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[Neoplasia](#). 2011 Apr;13(4):374-85.

Identification and Characterization of KCASH2 and KCASH3, 2 Novel Cullin3 Adaptors Suppressing Histone Deacetylase and Hedgehog Activity in Medulloblastoma.

De Smaele E, Di Marcotullio L, Moretti M, Pelloni M, Occhione MA, Infante P, Cucchi D, Greco A, Pietrosanti L, Todorovic J, Coni S, Canettieri G, Ferretti E, Bei R, Maroder M, Screpanti I, Gulino A.

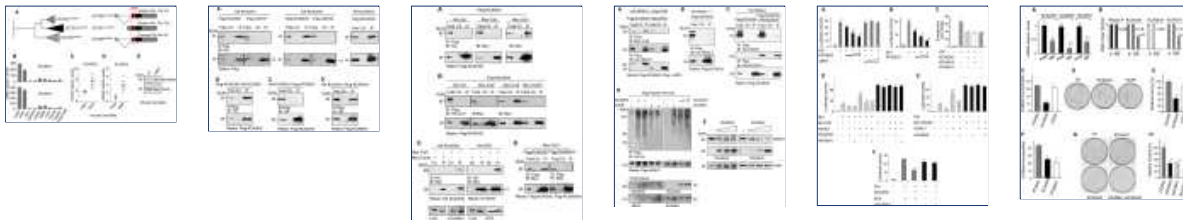
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Abstract

Medulloblastoma is the most common pediatric malignant brain tumor, arising from aberrant cerebellar precursors' development, a process mainly controlled by Hedgehog (Hh) signaling pathway. Histone deacetylase HDAC1 has been recently shown to modulate Hh signaling, deacetylating its effectors Gli1/2 and enhancing their transcriptional activity. Therefore, HDAC may represent a potential therapeutic target for Hh-dependent tumors, but still little information is available on the physiological mechanisms of HDAC regulation. The putative tumor suppressor REN(KCTD11) acts through ubiquitination-dependent degradation of HDAC1, thereby affecting Hh activity and medulloblastoma growth. We identify and characterize here two REN(KCTD11) homologues, defining a new family of proteins named KCASH, as "KCTD containing, Cullin3 adaptor, suppressor of Hedgehog." Indeed, the novel genes (KCASH2(KCTD21) and KCASH3(KCTD6)) share with REN(KCTD11) a number of features, such as a BTB domain required for the formation of a Cullin3 ubiquitin ligase complex and HDAC1 ubiquitination and degradation capability, suppressing the acetylation-dependent Hh/Gli signaling. Expression of KCASH2 and -3 is observed in cerebellum, whereas epigenetic silencing and allelic deletion are observed in human medulloblastoma. Rescuing KCASHs expression reduces the Hedgehog-dependent medulloblastoma growth, suggesting that loss of members of this novel family of native HDAC inhibitors is crucial in sustaining Hh pathway-mediated tumorigenesis. Accordingly, they might represent a promising class of endogenous "agents" through which this pathway may be targeted.

PMID: 21472142 [PubMed - in process] PMCID: PMC3071086 [Free PMC Article](#)

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