Medulloblastoma Growth is Halted by Inhibiting Jak2-mediated Phosphorylation of Atoh1

Akash J. Patel MD; Tiemo Klisch PhD; Anna Vainshtein PhD; Huda Y Zoghbi MD

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Introduction

Treatment for medulloblastoma, the most common malignant primary brain tumor in children, remains limited to surgical resection, radiation, and traditional chemotherapy; the 10-year survival rate is less than 50%. Seeking to identify key factors that drive tumor development in order to establish better therapies, we found that the transcription factor Atonal homologue 1 (Atoh1) is required for the development of Sonic Hedgehog (SHH)-type medulloblastoma in mice.

Methods

Using the Nd2::SmoA1 transgenic mice, harboring a constitutively active sonic hedgehog pathway, we explored how Atoh1 is involved in medulloblastoma development. We used immunoprecipitation-mass spectrometry for Atoh1 in the tumor initiating cells to identify phosphorylation events that occur in the tumors. The interaction of Jak2 and Atoh1 was confirmed using the bimolecular fluorescence complementation assay. Atoh1 phosphomimetic and phospho-dead mutants were cloned for studies and the Y78 phosphorylation site was investigated using inducible medulloblastoma cell lines. Proliferation was measured using an MTT proliferation assay. Xenograft transplants of inducible cell-lines of wild-type atoh1, phosphor-mimetic and phospho-dead atoh1 were used to compare tumor formation as it relates to this phosphorylation event.

Learning Objectives

Understand how a novel Jak2-Atoh1 signaling cascade promotes medulloblastoma formation

Results

Heterozygosity of Atoh1 reduced tumor occurrence and prolonged survival. More importantly, we discovered that tyrosine 78 of Atoh1 is phosphorylated by a novel Jak2-mediated pathway only in tumor-initiating cells and in human SHH-type medulloblastoma. We show that phosphorylation of this site stabilizes Atoh1 protein, increases its transcriptional activity, and is independent of the canonical Jak2 signaling cascades, whereas inhibiting Jak2 impairs tumor growth in vivo.

Conclusions

We found that the transcription factor Atoh1 is required for the development of Sonic Hedgehog (SHH)-type medulloblastoma in mice. Atoh1 is a transcription factor critical in hindbrain development, that is no longer expressed post-natally, making it an ideal therapeutic target. We have identified a Jak2-mediated phosphorylation event that occurs only in medulloblastoma initiating cells and is necessary for tumor formation. Inhibition of Jak2-mediated Atoh1 phosphorylation could provide a viable therapy for medulloblastoma.

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