SINGLE-CELL RNA SEQUENCING REVEALS H3K27M GLIOMA ONCgenic PROGRAMS

Gliomas harboring histone H3 lysine 27 mutations (H3K27M) occur primarily in the midline of the central nervous system in young children. This spatiotemporal restriction suggests that H3K27M mutations may transform a specific cell type during development, but it is not clear how developmental cell states may affect susceptibility to H3K27M-mediated gliomagenesis in patients. To better understand the cellular architecture of H3K27M-positive glioma, Filbin, Tirosh, Hovestadt, and colleagues performed single-cell RNA sequencing on 2,458 cells from 6 primary H3K27M-positive gliomas. Malignant H3K27M glioma cells exhibited patterns of intratumoral heterogeneity and could be distinguished based on the expression of four main programs: cell cycle, astrocytic-like (AC-like), oligodendrocytic-like (OC-like), and oligodendrocyte precursor cell (OPC)-like programs. OPC-like cells were the most prevalent subpopulation, were enriched for cell-cycle programs, and were sensitive to depletion of the OPC lineage factor PDGFRA. Analysis of copy-number variations and inferred haplotypes in two H3K27M-positive tumors revealed distinct genetic subclones with similar developmental hierarchies.

Further, all H3K27M-positive cells displayed high expression of a unique program, including the PRC1 subunit BMI1, which provided an additional vulnerability for these tumors. Additionally, single-cell RNA sequencing of 863 cells from several glioma models—a patient-derived xenograft, gliomaspheres, and differentiated glioma cells—showed the PDX most closely resembling the primary gliomas, whereas the in vitro models recapitulated some, but not all, tumor compartments. Gliomaspheres, which partially recapitulated the OPC-like state, exhibited tumor-initiating capacity, whereas more differentiated AC-like glioma cells did not. Collectively, these findings support the importance of cellular state in the properties of H3K27M-positive glioma, with dominant stem-like OPC-like cells promoting glioma self-renewal and tumor propagation. This study also highlights that both cellular lineages and genetics provide therapeutic opportunities in this disease.

Germline *IKZF1* Variants Predispose Children to Developing B-ALL

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