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Lymphomas

HELLS-DRIVEN CHROMATIN REMODELING DEFINES TRANSCRIPTIONAL PROGRAMS AND THERAPEUTIC VULNERABILITIES IN ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA

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Introduction: Chromatin remodelers regulate DNA–nucleosome interactions, shaping chromatin structure, accessibility, and gene expression. Their dysregulation is frequent in cancer and often represents a therapeutic vulnerability. HELLS, a key remodeler, preserves genome stability and controls gene expression in aggressive T-cell lymphomas, including ALK–anaplastic large cell lymphoma (ALCL). Previous studies showed that HELLS knockdown sensitizes ALCL cells to chemotherapy, highlighting its potential as a therapeutic target. This study aimed to define the transcriptional role of HELLS and evaluate its therapeutic relevance in ALCL.

Methods: We analyzed formalin-fixed, paraffin-embedded biopsies from diagnostic and relapsed ALCL patients (n= 44) and performed integrated multi-omics analyses (RNA-seq, ChIP-seq, ATAC-seq, and Connectivity Map) alongside functional assays.

Results: To explore the transcriptional function of HELLS, we performed HELLS Chromatin immunoprecipitation sequencing (ChIP-seq) analysis and intersected these data with the list of HELLS-dependent genes we previously identified by performing RNA sequencing. Out of the 729 genes significantly affected by $HELLS^{KD}$, 64% of the total were directly bound by HELLS based on ChIP-seq analysis. We termed these genes HELLS-direct genes otherwise named as HDGs. These genes belong to pathways known to drive the aggressiveness of ALK^{-}ALCL like JAK/STAT signaling, Rho-GTPase and DNA damage. NCounter profiling in a cohort of 44 ALCL patients (15 ALK^{+}, 29 ALK^{-}) confirmed their clinical relevance and the association between HELLS and its HDGs in patients. By integrating the effects of the KD of HELLS on the binding profile of RNAPII by ChIP-seq, we observed RNAPII elongation defects in ~60% of HDGs and changes in RNAPII occupancy in ~40% of HDGs. Notably, this last set of genes associated with these promoters belongs to T-cell mediated immunity and PD-L1/PD1 signaling, indicating a previously unrecognized potential role of HELLS in immune-related signaling pathways. These data suggest that, depending on targets, HELLS may foster transcription via two different mechanisms: by promoting RNAPII loading and by facilitating RNAPII elongation along the gene body. To test this hypothesis, we evaluated changes in accessibility by performing ATAC-seq and H3K4me3 profiling, demonstrating that HELLS promotes chromatin accessibility and transcriptional activation at immune-related loci. To investigate the therapeutic potential of HELLS, we performed a drug repurposing analysis based on the HDG signature, which identified PI3K, JAK/STAT, and DNA-PK as synergistic targets. In vitro, HELLS depletion combined with Ruxolitinib (JAKi) or AZD7648 (DNA-PKi) induced synthetic lethality.

Conclusions: This study shows that HELLS drives immune gene expression via chromatin remodeling in ALK^{-}ALCL, and its inhibition reveals combinatorial vulnerabilities supporting dual targeting of JAK/STAT or DNA-PK pathways.