TUMORIGENESIS

The origins of glioma

The cell of origin for glioma has been an issue for discussion, with evidence pointing to neural stem cells (NSCs), or NSC-derived astrocytes or oligodendrocyte precursor cells (OPCs). Using mosaic mouse models, Liu and colleagues identify the cell of origin for glioma that is caused by inactivating mutations in neurofibromatosis 1 (*Nf1*) and *Trp53*.

> “OPCs are the cell of origin for glioma that is associated with mutations in NF1 and p53.”

To investigate the glioma cell of origin Liu and colleagues followed NSC-derived cell lineages (neurons, astrocytes, OPCs and oligodendrocytes) during tumorigenesis. They did this by using mosaic mouse models that, through tissue-specific cre-mediated mitotic recombination, generate cells in a specific tissue or cell type with homozygous mutations in *Nf1* and *Trp53* that are labelled with green fluorescent protein (GFP) and wild-type daughter cells that are labelled with red fluorescent protein (RFP). So, the authors first targeted embryonic and adult NSCs and assessed the ratio of GFP^+ cells to RFP^+ cells in each NSC-derived cell lineage. The mice developed GFP^+ tumours within ~5 months at almost full penetrance. The tumours that formed were pathologically heterogeneous, with some exhibiting astrocytic features and others showing features of malignant glioma. However, the transcriptome profiles of these tumours were similar, indicating that they were of the same lineage.

Prior to tumour development, GFP^+ cells were progressively more over-represented, and a subset exhibited an increased proliferation rate and a prolonged ability to divide compared with RFP^+ cells. The authors hypothesized that the cell lineage undergoing the most expansion and sustained proliferation was the cell of origin. They found minor or no expansion of GFP^+ NSCs, astrocytes, neurons and oligodendrocytes, whereas GFP^+ OPCs increased ~130-fold compared with RFP^+ cells and constituted the major type of proliferating mutant cells in the brain parenchyma. The GFP^+ OPCs appeared to have an impaired ability to differentiate, given that this increase was not reflected in GFP^+ oligodendrocytes (which are derived from OPCs). Further analyses showed that many of the GFP^+ OPCs were not dividing and had no pathological features, indicating that the expansion represented a pre-tumorigenic stage. Cell type-specific markers in the tumours that formed were similar to those that had been identified by previous analyses of other glioma mouse models and patient samples. Moreover, transcriptome analysis of the GFP^+ tumour cells confirmed that the cells resembled OPCs, indicating that OPCs were the cell of origin in this model.

So, can mutant OPCs produce gliomas? The authors generated mosaic mice that expressed cre under the OPC-specific chondroitin sulfate proteoglycan 4 (*Cspg4*; also known as *Ng2*) promoter. Consistent with the NSC-mosaic mice, these OPC-mosaic mice developed tumours and exhibited the same pre-tumorigenic overexpansion of GFP^+ OPCs, confirming that OPCs are the cell of origin.

Comparison to human glioma transcriptome profiles revealed that the gliomas formed in these mice correlated with the proneural subtype of human glioma. Together, these data indicate that OPCs are the cell of origin for glioma that is associated with mutations in NF1 and p53. Moreover, the mosaic mouse model provides a system with which to examine early tumorigenic changes and the cell of origin for other types of cancer.

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ORIGINAL RESEARCH PAPER Liu, C. *et al.* Mosaic analysis with double markers reveals tumor cell of origin in glioma. *Cell* **146**, 209–221 (2011)
FURTHER READING Huse, J. T. & Holland, E. C. Targeting brain cancer: advances in the molecular pathology of malignant glioma and medulloblastoma. *Nature Rev. Cancer* **10**, 319–331 (2010)