HDAC6 inhibition decreases leukemic stem cell expansion driven by Hedgehog hyperactivation by restoring primary ciliogenesis

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Aberrant activation of the Hh pathway promotes cell proliferation and multi-drug resistance (MDR) in several cancers, including Acute Myeloid Leukemia (AML). Notably, only one Hh inhibitor, glasdegib, has been approved for AML treatment, and most patients eventually relapse, highlighting the urgent need to discover new therapeutic targets. Hh signal is transduced through the membrane of the primary cilium, a structure expressed by non-proliferating mammalian cells, whose stabilization depends on the activity of HDAC6. Here we describe a positive correlation between *Hh*, *HDAC6*, and *MDR* genes in a cohort of adult AML patients, human leukemic cell lines, and a zebrafish model of Hh overexpression. The hyper-activation of *Hh* or HDAC6 in zebrafish drove the increased proliferation of hematopoietic stem and progenitor cells (HSPCs). Interestingly, this phenotype was rescued by inhibition of HDAC6 but not of *Hh*. Also, in human leukemic cell lines, a reduction in vitality was obtained through HDAC6, but not Hh inhibition. Our data showed the presence of a cross-talk between Hh and HDAC6 mediated by stabilization of the primary cilium, which we detect for the first time in zebrafish HSPCs. Inhibition of HDAC6 activity alone or in combination therapy with the chemotherapeutic agent cytarabine, efficiently rescued the hematopoietic phenotype. Our results open the possibility to introduce HDAC6 as therapeutic target to reduce proliferation of leukemic blasts in AML patients.

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