Abstracts

CELL SIGNALING AND SIGNALING PATHWAYS

CS-01. THE PHOSPHORYLATION OF ATOH1 LEADS TO ITS DEGRADATION MEDIATED BY THE E3 UBIQUITIN LIGASE HUWE1 IN GRANULE NEURON PROGENITORS


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Medulloblastoma is the most common malignant pediatric brain tumor and is divided in four subgroups by gene profiling. The well-known subgroup harboring an activation of the Sonic Hedgehog (SHH)/Patched (PTCH) pathway shows an upregulation of the pro-neural basic helix-loop-helix transcription factor Atoh1. Atoh1 is essential for cerebellum development and more specifically for the formation of the granule neuron progenitors (GNPs), which are the cells of origin of SHH induced medulloblastoma. In tumoral context, Atoh1 acts as a pro-tumor factor in cooperation with SHH/PTCH pathway and its inhibition prevents medulloblastoma proliferation in vitro and in vivo. However, to date, mechanisms underlying Atoh1 regulation remained to be elucidated. We recently found that the mitogen SHH, by regulating Atoh1 phosphorylation, can protect Atoh1 against Huw1-mediated degradation. We also showed that Atoh1 degradation by the E3 ubiquitin ligase Huw1 was required for proper cerebellum development. Moreover, low expression of HUWE1 in human Sonic Hedgehog medulloblastoma subgroup was associated with a poor survival rate of patients. Together, we uncovered a signaling pathway that controls the balance between neuronal proliferation and differentiation in GNPs and that could be further targeted in order to elaborate new therapeutic strategies.

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