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TUMORIGENESIS

Origins

Opinion is split over whether tumours derive from stem cells or terminally differentiated cells but, for glioma, Bachoo, Maher and their colleagues now report that the cell type of origin doesn't matter — as long as a cell accumulates a defining set of mutations.

Experiments in mouse models have shown that mutations in the *Cdkn2a* gene that inactivate both its products — the tumour suppressors Ink4a and Arf — can lead to glioma formation when combined with activation of the epidermal growth-factor receptor (Egfr). This combination is more tumorigenic when Egfr is expressed in nestin-expressing neural stem cells and early glial progenitors than when targeted to mature astrocytes. Does this indicate that gliomas derive from undifferentiated cells? The authors used defined populations of neural stem cells (NSCs) and astrocytes to find out.

Inactivation of *Cdkn2a* had a more profound effect on astrocytes than it did on NSCs. Cultured *Cdkn2a*^{-/-} NSCs proliferated normally, whereas *Cdkn2a*^{-/-} astrocytes proliferated much more rapidly than those from wild-type mice, and lost their normal senescence response. Loss of Ink4a and Arf also altered the response of astrocytes to Egfr: *Cdkn2a*^{+/-} astrocytes treated with Egfr retained the features of fully differentiated astrocytes, whereas *Cdkn2a*^{-/-} astrocytes became anchorage independent and grew as 'neurospheres' — behaviour that is characteristic of NSCs. They also lost

expression of astrocyte markers and began to express NSC markers. Transfection with Egfr* — a constitutively active Egfr mutant found in human gliomas — or transfection with wild-type Egfr plus treatment with Egfr, caused dedifferentiation of *Cdkn2a*^{-/-}, but not *Cdkn2a*^{+/-}, astrocytes.

But can these cells form tumours? Injection of Egfr*/*Cdkn2a*^{-/-}, but not Egfr*/*Cdkn2a*^{+/-}, astrocytes or NSCs into the brains of immunodeficient mice led to high-grade glioma formation. Regardless of the cell type of origin, the tumours were poorly differentiated and had similar immunohistochemical profiles, indicating that astrocytes underwent dedifferentiation during tumorigenesis.

Similar tumours could also be induced in *Cdkn2a*^{-/-} mice (but not in mice that were wild type for either Ink4a, Arf or both) by infusing Egfr for seven days, confirming the specificity and cooperativity of these two pathways *in vivo*.

So, in gliomagenesis at least, it's not where you come from but where you're going that matters. Will these rules (or lack thereof) hold true for epithelial tumours? And once they've dedifferentiated, do *Cdkn2a*^{-/-} glioma cells continue to rely on activated

Egfr? As well as ending a long-standing debate, this work could have important implications for glioma therapy.

Cath Brooksbank

References and links

ORIGINAL RESEARCH PAPER Bachoo, R. M. *et al.* Epidermal growth factor receptor and *Ink4a/Arf*: convergent mechanisms for governing terminal differentiation and transformation along the neural stem cell to astrocyte axis. *Cancer Cell* **1**, 269–277 (2002)

FURTHER READING

Holland, E. C. Gliomagenesis. Genetic alterations and mouse models. *Nature Rev. Genet.* **2**, 120–129 (2001)

WEB SITE

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<http://www.hms.harvard.edu/dms/bbs/fac/depinho.html>