Aberrant expression patterns of various long non-coding RNAs (lncRNAs) involved in glioblastoma**

| LncRNAs | Expression pattern | Mechanism | Aberrant phenotype | References |
|---|---|---|---|---|
| HOTAIR | ↑ | interacts with the PRC2 complex | promotes cell cycle progression | 22–24 |
| | | HOTAIR/miR-326/FGF1 axis | promotes malignancy | |
| | | enhances the tight junction by binding to miR-148b-3p as a ceRNA | decreases the blood-tumor barrier (BTB) permeability | |
| HOTAIRMI | ↑ | acts as sponge for miR-129-5p and miR-493-3p | functions as ceRNA and promotes cell invasion and migration | 25,26 |
| | | | associated with inflammation and T cell-mediated immune response initiation | |
| TUNAR | ↑ | positive regulator of neuronal development | involved in cancer progression, cell cycle conduct, and pluripotency | 27 |
| LincROR | | acts as a tumor suppressor | promotes proliferation and enhances glioma stem cell forming ability | 28 |
| | | negatively correlated with KLF4 | | |
| H19 | ↑ | by reducing the miR-29a, it upregulates the VASH2 expression | promotes invasion and angiogenesis, along with tube formation | 29 |
| | | derives the miR-675, which in turn suppresses CDK6 directly | promotes proliferation and migration | |
| CRNDE | ↑ | modulates the mTOR signaling pathway | promotes growth and invasion | 30–32 |
| | | attenuates the axis of miR-384/PIWIL4 /STAT3 | facilitates proliferation and invasion and inhibits apoptosis | |
| | | protects Bcl-2 and Wnt2 by binding to miR-136-5p as a ceRNA | glioma cells migration and the capacity to invade are enhanced | |
| XIST | ↑ | expression of ZO-2 and FOXC1 transcription factor as a miR-137 sponge are improved | decreases blood-tumor barrier permeability | 33–35 |
| | | forms silencing complex RISC with miR-152 induced by RNA | promotes angiogenesis, GSC proliferation, migration, and invasive capacities | |
| NEAT1 | ↑ | mediates H3K27me3 in target promoters by binding to EZH2 | promotes growth and capacity to invade | 36 |
| TUG1 | ↑↓ | inhibits miR-144, which in turn reverses the effect of miR-144 on occludin, ZO-1, and claudin-5 | regulates blood-tumor barrier permeability | 37,38 |
| | | recruits polycomb to methylate locus-specific H3K27 histone | maintains stemness features of GSCs | |
| MALAT1 | ↓↑ | negatively regulates miR-155 | suppresses invasion and proliferation | 39–41 |
| | | targets miR-203 | involved in chemoresistance | |
| | | targets miR-140; interacts with nuclear factor YA | proliferation, blood-tumor barrier permeability, and chemosensitivity | |
| | | targets miR-101 | induces proliferation, migration, autophagy, apoptosis, and correlates with survival | |
| GAS5 | ↓ | the positive feedback loop of GAS5/miR-196a-5p/FOXO1 is formed | inhibits proliferation, migration, and invasion | 42 |
| CASC2 | ↓ | PTEN expression increases due to interaction with miR-181a | inhibit proliferations and increases TMZ sensitivity | 43 |
| NBAT-1 | ↓ | reduces the expression of the NRSF/REST neuronal-specific transcription factor | weakens proliferation, and neuroblastoma differentiation is increased | 44 |
| FOXM1-AS | ↑ | the smooth interaction of ALKBH5 and FOXM1 mRNA to demethylate FOXM1 mRNA | enhances reclamation and tumorigenesis of glioma stem-like cells | 45 |
| ECONEXIN | – | rise in TOP2A by wiping miR-411-5p | continues aggressive proliferation of glioma cells | 46 |
| SOX2OT | – | binds to miR-194-5p and miR-122, back-pedals SOX3 expression | boosts proliferation, migration, and invasion | 47 |
| HCP5 | – | forms a positive feedback loop of HCP5-miR-139-RUNX1 | causes proliferation, migration, and invasion | 48 |

*(Continued on next page)*

**Table 1. Continued**

| LncRNAs | Expression pattern | Mechanism | Aberrant phenotype | References |
|---|---|---|---|---|
| MEG3 | ↓ | acts in a p53-dependent manner; ceRNAs for miR-19a and miR-93 | inhibits glioma cell proliferation (*in vitro*) | 49,50 |
| UCA1 | ↑ | ceRNAs for miR-182 and miR-122 | promotes proliferation, invasion, and migration; modulates glycolysis and invasion of glioma | 51 |
| HOTTIP | ↓ | interacts via BRE, cycA and CDK2, p53 | promotes proliferation and apoptosis | 52 |
| HULC | ↑ | interacts with survivin, c-Myc, cyclin A/D1/E, p-Rb, Skp-1/2, CDK2/4 and EZH2, Bcl-2/Bax, caspase-3/8 | promotes proliferation invasion, migration, and angiogenesis | 53 |
| MDC1-AS | ↓ | upregulates antisense tumor-suppressing gene MDC1 | tumor suppressor; inhibits cell proliferation and cell cycle | 54 |
| TSLC1-AS1 | ↓ | – | inhibits cell proliferation, migration, and invasion | 55 |
| ADAMTS9-AS2 | ↓ | modulates the protein-coding gene ADAMTS9 | suppresses cell migration | 56 |
| ZEB1-ASI | ↑ | – | facilitates cell proliferation, migration, and invasion | 57 |
| TUSC 7 | ↓ | suppresses the levels of $IC_{50}$, TMZ, and MDR1 expression and escalates TMZ cytotoxicity in U87TR cells | inhibits TMZ resistance and tumor malignancy | 58 |
| LOC441204 | ↑ | involved with the β-catenin/p21/cdk4 cascade | associated with cell proliferation and growth | 59 |
| ANRIL | ↑ | associated with the expression of CBX7 (chromo box homolog 7) | cell proliferation and migration | 60 |

↑, upregulation; ↓, downregulation.

knockdown of *HOTAIRM1* resulted in inhibition of glioma proliferation, invasion, epithelial-to-mesenchymal transition (EMT), cell migration, and enhanced sensitivity to TMZ *in vitro*. Furthermore, *HOTAIRM1* functions as a ceRNA (competing endogenous RNA) to promote glioma cell invasion and migration by acting as a sponge for miR-129-5p and miR-495-3p. Additionally, a higher expression of *HOTAIRM1* was associated with increased inflammation and initiation of a T cell-mediated immune response. lncRNA *HOTAIRM1* was reported to promote glioma malignancy by forming a ceRNA network.

### TCL1 upstream neural differentiation-associated RNA (TUNAR)

*TUNAR* is a conserved lncRNA found in vertebrates and is significantly expressed in the central nervous system (CNS).[66] It is found to be a positive regulator of neuronal development and differentiation in humans, mice, and zebrafish, which indicates that downregulated *TUNAR* in brain tumors (GBM and lower-grade glioma [LGG]) is required to gain oncogenic characteristics.[67] Some reports suggest that lncRNAs such as *BCAR4* and *TUNAR* are found to be involved in cancer progression, cell cycle conduct, and pluripotency.[27] A recent comprehensive study by Reon et al.[68] analyzed the deregulated expression of three lncRNAs (*TUNAR*, *LINC00152*, *LINC01476*) and found that *TUNAR* and *LINC01476* were highly upregulated in GBMs compared to normal brain tissue.

### HOXA distal transcript antisense RNA (HOTTIP)

*HOTTIP*, an antisense transcript mapped at the distant end of the *HOXA* gene cluster, is related to the PRC2 and WDR5/MLL1 chromatin-modifying complexes and binds directly with WDR5. It is overexpressed in glioma tissues with high viability and hypoxia-treated glioma cells under hypoxic conditions. *HOTTIP* knockdown may inhibit hypoxia-induced EMT in glioma cells by increasing *miR-101*, which can regulate metastasis via modulation of ZEB1 expression. Based on these outcomes, *HOTTIP* may be a significant marker and therapeutic target in GBM.[52]

### Large intergenic noncoding RNA regulator of reprogramming (LINC-ROR)

*LINC ROR* is 2.6 kb long, a cytoplasmic lncRNA located on chromosome 18q21.3, and is involved in the modulation of cellular reprogramming.[28,69,70] Recently it was discovered that *lncRNA-ROR* mainly acts as an endogenous miRNA sponge in cancer cells to promote tumor development. Evidence reveals that *LINC-ROR*, p53, and caspase-3 are found to be upregulated in GBM patients.[69] In GBM, *LINC ROR* is involved in the process of DNA damage, suppresses the expression of p53 by binding to hnRNP, and can regulate cell apoptosis.[71] In another study, it was shown that upregulated expression of *KRUPPEL-like factor 4* (*KLF4*) results in proliferation by enhancing glioma stem cell (GSC) formation.

### H19 imprinted maternally expressed transcript (H19)

*H19* mapped on the chromosome 11p15.5 and is 2.3 kb long.[72,73] In glioma cells, binding of *H19* with c-Myc oncogene results in the induction of tumorigenesis.[73] Increasing evidence suggests that upregulated expression of *H19* in GBM tissues is associated with GBM patient survival. It has been reported that *miR-675*, a miRNA derived by the first exon of *H19*, could potentially promote migration through CDK6, regulate glioma cell proliferation, and induce glioma cell

invasion by targeting cadherin 13.[72] Few other miRNAs that participate in *H19*-induced glioma tumorigeneses are *miR-29a,51, miR-140,52,* and *miR-152.*[26] The depletion of *H19* by siRNAs is associated with decreased glioma invasion.[73] Higher expression of *H19* results in angiogenesis, stemness of GBM cells *in vitro*, and invasion.[74] Increased level of *H19* lncRNA promotes invasion, angiogenesis, and stemness of glioblastoma cells.[74] In the murine xenograft model, overexpression of *H19* is associated with increased tumor growth. Suppressing *H19* modulates tumorigenicity and stemness in U251 and U87 MG glioma cells.[75] Upregulated *H19* promotes TMZ resistance in U251 and M059J glioma cell lines as studied by Jia et al.[76] The study has reported that the resistant cells have higher *H19* expression than do non-resistant cells, and silencing of *H19* resulted in downregulation of EMT markers and Wnt/β-catenin markers.[58,76]

### Taurine upregulated gene 1 (TUG1)

*TUG1* is nearly 7.1 kb long and resides on chromosome 22q12. It is highly upregulated in GSCs.[77] The expression of the *TUG1* is highly dependent on Notch1 activation in GSCs. In the cytoplasm, *TUG1* functions to promote self-renewal by sponging *miR-145*, whereas in the nucleus it recruits polycomb repressive complex 1/2 (PRC1/2) to suppress the proliferation of genes by locus-specific methylation of histone H3K27 via YY1-binding activity.[37] Studies conducted based on gain and loss of function showed that dysregulation of *TUG1* affects apoptosis and cell proliferation.[78]

### Colorectal neoplasia differentially expressed (CRNDE)

*CRNDE* is mapped on the 16th human chromosome and is 1,059 nt long.[30,61] The higher expression of *CRNDE* was shown to play a regulatory role in glioma development.[25] A microarray analysis-based study performed by Hu and colleagues[26] revealed that *CRNDE* is involved in glioma recurrence, and higher expression of *CRNDE* contributed to cell apoptosis while it inhibited cell proliferation in glioma. *CRNDE* has many transcriptional isoforms because of alternative splicing.[61] In glioma cells, *CRDNE* is regulated via the mTOR signaling pathway. The upregulation of *CRNDE* promotes tumor formation in a murine model and in the *in vitro* invasion system.[30] Another role of this lncRNA includes the regulation of PIWIL4 mediating gene silencing, leading to the promotion of gliomagenesis via activation of STAT3 signaling.[61]

### Mediator of DNA damage checkpoint protein 1 antisense (MDC1-AS)

*MDC1-AS* is an antisense transcript of tumor suppressor *MDC1.*[54] However, its function is undetermined. *MDC1-AS* positively regulates the expression of *MDC1* and inhibits the proliferation and cycle of U87MG and U251 cell lines when overexpressed.[54] In glioma cells, *MDC1-AS* acts as a tumor suppressor by upregulating its antisense tumor-suppressing gene *MDC1.*[54]

### Maternally expressed gene 3 (MEG3)

*MEG3* is transcribed from the maternal allele.[79,80] The lower expression of *MEG3* has been found to behave as a tumor suppressor in glioma and is capable of activating both p53-dependent and p53-independent pathways.[61] The overexpression of *MEG3* inhibits cancer cell growth by hypomethylating *MEG3.*[81] When *MEG3* is overexpressed, the p53 level is elevated due to MDM2 downregulation.[82] A study revealed that *MEG3* may compete with *miR-19a and miR-93* ceRNAs to inhibit the cellular growth of GBM.[83,84] Also, increased *MEG3* and Wnt/β-catenin expression in glioma cells was shown to inhibit cell growth and metastasis.[49]

### X-inactive specific transcript (XIST)

*XIST* is involved in X chromosome inactivation in mammals to balance gene expression between sexes.[61] In general, *XIST* knockout studies in glioblastoma cells revealed attenuated cell growth and uptake of glucose by sponging *miR-126* via the IRSI/phosphatidylinositol 3-kinase (PI3K)/Akt pathway.[85] *XIST* knockdown causes upregulation of *miR-152*, leading to the suppression of GSC proliferation, migration, invasion, and tumorigenic potential.[33] *XIST* knockdown improved the brain-tumor barrier (BTB) permeability to repress angiogenesis in glioma.[33] Mechanistically, *XIST* can regulate the expression of the transcription factor (TF) forkhead box C1 (FOXC1) and zonula occludens 2 (ZO-2).[33] Gene expression analysis studies found that *XIST* is overexpressed in glioma endothelial cells.[61] Consequently, a few other studies show how the behavior of *XIST* as ceRNAs suppress the action of miRNAs, thus conferring chemoresistance and oncogenic properties to glioma cells.[34,61,86]

### Tumor suppressor in lung cancer-1 antisense-1 (TSLC1-AS1)

This lncRNA is the antisense transcript of a tumor suppressor.[55] *TSLC1-AS1* expression is downregulated in tumor specimens[55] and acts as a *TSLC1* expression mediator.[55] *TSLC1-AS1*'s overexpression results in *TSLC1* upregulation and inhibits proliferation, migration, and invasion of U87 cells.[55] This regulation may require a new modulator instead of promoter hypermethylation.[55]

### Highly upregulated in liver cancer (HULC)

*HULC* is a lncRNA located on chromosome 6p24.3.[53] Upregulation of *HULC* promotes proliferation and colony formation of glioma cells.[53] The underlying molecular mechanisms of *HULC* overexpression in glioma remain undetermined. In the case of hepatocellular carcinoma (HCC) cells, by sequestering *miR-200a-3p*, the increase in *HULC* gene expression and activity was associated with improved EMT-related parameters.[53] Therefore, the HULC-EMT pathway could cause cell migration and invasion.

### Nuclear paraspeckle assembly transcript 1 (NEAT1)

The lncRNA oncogene *NEAT1* is reportedly involved in promoting glioma development by suppressing miR-132.[87] This indirectly promotes *SOX2* expression involved in tumor formation of glioma.[87] *NEAT1* knockdown could potentially inhibit glioma cell proliferation and metastasis. The differential expression of *NEAT1* in astrocytomas and oligodendrogliomas was associated with lineage specificity and terminal differentiation of glial cells.[25] Moreover, *NEAT1* expression also relates to overall survival and may act as a prognostic candidate for LGG patients. Upregulated expression of *NEAT1* was related to poor outcomes in LGG patients and promoted proliferation, invasion,

and migration.[88] Interestingly, few studies have shown a *NEAT1* knockdown inhibitory effect on cell viability and invasion in gliomas.[87] It is known to upregulate the c-Met oncogene expression via *miR-449b-5p*, which negatively regulates c-Met expression levels. A recent study demonstrated that *NEAT1* is probably upregulated by the oncogenic epidermal growth factor receptor (EGFR) pathway where it acts as a scaffold molecule, promoting GBM tumorigenesis by recruiting histone-modifying enzyme.[87]

### ADAM metallopeptidase with thrombospondin type 1 motif, 9 antisense RNA 2 (ADAMTS9-AS2)

*ADAMTS9-AS2* is the antisense partner lncRNA of the protein-coding *ADAMTS9* gene, which is a well-recognized tumor suppressor.[56] *ADAMTS9-AS2* expression level is regulated by promoter hypermethylation and histone modification.[56] One study indicated that the high methylation level is responsible for the modulation of its inactivation in glioma cells.[56] Also, this study highlighted the ability of *ADAMTS9-AS2* to suppress cell migration by modulating the protein-coding gene *ADAMTS9*.[56] Reportedly, *ADAMTS9-AS2*'s overexpression inhibits the migration and invasion abilities of T98G cells, which allows increased tumor progression. *ADAMTS-AS2* was shown to be downregulated during tumorigenesis of glioma.[56]

### ZEB antisense RNA 1 (ZEB1-AS1)

*ZEB1-AS1* upregulation is correlated with tumor progression. ZEB1-AS1 has a significant effect on glioma cellular proliferation, migration, and invasion.[57] Recent reports have shown that the knockout of *ZEB1-AS1* attenuated tumor growth in the glioma murine model.[57] Thus, it is a tumor-promoting lncRNA in glioma cells. Similarly, in other loss-of-function studies, *ZEB1-AS1* was seen to effectively promote colorectal cancer cell proliferation, partially by suppressing p15 gene expression.[57]

### Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)

*MALAT1*, or nuclear-enriched transcript 2 (NEAT2), is located on chromosome 11q13.1.[39] *MALAT1* silencing leads to increased apoptosis of glioma cells and promotes TMZ resistance by *miR-203* suppression and TS function activation.[89] The downregulation of *MALAT1* reduced levels of TMZ resistance in U251 and U87 cell lines by regulating ZEB1 expression.[39] ZEB1 is synthesized by EMT, whose role has been recently identified in MDR. Furthermore, Cai et al.[90] showed that *MALAT1* shares crosstalk with TMZ resistance, and upregulated expression of *MALAT1* was found both *in vitro and in vivo* in glioma and was shown to direct binding with *miR-101* to decrease *miR-101* expression to regulate TMZ resistance. However, decreased expression of *MALAT1* in cells resulted in overexpression of *miR-101* followed by decreased levels of MGMT and glycogen synthase kinase-3β (GSK3B), indicating that both of these proteins are involved in the mechanism of TMZ resistance.[58,90]

### Growth arrest-specific 5 (GAS5)

*GAS5* is mapped on chromosome 1q25 and can inhibit tumor growth in gliomas.[42] One study revealed that *miR-196a-5p* is overexpressed in glioblastoma tissues. *GAS5* targets *miR-196a-5p*, which results in improved FOXO1 expression and a high transcriptional rate of *PID1* and *MIIP* genes. When FOXO1 is upregulated, it causes an increase in *GAS5* transcription. This results in the formation of a positive regulatory feedback loop. The *GAS5/miR-196a-5p*/FOXO1 axis suppresses GSC proliferation, migration, invasion, and apoptosis. These outcomes demonstrate that *GAS5* is a prominent target for glioma treatment.[42]

### Cancer susceptibility candidate 2 (CASC2)

*CASC2* is located on chromosome 10q26. Alternative splicing yields five *CASC2* exons, generating three lncRNAs: *CASC2a, CASC2b*, and *CASC2c*.[67] Exogenous *CACS2* was reported to inhibit the proliferation of glioma cells and amplify cell proliferation repression induced by TMZ. The regulation of sensitivity to TMZ chemotherapy by modulating *PTEN* is due to the *CASC2* and *miR-181a* interactions.[43] Correlation studies have found that *CASC2* positively correlates with *PTEN* and shares an inverse correlation with *miR-181a* in glioma tissues resistant to TMZ. Subsequently, *miR-181a* was inversely related to *PTEN*. Data revealed direct competitive binding with *miR-181a* between *CASC2* and *PTEN* mRNA. This indicates that glioma cells are sensitized to TMZ as the *miR-181a* expression is inhibited by *CASC2* directly targeting glioma cells.[43]

### Neuroblastoma associated transcript-1 (NBAT-1)

*NBAT-1* is mapped on the 6p22 chromosome. It controls the expression of genes involved in the proliferation and invasion of cells by EZH2 interaction epigenetically. Studies demonstrate that during upregulation of *NBAT-1* target genes, cell proliferation and invasion are affected in both EZH2 and *NBAT-1* knockdown cells. These genes act as a potential target of repression by *NBAT-1*/EZH2-mediated H3K27me3. *NBAT-1* also acts as a risk-assessing biomarker for neuroblastoma tumors. It also has a role in cellular proliferation and invasion. *NBAT-1*'s role in neuronal cell differentiation is linked to mechanisms and networks of genes involved in the development of neuroblastoma tumors and their progression. *NBAT-1*, along with *SOX9* and NRSF/REST downstream effectors, might be potential targets for the development of therapeutics.[44]

### Forkhead box M1 antisense (FOXM1-AS)

*FOXM1-AS* is a single lncRNA involved in the interaction between nascent transcripts *ALKBH5* and *FOXM1*. *LOC100507424* (*FOXM1-A*) is a lncRNA found on the 12th chromosome (chr12: 2945982–2968961, GRCh37/hg19), is transcribed in the direction opposite of *FOXM1*, and is 457 nt long, which are complementary to the last exon of *FOXM1* mRNA.[45] Its removal increases the m6A modification of *FOXM1* precursor (pre-)mRNA. Furthermore, *FOXM1-AS* knockdown reduced the expression of FLAG-FOXM1 in a similar pattern to *ALKBH5* knockdown, which decreased both the activity of *FOXM1* 3 UTR luciferase and collaboration of *HuR* and *FOXM1* RNA. Therefore, *FOXM1-AS* vitalizes *FOXM1* expression and aids in maintaining GSCs.[45]

### ECONEXIN

The *ECONEXIN/C130071C03Rik* expression seems to be regulated indirectly by Tp53 and Nf1. It shows sequence homology of 80% or

more to their promoter region.[46] *ECONEXIN* is predominantly located in the cytoplasm; it has two *miR-411-5p* binding sites. *ECONEXIN*'s binding to the AGO2 protein and *miR-411-5p*, which is a part of the RNA complex for silencing, indicates that it plays a role in miRNA regulation through the mechanism of silencing complex induced by RNA. Lack of *ECONEXIN* in cells causes an inclined *miR-411-5p* level. Thus, it regulates *miR-411-5p* through its role as a miRNA sponge for entrapping *miR-411-5p*, resulting in the upregulation of *TOP2A* upon glioma formation.[46]

### SOX2OT
*SOX2OT* is a lncRNA located on chromosome 3q26.3 (Chr3q26.3).[47] *SOX2OT* elimination suppresses cellular proliferation, migration, and invasion, escalating GSCs apoptosis. It also affects apoptosis via the upregulation of *miR-194-5p* and *miR-122* expression, which can downregulate *SOX3* expression by *SOX2OT*, leading to the activation of *TDGF-1* expression. This affects GSC biology via the JAK/STAT pathway. The feedback loop of *SOX2OT-miR-194-5p/miR-122-SOX3-TDGF-1* plays a vital role in modulating the biology of GSCs.[47]

### Histocompatibility leukocyte antigen (HLA) complex P5 (HCP5)
*HCP5* is located on chromosome 6p21.3. *HCP5* knockdown restricts cell proliferation, migration, and invasion and promotes apoptosis in glioma cells.[48] *HCP5* regulates the malignancy of glioma cells by binding to *miR-139*, which functions as a tumor suppressor. *HCP5*'s elimination also downregulates the RUNX1 TF, which can promote the expression of *AEG-1* involved in a sequence of oncogenic effects in glioma cells.[48] RUNX1 plays a part in *miR-139*-mediated inhibition of malignancy in glioma cells. *HCP5* downregulates *miR-139* to upregulate RUNX1. Also, interestingly, being primarily expressed in immune system cells, lncRNA *HCP5* may have a vital role in autoimmunity.

### Urothelial carcinoma-associated 1 (UCA1)
*UCA1*, a lncRNA mapped on chromosome 19p13.12, is a globally identified oncogenic gene in a variety of malignant tumors.[51] It was primarily diagnosed with bladder cancer. *UCA1* modulates the biological growth of glioblastoma cells by negatively mediating *miR-193a* expression, which negatively modulates *CDK6* by directly targeting its 3′ UTR. However, it was discovered that *CDK6* stimulates PI3K/AKT and MAPK cascades, along with the Notch signaling pathway. *UCA1* along with *miR-193* may impact these signal cascades via regulating the expression of *CDK6*. *UCA1* silently represses glioblastoma cell (U-118 MG and A172) potential and weakens migration and cell invasion. However, it aids apoptotic progress through *miR-193a*-mediated *CDK6* silencing, while inhibiting the PI3K/AKT, MAPK, and Notch pathways.[51] This proves that the lncRNA *UCA1* could be a valuable therapeutic target.

### Tumor suppressor candidate 7 (TUSC7)
*TUSC7* is an antisense lncRNA that has four exons mapped at 3q13.3.[91] According to Pasic et al.,[92] it was primarily detected in osteosarcoma. Recently, a few studies reported that low *TUSC7* expression significantly suppresses tumor growth. *TUSC7* expression was

interconnected negatively with TMZ resistance.[58] Its overexpression reduces levels of half-maximal inhibitory concentration ($IC_{50}$) of TMZ and MDR1 expression, and it escalates TMZ cytotoxicity in U87TR cells. Up-modulation of *miR-10a* improves MDR1 expression and $IC_{50}$ of TMZ, increases cell viability and division, and restricts U87TR cell apoptosis. Furthermore, *TUSC7* inhibits the resistance of TMZ in U87TR cells through *miR-10a* interaction. *TUSC7* downregulation in glioma worked as a prognostic biological marker for glioma patients and restricted malignant behavior.[91]

### LOC441204
Lin and colleagues[59] investigated the role of *LOC441204* in brain tumor samples using oligonucleotide microarray analysis. The study reported an increased expression of *LOC441204* that was positively associated with tumor size and grade. Evidence indicates that the diminution of *LOC441204* in T98 human glioma cells led to a considerable decrease in proliferative ability and amplified β-catenin degradation. Moreover, *LOC441204* accelerated the cell proliferation ability of glioma cell lines via a mechanism involving the β-catenin/p21/cdk4 cascade. Therefore, these results strongly support the fact that *LOC441204* is a novel oncogene and may serve as a promising cell growth marker for glioma progression.

### Antisense non-coding RNA in the INK4 locus (ANRIL)
Paul et al.[60] investigated the role of oncogenic lncRNA *ANRIL* concerning glioma biology. In general, lncRNA *ANRIL* transcribes antisense to the *INK4b-ARF-INK4a* locus that encodes CDKN2B and CDKN2, the two cyclin-dependent kinase inhibitors, as well as ARF that binds to MDM2 and results in its degradation, thereby activating p53. Knocking out *ANRIL* in LN229 and T98G glioma cell lines inhibited colony formation and cell proliferation. In general, *ANRIL* is upregulated in glioma cell lines; however, *ANRIL* is co-deleted with a homozygous deletion of the *INK4b/ARF/INK4a* locus in GBMs. This is positively associated with the upregulation of all genes present in the locus, i.e., *ANRIL, CDKN2A,* and *CDKN2B*. Thus, the lack of *ANRIL*-mediated suppression of the *INK4b-ARFINK4a* locus is possibly due to the lower expression of *CBX7* (chromo box homolog 7), a co-repressor molecule in GBMs.

### lncRNAs involved in chemoresistance
Zhang et al.[93] developed TMZ (Temodar), an oral chemotherapeutic drug for clinical use in glioma with the best therapeutic efficacy against patients with high-grade gliomas. A substantial proportion of patients suffering from GBM have inherent or acquired TMZ resistance that significantly deters the clinical outcome.[90,94] Since chemoresistance is the main hurdle to a better outcome of GBM chemotherapy, the mechanism of this resistance needs to be understood, and we have to identify a unique therapeutic target. Our current understanding is that *MALAT1* boosts the chemoresistance by suppressing the *miR-101* pathway of signaling via direct GBM cell binding.[90] Another lncRNA *AC023115.3* competes with endogenous RNA for *miR-26a* and constricts the *miR-26a* inhibitory effect on GSK3β. It promotes Mcl1 deterioration by inducing a GSK3β increase and autophagy decline. Furthermore, *AC023115.3* enhances the glioma cell's
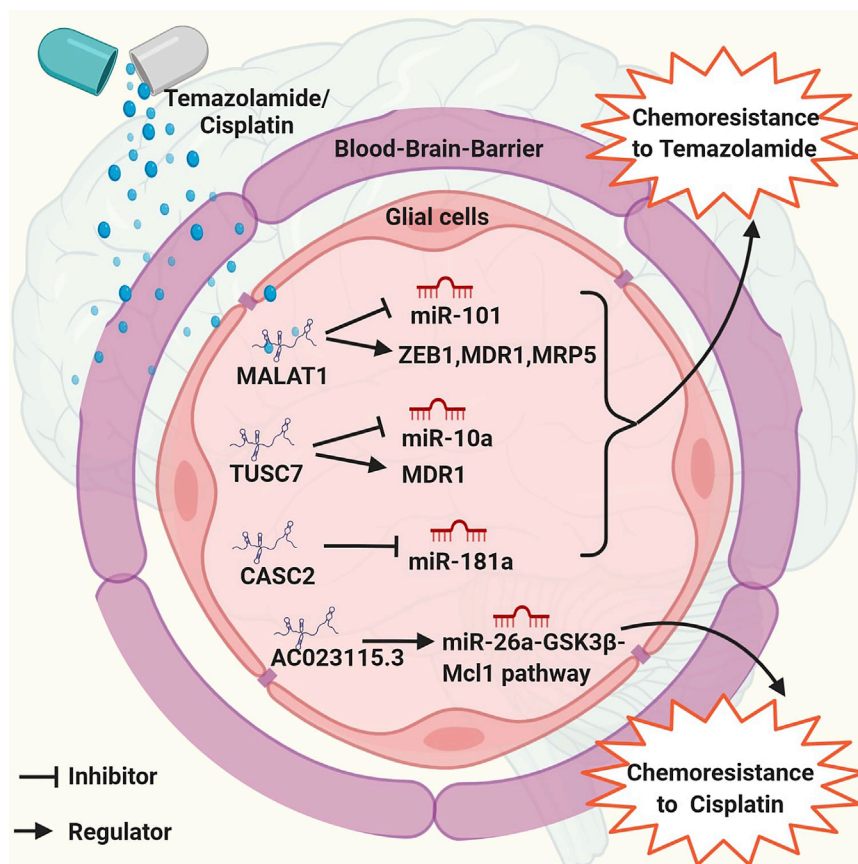
Figure 2. Illustration of how the mechanism of chemoresistance in glioma to temozolomide (TMZ) and cisplatin with the involvement of lncRNAs, CASC2, MALAT1, and TUSC7 promotes chemoresistance to TMZ by suppressing the miRNAs while AC023115.3 mainly targets the mcl1 pathway and enhances glioma cell chemosensitivity to cisplatin

tended to be clustered most significantly in immune-related biological processes in Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Therefore, understanding the molecular mechanisms of these novel lncRNAs biomarkers during the tumorigenesis and malignant progression of gliomas may provide novel diagnostic, prognostic, and therapeutic targets for gliomas.[96]

A study by Dong and colleagues[97] used lncRNA gene network analysis to identify *ASLNC22381* and *ASLNC20819* lncRNAs that exhibited significantly higher expression in growth factor-related insulin growth factor (IGF)-1 pathway, leading to recurrence and malignant progression of GBM. Furthermore, the differential expression of lncRNAs in glioma compared to normal brain tissue may have a regulatory function in the PPAR signaling pathways that may be involved in the pathogenesis of GBM.

chemosensitivity to cisplatin by regulating the *miR-26a-GSK3β-Mcl1* pathway. These data indicate that the *AC023115.3-miR-26a-GSK3β* signaling axis plays a vital role in the reduction of the chemoresistance of gliomas.[94]

Recently, lncRNAs have been identified as playing a role in chemotherapy resistance in multiple cancers[95] (Figure 2). lncRNA *RP11-838N2.4* can strengthen the *in vivo* and *in vitro* cytotoxic effects of TMZ on GBM cells. lncRNA *RP11-838N2.4* plays the role of an endogenous sponge, curbing the function of *miR-10a* via conserved sequences and strengthening the expression of *EphA8*, which enhances the rate of cell apoptosis. This leads to intensification of the sensitivity of GBM cells to TMZ. Transforming growth factor β (TGF-β) activity is impeded by lncRNA *RP11-838N2.4*, which is *miR-10a*-independent. lncRNA *RP11- 838N2.4* characterization might aid in approaches for heightening TMZ efficacy.[95]

## PARTIALLY STUDIED lncRNAs IN GLIOMA
Chen et al.[96] used a Cox regression analysis and identified four independent lncRNA biomarkers named *AK098425*, *AL833059*, *AK056155*, and *CR613436*. These were positively associated with the clinical outcome of patients with GBM. Later, functional analysis revealed that the genes co-expressed with these four lncRNAs

Studies conducted by Zhang et al.[25] on differential lncRNA expression signatures revealed that different lncRNA expression profiles may be potentially involved in distinguishing between astrocytic and oligodendroglial tumors, as well as between grades of the gliomas. For example, *LOC400043* was found to be upregulated with increasing malignancy grades while a dramatic increase in the expression level of *LOC400043* was reported to play an important role in gliomagenesis.

*RFPL1S* was reported to function as a regulator of cell-cycle progression, and it was reported as antisense of the coding gene *RFPL1* and found to play an essential role in the post-transcriptional regulation of the *RFPL1*. Furthermore, the differential expression of *DLX6-AS* between astrocytomas and oligodendrogliomas was displayed to be associated with lineage specificity and terminal differentiation of glial cells.[25]

A clinical-based investigation performed by Hegi and colleagues[98] reported that *prominin-1* lncRNA (or CD133) is a predictor of poor survival in patients treated with chemoradiotherapy. Interestingly, its expression was associated with resistance and it maintains a self-renewal

signature. This indicates that a tumor stem cell phenotype is involved in the escape of glioblastoma from chemoradiotherapy. Moreover, multivariate analysis revealed the two major clusters characterized by *EGFR* and *HOX* (homeobox) gene expression. These are two autonomous prognostic factors for O-6-methylguanine-DNA methyltransferase (MGMT) methylation status and are associated with cell adhesion, innate immune response, and tumor vascularization.

Lin et al.[99] predicted the role of potential oncogenic lncRNAs such as *CARD8-AS1* and *PWAR6*. These are dynamically expressed lncRNAs and are regulated by grade-specific TFs. These TFs show higher expression with increasing grades of glioma. Some TF regulators such as SPI1 and PLAU play a critical function in glioma and are associated with tissue remodeling and wound repair. Moreover, *CARD8-AS1* and *PWAR6* have a significant role in the process of the metastatic potential of glioma cell lines *in vitro*, in DNA repair, the EMT, regulating immune responses, and patient survival. Therefore, these oncogenic lncRNAs can serve as promising candidates for prognostic biomarkers in glioma.[99]

Li and colleagues[100] have evaluated the role of lncRNAs in GBM that showed epigenetic dysregulation in promoter regions, most of which were hypomethylated. Their study identified six lncRNAs of note; one of them, *PRRT3-AS1*, was among the most hypermethylated lncRNAs and maybe a potential biomarker of GBM prognosis. Furthermore, it was revealed that the aberrant methylation of either hypermethylated or hypomethylated lncRNAs may result in the disruption of some pathways such as mTOR signaling, apoptosis, ErbB signaling, and FoxO signaling pathways.

Studies conducted by Matjašič et al.[101] examined the expression level of several lncRNAs and certain lncRNA-associated miRNAs, which reported that there is a significant change in the expression between the analyzed glioma subtypes and grades. For example, expression levels of seven lncRNAs (*7SL, EGO-A, HOTAIR, JPX, MEG3, RNCR3*, and *ZFAS1*) and four miRNAs (*miR-770, miR-125b, miR-124a,* and *miR-196a*) showed major association with overall survival considering only the expression of astrocytoma, primary GBMs, and oligodendroglioma.

lncRNA *7SL* is downregulated in astrocytic tumors and upregulated in oligodendroglioma and oligoastrocytoma. This difference may be an additional genetic parameter for differentiating these subtypes from each other; upregulated expression of EGO-A (eosinophil granule ontogeny isoform A) was observed in all glioma subtypes, except secondary GBMs. EGO-A host gene ITPR1 (inositol triphosphate receptor type 1) is encoded near to a transcriptional regulator, *EGR-1* (early growth response 1), that is responsible for the induction of mitosis, cell differentiation, and growth. The expression of the *EGR-1* gene in glioma cells is induced by overexpression of the EGFR gene and platelet-derived GFR (PDGFR) gene.[101,102]

*RNCR3* (retinal noncoding RNA3) is overexpressed in the brain and acts as a sponge for *miR-124a*. *RNCR3* is a precursor for *miR-124a*

and both are downregulated in primary and secondary GBMs. A lower expression of *RNCR3* was correlated with a lower survival probability.[101]

Zottel et al.[58] have reviewed a few lncRNAs that are involved in resistance to TMZ in glioblastoma including *RP11-838N2.4, NC-TALC, NONHSAT163779*, *ADAMTS9* antisense RNA2 (ADAMTS9-AS2), P73 antisense RNA 1T non-protein-coding (*TP73-AS1*), *AC003092.1*, and SET binding factor 2 antisense RNA 1 (*lncSBF2-AS1*).

Recently, Cheng and colleagues[103] discussed the function of exosomal lncRNAs in glioma progression and clinical applications. Exosomes are small endosomes derived from extracellular vesicles (EVs) of 40–150 nm in diameter. These are secreted by different cells in the body and almost from all body fluids, including urine, blood, saliva, breast milk, and cerebrospinal fluid (CSF).[104] Some of the exosomal lncRNAs, such as lncRNA-*AHIF* and lncRNA-*ATB*, were reported to be involved in invasion and cell proliferation in gliomas; lincRNA-*POU3F3* and lincRNA-*CCAT2* played a significant role in the regulation of angiogenesis in gliomas, and lncRNA-*SBF2-AS1* enhances chemoresistance to TMZ. Alternatively, few other exosomal lncRNAs such as *circATP8B4* and lncRNA-*AHIF* were reported to promote cell radioresistance and invasion. Furthermore, the exosomal lncRNAs may have a promising clinical function in glioma diagnosis because of their distinctive characteristics such as small size, the ability to circulate freely or package into exosomes, their double-layer phospholipid membrane acting as a seal to protect ncRNAs from the ribonuclease-mediated degradation, and their ability to cross the blood-brain barrier (BBB), thereby suggesting their role as potential biomarkers. For instance, patients with recurrent GBM showed increased serum levels of *SBF2-AS1* exosomal lncRNAs that were associated with poor response to TMZ therapy and worse prognosis.[63]

Lin et al.[88] have identified six aberrantly expressed lncRNAs of prognostic significance with their ceRNA networks against LGGs. Based on The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) RNA sequencing (RNA-seq) databases, six differentially expressed lncRNAs between LGG and normal brain tissue were screened, i.e., *AC021739.2, AL031722.1, AL354740.1, FGD5-AS1* (FGD5 antisense RNA1), *LINC00844*. and *NEAT1*. These were associated with overall survival and may act as prognostic candidates for LGG patients. For instance, *FGD5-AS1* was found to be a prospective therapeutic target for LGG; in contrast, upregulated expression of *LINC00844* showed a favorable prognosis, whereas information on the remaining lncRNAs (*AC021739.2, AL031722.1,* and *AL354740.1*) is limited. Furthermore, based on the connectivity map (CMap) dataset, six putative drugs (irinotecan, camptothecin, mitoxantrone, azacitidine, mestranol, and enilconazole) were used for glioma treatment that potentially targeted glioma-associated pathways, such as the JAK-STAT signaling pathway, the TGF-β signaling pathway, the HIF-1 signaling pathway, and the mitogen-activated protein kinase (MAPK) signaling pathway.
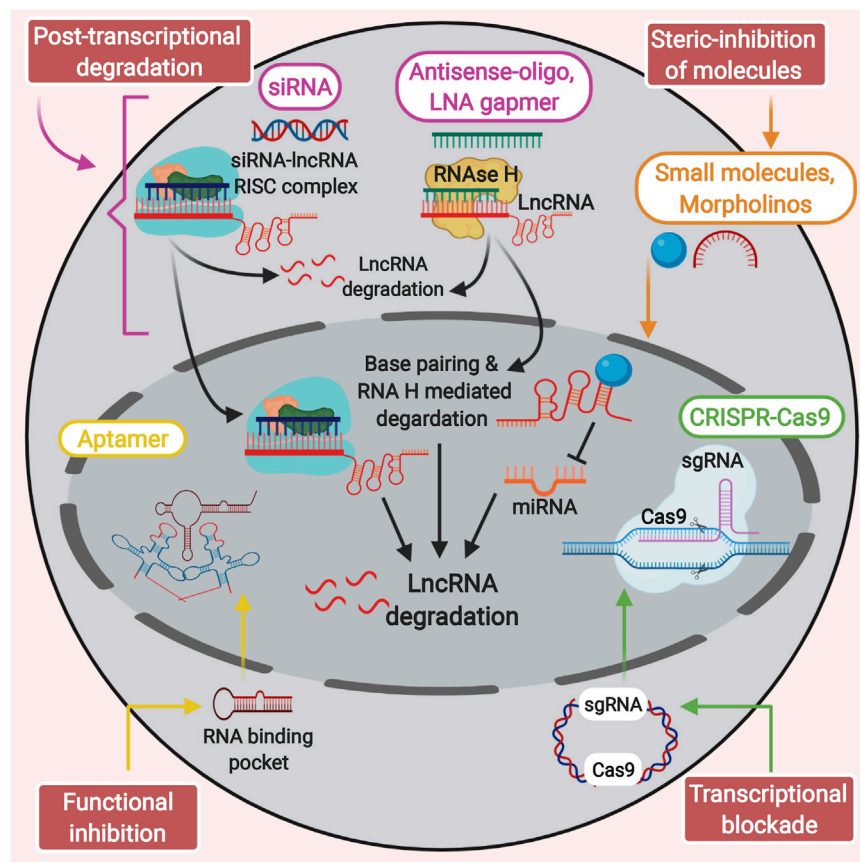
**Figure 3. Depiction of the most widely recognized approaches to focus on the RNA of interest**
To post-transcriptionally disintegrate the desired RNAs, RNA interference recruits the RISC complex to post-transcriptionally disintegrate the target RNAs; antisense oligonucleotides (ASOs) degrade the RNA of interest through an RNase H-dependent mechanism; CRISPR-Cas9 is used to accomplish transcriptional silencing; and small molecules such as morpholinos and tailored ASOs are used to hinder interactions between the lncRNA and the protein.

## Post-transcriptional degradation

Post-transcriptional degradation is the most widely recognized method used to focus on the desired RNA. The development of the RNA-RNA or RNA-DNA duplex is a profoundly explicit procedure that has permitted specialists to examine the capabilities of oligonucleotide-based therapeutics. These therapeutics offer higher efficacy, improved stability, and reduced off-target effects compared to traditional treatment options.[105,106]

There are two significant methodologies utilized. One is RNA interference (RNAi): in this methodology, siRNAs stimulate dicer action in the cytoplasm and recruit the RISC (RNA-induced silencing complex) to post-transcriptionally disintegrate the desired RNAs. This strategy has been utilized to target mRNAs in various neurotic conditions, such as malignancies, neurological ailments, and metabolic disorders.[107] The other methodology is antisense oligonucleotides (ASOs), which are promising therapeutics that target and degrade the RNA of interest through the RNase H-dependent mechanism. The binding of ASOs to the desired RNA can restrain or change the expression of the gene via a steric blockade, alternating the splicing mechanism, and degradation. For instance, intravenous treatment with ASOs targeting TUG1 coupled with a drug delivery system induces GSC differentiation and efficiently represses GSC growth *in vivo*.[37] The improvement of locked nucleic acids (LNAs) and *S*-constrained ethyl (cEt) alterations represent a portion of the advances in ASOs with improved strength and have promising pharmacokinetic profiles for different malignant growth-related and neurological sicknesses.[108–110]

Another subset of ncRNAs is natural antisense RNAs (NATs), which coincide with protein-coding genes and are transcribed in the reverse direction. Upregulated expression of NATs in malignant growth results in the suppression of the related tumor suppressor genes.[111] The inhibition of NATs via ASOs, referred to as "antagoNATs," may increase the expression of tumor suppressor genes. AntagoNATs are linear, synthetically altered LNAs, or different ASOs.[111,112] TUG1

A microarray analysis-based study performed by Hu and colleagues[26] revealed some differentially expressed lncRNAs in recurrent gliomas relative to primary glioma. For example, some lncRNAs such as *AC016745.3*, *XLOC_001711*, and *RP11-128A17.1* have significant roles in glioma recurrence. Furthermore, the report suggests that mRNA in the lncRNA-mRNA pair may be the target of lncRNA. For example, higher expression of *FOXD4L1* (forkhead box protein D4-like 1) correspond to increased expression of enhancer lncRNA *AC016745.3* that is involved in increasing the expression of genes that lead to the maintenance of proliferative neural precursors. Decreased expression of mRNA *RPRM* (reprimo) in pituitary tumors is related to decreased lncRNA *XLOC_001711* expression that acts as a tumor suppressor. Another highly expressed sense mRNA, *MEIS2* (myeloid ecotropic insertion site 2), corresponds to increased expression of antisense lncRNA *RP11-128A17.1*, thereby promoting cell proliferation in human neuroblastoma cell lines.

## THERAPEUTIC APPROACHES TARGETING lncRNAs IN GLIOMA

lncRNAs have a significant role at various stages of tumor onset and progression in GBM. Therefore, targeting both nuclear and cytoplasmic lncRNAs may allow us to discover additional therapeutic applications (Figure 3).

is targeted with ASOs intravenously mix with a medication delivery system that results in the induction of differentiation in GSCs and *in vivo* growth suppression of tumors.[37] To protect ASOs, chemical modification at the ends is performed with the addition of 2′-*O*-methyl and LNA at both the 5′ and 3′ ends that protects it from degradation and helps in the maintenance of constant ASO levels. A preclinical trial demonstrated that *MALAT1* ASO, when administered subcutaneously in the MMTV-PyMT mouse model of luminal B breast malignancy, leads to the separation of early tumors with an almost 80% decrease in metastasis compared to non-specific ASOs.[113] These investigations showed that *MALAT1* ASO may be developed as a possible restorative for metastatic ailment in a few disease types, yet further assessment is required.[114] The contemporary and clinically progressed oligonucleotides, peptide nucleic acids (PNAs), are exclusively nucleic acids linked with a neutral-charged peptide spine and are thermally steady in the tumor microenvironment. These are altered *in vivo* for their utilization in "anti-ncRNA treatment."[115] The PNAs-based technique might be effective in solid tumors, such as gliomas.[116]

### Steric blockade

lncRNA genes can be regulated by the steric shunt of the promoter or by utilizing genome-altering strategies such as CRISPR-Cas9.[117] In this methodology, a transcriptional repressor is combined with dead-Cas9, and this complex is guided by guide RNAs to a particular gene promoter to accomplish transcriptional silencing.[118] The altering of genome, epigenome, or RNA intervened by CRISPR-Cas9 is a promising methodology for targeting lncRNAs expressed in glioma and could be profitable over regular quality treatment approaches.[119]

### Steric inhibition

The interactions between the lncRNA and the protein can be hindered by utilizing small molecules such as morpholinos and tailored ASOs, which are incapable of using the RNA degradation pathway. These can bring about loss of function by specifically binding to the RNA and blocking the RNA and the protein boundary.[120] lncRNAs are capable of forming stable secondary and tertiary structures that can be precisely mapped using SHAPE and PARIS, which are RNA structure determination assays.[121–123] Small molecule inhibitors for bromodomain and extra-terminal (BET) proteins decrease the level of several oncogenes involved in the succession of GBM. For instance, BET domain proteins diminish the expression of *HOTAIR*, and the utilization of BET inhibitors can re-establish the tumor growth brought about by oncogenic lncRNAs.[124]

## CONCLUSIONS

Glioblastoma is one of the most lethal brain diseases. Clinical advances in surgery and radiotherapy have proved to be useful; however, the development of non-invasive methods is still a prerequisite for truly great treatment options. Within the last few years, ncRNAs have gained a fresh impetus in the field of glioma research and could be utilized as a promising tool for targeted therapy. lncRNAs are known to participate in various cellular regulatory pathways that

modulate the process of tumorigenesis. Numerous deregulated lncRNAs have been associated with GBM and are involved in almost all of the features of this malignancy, including cell multiplication, movement, angiogenesis, stemness, tumor relapse, severity, and chemoresistance. The cutting-edge biochemical and molecular methodologies have unequivocally helped in elucidating how lncRNAs control and regulate various functions. Although it is promising to find novel diagnostics and therapeutics to improve glioma survival using lncRNAs, to date, the attributes of most of these ncRNAs are indefinite. The distribution of drugs across the intact BBB into the brain is a critical factor to consider during the development of valuable therapies. The therapeutics based on lncRNAs are restricted to only *in vivo* application because of low stability and poor drug uptake. Thus, future investigations need to give more consideration to recognizing cell-to-cell heterogeneity of lncRNAs in gliomas that will help in the development of novel RNA-based methodology to treat such a malignancy and bring new trust in patients with GBM.

## AUTHOR CONTRIBUTIONS

A.K.P. conceived the idea of this review. A.K.P., B.Y., and S.P. wrote the manuscript and presented the concepts in the manuscript. A.K.P., M.G., B.Y., Y.R., M.P., A.G., and S.P. designed and created the figures, revised the paper, and made final corrections. All authors have read and agreed to the published version of the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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