ATOH1

This protein belongs to the basic helix-loop-helix (BHLH) family of transcription factors. It activates E-box-dependent transcription along with TCF3 (E47).

ATOH1 is required for the formation of both neural and non-neural cell types. Using genetic deletion in mice, Atoh1 has been shown to be essential for the formation of cerebellar granule neurons, inner ear hair cells, spinal cord interneurons, Merkel cells of the skin, and intestinal secretory cells (goblet, enteroendocrine, and Paneth cells). ATOH1 is a mammalian homolog of the Drosophila melanogaster gene atonal. ATOH1 is considered part of the Notch signaling pathway.

In 2009, ATOH1 was identified as a tumor suppressor gene.

Mou et al. speculated that ATOH1 may influence the efficacy of Immune checkpoint inhibitors therapy in patients with colorectal adenocarcinoma by affecting the immune microenvironment and immunogenicity of the tumor [1)].

Kervarrec et al. demonstrated MCPyV-large T antigens' capacity to inhibit the degradation of the MC master regulator Atonal bHLH transcription factor 1 (ATOH1) [2)].

Signaling networks controlled by Sonic hedgehog (SHH) and the transcription factor Atoh1 regulate the proliferation and differentiation of cerebellar granule neuron progenitors (GNPs). Deregulations in those developmental processes lead to medulloblastoma formation, the most common malignant brain tumor in childhood. Although the protein Atoh1 is a key factor during both cerebellar development and medulloblastoma formation, up-to-date detailed mechanisms underlying its function and regulation have remained poorly understood. Here, we report that SHH regulates Atoh1 stability by preventing its phosphodependent degradation by the E3 ubiquitin ligase Huwe1. Our results reveal that SHH and Atoh1 contribute to a positive autoregulatory loop promoting neuronal precursor expansion. Consequently, Huwe1 loss in mouse SHH medulloblastoma illustrates the disruption of this developmental mechanism in cancer. Hence, the crosstalk between SHH signaling and Atoh1 during cerebellar development highlights a collaborative network that could be further targeted in medulloblastoma [3)].

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studied the role of Sox2 in cerebellar development. They found that the external germinal layer (EGL) is derived from embryonic Sox2+ precursors and that the EGL maintains a rare fraction of Sox2+ cells during the first postnatal week. Through lineage tracing and single-cell analysis, they demonstrated that these Sox2+ cells are within the Atoh1+ lineage, contribute extensively to adult granule neurons, and resemble Sox2+ tumor cells. Critically, constitutive activation of the SHH pathway leads to their aberrant persistence in the EGL and rapid tumor onset. They proposed that failure to eliminate this rare but potent developmental population is the tumor initiation mechanism in SHH-subgroup MB [4)].

showed that the transcription factor Atonal homologue 1 (Atoh1) is required for Shh-type medulloblastoma development in mice. To determine whether reducing either Atoh1 levels or activity in tumors after their development is beneficial, we studied Atoh1 dosage and modifications in Shh-type medulloblastoma. Heterozygosity of Atoh1 reduced tumor occurrence and prolonged survival. We discovered tyrosine 78 of Atoh1 is phosphorylated by a Jak2-mediated pathway only in tumor-initiating cells and in human SHH-type medulloblastoma. Phosphorylation of tyrosine 78 stabilizes Atoh1, increases Atoh1's transcriptional activity, and is independent of canonical Jak2 signaling. Importantly, inhibition of Jak2 impairs tyrosine 78 phosphorylation and tumor growth in vivo. Taken together, inhibiting Jak2-mediated tyrosine 78 phosphorylation could provide a viable therapy for medulloblastoma [5].

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