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The Potential Roles and Applications of the long non-coding RNA-Interactome in *glioblastoma* Etiology and Treatment

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a heterogenous population of largely evolutionary preserved transcripts, over 200nt in length which play important roles in human health and disease. These versatile and numerous transcripts can possess RNA:Protein, RNA:RNA, and RNA:DNA binding potential. Some lncRNAs also encode short peptides which can have biological significance. Many, if not a plurality of known lncRNAs, are expressed in the brain, believed to help encode complex information and facilitate various neurologic processes. In fact, lncRNA expression appears to be positively correlated with organism and organ complexity in stark contrast to coding genes. *Glioblastoma* (GBM) is the most common primary brain tumor with a dismal prognosis. The 5-year survival rate for GBM is around 7% with a median survival of between 14-16mos. GBM standard of care has not changed much in past decades and there is a need for new therapeutic strategies. In this review we focus on six lncRNAs of significance to cancer highlighting their potential applications in GBM treatment. These lncRNAs are MALAT1/NEAT2, HOTAIR, ZFAS1, SOX2-OT, CASC19/PCAT2, and SAMMSON. Some of these lncRNAs are well characterized across numerous cancers, but most are poorly characterized in the context of GBM or glioma. Many lncRNAs, including those highlighted herein, have been implicated in therapy resistance including chemoresistance and radiation resistance. Some of these transcripts can be found in patient serum. lncRNAs then present potential as theragnostic, prognostic, and diagnostic potential for GBM and other cancers. They may also represent therapeutic opportunities directly and as concomitant therapies to address resistance mechanisms.

Keywords: long non-coding RNA, interactome, *Glioblastoma*, MALAT1/ NEAT2, HOTAIR, ZFAS1, SOX2-OT, CASC19/PCAT2, SAMMSON.

Introduction

Long non-coding RNAs (lncRNAs) are a class of non-coding RNA (ncRNA) molecules with a defined length of greater than 200 nucleotides, sometimes as great as 100kb or more. Their length facilitates the formation of complex secondary and tertiary structures which may interact with various other molecules. These transcripts can be classified as intronic, intergenic, sense, antisense, or bidirectional overlapping protein coding regions. Many of these transcripts can interact with RNA, DNA, and/or proteins or peptides affecting gene regulation, biomolecule translocation, and biochemical functions. Interactions between lncRNAs and other biomolecules can be abundant and non-specific. In this review we refer to the "lncRNA-interactome" meaning all of the potential binding partners and loci where lncRNAs can exert influence. Regulation by lncRNAs is vastly complex with some transcripts serving as both tumor suppressors as well as pro-tumor oncogenes. Largely this distinction is dependent on interacting partners and sub-localization.

It has been observed that unlike with protein coding genes, ncRNA diversity and expression correlate positively with organism and organ complexity[1]. More than a third of known lncRNAs are specific to primates[2]. In fact, the human nervous system, in particular the brain, has been found to possess the greatest number of lncRNA species compared to all other organisms or organs studied to date [1,3,4]. It should be no surprise then that lncRNAs play an instrumental role in gliomagenesis and progression. A distinct barrier to lncRNA research has and is a continued lack of standardization with regard to characterization and study of these transcripts. There are a number of annotated databases (lncRNAdb[5], LNCipedia[6], LncExpDB[7], LncRNAWiki[8], LncBook[9], Lnc2Cancer[10], and others) useful for the study of lncRNAs, but nomenclature differences as well as biological factors such as alternative splicing contribute to confusion when it comes to assigning phenotypic relevance to particular transcripts. In some cases, the same transcripts under different names can be duplicative while in others, unique transcripts could go unannotated and missed due to a lack of clarity in characterization or labeling. These and other challenges with the study of lncRNAs are in part what make this field akin to the wild west of cellular biology with potentially numerous treasure hordes yet to be uncovered.

Perhaps the greatest influence lncRNA transcripts have over cellular biology is through RNA:DNA interactions. lncRNAs can form triple helices (triplex) with DNA in a parallel or antiparallel manner potentially exerting regulatory effects in cis to the triplex site. These transcripts are often evolutionarily conserved and contain transposable elements occasionally with DNA binding domains preserved[11]. These potentially functional domains may play an important role in lncRNA regulatory etiology meriting further investigation. lncRNAs can serve as scaffolds or recruitment factors bringing transcriptional or epigenetic machinery proximally to these DNA interaction sites. They can also facilitate enhancer or super enhancer elements in trans, far distal to their encoding loci. These are just some of the many ways lncRNAs affect transcriptional regulation.

lncRNA transcripts may also interact with other RNAs to affect posttranscriptional processes such as modifications or splicing. An obvious example of RNA:RNA interaction is that of lncRNAs with other ncRNA species, namely, micro RNAs (miRNAs). lncRNAs act as decoys or molecular sponges sequestering miRNAs, peptides, proteins, or transcription factors to exert regulatory influence. lncRNA transcripts interacting with other nucleic acid-based molecules can help recruit translational machinery to coding genes which are proximal or overlapping to the lncRNA loci. lncRNAs can even interact with themselves through back-splicing junctions leading to circularization forming circular RNAs (circRNA). These highly stable transcripts can be found secreted in body fluids including peripheral blood, saliva, or urine. circRNAs are thus ideal candidates for biomarker studies due to their ubiquitousness and stability.

Glioblastoma (GBM) is the most common primary brain tumor with a median survival between 14-16mos. GBM, or grade IV glioma, can be characterized by tumor cell of origin such as astrocytoma, oligodendroglioma, or ependymoma[12]. In 2016, molecular classifications of GBM were added including IDH1/2 (isocitrate dehydrogenase) mutational status, 1p/19q deletion status, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. There are four canonical molecular subtypes of GBM including classical, mesenchymal, neural, and proneural. GBM is treated by adjuvant chemoradiation with temozolomide (TMZ) followed by maximal safe surgical resection and concomitant chemoradiation. The past several decades of research have failed to extend survival in GBM patients largely thanks to a dearth of accurate preclinical testing models and due to the high degree of intra and intertumoral heterogeneity inherent to these tumors[13]. Thus, uncovering new therapeutic avenues in GBM remains a high priority.

The roles of lncRNAs in cancer are continuing to be explored with many being found to affect cancer hallmark traits. In this review, we highlight six significant lncRNAs which have been implicated in GBM pathophysiology with emphasis on applications for GBM treatment potential. The lncRNA MALAT1 is the first lncRNA transcript explored herein which has been studied previously in the context of GBM treatment. HOTAIR is a lncRNA transcript recently implicated in numerous oncologic processes, gliomas included. ZFAS1 is a less understood lncRNA in cancer biology but has been implicated in GBM pathophysiology. SOX2OT (SOX2-OT) has emerged as having potential implications for treatment resistances in a variety of cancers. CASC19 (PCAT2) is a lesser-known transcript studied in the context of other cancers, but not yet examined thoroughly in GBM. SAMMSON is the least known lncRNA covered in this review, but its potential applications for GBM treatment are potentially significant.

MALAT1/ NEAT2:

Metastasis-associated lung cancer transcript 1 (MALAT1), also known as nuclear-enriched abundant transcript 2 (NEAT2), is a lncRNA believed to play oncogenic roles in several cancers. MALAT1 is also among the highest expressed lncRNA in normal tissues[12]. MALAT1 has an overall length of around 8.7kb and is located on human chromosome 11q13.1 and encodes a peptide containing 213 amino acids[14]. MALAT1 exhibits strong evolutionary conservation which is suggestive of key roles in biological and disease processes[15]. In the cell, MALAT1 is commonly localized to nuclear speckles and has been reported to play a role in the regulation of pre-mRNA splicing[16]. Upon literature search of PubMed, "lncRNA" + "MALAT1" results in 1,335 records in the past 5 years. Adding the term "glioblastoma" results in 21 records.

MALAT1's relationship to GBM as a protooncogene and/or tumor suppressor depends on its interactions with several miRNAs[15]. Acting as a molecular sponge or decoy for miRNA-101, MALAT1 increases chemoresistance to temozolomide through enhanced epithelial-mesenchymal transition (EMT) and reduces apoptosis through downregulation of Ras-related protein RAP-1b (Rap1B)[12,17]. However, MALAT1-mediated repression of miR-155 suppresses tumor growth via ERK/MAPK and MMP2 signaling suppression and subsequent increases in FBXW7 transcript levels[18]. Further, MALAT1 sequestration of miR-101 was also found to affect levels of MGMT and Glycogen synthase kinase-3 beta (GSK3B), which both decrease with suppression of MALAT1 indicating another potential link to TMZ sensitivity[19].

A recent study found that the RNA modification - N6-methyladenosine (m6A) is elevated in GBM and occurred at a high frequency in MALAT1[20]. MALAT1 affects glioma stem cell viability and proliferation through upregulation of sex determining region Y-box 2 (SOX2)[21]. MALAT1 has also been implicated in aberrant metabolism including a potential role in hyperglycemia-related tumor progression for patients with both diabetes mellitus and GBM[22]. In GBM-diabetes mellitus patient-derived cells, GLUT3 suppression induced

SOX2 and MALAT1 expression influencing the migratory/invasive potential of glioma cells[23]. MALAT1 expression has been found to be positively correlated with GBM tumor aggressiveness, independent of IDH mutation suggesting a potential prognostic role of MALAT1 in GBM[24]. In another study of adult and pediatric GBM, high MALAT1 expression was found to coincide with the presence of TERT C228T mutation predicting poorer overall prognosis[25]. MALAT1 expression concurrent with TERT mutation then may be a prognostic factor or even present a novel treatment opportunity.

Co-expression analysis demonstrates that MALAT1 is associated with MRP5, TYMS, BCRP, and mTOR[26]. MALAT1 overexpression has been found in TMZ-resistant glioma cells compared to sensitive cells[27]. Silencing MALAT1 expression reduced the expression of multidrug resistance protein 1 (MDR1), multidrug resistance-associated protein 5 (MRP5), low-density lipoprotein receptor-related protein 1 (LRP1), and zinc finger E-box-binding homeobox 1 (ZEB1) indicating reduced EMT and drug resistance[28]. At the single cell analysis level, a subset of neuronal glioma stem cells was found to have higher expression of MALAT1, enriched in the nuclear fraction[29]. Importantly, recent research by Mazur et.al. has shown that neurosphere culture conditions, including the presence of fetal bovine serum, affects the abundance of MALAT1 and other lncRNA transcripts making culture conditions a potential confounding factor for its study[30]. Another study of HSV-G47Δ infected glioma stem cells demonstrated that MALAT1 among other key lncRNAs are significantly downregulated under hypoxic conditions[31]. These findings highlight the importance of research model considerations in studying lncRNAs related to GBM.

Future research into MALAT1 in the context of GBM should utilize clinically relevant *in vivo* models mimicking the current standard of care including TMZ and radiation exposure. Specifically, it is important to identify the binding partners including miRNAs and proteins associated with MALAT1 malignant processes including drug/radiation resistance. The linkage between diabetes/ hyperglycemia and MALAT1 expression could indicate a metabolic role for MALAT1 in GBM cells under nutrient depleted conditions. Furthermore, MALAT1 expression levels could be theragnostic offering insight into therapy responsiveness alone or in combination with other markers.

HOTAIR:

HOX transcript antisense intergenic RNA (HOTAIR) is located on chromosome 12q13.13 overlapping a part of the homeobox superfamily of genes (HOXD)[32]. It has been shown that interactions of the 5′ end of HOTAIR with polycomb repressive complex 2 (PRC2) can drive target gene epigenetic silencing[33]. HOTAIR has also been found in extracellular vesicles (EVs) which can be isolated from patient blood serum[34]. Upon literature search of PubMed, "lncRNA" + "HOTAIR" results in 658 records in the past 5 years. Adding the term "glioblastoma" results in 19 records.

Guo et.al. found HOTAIR abundance is positively correlated with TRPM7 expression, suggesting that TRPM7 positively regulates HOTAIR expression[35]. Further, they found that HOTAIR directly interacts with miR-301a-3p and that the sponging of miR-301a-3p resulted in upregulated expression of FOSL1. This suggests an oncogenic role for HOTAIR through disinhibition of FOSL1 increasing glioma cell survival and invasive potential. HOTAIR also interacts with miR-1 and miR-206 sponging these miRNAs to induce expression of YY1[36]. The YY1 transcription factor has been shown to regulate oncogenic processes through modulation of PI3K/AKT and Wnt signaling pathways suggesting this axis as a potential therapeutic avenue[37]. GBM subtype -specific expression levels of HOTAIR have shown higher levels of HOTAIR in classical and mesenchymal subtypes compared to neural or proneural[38]. Glioma invasion has also been linked to HOTAIR-mediated upregulation of matrix metalloproteinase-7 (MMP-7), matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF)[39].

As previously referenced, HOTAIR interacts with the PRC2 complex, specifically with EZH2 to affect gene regulation in GBM. Disruption of this interaction has been found to increase ATF3 expression inhibiting recruitment of p300, p-p65, p-Stat3 and SP1 to the MGMT promoter[40]. Yang et.al. also find that besides the suppression of MGMT, disruption of HOTAIR/EZH2 increases CDKN1A expression and impairs DNA double-strand break repair by inhibiting the ATF3-p38-E2F1 pathway. Combining EZH2 disruption with LSD1 inhibition blocks cell cycle progression by targeting CDKN1A leading to promotion of apoptosis mediated by BBC3[41].

HOTAIR is not only associated with gene repression but also serves as a scaffold for interactions with super enhancer elements[42]. Combining ChIRP-seq and RNAseq data, the authors identified 26 genes directly regulated by HOTAIR-associated super enhancers including MEST. The prooncogenic phenotype conferred by HOTAIR was rescued with MEST overexpression in a HOTAIR KD model. HOTAIR expression in GBM tissues can also be mediated by EVs containing HOTAIR transcripts which are transferred between cells, conferring TMZ resistance[34]. This is accomplished by sponging miR-256b-3p which in turn upregulates epithelial V-like antigen 1 (EVA1). Furthermore, HOTAIR has been found to stably exist in serum exosomes potentially suggesting diagnostic value in GBM[43]. HOTAIR has recently been found to promote GBM cell invasion via β-catenin signaling[44]. This along with activation of NF-κB signaling facilitates immune escape making HOTAIR a potent oncogene and potential therapeutic target in GBM[45]. Co-therapy with anti-peroxisome proliferator-activated receptor alpha (PPARα) and si-mediated HOTAIR KD was shown to inhibit invasive and proliferative potential *in vitro*[46].

Collating this evidence suggests strongly a potential therapeutic and theragnostic role for HOTAIR in GBM. The stability of HOTAIR in serum EVs could be used as an indicator of minimal residual disease (MRD) in clinical studies. This could be useful for predicting recurrence and measuring therapeutic response. Further clinical and *in* vivo research is needed to evaluate HOTAIR as a biomarker for GBM and other cancers.

ZFAS1:

Zinc Finger NFX1-Type Containing 1 (ZNFX1) antisense RNA 1 (ZFAS1), like other lncRNAs, possesses RNA:RNA and RNA:DNA binding potential[13]. ZFAS1 is found on chromosome 20q13.13, has 14 transcripts created through alternative splicing, and is considered an oncogene in most types of cancer[47]. ZFAS1 also has an open reading frame which is translated into a small peptide with prooncogenic functions in hepatocellular carcinoma[48]. ZFAS1 is also implicated in multiple non-neoplastic conditions such as arthritis and epilepsy[47]. Upon literature search of PubMed, "lncRNA" + "ZFAS1" results in 163 records in the past 5 years. Adding the term "glioblastoma" results in 1 record.

ZFAS1 overexpression in glioma is associated with ascending histologic grades, poor prognosis, and increased tumor size[49]. ZFAS1 in glioma and other cancers seems to exert regulatory control through interactions with numerous miRNAs[47]. In gliomas, ZFAS1 through miRNA sponging seems to modulate HK2 expression as well as regulating the expression of proteolipid protein 2 (PLP2)[47, 50]. ZFAS1 was also found to have positive correlations with stemness-related gene MAPRE2 while having simultaneous negative correlation with cell-cycle gene RFC3[13]. In this study, ZFAS1 generally was upregulated in radiation resistant tumors verse radiation sensitive tumors. This evidence suggests that ZFAS1 could serve as a "master" regulator of multiple oncogenic processes in GBM including mediating therapy resistance. m6A (N6-methyladenosine) modifications in ZFAS1 were also found to have significant positive correlation in glioma[51]. It is possible then that RNA modifications, such as m6A may be associated with regulation of ZFAS1 and of GBM pathogenesis. ZFAS1 thus is an ideal candidate for further characterization in the context of GBM.

If it is to be believed that ZFAS1 could be a regulator or switch in GBM for multiple oncogenic processes, then future research should explore the effects of KD or OE of ZFAS1 in GBM models. Furthermore, identifying and validating ZFAS1 binding partners as well as binding/triplex sites in euchromatin regions will shed further light on this lncRNAs role in oncogenic processes.

SOX2OT/SOX2-OT:

SOX2OT is located proximal to sex determining region Y-box 2 (SOX2) on chromosome 3q26.33. Several studies suggest that SOX2OT acts as a molecular sponge for miRNAs, thus affecting downstream regulation of various pathways[52, 53]. In non-small cell lung cancer (NSCLC), SOX2OT sponging of miR-30d-5p upregulates PDK1 expression driving PD-L1 checkpoint escape through the mTOR signaling pathway[54]. Also in NSCLC, it was found that SOX2OT played an oncogenic role by regulating miR-122-3p/FOXO1 and miR-194-5p/FOXA1 as a miRNA molecular sponge[53]. SOX2OT has been found to promote stemness of neoplastic cells in NSCLC and in esophageal squamous cell carcinoma (ESCC)[55, 56]. A number of studies across cancers have suggested that SOX2OT plays a role in regulating its neighboring SOX2 gene[53,57,58]. SOX2 and two splice variants of SOX2OT (SOX2OT-S1 and SOX2OT-S2) are co-upregulated in brain tumors (gliomas, meningiomas and pituitary adenomas) as well as in ESCC[59, 60]. Upon literature search of PubMed, "lncRNA" + "SOX2OT" results in 89 records in the past 5 years. Adding the term "glioblastoma" results in 5 records.

SOX2OT was shown to be upregulated in GBM patients verses normal controls[26]. SOX2OT expression is associated with TMZ chemoresistance in glioma cells[61]. Loss or suppression of SOX2OT in glioma cells resulted in decreased viability when treated with TMZ. This suggests that SOX2OT is involved with TMZ sensitivity and glioma cell proliferation. Further, in this same study RIP-qPCR showed that SOX2OT co-precipitated with ALKBH5, an RNA demethylase which can affect m6A modifications[61]. SOX2OT may therefore act as a scaffold for this and other epigenetic/post-transcriptional modifiers. SOX2OT has been shown to decrease in expression in radiation resistant GBM patient-derived xenografts (PDX) compared to radiation sensitive cells[13]. Another study found that SOX2OT sponges miR-192-5p which helps activate ERK signaling via RAB2A increased expression[58]. Elevated ERK signaling in turn promotes glioma growth and cell proliferation. A recent study of several lncRNAs found that *in vitro* microenvironment influences the molecular profile and phenotype of glioma cells[26]. This again highlights the importance of patient-derived tumor models' ability to recapitulate the patient tumor environment. This and evidence in other cancers suggest that SOX2OT could be a potent oncogene in GBM and could represent a novel therapeutic avenue for treating these tumors.

Delineating the roles of SOX2Ots splice variants in GBM is an important future direction. Identifying the binding partners of the splice variants may facilitate understanding of their roles in oncogenic processes and inform therapeutic designs for siRNA or RNAi agents. Findings in other cancers such as NSCLC and ESCC could be used to guide or inform conserved oncogenic functions of SOX2OT in brain tumors.

CASC19/ PCAT2:

Cancer susceptibility 19 (CASC19) or prostate cancer-associated transcript 2 (PCAT2) can be found on chromosome 8q24.21. Unlike other longer lncRNAs such as MALAT1 or KCNQ1OT1, CASC19 is a mere 324bp in length[62]. CASC19 has been found to be oncogenic in a number of human cancers, and it has been identified as a key gene regulating radiosensitivity and response to radiotherapy[13, 62]. In nasopharyngeal carcinoma, it has been found to enhance radioresistance by augmenting AMPK-mTOR signaling and as a molecular sponge through the miR-340-3p/FKBP5 axis[63,64]. In NSCLC CASC19 was found as part of a

radioresponse-related gene expression signature predicting risk classification and prognosis[65]. Furthermore, CASC19/PCAT2 has been found to be associated with increased chromatin instability through local ectopic recruitment of centromere associated proteins CENP-A/C[66]. Recent evidence suggests CASC19 as a potential therapeutic target in human neoplasms as well as a potential role as a biomarker for therapeutic response and diagnosis. Upon literature search of PubMed, "lncRNA" + "CASC19" OR "PCAT2" results in 29 records in the past 5 years. Adding the term "glioblastoma" results in 0 records.

CASC19 expression was significantly upregulated in glioma which was also positively associated with tumor diameter and pathological grade[67]. This study further found that CASC19 promoted glioma cell proliferation and metastasis, purportedly through sponging miR-454-3p which targets RAB5A. CASC19 has also been found upregulated in an EGFRVIII mutant model of radiation resistance potentially suggesting a relationship between EGFR mutant GBM and CASC19-mediated radioresistance[13]. The relative lack of research around CASC19s potential role in glioma in the past decade makes this a promising, novel area of research meriting further exploration.

CASC19 may be a small transcript compared to other oncogenic RNAs; however, it merits further study into the potentially broad impacts of this transcript especially in the context of therapy resistance. Its relationship and role in chromatin instability could be explored utilizing ATACseq and CHIPseq protocols in the context of CASC19 OE. This transcript's miRNA-mediated regulatory roles in GBM may also be informed by findings in other neoplasms. Furthermore, the potential association between EGFRVIII and CASC19 should be validated and explored.

SAMMSON/ LINC01212:

The lncRNA SAMMSON (Survival Associated Mitochondrial Melanoma Specific Oncogenic Non-coding RNA) formerly known as LINC01212, can be found in chromosome region 3p13-3p14[68]. SAMMSON contains 4 exons and has 28 or more transcripts produced through alternative splicing[69]. In melanoma, SAMMSON has been found to mediate adaptive resistance to RAF-inhibition therapy[70]. SAMMSON promotes uveal melanoma progression by interacting with various proteins involved in mitochondrial translation, promoting mitochondrial function[71]. It has also been found to regulate chemosensitivity in breast cancer cells[72]. Upon literature search of PubMed, "lncRNA" + "SAMMSON" results in 16 records in the past 5 years. Adding the term "glioblastoma" results in 3 records.

In GBM cells, the knockdown of SAMMSON was found to result in the inactivation of malignant signaling of the PI3K/Akt pathway[73]. In this study, it was found that SAMMSON affects GBM cell viability, invasive potential, and antiapoptotic mechanisms. Additionally, SAMMSON has been shown to have increased expression in radiation resistant cells compared to parental sensitive cells[13]. Also, SAMMSON has been found upregulated playing a role in promoting cell proliferation in GBM cells through its interactions with miR-622[74]. Like CASC19, SAMMSON is relatively understudied in the context of GBM or glioma. This again represents an opportunity area for new research to explore further.

Identification and quantification of SAMMSON splice variants in brain tumors should be explored further. Understanding the prevalence and function of specific splice variants could inform targeted drug design. SAMMSONs role in therapy resistance and prooncogenic processes could be related to specific splice variants and their binding partners. Specifically, further research is indicated for the role of SAMMSON in GBM cell survival and radiation resistance.

Conclusions:

The elucidation of lncRNA function should be multifactorial. The genetic loci proximal to the encoding portion of a lncRNA is important, as are the transcripts inherent RNA, DNA, and protein

interaction(s). RNA:DNA predicted interactions can be numerous resulting in a host of potential lncRNA targets on the genome-wide scale. lncRNAs can act as enhancer elements for gene expression in cis or in trans. It is important to filter these potential interaction loci by matching lncRNA interactomes with RNAseq, CHIPseq, ATACseq, and other profiling methods. Methods such as CLIP (Cross-linking and immunoprecipitation) or ChIRP (Chromatin Isolation by RNA purification), and variations thereon, can be combined with NGS approaches to begin translating the lncRNA code and to elucidate functional roles of these transcripts. Functional screens and reporter assays can further reduce the lncRNA-interactome to home in on biologically relevant roles of lncRNAs in tissues and cancer. Furthermore, cellular regulation by lncRNAs almost certainly occurs in a spaciotemporal manner depending on cell cycle, subcellular localization, and cellular metabolism in a manner which is also cell/tissue specific. lncRNAs can also host multiple alternatively spliced transcripts and several open reading frames for small peptides. As such, lncRNA regulation belies levels of complexity which are not always immediately appreciated. Another potential barrier to lncRNA research is a lack of accurate preclinical models and the influence of cultivation conditions on models of glioma in the lab. Further research into the creation of preclinical models for GBM which recapitulate patient conditions remains of paramount importance.

To conclude, GBM pathophysiology has been shown to involve regulation by lncRNAs. These abundant, heterogeneous transcripts are potent regulators of gene and epigenetic regulation. Decades of research in GBM have not resulted in significant improvements in survival metrics for patients. lncRNAs may represent a promising therapeutic avenue for the future treatment of GBM. Some lncRNAs in particular: SOX2OT, ZFAS1, CASC19, and SAMMSON show evidence of involvement in GBM, but have not been thoroughly investigated in this context. More research into the lncRNA transcripts highlighted herein as well as into lncRNAs generally is indicated to expose novel theragnostic and therapeutic potential of these transcripts in gliomas.

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