**Exploring phenotypic mosaicism in a mouse model of glioma to understand intratumoral heterogeneity and cellular states in GBM.**

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**Abstract**

The lethality of glioblastoma multiforme (GBM) and the failure of treatment is largely attributable to the heterogeneous properties of this cancer. We aim specifically to characterize the driving event for GBMs to acquire a heterogeneous phenotype during progression. Central to achieving this goal is the ability to interrogate possible sources of heterogeneity that guide cellular states that are similar to those identified in human patients. We therefore employ a mouse model of glioma that recapitulates the pathophysiology and gene expression signatures of human GBM. While initiated with identical oncogenic drivers, this mouse model unexpectedly displays heterogeneous phenotypes between animals. Our preliminary data using time-series single-cell transcriptomics approach shows that transformed cells, even without acquiring additional genetic alterations, switch cellular states at the beginning of tumor formation and one population commit themselves to expand to establish gliomas that are mainly comprised of one cell type. We further observe the strong association of microenvironmental cues with glioma cell populations and their roles in the state transitioning of glioma cells. Through the characterization of mechanisms that drive phenotypic mosaicism, we hope to uncover general principles that govern tumor progression and heterogeneity, and then ultimately provide novel therapeutic strategies to cure GBM.