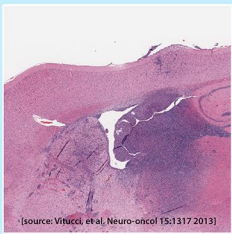




MADISON BUTLER

Faculty Research Mentor: Dr. Ryan Miller
Department of Pathology and Laboratory Medicine



H&E staining of orthotopic allograft model exhibiting characteristics of GBM

The Role of EGFRvIII and PTEN Deletion in Dynamic Kinome Reprogramming

Glioblastoma (GBM), a grade IV astrocytoma, is the most common malignant primary brain tumor. Receptor tyrosine kinase (RTK) pathways are frequently mutated in GBM, including alterations in the RTK Epidermal Growth Factor Receptor (EGFR). Moreover, EGFR variant III (EGFRvIII) is the most common activating mutation in GBM. Given its frequency, specificity, and role in promoting gliomagenesis, EGFR dysfunction is a prime target for drug treatment. However, multiple resistance mechanisms, such as co-occurrence of EGFRvIII and deletion of the tumor suppressor PTEN, prevent effective treatment via activation of alternate kinase pathways. To determine the role of EGFRvIII and PTEN deletion mutations in kinome responses to tyrosine kinase inhibitors (TKI), we examined immortalized murine astrocytes derived from non-germline genetically engineered mouse models expressing five core genotypes: wild-type EGFR + wild-type PTEN (C), wild-type EGFR + PTEN deletion (CP), EGFRvIII + wild-type PTEN (CEv3), overexpressed wild-type EGFR + wild-type PTEN (CE), and EGFRvIII + PTEN deletion (CEv3P). We used multiplexed inhibitor bead affinity chromatography and mass spectrometry (MIB-MS) and RNA sequencing to determine the baseline transcriptomes and kinomes of each genotype. We determined that cell lines exhibited differential baseline RNA expression and kinase activity as a result of EGFRvIII and/or PTEN deletion relative to C astrocytes and across genotypes. The observed differentially-activated kinases represent potential targets for dual treatment with EGFR TKI. We are currently examining changes in the kinome profile of each cell line after treatment with Afatinib, a second-generation tyrosine kinase inhibitor. These results will help define the kinase networks involved in tumor resistance to TKI and may aid in the identification of potential personalized combination therapy with EGFR TKI for GBM patients.