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ZBTB7A loss accelerates RUNX1::RUNX1T19a-driven leukemia by enhancing erythroid block and aberrant myeloid progenitor expansion

ZBTB7A is a transcription factor critical for hematopoietic lineage commitment, particularly in promoting erythroid differentiation. In acute myeloid leukemia (AML), ZBTB7A mutations are frequently associated with the t(8;21) translocation, which generates the RUNX1::RUNX1T1 fusion and defines a patient subgroup with relatively favorable outcomes. However, relapse remains a significant clinical challenge, highlighting the need for novel therapeutic strategies. To investigate the cooperative role of ZBTB7A loss in RUNX1::RUNX1T1-driven leukemogenesis, we established a murine model by transplanting sub-lethally irradiated C57BL/6J mice with Cas9-EGFP bone marrow (BM) progenitors transduced with a construct encoding RUNX1::RUNX1T1 (9a variant), tdTomato, and either a Zbtb7a-targeting or non-targeting sgRNA. Strikingly, only mice receiving ZBTB7A knockout cells developed leukemia (latency: 99 days), whereas control mice remained in a preleukemic state for nearly 200 days. Leukemic mice exhibited anemia, elevated leukocyte counts, bone marrow infiltration (>20% blasts), and organomegaly. Immunophenotyping of BM double-positive EGFP and tdTomato leukemic cells revealed a predominant population lacking Sca-1, but positive for c-Kit and CD43, markers consistent with megakaryocyte-erythroid progenitor (MEP)-like leukemia-initiating cells. Besides, approximately 50% of the double-positive cells were also CD71+ and TER119–, indicating a differentiation block at the proerythroblast stage. However, within the Lin–Sca-1–c-Kit+ compartment, a typical MEP population coexisted with an aberrant CD16/32+ CD34–subset, suggesting skewing toward a granulocyte-monocyte progenitor (GMP)-like profile. Ongoing ex vivo colony-forming assays and single-cell RNA sequencing will further elucidate the nature of RUNX1::RUNX1T1 + ZBTB7A-deficient leukemia, with the ultimate goal of identifying novel therapeutic vulnerabilities associated with ZBTB7A loss.

Research type

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