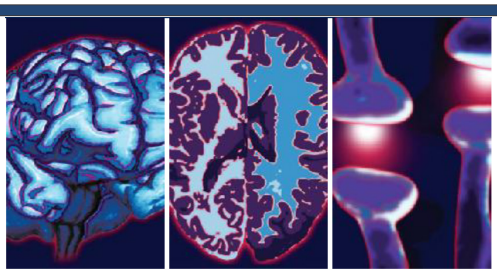
Review Article



Overview of the Multifaceted Functions of lncRNA HOTAIR in Glioblastoma.

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ABSTRACT

Glioblastoma is an aggressive primary brain tumor. Recurrence is a major clinical problem. Several biological features favor recurrence of these tumors following surgery. Therapies to prolong survival are not completely effective. Non-coding genetic elements play a key role in the process of gliomagenesis. Non-coding RNAs are novel regulatory RNAs that play key roles in various processes as gene regulation, cell differentiation, and proliferation. Interestingly, some lncRNAs may act as tumor suppressors while others are oncogenic. In this review, we are going to illustrate the role of a well-known lncRNA HOX Transcript Antisense Intergenic RNA (HOTAIR) in glioma and highlight the possible functions in glioma.

Keywords: Glioblastoma, long non-coding RNAs, microRNAs, brain tumor

Introduction

Glioblastoma Multiforme (GBM) is a primary brain tumor notorious for aggressive behavior [1]. The survival rate after one year is about 39.7% with a high rate of recurrence [2]. The recurrence of GBM is a complex multifactorial process. The best outcome reported was related to the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) clinical trials [3]. Epigenetics are extensively involved in the virulence of GBM. Several factors contribute to treatment failure such as the heterogeneity of the GBM microenvironment, repository of stem cells with great regenerative activity, and developing resistance to common therapies.

Non-coding RNAs (ncRNAs) are recent classes of RNA molecules that play essential roles in different processes as gene regulation, cell differentiation and growth [4]. The non-coding elements represent a large moiety of the human genome, however, its main functions are poorly understood [5,6]. The mechanism through which ncRNA regulates biological functions needs to be more elucidated. Non-coding RNA is classified into short and long types according to the nucleotide length. Small ncRNAs (20-200 nucleotides) include microRNAs (miRNAs), small nuclear RNAs (snRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), Piwi-interacting RNAs (piRNAs) [7].

Long non-coding RNAs are composed of more than 200 nucleotides and could control genes that regulate the cell cycle, apoptosis, and cellular growth [8]. Mounting research

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suggests a possible role of lncRNAs in different cancers including glioma [9]. For example, a lncRNA Nuclear Enriched Abundant Transcript 1 (*NEAT1*) enhances invasion of GBM cells and inhibits apoptosis [9]. Another lncRNA H19 was found to correlate with glioma grade and invasiveness [10]. The Tumor Suppressor Candidate 7 (*TUSC7*), is a LncRNA that inhibits invasion and migration of glioma cells and correlates with prognosis [10,11]. In this review article, we are going to highlight the potential roles of a well-known lncRNA HOX Transcript Antisense Intergenic RNA (HOTAIR) in glioma.

Literature Review

▪ Mechanism of action

The lncRNA HOX Transcript Antisense Intergenic RNA (HOTAIR) was the first *lncRNA* to be identified [12]. It relates to the homeobox super-families and comprises 2158 nucleotides. It is transcribed from the *HOXC* locus on chromosome 12q13.13 [13]. Polycomb-Repressive Complex 2 (PRC2) is a chromatin modifying complex and a binding target for HOTAIR [14]. PRC2 complex induces lysine methylation on histone H3. *H3K27* methylation is considered a gene silencing way and is assisted by histone methyl transferase (Enhancer of Zeste Homolog 2 (*EZH2*) [15]. Through interaction with histone lysine-specific demethylase (*KDM1*), HOTAIR can silence different genes [16].

KDM1 can combine with RE1-Silencing Transcription factor (REST) and cofactor Corepressor for Element-1-Silencing Transcription Factor (CoREST) to promote gene silencing. In early embryo life, HOTAIR is expressed in certain locations such as hind limb bud, and posterior trunk. HOTAIR also can regulate the cell cycle proteins through controlling Cyclin-Dependent Kinase 2 (*CDK2*), *CDK4*, and Cyclin D1 [17]. Aberrant HOTAIR expression has been correlated with growth, and recurrence by affecting downstream targets [18-20].

▪ Molecular interactions involving HOTAIR in GBM

HOTAIR exhibited oncogenic potential in breast and renal cancer by enhancing cell proliferation, suppressing apoptosis, and promoting invasion [21,22]. HOTAIR was expressed in glioma at a high rate compared to normal brain tissues [23]. A certain study showed that HOTAIR knockdown dismantled GBM mouse model [24]. HOTAIR is highly expressed in both classic and mesenchymal glioma subtypes compared to neural and proneural subtypes [25]. HOTAIR was identified as a marker that correlates for tumor grade and outcome given the fact that low-grade glioma has lower expression levels of HOTAIR compared with high-grade tumors [25]. Studies evaluating the role of HOTAIR in GBM are summarized in Table 1.

Table 1: A sample of experimental studies investigating HOTAIR in glioblastoma.

Role of HOX Transcript Antisense Intergenic RNA (HOTAIR)	Reference
HOTAIR inhibits the transcription of Neuroleukin (NLK) in U87, Glioblastoma Multiforme (GBM) cells, regulate Wnt/β-catenin pathway, inhibit cell cycle arrest and promote cell migration.	[70]
HOTAIR mRNA levels are increased in A172 glioma cells compared to normal astrocytes.	[71]
miR-141 directly binds to the 3 UTR of HOTAIR in U251 and U87 glioma cells, inhibiting its expression.	[72]
miR-148b-3p downregulates the expression of tight junction-related proteins including ZO-1, clauidin-5, and occludin.	[69]
HOTAIR rs920778 and rs12826786 frequencies do not differ between glioma patients and controls.	[73]
HOTAIR levels positively correlate with Matrix Metalloproteinase-7 (MMP-7), Matrix Metalloproteinase-9 (MMP-9), and Vascular Endothelial Growth Factor (VEGF) levels in human glioma.	[74]
HOTAIR upregulates the expression of hexokinase 2 by downregulating miR-125.	[75]
HOTAIR is upregulated in temozolomide-resistant GBM cells. Serum exosome HOTAIR levels are higher in GBM patients' resistant to temozolomide compared with responders.	[68]

HOTAIR activity could be controlled by other ncRNAs. Homeobox Protein A9, (*HOXA9*) stimulates the expression of HOTAIR in glioma.

The upregulation of HOXA9 was associated with abnormally aggressive behavior [26]. As mentioned before, HOTAIR can induce gene silencing depending on *EZH2*, meanwhile, *HOXA9* is regulated by the Phosphatidylinositol 3-Kinase (PI3K) pathway and the inhibition of *EZH2*-mediated histone methylation [23, 27].

Another study evaluated the role of Programmed Cell Death Protein 4 (PDCD4) in the progression of GBM. The overexpression of PDCD4 in glioma cells down regulated cellular proliferation suggesting that PDCD4 could function as a tumor suppressor.

Lower expression levels of PDCD4 are associated with upregulated Histone H3 methylation mediated by HOTAIR [28]. Exposure of glioma cells to a Bromodomain and Extra-Terminal (BET inhibitor) (I-BET151) downregulated the expression of HOTAIR and halted cell proliferation through cell cycle arrest. Moreover, the upregulation of HOTAIR abolished the anti-cancer effect of I-BET151. [29].

The role of HOTAIR as a tumor suppressor gene needs further scrutinization [30].

▪ HOTAIR can influence cell-cycle related genes in GBM

Long non-coding RNAs (lncRNAs) can regulate the cell cycle through several ways [31,32]. Antisense Noncoding RNA in the INK4 Locus (ANRIL), for example, downregulates p15INK4B expression, and Metastasis Associated Lung Adenocarcinoma Transcript (MALAT1) controls B-MYB that controls cell cycle progression [33,34].

In LN229 and U87 cells, the downregulating HOTAIR resulted in G0 or G1 stage block [35]. The downregulation of Cyclin D1, Cyclin E, Cyclin-Dependent Kinase 2 (*CDK2*), *CDK4*, and the enhanced expression of other proteins such as p21 and p16 was associated with HOTAIR downregulation. HOTAIR regulates a group of 18 genes that constitute a cell-cycle related mRNA network. HOTAIR controls cell cycle in glioma cells by regulating Forkhead Box Protein M1 (FoxM1) and Aurora Kinase B (AURKB) that are involved in mitosis. Several genes such as *ASPM, NCAPG, CDC6, CHEK1, CEP55* play a role in gliomagenesis, through their effect on cell cycle progression [36-39].

HOTAIR affected the expression of some cell-cycle related genes such as *CDC6, NCAPG, CENPE*, and *PLK4*. As mentioned earlier, HOTAIR can induce gene silencing depending on *EZH2* through histone methylation [40]. *EZH2* inhibition was reported to stop cell cycle progress at the G0 or G1 phase of GBM cells favoring it as a therapeutic target.

▪ Prominent interactions of HOTAIR with micro-RNA in GBM

lncRNAs can control the activity of several mRNAs [41]. lncRNAs can compete with micro RNAs displacing them from binding sites [42]. In breast cancer, HOTAIR miR-7 relation is a clear example and in gastric cancer, its pro oncogenic effect was through competing with miR-331-3p [42,43].

HOTAIR/*miR-326*: A study has shown that the expression of *miR-326* is downregulated in glioma tissues. Knocking down HOTAIR resulted in the overexpression of *miR-326* which resulted in downregulating Fibroblast Growth Factor 1 (FGF1) in U87 cells impacting cellular proliferation (Figure 1).

HOTAIR/*miR-15b*: A study found that HOTAIR reduced *miR-15b* expression in glioma cells which may have oncogenic potential [44]. miR-15b could upregulate p53 expression. HOTAIR, *miR-15b*, and p53 is a closed loop that controls glioma progression.

HOTAIR/*miR-125a*: *miR-125a-5p* was reported to inhibit glioblastoma cell proliferation, and HOTAIR has been demonstrated to reduce *miR-125a* expression [45,46]. Schisandrin B, an herbal extract, reduced HOTAIR expression in glioma cell lines by targeting the mammalian Target of Rapamycin (mTOR) expression [47].

HOTAIR/*miR-219*: *miR-219-5p* inhibits glial cell proliferation by targeting tyrosine kinase and Epidermal Growth Factor Receptor Mutation (EGFR) [48]. HOTAIR has been also shown to inhibit *miR-219* in U87 cells, resulting in increased Cyclin D1 levels and cellular proliferation [49].

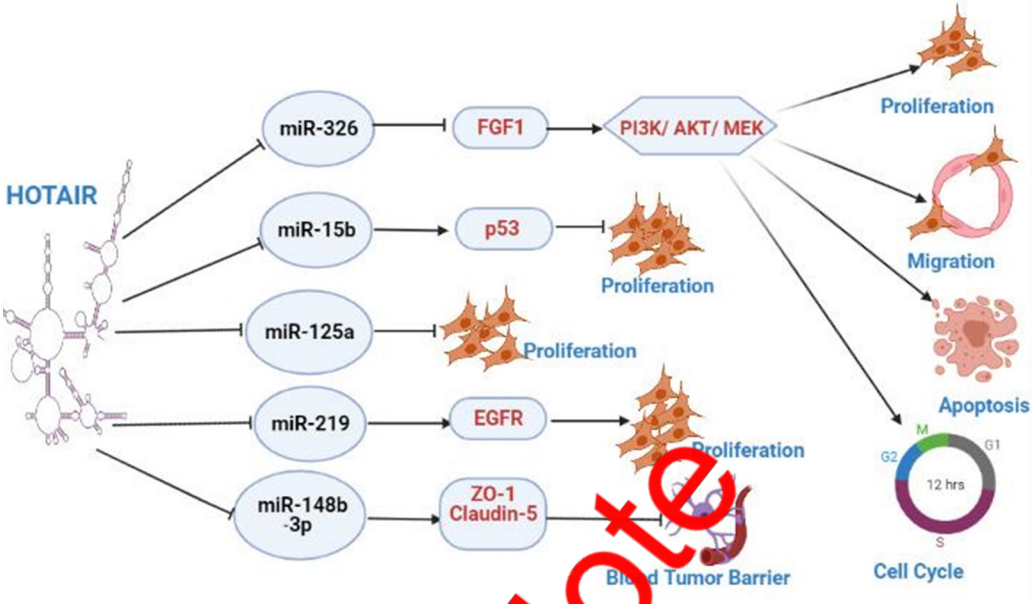

Figure1: HOTAIR can interact with several other non-coding mRNAs and affect their activities which eventually affect cellular proliferation, apoptosis and cell cycle. *MiR-326* inhibition resulted in decreased Fibroblast Growth Factor 1 (FGF1) that mediates the activity of the pathway Phosphatidylinositol 3-Kinase (PI3K)/AKT/MEK which affects proliferation, migration and apoptosis. *MiR-15* inhibition by HOTAIR will affect the level of p53 which is a tumor suppressor gene. Inhibition of *miR-148b-3p* by HOTAIR results in decreased expression of tight junction proteins which affects the tumor brain barrier permeability.

Discussion

▪ HOTAIR and angiogenesis

Angiogenesis is controlled by hypoxia mediators, the most well-known ones are Hypoxia Inducible Factor (HIF) and Vascular Endothelial Growth Factor (VEGF) [50,51]. Both HIF and VEGF work together to promote a vascular niche for glioma cells. In nasopharyngeal carcinoma cells, HOTAIR enhanced angiogenesis by activating the transcription promoter of Vascular Endothelial Growth Factor A (VEGFA) [52]. It may act through the formation of extracellular vesicles as it was detected in the supernatant of GBM culture [53]. Comprehensive studies are needed to evaluate the role of HOTAIR in terms of glioma vascularization.

▪ Potential use of HOTAIR as a diagnostic marker in GBM

An absolute need for a non-invasive accurate marker for clinical implications in patients diagnosed with high-grade gliomas is demanding. The possibility for certain body fluid markers to be used for clinical prediction of glioma is still under investigation. Markers that can monitor response to therapy are essential especially for an aggressive disease like GBM. Differentiating true GBM recurrence from pseudo-progression seems difficult and technically challenging. Conventional Magnetic Resonance Imaging (MRI) could not easily pick the exact differences between both conditions. A serum biomarker could be a tool to aid in the clinical differentiation in both situations.

Glial Fibrillary Acidic Protein (GFAP), lactate, *miR-504*, have been reported as potential candidates for diagnosing GBM [54-56]. The stability of lncRNAs secondary structures makes them perfect biomarkers [57]. HOTAIR has been identified as a possible serum marker in other cancers [58,59]. Its concentration was lower after the surgical treatment of a recurrent GBM and the reduction was more noticeable further weeks after surgery. Further experimental and clinical work should be implemented to evaluate the sensitivity and predictability of HOTAIR as a novel serum biomarker in patients diagnosed with GBM.

▪ HOTAIR as a potential therapeutic target in GBM

As discussed earlier, HOTAIR can regulate glioma progression in an EZH2-dependent

manner through epigenetic role. Therefore, targeting of HOTAIR-EZH2 interaction may be utilized as a possible therapeutic approach. *AC1Q3QWB* that targeted HOTAIR-EZH2, was found to inhibit glioma cell proliferation, with a resultant increase in CWF19L1 that works as a tumor suppressor gene [60,61]. The Bromodomain and Extra-Terminal (BET) proteins are epigenetic modulators that have been used as therapeutic tools for some cancers with profound epigenetic changes [62]. In a published study, I-BET151 treatment and *BRD4* depletion reduced the overexpression of HOTAIR in glioma cells through an effect on transcription factors [63].

RNAi are tools that could inhibit specific genes, including short interfering RNAs (siRNAs) which are short double-stranded RNAs targeting complementary RNA molecules, resulting in gene suppression [64]. Carriers of nucleic acids could be used to deliver these siRNAs into tumor cells. Due to their high stability, iron oxide nanoparticles and specifically Super Paramagnetic Iron Oxide Nanoparticles (SPIONs) have been used widely in the delivery [65]. A study has demonstrated the successful delivery of siHOTAIR that subsequently inhibited glioma stem cell proliferation [66]. In a study by Zhang et al., deleting the HOTAIR regulatory element improved the sensitivity of glioma cells to Temozolomide. [67].

In Temozolomide-resistant GBM cells, HOTAIR was upregulated, while temozolomide resistance was enhanced upon the exosome-mediated transfer of HOTAIR by a mechanism involving *miR-519a-3p* downregulation [68-70]. Poor penetration of the blood-brain barrier and failure to achieve a maximal intratumoral concentration is a common hurdle facing chemotherapy. HOTAIR knockdown resulted in improving brain-tumor barrier permeability by a mechanism involving the *miR-148b-3p* targeting. *miR-148b-3p* affects the microvascular endothelial cells which control the expression of proteins involved in Blood-Brain Barrier (BBB) integrity as Zonula Occludens (ZO-1), Claudin-5, and Occludin [71-75].

Conclusions

There is a compelling need for clinical studies that could uncover the HOTAIR role in GBM. Therapies to prolong survival in patients diagnosed with GBM are traditional and their effect on survival is not remarkable. More understanding of the biology of HOTAIR will enable researchers to develop new strategies and diagnostic markers that will eventually apply in clinical trials. Elevated expression of HOTAIR in glioma correlates with higher tumor grade and poor prognosis. Mechanistically, HOTAIR influences the expression of several cell cycle-related genes and interacts with various microRNAs, contributing to tumor growth, resistance to apoptosis, and increased invasion. Targeting HOTAIR-*EZH2* interactions, utilizing RNA interference strategies, and employing BET inhibitors like I-BET151 have shown potential results in preclinical models.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization about the material described in the manuscript.

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