PTEN Loss Mitigates the Response of Medulloblastoma to Hedgehog Pathway Inhibition.

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Abstract
Medulloblastoma is a cancer of the cerebellum, for which there is currently no approved targeted therapy. Recent transcriptomics approaches have demonstrated that medulloblastoma is composed of molecularly distinct subgroups, one of which is characterized by activation of the Hedgehog pathway, which in mouse models is sufficient to drive medulloblastoma development. There is thus considerable interest in targeting the Hedgehog pathway for therapeutic benefit in medulloblastoma, particularly given the recent approval of the Hedgehog pathway inhibitor vismodegib for metastatic and locally advanced basal cell carcinoma. Like other molecularly targeted therapies, however, there have been reports of acquired resistance to vismodegib, driven by secondary Hedgehog pathway mutations and potentially by activation of the phosphatidylinositol 3-kinase (PI3K) pathway. Given that acquired resistance to vismodegib may occur as a result of inappropriate PI3K pathway activation, we asked if loss of the PI3K pathway regulator, phosphatase and tensin homologue (Pten), which has been reported to occur in patients within the Hedgehog subgroup, would constitute a mechanism of innate resistance to vismodegib in Hedgehog-driven medulloblastoma. We find that Hedgehog pathway inhibition successfully restraints growth of Pten-deficient medulloblastoma in this mouse model, but does not drive tumor regression, as it does in Pten-wild-type medulloblastoma. Combined inhibition of the Hedgehog and PI3K pathways may lead to superior antitumor activity in PTEN-deficient medulloblastoma in the clinic. Cancer Res; 73(23); 1-9. ©2013 AACR.

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