(S106) ONCOGENIC MECHANISMS AND THERAPEUTIC TARGETING OF THE HIGH-RISK CDX2/UBTF B-ALL

Topic: 01. Acute lymphoblastic leukemia - Biology & translational research

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Background

CDX2/UBTF B-cell acute lymphoblastic leukemia (B-ALL) is a recently described adult subtype characterized by the systematic association of two alterations: strong ectopic expression of the CDX2 gene and the presence of the chimeric fusion protein UBTF::ATXN7L3. This entity is associated with a very poor treatment response, with a 3-year cumulative relapse incidence of 75% highlighting the urgent need for novel therapeutic strategies.

Aims

We aimed to identify effective therapeutic vulnerabilities in CDX2/UBTF B-ALL and investigate the molecular mechanisms through which CDX2 and UBTF::ATXN7L3 likely cooperate to drive leukemogenesis.

Methods

Transcriptomic analysis was performed on 29 CDX2/UBTF B-ALL and compared to 981 other B-ALL cases. Patient-derived xenograft (PDX) models were established in NSG mice, including one luciferase-expressing model. A large-scale ex vivo pharmacologic screen was conducted using four independent CDX2/UBTF PDX models co-cultured on stromal cells. Pre-clinical experiments in NSG mice were performed with leukemic infiltration monitoring by bioluminescence imaging and bone marrow assessment by flow cytometry. Co-immunoprecipitation (co-IP) assays were performed in HEK293T transfected with CDX2 and UBTF::ATXN7L3 constructs. ATACseq and CUT&RUN experiments were performed in PDX cells to investigate chromatin accessibility and transcription factor occupancy.

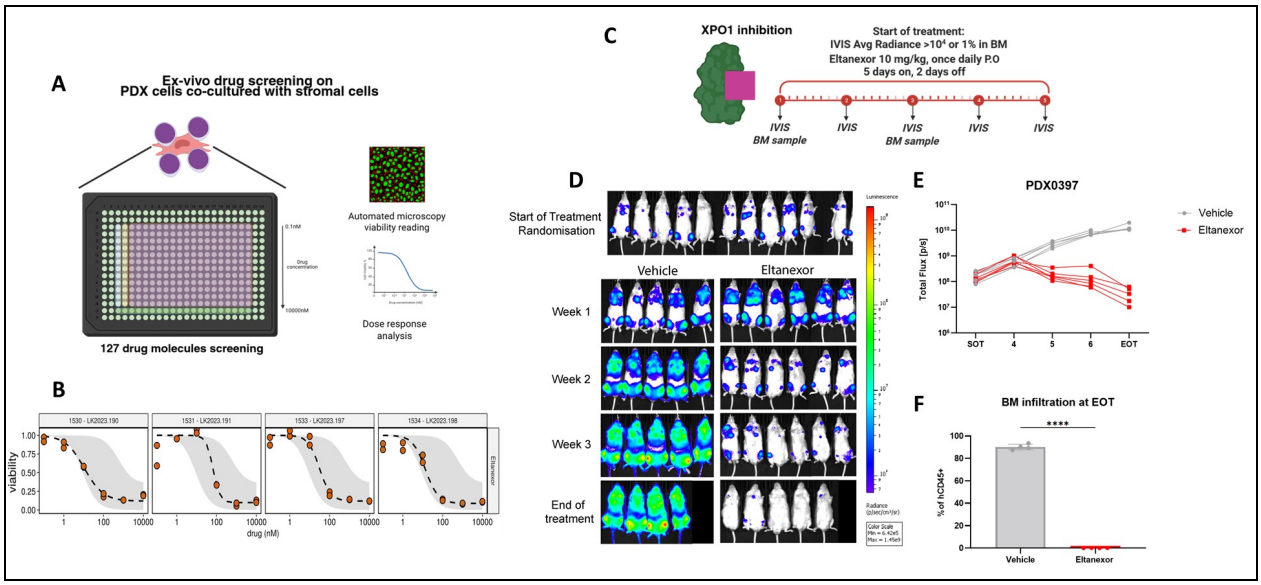
Results

Ex vivo drug screening including four distinct CDX2/UBTF PDX models identified XPO1 inhibitors among the most potent compounds in our models. Notably, CDX2/UBTF B-ALL displayed significantly greater sensitivity to XPO1 inhibition compared with a large reference dataset from other B-ALL subtypes. In vivo, eltanexor treatment induced a dramatic reduction of leukemic burden in 3 PDX models (3-log reduction in total bioluminescence flux $p<0.05$, 34% vs 1% blasts, $p < 0.05$, 57% vs 0.02% blasts, $p < 0.05$, respectively).
Interestingly, the nuclear export protein XPO1 was recently shown to be involved in chromatin binding complexes with oncoproteins that drive HOX/MEIS1 dependent-leukemogenesis. CDX2/UBTF B-ALL also harbor HOXA/MEIS expression, which prompted us to investigate a possible role of XPO1 in CDX2/UBTF leukemogenic program. By co-IP in transfected HEK293T cells we demonstrated physical interaction between both driver oncoproteins, CDX2 and UBTF::ATXN7L3, and XPO1. Furthermore, CUT&RUN and ATACseq experiments revealed shared chromatin occupancy of CDX2, UBTF, and XPO1 at regulatory regions of genes specifically expressed in this leukemia subtype.

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Summary/Conclusion

Our study identifies XPO1 inhibition as a promising therapeutic strategy in chemotherapy-resistant CDX2/UBTF B-ALL. Moreover, our findings support a model in which CDX2/UBTF leukemogenesis depends on an XPO1-containing chromatin regulatory complex, thereby creating a targetable dependency. Ongoing analyses aim to clarify the transcriptional and epigenetic consequences of XPO1 inhibition and to further validate this therapeutic approach for clinical translation.



CDX2/UBTF B-ALL are sensitive to XPO1 inhibitors (A) Experimental setup of the ex-vivo drug screening (B) Dose response curves to the XPO1 inhibitor Eltanexor in 4 independent CDX2/UBTF PDX with the projection (in grey) of the 10th and 90th quantile of the cohort (C) Experimental setup of in-vivo treatment in NSG mice with 10mg/kg Eltanexor (D) Bio-luminescence images (E) Bio-luminescence total flux quantification (F) Bone marrow aspirates after 4 weeks of treatment.

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