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Cell, Tumor, and Stem Cell Biology

Pten Haploinsufficiency Accelerates Formation of High-Grade Astrocytomas

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We previously reported that central nervous system (CNS) inactivation of *Nf1* and *p53* tumor suppressor genes in mice results in the development of low-grade to high-grade progressive astrocytomas. When the tumors achieve high grade, they are frequently accompanied by Akt activation, reminiscent of the frequent association of *PTEN* mutations in human high-grade glioma. In the present study, we introduced CNS heterozygosity of *Pten* into the *Nf1/p53* astrocytoma model. Resulting mice had accelerated morbidity, shortened survival, and full penetrance of high-grade astrocytomas. Haploinsufficiency of *Pten* accelerated formation of grade 3 astrocytomas, whereas

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loss of *Pten* heterozygosity and Akt activation coincided with progression into grade 4 tumors. These data suggest that successive loss of each *Pten* allele may contribute to *de novo* formation of high-grade astrocytoma and progression into glioblastoma, respectively, thus providing insight into the etiology of primary glioblastoma. The presence of ectopically migrating neural stem/progenitor lineage cells in presymptomatic *Pten*-deficient mutant brains supports the notion that these tumors may arise from stem/progenitor cells. [Cancer Res 2008;68(9):3286–94]

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