Targeting Hedgehog and HDAC6 in acute myeloid leukemia in in vitro and zebrafish models

Oral presentation

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In patients with Acute Myeloid Leukemia (AML) unknown drug-resistance mechanisms, driven by the abnormal activationof the Hedgehog (Hh) signaling, hamper the achievement of chemotherapy response. However, only one Hh inhibitor(glasdegib) is currently in use for AML treatment.Therefore, new therapeutic approaches are needed, and new moleculartargets could be identified in the Hh signal cascade. The Hh pathway localizes on the membrane of the primary cilium, a microtubular structure derived from the centrosome and, therefore, expressed by non-proliferating mammalian cells.Since cancer cells, including AML cell lines, are characterized by a high rate of proliferation, they fail to present the primary cilium on their surface. Novel approaches to restore this structure on the surface of cancer cells are under investigation and most of them target the histone deacetylase HDAC6 as it controls cilium reabsorption. In our preliminary results, we verified that in AML patients' blood samples the expression levels of the Hh signaling are higher than healthy controls. Moreover, we demonstrated a positive correlation between Hh, HDAC6 and genes that confer tumor resistance (MDRs) both in patients and human AML cell lines. We confirmed the increased expression of hdac6 and MDRs also in a zebrafish model carrying the overexpression of the Hh pathway. In zebrafish we found that Hh hyperactivation generates a pre-leukemic phenotype, characterized by the hyperproliferation of the hematopoietic stem and progenitor cells (HSPCs). Interestingly, we rescued this hematopoietic phenotype with the HDAC6 inhibitor TubastatinA, but not with the Hh inhibitor cyclopamine. In line with this, the overexpression of the HDAC6 in zebrafish induced the hyperproliferation of HSPCs, confirming the role of HDAC6 hyperactivation in the pre-leukemic phenotype induction. To dissect the role of Hh/HDAC6 signaling in AML resistance and relapse we took advantage of zebrafish with Hh or HDAC6 overexpression or AML models and in vitro human AML cell lines in which we investigated the efficacy of a combination treatment with Hh and HDAC6 inhibitors and common chemotherapic agents.