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Identification of regulatory programs for glioblastoma cellular hierarchy using single- cell multi-omic profiling

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Scientific Abstract:

Glioblastoma (GBM) is the most lethal malignant brain tumor with a dismal median survival of less than 15 months. GBMs contain heterogeneous cell populations, including a glioblastoma stem cell (GSC) population that drives tumor growth and mediates therapeutic resistance. It has been postulated that the cellular hierarchy of GBM recapitulates the normal brain development program. The cell type diversity and gene expression dynamics of GBM development have been analyzed using single-cell RNA. However, the gene regulatory programs that drive GSC self-renewal and differentiation are not fully understood. This proposed project tests the hypothesis that GSCs can be identified using epigenetic signatures and that GSC differentiation is driven by cell-type specific gene regulatory programs. To comprehensively depict the regulatory and epigenetic program of GBM, we will apply two newly developed and complementary single-cell multi-omic profiling methods. The first method snmC2T-seq jointly interrogates the whole transcriptome, DNA methylome and chromatin accessibility from single nuclei. The second method sn-m3C-seq generates cell-type specific chromatin architecture maps by jointly profiling the DNA methylome and chromatin conformation. The proposed project will reveal cell-type specific gene regulatory programs that drive GBM progression and provide potential new therapeutic targets, in regulatory and epigenetic pathways, for treating GBM.

Lay Abstract:

Cell type heterogeneity is a major contributor to the therapeutic resistance of glioblastoma. The goal of this project is to understand the molecular identity of different cell types in glioblastoma tumors. Using single-cell strategies, the project will reveal the gene regulatory programs that drive the progression of glioblastoma.