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Acute Leukemias

BIALLELIC LOSS OF RB1 AND LPAR6 AT 13Q14 DRIVES KEY CELL CYCLE ABNORMALITIES IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Cell cycle dysregulation occurs in 70% of T-ALL/LBL cases and may result from diverse genetic alterations affecting CDKN2AB, CDKN1B, TP53, and/or RB1. RB1 maps to 13q14, the second most frequently deleted region in T-ALL/LBL (14%). These deletions often encompass DLEU1/2, long non-coding RNAs recurrently deleted in chronic lymphocytic leukemia, and/or RB1. Notably, an internal intron of RB1 harbors LPAR6, a G protein–coupled receptor that regulates cell proliferation and invasiveness, acting as either an oncogene or a tumor suppressor.

Aim: Occurrence and functional impact of 13q14 deletions affecting RB1 and LPAR6.

Methods: SNP array was used to identify copy number alterations in a cohort of 319 T-ALL/LBLs. Genomic studies included CI-FISH (La Starza R, 2020), which provided the genetic classification of 282 cases according to the main genetic subgroups, targeted custom NGS, and Whole Genome Sequencing (WGS). Gene expression studies were conducted by Whole Transcriptome Expression array (Bardelli V, 2025) and quantitative RT-PCR. Drug Response Profiling (DRP) (Pagliaro L, SIE 2025) on 70 drugs provided additional ex vivo functional data for a selection of 19 typical T-ALL cases.

Results: A focal biallelic deletion encompassing RB1 and LPAR6 (RB1–LPAR6bDEL) was detected in 18 of 319 cases (6%) and showed a significant association with a cortical immunophenotype and the TLX1 molecular subtype. This alteration frequently co-occurred with lesions affecting other cell cycle regulators (CDKN2A/B, CDKN1B, CCND2) in 94% of cases, as well as with NOTCH1/FBXW7 mutations (83%) and/or alterations in JAK/STAT pathway members (72%). WGS confirmed the biallelic deletion and identified an RCBTB2::LPAR6 fusion in the four cases defining the minimal common deleted region. Cases harboring the RB1–LPAR6bDEL displayed significant downregulation of RB1 and LPAR6 and concomitant upregulation of E2F1, E2F2, and E2F7, members of the E2F transcription factor family involved in cell cycle regulation and DNA replication/repair. GSEA and pathway analysis demonstrated significant enrichment of E2F1-related signatures and of gene sets involved in DNA replication, cell cycle progression, and DNA repair, together with enrichment for NOTCH and MYC target genes and activation of the Wnt signaling pathway. Finally, we observed that RB1–LPAR6bDEL T-ALLs exhibited higher ex vivo sensitivity to BCL2 inhibition, along with greater chemoresistance when compared to controls.

Conclusions: The RB1–LPAR6bDEL in cortical TLX1-positive T-ALL/LBL functionally recapitulates the effect of pRB phosphorylation, resulting in E2F1, E2F2, and E2F3 accumulation and subsequent S-phase entry and cell proliferation. Regarding the haploinsufficiency of LPAR6, which resembles that observed in normal CD34-positive cells, and the identification of the RCBTB2::LPAR6 fusion, further studies are warranted to elucidate their potential leukemogenic roles and the therapeutic implications.