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Club de lecture

Histone deacetylase and Cullin3-REN(KCTD11) ubiquitin ligase interplay regulates Hedgehog signalling through Gli acetylation

Canettieri G, Di Marcotullio L, Greco A, Coni S, Antonucci L, Infante P, Pietrosanti L, De Smaele E, Ferretti E, Miele E, Pelloni M, De Simone G, Pedone EM, Gallinari P, Giorgi A, Steinühler C, Vitagliano L, Pedone C, Schinin ME, Screpanti I, Gulino A.

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Abstract

Hedgehog signalling is crucial for development and is deregulated in several tumours, including medulloblastoma. Regulation of the transcriptional activity of Gli (glioma-associated oncogene) proteins, effectors of the Hedgehog pathway, is poorly understood. We show here that Gli1 and Gli2 are acetylated proteins and that their HDAC-mediated deacetylation promotes transcriptional activation and sustains a positive autoregulatory loop through Hedgehog-induced upregulation of HDAC1. This mechanism is turned off by HDAC1 degradation through an E3 ubiquitin ligase complex formed by Cullin3 and REN, a Gli antagonist lost in human medulloblastoma. Whereas high HDAC1 and low REN expression in neural progenitors and medulloblastomas correlates with active Hedgehog signalling, loss of HDAC activity suppresses Hedgehog-dependent growth of neural progenitors and tumour cells. Consistent with this, abrogation of Gli1 acetylation enhances cellular proliferation and transformation. These data identify an integrated HDAC- and ubiquitin-mediated circuitry, where acetylation of Gli proteins functions as an unexpected key transcriptional checkpoint of Hedgehog signalling.

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