A quantitative study of two critical lncRNAs in patients with glioma

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Background

Glioma is one of the most common types of central nervous system tumors, which includes low-grade (I & II) and high-grade (III & IV) tumors. Low-grade gliomas are generally slower-growing tumors than account for 10% of intracranial tumors and 20% of all gliomas. High-grade gliomas (Malignant gliomas) account for approximately half of the primary brain tumors and 80% of Gliomas.

Clinical presentation: The presenting symptoms are classified as generalized or focal. Headache in high grades and seizures in low grades are more common.

Diagnostic workup: The initial workup of patients with brain tumors must include a comprehensive history, physical examination, and diagnostic imaging. MRI is the imaging modality of choice for most CNS tumors. MRI with Gadolinium provides an improved ability to discern tumors from other pathologic entities, one tumor type from another, and putatively higher from lower grade malignancies.

Pathology: Recent advancement in molecular biology in CNS tumors has dramatically changed the diagnosis and treatment of these tumors. In 2016 WHO revised its classification system for pathologic subtypes of CNS tumors to combine histology with molecular parameters such as IDH1 mutation, 1p19q co-deletion, and H3 K27M mutation for gliomas.

Due to the recent genomic approaches that have had a profound effect on our understanding and classification of brain tumors, we did this investigation on two important lncRNAs including MEG3 and MDC1-AS1 to evaluate their expression in gliomas and their possible role in creation, promotion and even management of these tumors including precise diagnosis and dedicated treatment such as targeted therapy.

lncRNAs are non-protein coding transcripts that overstep 200 nucleotides in length. By complementary base pairing with mRNAs or forming complexes with RNA binding proteins (RBPs) may consolidate mRNA stability and splicing. Also, They participate in the ceRNA network. A remarkable topic for lncRNAs is their potential ability for induction or suppression of tumorigenesis in numerous types of well-known tumors such as gastric, colorectal and, breast cancers.

Results

Our investigation indicates that lncRNAs, including MEG3 and MDC1-AS1, are down-regulated (p-value = 0.001) in high-grade tumors (Grades III & IV) in comparison to low-grade tumors (Grades I & II) and non-tumoral tissues.

![Figure 1](image1.png)

Figure 1. Methylation imaging staining of brain tumors

- High-grade glioma demonstrating an enhancing lesion with central necrosis and tumor necrosis.
- Low-grade glioma illustrating a non-enhancing lesion.

![Figure 2](image2.png)

Figure 2. (A) Low-grade glioma (B) High-grade glioma (GBM)

Material & Methods

- 150 paraffin-embedded tissue blocks were provided.
- Total RNAs were extracted and Complementary DNA (cDNA) synthesis was done.
- qPCR was used to evaluate the expression of lncRNAs.
- Statistical analysis was done.

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<tr>
<th>lncRNA</th>
<th>Glioma Patients (n=37)</th>
<th>Control (n=5)</th>
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<tr>
<td>Age</td>
<td>Mean ± SD (years)</td>
<td>63.7 ± 4.6</td>
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<tr>
<td>Grade</td>
<td>Low (grade I &amp; II)</td>
<td>16-57</td>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>35 (94.5%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>4 (10.85%)</td>
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<tr>
<td></td>
<td>Total (n)</td>
<td>39 (100%)</td>
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<tr>
<th>lncRNA</th>
<th>MEG3 (p-value)</th>
<th>MEG1 (p-value)</th>
<th>MDC1-AS1 (p-value)</th>
<th>MEG1-AS1 (p-value)</th>
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<td>High-grade glioma</td>
<td>0.027</td>
<td>0.019</td>
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</tbody>
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![Figure 3](image3.png)

Table 3. lncRNA expression in gliomas

![Figure 4](image4.png)

Figure 4. Relative gene expression of MEG3 and MDC1-AS1.

Discussion

Genomic approaches have had a profound effect on our understanding and classification of brain tumors. After completion of numerous large-cohort sequencing studies, a consensus list of mutant oncogenes and tumor suppressors has been forming for most disease entities. Although many mutations are found commonly across the entire landscape of neoplasia, a significant fraction is specific to individual tumor types.

According to these findings, in 2016, WHO revised its classification system for pathologic subtypes of CNS tumors to combine histology with molecular parameters, such as IDH1 mutation, 1p19q co-deletion, and H3 K27M mutation for gliomas.

Besides, recent studies indicate that molecular features may be more predictive of underlying behavior than what we knew before and are playing an increasingly important role in the clinical approach and particular treatment of glial tumors. Among these researches, numerous studies suggest non-coding RNAs could be promising diagnostic biomarkers and therapeutic targets in many cancers, including gliomas.

lncRNAs are a highly diversified group of DNA transcripts. Some studies combined computational and experimental methods to identify lncRNAs and their roles in tumor biology. The combinatorial approach could help us to discover not only the prognostic and predictive value of lncRNAs but also their therapeutic potential.

Maternally expressed gene 3 (MEG3) is a maternally imprinted gene encodes an approximately 1.6 kb lncRNA. MEG3 acts as a tumor suppressor through the accumulation of p53 protein, which activates its downstream target genes. Mediator of DNA damage checkpoint protein 1 (MDC1) acts as a robust tumor suppressor via DNA damage repair and may be involved in the carcinogenesis of cancer. MDC1-AS1 is a natural antisense transcript of MDC1, which regulates its expression and exhibits an inhibitory role on promotion glioma tumor cells through its up-regulation of MDC1.

In our research, the expression of lncRNAs MEG3 and MDC1-AS1 were down-regulated in high-grade glioma in comparison with low-grade gliomas and normal tissues significantly (p-value = 0.001). Based on our previous knowledge and these new findings, the down-regulation of MEG3 and MDC1-AS1 may correlate with higher grading of gliomas and have profound relation with lower survival in these high-grade tumors.

In conclusion, these consequences indicate that lncRNAs may have a critical role in the diagnostic and therapeutic management of glial tumors in the future, especially in the era of personalized medicine. Although for complete cognition and perception of their importance in the management of glioma, more studies and complementary investigations are necessary.

References


Conflict of Interest

The authors declare no conflicts of interest with this work.