

## Letter

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### p53 and Pten control neural and glioma stem/progenitor cell renewal and differentiation

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**Glioblastoma (GBM) is a highly lethal brain tumour presenting as one of two subtypes with distinct clinical histories and molecular profiles. The primary GBM subtype presents acutely as a high-grade disease that typically harbours mutations in *EGFR*, *PTEN* and *INK4A/ARF* (also known as *CDKN2A*), and the secondary GBM subtype evolves from the slow progression of a low-grade disease that classically possesses *PDGF* and *TP53* events<sup>1,2,3</sup>. Here we show that concomitant central nervous system (CNS)-specific deletion of *p53* and *Pten* in the mouse CNS generates a penetrant acute-onset high-grade malignant glioma phenotype with notable clinical, pathological and molecular resemblance to primary GBM in humans. This genetic observation prompted *TP53* and *PTEN* mutational analysis in human primary GBM, demonstrating unexpectedly frequent inactivating mutations of *TP53* as well as the expected *PTEN* mutations. Integrated transcriptomic profiling, *in silico* promoter analysis and functional studies of murine neural stem cells (NSCs) established that dual, but not singular, inactivation of *p53* and *Pten* promotes an undifferentiated state with high renewal potential and drives increased Myc protein levels and its associated signature. Functional studies validated increased Myc activity as a potent contributor to the impaired differentiation and enhanced renewal of NSCs doubly null for *p53* and *Pten* (*p53*<sup>-/-</sup> *Pten*<sup>-/-</sup>) as well as tumour neurospheres (TNSs) derived from this model. Myc also serves to maintain robust tumorigenic potential of *p53*<sup>-/-</sup> *Pten*<sup>-/-</sup> TNSs. These murine modelling studies, together with confirmatory transcriptomic/promoter studies in human primary GBM, validate a pathogenetic role of a common tumour suppressor mutation profile in human primary GBM and establish Myc as an important target for cooperative actions of p53 and Pten in the regulation of normal and malignant stem/progenitor cell differentiation, self-renewal and tumorigenic potential.**