August 24th 2023

Layman Summary of Progress (2022-2023)

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Background: Glioblastoma (GBM) tumors exhibit heterogeneity, evade immunotherapy, and display aggressive recurrence, leading to unfavorable clinical outcomes. This project integrates bioinformatic and genetic tools to validate GL261 and CT2A as murine models for human GBM. Additionally, these models are employed to identify gene expression regulators (namely, transcription factors) within GBM cells. The goal is to understand how heterogeneous GBM tumors can be reprogramed into uniform states.

Progress: Two distinct mouse models of glioblastoma, CT2A and GL261, were implanted into mouse brains. Subsequent single-cell transcriptomic profiling was employed to generate high-resolution data, effectively characterizing both the tumors and their surrounding microenvironment. With this approach we found that the transcriptomic profile of tumors engrafted in mice resembled human glioblastomas, and that the mouse tumors were as diverse as patient tumors, thereby supporting the validity of these mouse models. Additionally, functional genetic screenings conducted on CT2A and GL261 cells indicated that these models recapitulate several genetic dependencies unique to human GBM. This suggests that these mouse models share therapeutic vulnerabilities with their human counterparts.

Using a collection of public and in-house GBM datasets profiled using single-cell transcriptomics, we employed machine-learning methods to predict which transcription factors regulate GBM state. Using a complementary genome wide CRISPR screening approach, we also identified genes that enable glioma cells to evade killing mediated by cytotoxic T lymphocytes (CTLs), macrophages and NK cells. Although this alternate approach did not yield any additional transcription factors, it did highlight the critical role of the autophagy pathway in regulating glioma-intrinsic immune evasion.

Among the transcription factors uncovered through the bioinformatic approach, four potential candidates were identified. Genetic perturbation of these transcription factors confirmed their role in regulating glioma cell state. Ongoing efforts aim to elucidate the impact of these perturbations on the surrounding immune microenvironment within these models. The anticipated outcome of these findings is a deeper understanding of how transcription factors influence GBM states and subsequently shape the resulting immune responses.