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"Targeting the Cerebrovasculature to Combat Glioblastoma Multiforme"

Glioblastoma multiforme (GBM) is the most common and deadly form of primary brain cancer. Standard treatment for glioma remains surgical resection of the bulk tumor, radiation, and chemotherapy. Despite identifying the key genetic drivers of GBM, few drugs/small molecules have been found that effectively disrupt these proteins and their associated pathways, or affect the tumor microenvironment in GBM. Due to its invasive nature, total eradication of the tumor is nearly impossible, making recurrence after intervention inevitable. ***With a median survival of 15 months, and less than 6% of patients surviving more than 5 years, new paradigms for combating GBM are desperately needed.***

Two defining clinical features of GBM are a dysfunctional blood brain barrier (BBB) and excessive angiogenesis. Using a CRISPR/Cas9 native mouse, we identified progressive alteration of vessel function and morphogenesis during glioma progression. We also found that tumor stem cell derived endothelial cells are a rare subpopulation that contributes to vessels within the tumor, albeit to a limited degree. Bulk and single cell transcriptional profiling of human patient samples, patient derived xenograft (PDOX) mouse models, and a CRISPR/CAS9 native mouse model of GBM showed that a pro-angiogenic VEGF-MAPK-ETS-BRD4 signature differentiated high grade glioma from low grade glioma. Extensive endothelial heterogeneity within the tumor and tumor microenvironment defines GBM and we provide insights into the diverse cellular and molecular mechanisms that drive glioma vascularization and angiogenesis during tumorigenesis. Finally, we also show targeting this VEGF-BRD4 axis impacts glioma progression and survival in PDOX and CRISPR mouse models of glioma.

Key idea 1: GBM features extensive heterogeneity in the endothelium and tumor microenvironment.

Key idea 2: A VEGF-MAPK-ETS-BRD4 angiogenic signature distinguishes high grade glioma from low grade glioma.

Key idea 3: Targeting the VEGF-MAPK-ETS-BRD4 axis may disrupt glioma progression.