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Blood 142 (2023) 5689

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

602.MYELOID ONCOGENESIS: BASIC

Combined Deficiency of Chromosome 7 Myeloid Tumor Suppressors Enhances Chemotherapy Resistance

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Monosomy 7 and del(7q) [-7/del(7q)] are recurrent in myeloid neoplasms and associated with chemoresistance. -7/del(7q) is identified in up to half of therapy-related myeloid neoplasms (t-MN), high-risk secondary malignancies arising after prior exposure to chemotherapy or radiation. -7/del(7q) is also detected in clonal hematopoiesis, suggesting chromosome 7 aberrations can be early events in disease etiology. Despite this prevalence, the pathogenesis of -7/del(7q) in leukemogenesis remains unclear. We previously reported that deficiency of the transcription factor *CUX1*, a 7q-encoded tumor suppressor gene, promotes hematopoietic stem and progenitor cell drug resistance and t-MN transformation. Herein, we determined the combined impact of *CUX1* loss with additional 7q tumor suppressor genes. To this end, we established a CRISPR/Cas9-based murine model of del(7q) clonal hematopoiesis and drug resistance. After targeting four 7q genes simultaneously, combined deficiency of CUX1 and the histone methyltransferase EZH2 uniquely promoted clonal outgrowth under genotoxic pressure *in vivo* and *in vitro*. Mechanistically, clonal selection is due, in part, to decreased apoptosis after chemotherapy exposure. RNA-seq in the absence of genotoxic insult revealed that *Cux1* and *Ezh2* loss has an additive transcriptional impact that is enriched for -7/del(7q) patient-derived gene signatures. Overall, we reveal a previously unknown genetic interaction between the 7q genes *CUX1* and *EZH2*, supporting the concept of 7q as a contiguous gene syndrome region . A refined understanding of the molecular pathways driving del(7q) pathogenesis and drug resistance will enable development of therapies designed to counter or prevent these high-risk malignancies. In addition, we report a tractable approach for interrogating the pathogenesis of aneuploid events more broadly in cancer.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189308