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[Clin Cancer Res](#). 2011 Jun 1;17(11):3590-9.

BRAF Activation Induces Transformation and Then Senescence in Human Neural Stem Cells: A Pilocytic Astrocytoma Model.

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Abstract

PURPOSE: BRAF is frequently activated by gene fusion or point mutation in pilocytic astrocytoma, the most common pediatric brain tumor. We investigated the functional effect of constitutive BRAF activation in normal human neural stem and progenitor cells to determine its role in tumor induction in the brain.

EXPERIMENTAL DESIGN: The constitutively active BRAF(V600E) allele was introduced into human neurospheres, and its effects on MAPK (mitogen-activated protein kinase) signaling, proliferation, soft agarose colony formation, stem cell phenotype, and induction of cellular senescence were assayed. Immunohistochemistry was used to examine p16(INK4a) levels in pilocytic astrocytoma.

RESULTS: BRAF(V600E) expression initially strongly promoted colony formation but did not lead to significantly increased proliferation. BRAF(V600E)-expressing cells subsequently stopped proliferating and induced markers of oncogene-induced senescence including acidic β -galactosidase, PAI-1, and p16(INK4a) whereas controls did not. Onset of senescence was associated with decreased expression of neural stem cell markers including SOX2. Primary pilocytic astrocytoma cultures also showed induction of acidic β -galactosidase activity. Immunohistochemical examination of 66 pilocytic astrocytomas revealed p16(INK4a) immunoreactivity in the majority of cases, but patients with tumors negative for p16(INK4a) had significantly shorter overall survival.

CONCLUSIONS: BRAF activation in human neural stem and progenitor cells initially promotes clonogenic growth in soft agarose, suggesting partial cellular transformation, but oncogene-induced senescence subsequently limits proliferation. Induction of senescence by BRAF may help explain the low-grade pathobiology of pilocytic astrocytoma, whereas worse clinical outcomes associated with tumors lacking p16(INK4a) expression could reflect failure to induce senescence or an escape from oncogene-induced senescence. *Clin Cancer Res*; 17(11); 3590-9. ©2011 AACR.

PMID: 21636552 [PubMed - in process]

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