

XING FAN
Neuropathology

Notch2 promotes, and Notch1 inhibits, the growth of embryonal brain tumors

Xing Fan, Charles Eberhart

Notch signaling plays an important role in the maintenance and proliferation of central nervous system progenitor cells, but its involvement in the pathogenesis of progenitor cell derived brain tumors such as medulloblastoma is unknown. We demonstrate that Notch2 receptor transcripts are highly expressed in medulloblastomas, while Notch1 is scarce or undetectable. This parallels normal cerebellar development, with Notch2 predominantly expressed in proliferating progenitors and Notch1 in post-mitotic differentiating cells. Expression of truncated, constitutively active Notch1 or Notch2 in embryonal brain tumor cell lines caused opposite effects on tumor growth consistent with this developmental pattern. Cell proliferation, soft agar colony formation and xenograft growth were all promoted by Notch2 and inhibited by Notch1. Given the oncogenic effects of Notch2, we analyzed its gene dosage in 40 embryonal brain tumors, detecting increased copy number in 15% of cases. In addition, increased Notch activity in medulloblastomas, as evidenced by Hes1 protein expression, was associated with significantly shorter patient survival ($P = 0.01$). Finally, inhibition of Notch signaling arrested tumor growth in vitro and may be useful therapeutically. Our data indicate that Notch1 and Notch2 can have opposite effects on the growth of a single tumor type, and suggest Notch2 can be activated by gene amplification in human tumors.