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internal seminar

Biometra seminars

HDAC6 AND HDAC8 IN ACUTE MYELOID LEUKEMIA: LESSONS FROM ZEBRAFISH

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Aberrant expression and activity of epigenetic modifiers belonging to the histone deacetylase (HDAC) family have been reported in patients with acute myeloid leukemia (AML). The zebrafish model, in which the mechanisms involved in hematopoiesis are conserved with those of higher vertebrates, represents an ideal tool for studying the role of the different HDAC in leukemia. Using transgenic embryos with green-labeled hematopoietic stem and progenitor cells (HSPCs), we demonstrated that HDAC6 and HDAC8 overexpression leads to an increase in the HSPCs population. This phenotype, which resembles a pre-AML state, was reversed by treating the embryos with selective HDAC6 (TubastatinA) and HDAC8 (PCI-34051) inhibitors. Searching for the molecular mechanisms underlining the hematopoietic phenotype, we found that HDAC8 and HDAC6 promote the pre-AML phenotype acting on Wnt and Hh signaling pathways. The new frontier in the management of AML patients is represented by combination treatments and we showed that HDAC6- and HDAC8-specific inhibitors can be used in these settings together with chemotherapic agents. We showed that TubastatinA and PCI-34051 synergize with cytarabine to suppress the leukemic phenotype of two AML zebrafish models and reduce the viability of AML cell lines. In summary, using the zebrafish model, we demonstrated the efficacy of TubastatinA and PCI-34051, which could be exploited also for the treatment of tumors carrying HDAC6 and HDAC8 overexpression.

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