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INSTITUT LADY DAVIS DE RECHERCHES MÉDICALES | LADY DAVIS INSTITUTE FOR MEDICAL RESEARCH

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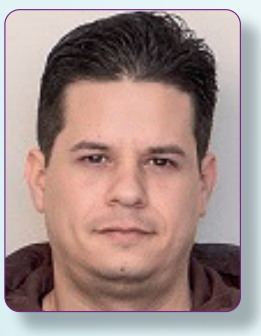

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blood advances

The E3 ubiquitin ligase Herc1 modulates the response to nucleoside analogs in acute myeloid leukemia

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For several decades, induction therapy with nucleoside analogs, in particular cytarabine (Ara-C) and, to a lesser extent, fludarabine, has been the standard of care for patients diagnosed with acute myeloid leukemia (AML). Still, the anti-tumor efficacy of nucleoside analogs is often limited by intrinsic and acquired drug resistance, thereby leading to poor therapeutic response and suboptimal clinical outcomes. Half of adult patients relapse from standard-of-care chemotherapy within three years, and the overall five-year survival rate in adults is around 30%, thereby highlighting the critical need to better understand the determinants of chemo-responsiveness in AML cells.

In this study, we used genome-wide CRISPR-based pharmacogenomic screening to map the genetic factors that modulate the response to nucleoside analogs in AML and identified the E3 ubiquitin ligase Herc1 as a key modulator of Ara-C response in the MLL/AF9 (MA) and the HOXA9/MEIS1 (HM) murine AML models both in vitro and in vivo. Loss of HERC1 enhanced nucleoside analog-induced cell death in both murine and human AML cell lines by compromising cell cycle progression.

In-depth proteomic analysis and subsequent validation identified deoxycytidine kinase Dck as a novel target of Herc1 in MA and HM murine cells. We observed that HERC1 is overexpressed in AML compared to other cancer types and higher HERC1 expression is associated with shorter overall survival of patients with AML in the TCGA and BEAT-AML cohorts.

Collectively, this study highlights the importance of HERC1 in the response of AML cells to nucleoside analogs, thereby establishing this E3 ubiquitin ligase as a novel predictive biomarker and potential therapeutic target for the treatment of AML.

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