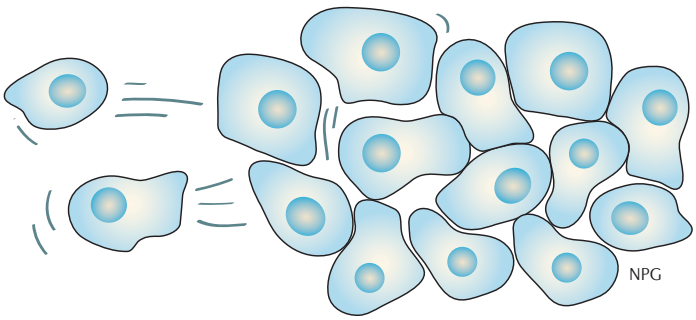
GLIOMA

Tumour cells in reverse

Previous studies have suggested that various types of progenitor or stem cells are probably the cells of origin for glioma. However, in a new study published in *Science*, Inder Verma and colleagues provide evidence that mature neurons and astrocytes can also serve as the cell of origin for gliomas, making the picture a bit more complex.

Two tumour suppressors commonly lost in glioma are p53 and neurofibromatosis type 1 (NF1; a RAS GTPase-activating protein (GAP)); indeed, the loss of both proteins causes aggressive gliomas to form in mice. Using synapsin I (*Syn1*)-Cre mice, which express Cre specifically in mature neurons, the authors first demonstrated that cortical injection of a lentivirus construct expressing short hairpin RNAs (shRNAs) against both *Trp53* and *Nf1*, as well as green fluorescent protein (GFP) and a Cre-regulated red fluorescent protein (RFP), resulted in the formation of mixed GFP^+/RFP^- and GFP^+/RFP^+ gliomas. As RFP should only be deleted in neurons, these data suggest that the tumour cells that are only GFP^+ are of neuronal origin. Lentiviral vectors expressing *Trp53* shRNA, GFP and a Cre-inducible oncogenic *Hras* ($Hras^{V12}$) — HRAS is constitutively active in gliomas following NF1 loss — produced similar results. In addition, primary neurons isolated from *Syn1*-Cre mice and transduced *in vitro* with lentivirus expressing *Trp53* and *Nf1* shRNAs could form histologically similar tumours when transplanted into immunodeficient mice. Finally, tumours also formed following injection of the lentiviral vector expressing *Trp53* shRNA and Cre-inducible $Hras^{V12}$ into calcium/calmodulin-dependent protein kinase II-α (*Camk2a*)-Cre mice, which also express Cre in mature neurons. Taken together, these data suggest that mature neurons can be transformed and can produce gliomas. Interestingly, tumours also formed following the injection of the lentiviral construct expressing *Trp53* shRNA and Cre-inducible $Hras^{V12}$ in mice expressing Cre primarily in differentiated astrocytes (glial fibrillary acidic protein (*Gfap*)-Cre mice).

> “mature neurons can be transformed and can produce gliomas”



In order to further study these tumours, the authors then looked at the expression of differentiation markers at various stages, using both imaging and gene expression analyses. At early stages, virus-transduced cells expressed the expected markers of differentiation (such as GFAP), but did not express stem or progenitor cell markers (such as nestin). However, as the tumours progressed, the expression of differentiation markers decreased concomitantly with an increase in the expression of stem or progenitor cell markers, suggesting that the cells undergo dedifferentiation. This observation was supported by an *in vitro* model. Primary astrocytes from *Gfap*-Cre mice were transduced *in vitro* with one of the two lentiviral constructs, then transplanted into immunodeficient mice. The cells in the tumours that formed primarily expressed progenitor markers, although a few cells expressed a neuronal marker. Interestingly, virus-transduced astrocytes or neurons displayed stem cell properties *in vitro*, changing their morphology and forming neurospheres in culture, and this required p53 loss combined with either NF1 loss or HRAS activation.

Are these data relevant to human gliomas? The authors found that tumours from *Gfap*-Cre or *Syn1*-Cre mice had gene expression profiles similar to those of the poor-prognosis mesenchymal subtype of human glioma, which typically exhibits loss or mutation of p53 and NF1.

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ORIGINAL RESEARCH PAPER Friedmann-Morvinski, D. *et al.* Dedifferentiation of neurons and astrocytes by oncogenes can induce gliomas in mice. *Science* 18 Oct 2012 (doi:10.1126/science1226929)