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Acute Leukemias

ECTOPIC ACTIVATION OF FOXF1 AND FENDRR BY T(14;16)(Q32;Q24) IDENTIFIES A HIGH-RISK T-ALL/MPAL SUBTYPE

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Introduction: Despite advances in elucidating the genomic landscape of T-cell acute lymphoblastic leukemia (T-ALL) and lineage ambiguous acute leukemia, many cases still lack defining genetic hallmarks, complicating risk stratification and treatment. Notably, the discovery of recurrent genomic alterations that transcend conventional immunophenotypic boundaries supports the notion that classification based solely on immunophenotype remains limited, particularly when applied to acute leukemias of ambiguous lineage (ALAL), such as mixed-phenotype acute leukemia (MPAL), and to early T-cell precursor acute lymphoblastic leukemia (ETP-ALL)[1-2]. Here we report a distinct genetic entity encompassing both MPAL and ETP-ALL, driven by a t(14;16)(q32;q24) translocation and aberrant expression of *FOXF1* and *FENDRR*.

Methods: We retrospectively investigated 1831 T-ALL and MPAL cases by either cytogenetics or whole-genome sequencing (WGS). Somatic variants and copy number alterations were identified through whole-genome sequencing (WGS), custom next-generation sequencing, and single nucleotide polymorphism arrays (SNPa). RNA sequencing (RNA-seq) was used to define transcriptomic clustering, gene expression signatures, and pathway enrichment across 1,370 T-ALL cases. H3K27ac HiChIP and ATAC-seq were performed to examine chromatin architecture and accessibility, and single-cell DNA and RNA sequencing was performed to dissect clonal and transcriptional heterogeneity. Ex vivo drug screening was performed using a library of 176 compounds.

Results: We identified 13 cases of ETP-ALL (n=9) and MPAL (n=4) with a t(14;16)(q32.2;q24) translocation that juxtaposes *FOXF1* and *FENDRR* near the *BCL11B* enhancer on chromosome 14, resulting in their ectopic activation. These cases exhibited a distinct gene expression profile with features of immature and myeloid potentials, consistent with developmental arrest at an early progenitor stage. Additional recurrent genomic features included bi-allelic *CDKN2A/B* deletions, *GATA3* loss-of-function mutations, and alterations in the NOTCH1 and JAK/STAT pathways. Single cell analyses suggested a model in which *FOXF1/FENDRR* deregulation is the primary oncogenic event, with *GATA3* inactivation restricting T-lineage maturation and enabling lineage plasticity. All cases showed an immature immunophenotype, with the expression of B-lymphoid markers as distinctive hallmark. All cases were refractory to front line therapies, but drug screening demonstrated that that co-targeting of BCL2--family proteins and the JAK/STAT were synergistic.

Conclusions: The identification of *FOXF1/FENDRR* as oncogenic drivers in immature T-ALL and MPAL defines a novel high-risk leukemia subtype marked by the t(14;16)(q32;q24) translocation. Its dismal prognosis calls for the implementation of tailored diagnostic strategies.

References:

1. DOI: 10.1038/s41586-018-0436-0
2. DOI: 10.1038/s41586-024-07807-0.