v Summary

Targeting CDK12/13 to Overcome Glucocorticoid Resistance in Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Although research has dramatically improved survival rates, a subgroup of relapsed or refractory patients continues to experience poor outcomes. A primary predictor of treatment success is the patient's initial response to glucocorticoids, a mainstay of ALL induction therapy. Glucocorticoids bind to the glucocorticoid receptor to initiate a vast transcriptional shift that drives pro-apoptotic pathways and metabolic reprogramming. The failure of resistant cells to execute these programs led to the hypothesis that targeting the CDK12/CDK13/CCNK complex, a master regulator of RNA polymerase II responsible for maintaining oncogenic transcription, could restore pro-apoptotic susceptibility. In this study, we found that CDK12, CDK13, and CCNK are upregulated in B-ALL, with a strong functional dependency on this complex across B- and T-ALL models in CRISPR screen. Pharmacological inhibition of CDK12/13 was highly cytotoxic to ALL cells, sparing healthy peripheral blood mononuclear cells, and acted synergistically with dexamethasone, predominantly in B-ALL. Mechanistically, CDK12/13 inhibition suppressed growth-associated programs (such as mTORC1, *MYC*, and *E2F* targets), downregulated DNA repair genes, and induced alternative splicing events. This disruption activated cellular stress responses and uniquely potentiated the glucocorticoid-responsive transcriptional program in otherwise dexamethasone-resistant cells. Ultimately, targeting the CDK12/13 axis induced DNA damage, G2 cell cycle arrest, and apoptosis in dexamethasone-resistant B-ALL cells, establishing combined CDK12/13 inhibition and glucocorticoid therapy as a mechanistically rational strategy to overcome glucocorticoid resistance in ALL.