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# Precancerous Cells Initiate Glioblastoma Evolution and Contribute to Intratumoral Heterogeneity

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## Abstract

Neural stem cells in the subventricular zone are identified as cells of origin harboring driver mutations in glioblastoma (GBM), which is the most devastating brain tumor with highly heterogeneous nature. However, the sequential transformation of a limited number of mutation-harboring neural stem cells into a distant tumor with high intratumoral heterogeneity remains poorly understood. In this study, we have identified transcriptionally distinct types of mutation-harboring precancerous cells in our spontaneous, somatic mouse model recapitulating human GBM evolution as well as in tumor-free subventricular zone tissues from patients. These precancerous cells emerge via oligodendrocyte lineage specification, exhibiting unique transcriptional programs involving dysregulated translations and extracellular matrix remodeling. Subsequently, they give rise to heterogeneous tumor cell populations by activating multiple programs crucial for gliomagenesis. Our findings highlight the pivotal role of precancerous cells in tumor evolution and intratumoral heterogeneity, suggesting their potential as a novel therapeutic target for GBM.

**Significance:** We identified mutation-harboring precancerous cells that emerge via oligodendrocyte progenitor cell fate specification and contribute to the evolution of GBM with intratumoral molecular heterogeneity. This single-cell atlas from the GBM mouse model and patients' tissues revealed distinct transitional states of precancerous cells and demonstrated step-wise acquisition of oncogenic programs during GBM progression. See related commentary by Lee and Suvà, p. 1312.

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