Nature Reviews Clinical Oncology | Published online 8 Nov 2016; doi:10.1038/nrclinonc.2016.182

GENETICS

New paediatric glioblastoma treatment option

Glioblastoma is an extremely aggressive cancer associated with an average survival of 12–18 months, and is incurable with current treatment options. Paediatric glioblastoma is highly heterogeneous and genetically distinct from its adult counterpart and, although some genetic causes have been identified, a substantial fraction of tumours still lack potential targets for novel therapies. Now, a study co-led by David Jones, Peter Lichter, and Stefan Pfister has shed light on previously unidentified gene fusions that could represent new drug targets.

The researchers performed integrative genetic analyses of 53 paediatric glioblastomas and used five *in vitro* model systems to identify previously unknown gene fusions involving the *MET* oncogene. Tumorigenesis induced by these *MET* fusions involved MAPK activation, resulting in compromised cell-cycle regulation. Moreover, pharmacological inhibition of MET suppressed tumour growth in xenograft models. This finding was also translated to the clinic — a child with a *MET*-fusion-expressing glioblastoma was treated with the MET inhibitor crizotinib, which led to symptom relief and tumour shrinkage. New lesions appeared, however, indicating that a combination treatment approach is warranted.

Jones comments: "the most-striking finding was that fusions of the known oncogene *MET* were detected in ~10% of patients. By developing a new mouse model, we showed that the fusion gene products are a druggable target in a subset of paediatric glioblastomas, and provided clinical proof-of-principle." This study demonstrates that "targeted inhibitors against MET might be a good therapeutic option for some patients, and that personalized therapy is of potential value in this setting." Future efforts to understand the mechanisms by which these tumour cells develop resistance to therapies are an ongoing priority.

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ORIGINAL ARTICLE Bender, S. *et al.* Recurrent *MET* fusion genes represent a drug target in pediatric glioblastoma. *Nat. Med.* http://dx.doi.org/10.1038/nm.4204 (2016)