Title: Non-coding RNA-mediated progression of IDH-mutant astrocytomas to grade 4 after treatment

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Keywords:

bioinfomatics and computational biology, cancer, microRNA, long non-coding RNA

Abstract

Low grade IDH-mutant (IDHmut) astrocytomas are heterogeneous brain tumors associated with a median overall survival of 7-10 years. However, patient survival is significantly worsened upon tumor progression to grade 4. Dysregulated non-coding RNAs (ncRNAs) have been linked to therapy resistance and invasion of the surrounding normal tissue in gliomas. Despite advances in the field, little is known about the role of ncRNAs in the progression of IDHmut astrocytomas.

We used a transcriptomic data-driven approach to uncover how ncRNAs mediate tumor progression at the molecular level. We collected matched tumor samples (before and after progression to grade 4) from six IDHmut astrocytoma patients and measured their coding and non-coding RNA expression profiles. By comparing our data with the Cancer Genome Atlas (TCGA) primary tumor cohort, and the Glioma Longitudinal AnalySiS (GLASS) longitudinal tumor cohort, we found that genes shared among all three datasets are related to cell proliferation, DNA repair and ERBB signaling. Genes unique to post-treatment progression are related to synaptic plasticity.

We calculated a Gene Regulatory Network to further elucidate the mechanisms through which noncoding RNAs contribute to the progression of IDH-mutant astrocytomas.

We found 32 differentially expressed (DE) microRNAs upon progression and identified 78 DE target genes. Gene set enrichment analysis showed that these 78 target genes were especially associated with cell proliferation. Furthermore, we observed 40 dysregulated long non-coding RNAs and 62 DE target genes enriched in neurodevelopment, cell proliferation, extracellular matrix and ERBB signaling.

A part of the ncRNAs has been previously implicated in radiation-induced responses.