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LOSS OF IKZF1 CONTRIBUTES TO CYTARABINE RESISTANCE IN B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

Topic: 01. Acute lymphoblastic leukemia - Biology & Translational Research

Keywords: ALL, Ara-C (cytarabine), Resistance

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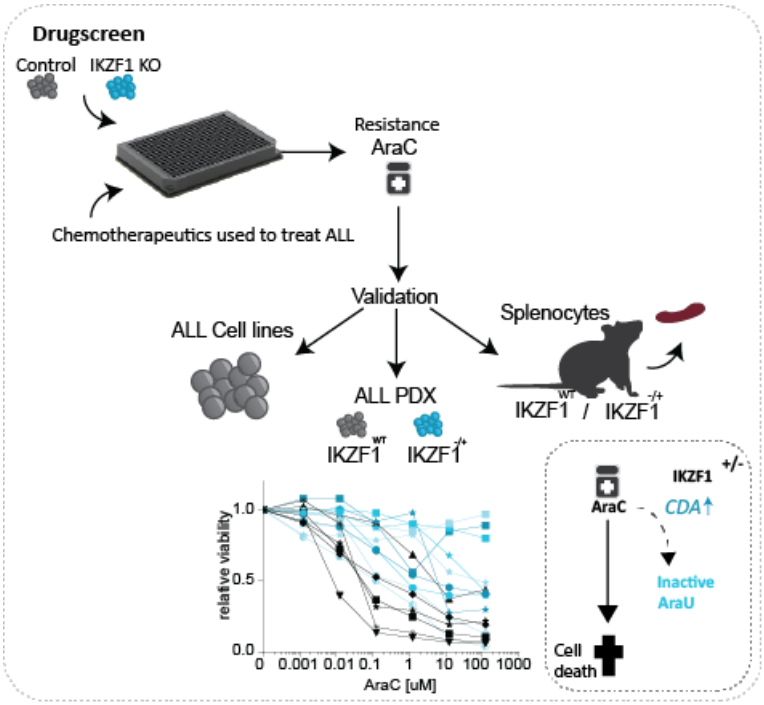
Background: Deletions and mutations affecting lymphoid transcription factor *IKZF1* occur in about 10-15% of patients with B cell precursor acute lymphoblastic leukemia (BCP-ALL) and predict a poor outcome. We have shown previously that loss of IKZF1 function compromises the therapeutic efficacy of glucocorticoids (GCs). Here, we investigated whether loss of IKZF1 function also affects therapy response to other chemotherapeutic agents used in the treatment of ALL.

Aims: To further optimize antimetabolite therapies for IKZF1 deleted leukemia to prevent relapse and therapy resistance.

Methods: We performed a drug screen including all chemotherapeutic agents used in the treatment of ALL. The results were validated using targeted knockouts, shRNA mediated knockdowns as well as a chemical induced breakdown of IKAROS. These assays were performed on ALL cell lines as well as murine splenocytes and ALL-patient derived xenografts.

Results: We observed that CRISPR/CAS9-mediated loss of *IKZF1* in SEM pre-B ALL cells markedly reduced the cellular response to the pyrimidine analogue cytarabine (AraC) relative to *IKZF1* wild type cells. The same drug resistance profile was observed upon shRNA-mediated knockdown of IKZF1 as well as in B-cells isolated from 8 to 14 weeks-old *Ikzf1*$^{+/-}$ mice. We confirmed these findings by *ex vivo* profiling of patient-derived xenografts (PDX), where we observed that *IKZF1*-deleted cases (n=10) were significantly (area under the curve (AUC) 78.690) more resistant to AraC than those wild type for *IKZF1* (n=6) (AUC 26.447). Loss of IKZF1 can also chemically be mimicked by the cereblon-E3 ligase Iberdomide, which specifically targets and breaks down members of the Ikaros protein family. Indeed, we observed that PDX wildtype for IKZF1, developed resistance to AraC in response to this drug. The metabolic enzyme cytidine deaminase (CDA) is an important determinant of AraC therapy response, both in ALL and acute myeloid leukemia (AML). Consistent with these findings, we observed that IKZF1 loss increases the expression of CDA in BCP-ALL cell lines as well as mouse primary B cells and PDX models. In addition, treatment of *IKZF1*$^{+/-}$ cells using pharmacological inhibitors of CDA, restored pyrimidine analogue sensitivity to control levels.

Image:



Summary/Conclusion: Together, these results demonstrate that loss of *IKZF1* confers resistance to AraC, both in experimental models and in patient-derived cells. We are currently performing CRISPR/CAS9 based reverse genetics screens to identify genes/pathways that enhance response to AraC or other antimetabolites. We expect that this approach will allow us to identify (hematopoietic cell-specific) pathways that can be targeted to sensitize responses to AraC in *IKZF1* deleted ALL and possibly AML. Preclinical validations of these findings, using representative PDX models, will guide the development of more effective antimetabolite therapies for this high-risk patient group.

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