Evolution of Oncogenic Signatures Within Glioblastoma Along a Spatiotemporal Axis

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Glioblastoma is a malignant tumor of the central nervous system distinguished by its intra-tumoral heterogeneity and inevitable recurrence. A longitudinal axis of genomic evolution has been identified between two spatially defined identities, tumor edge and core. This study sought to characterize this transition as a potential therapeutic target. Publicly available RNA-seq data was used to identify significant differentially expressed genes. These DEGs (n=105) were then further analyzed at both the individual gene level and at the whole genome level. Transcription factor enrichment analysis revealed the oncogenic transcription factor FOXM1 as a statistically significant mediator of downregulated target genes. Protein-protein interaction network analysis of DEGs revealed the oncogenic protein kinase MELK as over-represented within the core. The protein complex of MELK and FOXM1 has been characterized to transcriptionally regulate the enzymatic catalytic subunit EZH2, which in turn promotes radio-resistance. Clinically, the co-expression of EZH2 and MELK is induced in recurrent tumors. Small molecules and drugs that reverse this spatiotemporal gene expression signature were identified. Collectively, this systematic comparison of tumor core/edge and the identification of DEGs as critical instigators of therapeutic resistance provides a coherent portrait of the prognostically-significant shift in molecular phenotypes associated with the spatiotemporal axis. This intra-patient heterogeneity highlights the importance of eradication of the tumor edge to prevent the lethal GBM recurrence. Additionally, these data link this lethal axis to the edge-to-core transition and indicate MELK-FOXM1-driven EZH2 signaling as a therapeutic target in postsurgical GBM tumors.

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