Intratumoral Heterogeneity in Gene Expression within Single Glioblastoma Tumors

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Glioblastoma is a highly aggressive malignant tumor of the central nervous system defined by its inter- and intra-patient heterogeneity. However, understanding of molecular differences within single tumors of glioblastoma remains largely limited. This study aimed to determine whether glioblastoma tumors harbor a spatially-distinct gene program, and if so, sought to identify actionable therapeutic targets in the tumor core and edge lesions. First, transcriptional data analysis was performed using RNA-seq data of tumor specimens separated by primary/recurrence, age, and intra-tumoral spatial localization (e.g. tumor core and edge). Differentially expressed genes in both spatial groups were identified. Gene set enrichment analysis was then conducted on two sample sets of spatially annotated glioblastoma cell cultures, leading to identification of 8 oncogenic gene sets, including STK33. Gene ontology analysis found a link between core-upregulated genes to protein metabolism as well as the negative regulation of FGF receptor signaling. In contrast, the edge-upregulated genes were linked to immune/interferon and response to external stimuli. Additionally, correlation was assessed between gene expression and response to chemotherapy agents temozolomide and bevacizumab. Conclusively, the analysis of the differentially expressed genes (n=2381) exhibited the presence of the transcriptional intra-tumoral spatial edge-to-core axis, and resulted in identification of the STK33-mediated oncogenic gene set as statistically significant both in this intra-tumoral spatial identity as well as in temozolomide effectiveness. These findings may indicate a set of targetable genes that are selectively expressed within tumor core and edge.

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