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604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Aberrant 3'UTR Processing Regulates Leukemogenesis and Therapy Resistance

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A block in cellular differentiation is a hallmark of acute myeloid leukemia (AML) that promote clonal expansion and influence therapy response [1,2]. It has become evidently clear that non-genetic mechanisms are critical to prevent malignant cells to resume its lineage maturation trajectory [3,4]. However, there is still an incomplete understanding of gene regulatory pathways that induce differentiation arrest of leukemia cells. Here, we applied an immunophenotypic readout and positive selection CRISPR/Cas9 screens to identify suppressors of leukemia differentiation. These screens converged on ZBTB7A, a zinc finger transcription factor whose *loss-of-function* restricted AML maturation in the prescence of differentiation-inducing agents. Mechanstically, ZBTB7A ablation led to an elevated inflammatory state to stimulate leukemia proliferation. In addition, we found that genetic deletion of ZBTB7A and its paralog, ZBTB7B cooperatively suppresses myeloid differentiation and promotes resistance to several clinical compounds. Lastly, we identify that leukemic cells hijack multiple upstream 3'UTR processes, such as alternative polyadenylation and mRNA decay to downregulate *ZBTB7A* and *ZBTB7B* expression. Together, these data provide fundamental insight into non-genetic mechanisms that impede myeloid differentiation and mediate drug resistance.

Disclosures No relevant conflicts of interest to declare.

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