Defining the evolutionary mechanisms of IDH-mutant glioma progression through single-cell multi-omics innovation

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Abstract: Cancer evolution constitutes a foremost obstacle to effective treatment, driving malignant cells to adapt and overcome therapy. IDH-mutant gliomas (IDH-G) illustrate the quandary of cancer evolution: despite maximal treatment, the disease invariably progress and recurs. IDH-G evolution has been characterized in bulk studies at the genetic, epigenetic and transcriptional levels, but we lack an integrative perspective of its evolution at cellular resolution. Recent single-cell RNA-sequencing (scRNAseq) profiling of IDH-G at diagnosis showed that defined cellular states, developmental hierarchies and plasticity coordinate to fuel glioma growth. How these transcriptional cell states evolve and how genetic and epigenetic alterations jointly result in the aggressive transformation of indolent low-grade gliomas to high-grade lethal tumors remains unresolved. To address this, we seek to develop and apply multi-layered single-cell genomic technologies and analytics to a unique cohort of longitudinally sampled IDH-G. To define how cellular phenotypic plasticity and clonal evolution enable IDH-G cell fitness, we will pioneer multiplex GoT (genotyping of transcriptomes), to profile multiple somatic mutations and transcriptomes in high-throughput scRNAseq and *in situ* (spatial GoT) (Aim1). We will also seek to define the epigenetic encoding of IDH-G cellular states and integrate cellular state dynamics with lineage histories of IDH-G. To that end, we will concurrently profile DNA methylation and full-length transcriptome (aim2). Altogether, this research proposal seeks to pioneer the integrative analysis of epigenetic identity with genetic and transcriptional information to systematically dissect IDH-G evolution.