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GLIOBLASTOMA

Transforming fusions induce aneuploidy

PHOTODISC

> events that induce aneuploidy may be a cause of cancer

A long-standing question in cancer biology is whether aneuploidy is a cause or a consequence of cancer. Iavarone, Rabadan, Lasorella and colleagues have uncovered a recurrent oncogenic fusion protein in a subset of glioblastomas that can directly interfere with cell division, suggesting that events that induce aneuploidy may be a cause of cancer.

To look for fusion proteins in glioblastoma, the authors used massively parallel, paired-end sequencing of expressed transcripts (RNA–seq) in freshly isolated glioma stem-like cells (GSCs) from nine patients with glioblastoma. One GSC culture (GSC-1123) and its matched primary tumour contained an in-frame fusion of the tyrosine kinase domain of fibroblast growth factor receptor 3 (*FGFR3*) and the transforming acidic coiled-coil (TACC) domain of *TACC3*, which mediates the localization of TACC proteins to the mitotic spindle. Using a novel computational approach to detect gene fusions in whole-exome sequencing data (ExomeFuse), the authors also found the *FGFR3–TACC3* fusion in four samples from The Cancer Genome Atlas database that had outlier overexpression of both these proteins. Furthermore, screening of an additional 88 primary glioblastomas revealed one with the *FGFR3–TACC3* fusion and another with a similar *FGFR1–TACC1* fusion.

Are FGFR–TACC fusion proteins oncogenic? Cultured Rat1A fibroblasts could be transformed by expression of FGFR3–TACC3 or of FGFR1–TACC1, and expression of either fusion in astrocytes also lacking the *Ink4a–Arf* locus led to glioma-like tumour formation following subcutaneous injection in immuno-deficient mice. In addition, FGFR3–TACC3 expression and silencing of p53 in the brains of immunocompetent mice resulted in lethal brain tumours in seven of eight mice.

How do FGFR–TACC fusion proteins induce tumours? Interestingly, canonical FGFR signalling pathways did not seem to be activated despite constitutive kinase activation in FGFR3–TACC3, so the authors examined the fusion using confocal and time-lapse microscopy. They found that FGFR3–TACC3 localized at spindle poles during mitosis, and its expression led to mitotic delays and errors in chromosome segregation, resulting in a 2.5–5-fold increase in the proportion of cells with aneuploidy compared with controls, depending on the cell type. They also observed aneuploidy in the primary GSC-1123 cells.

Aneuploidy in Rat1A cells expressing FGFR3–TACC3 could be reversed by treatment with FGFR inhibitors, and growth of FGFR3–TACC3-expressing cells, including primary GSC-1123 cells, was inhibited by pharmacologically relevant concentrations of FGFR inhibitors *in vitro*. *In vivo*, FGFR inhibition prolonged the survival of mice bearing intracranial xenografts of FGFR3–TACC3-expressing astrocytes, indicating that patients with glioblastomas that express FGFR–TACC fusions might benefit from treatment with FGFR inhibitors.

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ORIGINAL RESEARCH PAPER Singh, D. *et al.* Transforming fusions of *FGFR* and *TACC* genes in human glioblastoma. *Science* 26 Jul 2012 (doi:10.1126/science.1220834)