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Title: High throughput drug screening reveals HDAC inhibitors as new therapeutic perspectives for Hepatoblastoma
Topic:
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Abstract:
Aim of the Study: Hepatoblastoma (HB) is the main form of pediatric liver cancer. While its treatment, mainly based on cisplatin, is effective in 80% of patients, it remains insufficiently efficient in high-risk cases due to the emergence of chemoresistance. Our previous work identified a proliferative and poorly differentiated transcriptomic subtype called Liver Progenitor linked to cisplatin resistance. Our project aims to identify innovative therapeutic approaches to overcome cisplatin resistance in this HB subset.

Methods: We screened 91 therapeutic compounds individually and 38 combinations, mainly paired with cisplatin, across 8 pediatric liver cancer cell lines. The most effective therapeutic conditions were subsequently validated using spheroid models. Transcriptomic analyses were performed on the 8 cell lines, 100 HB samples and 8 normal livers.

Main Results: The tested cell lines were primarily resistant to cisplatin and were enriched in the liver progenitor transcriptomic subgroup. Mitosis process inhibitors, proteasome inhibitors, and specific histone deacetylase (HDAC) inhibitors were the most efficient compounds in monotherapy. Notably, despite a wide range of efficiency, the six HDAC inhibitors showed similar sensitivity profiles. Further transcriptomic analysis revealed overexpression of HDAC1 and HDAC2, especially in the Liver Progenitor subtype, suggesting their potential role as therapeutic targets. Panobinostat was one of the most potent HDAC inhibitors and demonstrated a synergic or additive effect with cisplatin in reducing cell viability in monolayer culture and in spheroid models, respectively.

Conclusion: Panobinostat demonstrated promising anti-proliferative effects against cisplatin-resistant HB and may be combined with cisplatin for HB patients refractory to standard treatments.