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Genetic and Non-genetic Determinants of Cellular Architecture in IDH1-mutant Oligodendrogliomas and Astrocytomas Using Single Cell Transcriptome Analysis

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Introduction

Gliomas are among the most lethal malignancies and their histogenesis in humans remains unresolved. IDH1 mutational status and co-occurring genetic alterations define major clinical and prognostic classes of gliomas that closely mirror their histologic classification into astrocytic or oligodendroglial tumors. This suggests that distinct progenitor cells give rise to different glioma types, or conversely, that genetic mutations influence cellular lineages, generating tumors of different cellular composition.

Methods

We profiled 4,400 freshly isolated single cells from IDH1-mutant oligodendrogliomas and 7,500 single cells from IDH1-mutant astrocytomas by RNA-seq and reconstructed the architecture from consented patients. We identify distinct subpopulations of cells by coupling computational methods to find transcriptional signatures of cellular state with experimental validation using in situ RNA hybridization/immunohistochemistry. To identify subclones carrying unique genetic mutations, we combine mutation calling from whole exome sequencing on bulk tumor samples and from single-cell RNA sequencing to obtain a high-confidence set of mutations contained within subclones.

Results

We found that irrespective of their histologic sub-classification into astrocytic or oligodendroglial tumors, all IDH1 mutant gliomas share a similar cellular architecture that is distinct from IDH1 wildtype gliomas. In almost all cases, subclonal analysis defined by shared genetic mutations cause a shift in the distribution of cellular states within a tumor, but the overarching architecture is preserved. By directly comparing single cells between different glioma subtypes and from genetic subclones within the same tumor, we propose a model to decouple genetic and lineage determinants of cancer cell programs at single-cell resolution.

Conclusions

These data demonstrate that at least two contributions to glioma cellular architecture exist: 1) genetic influences, as identified by mutation and chromosomal aberrations within tumor subclones, and 2) non-genetic influences whereby progenitor-like tumor cells give rise to two dominant, more differentiated glial subpopulations of tumor cells, in a process akin to normal differentiation during neurodevelopment.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) describe the cellular architecture in IDH1 mutant gliomas using single cell RNA sequencing, 2) highlight differences in architecture between IDH1 mutant and IDH1 wildtype gliomas, 3) discuss genetic and non-genetic contributions to cellular architecture in IDH1 mutant gliomas, and 4) identify novel therapeutic vulnerabilities in IDH1 mutant gliomas based on their unique cellular architecture.

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