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Glioblastoma functional heterogeneity and enrichment of cancer stem cells with tumor recurrence

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Abstract

Glioblastoma (GBM) is an incurable disease with high intratumoral heterogeneity. Bioinformatic studies have examined transcriptional heterogeneity with differing conclusions. Here, we characterize GBM heterogeneity and highlight critical phenotypic and hierarchical roles for quiescent cancer stem cells (qCSCs). Unsupervised single-cell transcriptomic analysis of patient-derived xenografts (PDXs) delineates six GBM transcriptional states with unique tumor exclusive gene signatures, five of which display congruence with central nervous system (CNS) cell lineages. We employ a surrogate tumor evolution assay by serial xenograft transplantation to demonstrate faithful preservation of somatic mutations, transcriptome, and qCSCs. PDX chemotherapy results in CSC resistance and expansion, also seen in recurrent patient GBM. In aggregate, these novel GBM transcriptional signatures exclusively identify tumor cells and define the hierarchical landscape as stable biologically discernible cell types that allow capture of their evolution upon recurrence, emphasizing the importance of CSCs and demonstrating general relevance to all GBM.

Keywords: F3 receptor; cancer stem cells; chemoresistance; glioblastoma; heterogeneity; hierarchy; patient-derived xenograft; recurrence; single-cell RNA sequencing; temozolomide.