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Targeting subtype in ALL - Section 18

Current perspectives in T-ALL

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Take home messages

- To understand the biological differences between ETP ALL and T-ALL.
- To become familiar with major oncogenic drivers and targets with therapeutic potential in T-ALL.
- To appreciate different immunotherapy approaches in T-ALL.

Introduction

Transcriptomic and genomic profiling studies distinguish 2 major categories of T-cell acute lymphoblastic leukemia (T-ALL).[*1] Early T-cell precursor T-ALLs (ETP T-ALL) are characterized by a gene expression profile related to that of immature T-cell precursors, hematopoietic stem cells and myeloid progenitors.[*1] Genetically, these tumors show a pattern of mutations that overlaps with that of acute myeloid leukemia including high prevalence of activating mutations signaling factors, inactivating lesions in hematopoietic transcription factors and mutations targeting epigenetic regulators.[*1] In contrast, typical T-ALL tumors with transcriptional signatures related to those of developing thymocytes are characterized by deregulated cell cycle control and constitutively active NOTCH1 signaling.[*1]

Current state of the art

NOTCH1 signaling as therapeutic target

NOTCH1 signaling is a major driver of leukemia cell growth, metabolism, and survival in T-ALL.[2] Notably, small molecule gamma secretase inhibitors (GSIs) abrogate NOTCH1 signaling antagonizing the oncogenic effect of T-ALL-associated *NOTCH1* mutations[2] (Fig. 1). Early attempts to deploy GSIs as targeted therapy for T-ALL showed little success with limited therapeutic activity and marked intestinal toxicity, an on-target side effect derived from suppression of NOTCH signaling in the intestine.[2] However, GSI-induced NOTCH1 inhibition shows highly synergistic antileukemic effects with glucocorticoid against glucocorticoid resistant T-ALL and the combination of glucocorticoids with GSIs can effectively suppress the development of gastrointestinal toxicity derived from systemic inhibition of NOTCH-signaling.[3] In addition, multiple other therapeutics can also synergize with NOTCH1 inhibition in T-ALL[4] including suppression of NF-kappaB with bortezomib,[5] blocking mTOR with rapamycin[4,6] and inhibition of protein biosynthesis with withaferin.[4] Moreover, oncogenic NOTCH1 is also central for T-ALL cell metabolism[7] and inhibition of NOTCH1 signaling sensitizes leukemia cells to glutaminase inhibitors and render the dependent on autophagy for growth and survival.[7]

Cyclin-CDK complexes as therapeutic targets in T-ALL

Deregulated cell cycle progression as result of 9p deletions and consequent loss of CDKN2A-encoded tumor suppressor genes is a hallmark of T-ALL.[*1] Consequently, pharmacologic inhibition of CDK4/CDK6 which effectively restores cell cycle control mimicking the activity of P16/INK4A effectively suppresses T-ALL cell proliferation[8] (Fig. 1).

Targeting the *PI3K* pathway

PTEN, a tumor suppressor gene encoding a lipid phosphatase inhibitor of PI3K-mTOR signaling is lost in 10% to 20% of T-ALLs.[*1] Constitutively active PI3K signaling drives cell primarily cell growth and metabolism, but also proliferation and survival in T-ALL.[9] PI3K and mTOR inhibitors are in clinical development and can induce strong antileukemic effects in preclinical models of PTEN deficient T-ALL[10] (Fig. 1). In addition, constitutively active PI3K-mTOR signaling can interfere with the antileukemic effects of glucocorticoids[*11] supporting a role for glucocorticoid plus PI3K-mTOR inhibitor combination therapies for the treatment of T-ALL.[10,*11]

Targeting the *JAK/STAT* pathway

Cytokines promote cell proliferation and survival in early lymphoid progenitor cells and in leukemia lymphoblasts signaling via the JAK-STAT pathway. Activating mutations in the *IL7R*, *JAK1*, *JAK3*, and *STAT5* genes that induce increased JAK-STAT

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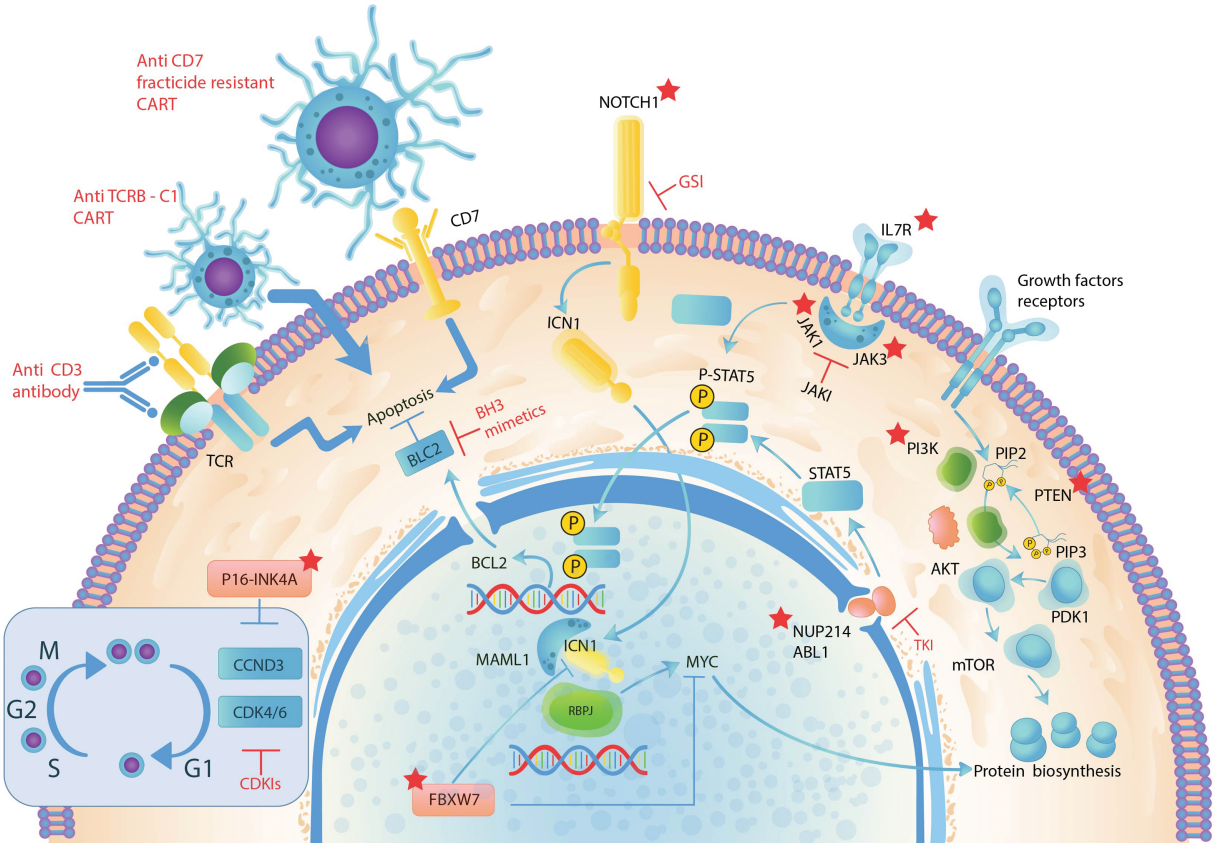

Figure 1. Oncogenic pathways, therapeutic targets, and immunotherapy-based treatments in T-ALL. Factors targeted by oncogenic mutations are marked with red stars. Targeted therapies are shown in red. CDKi: cyclin kinase inhibitor, GSI: γ-secretase inhibitor, PI3Ki: phosphatidylinositol 3 kinase inhibitor, JAKi: Janus kinase inhibitor, TKi: tyrosine kinase inhibitor ICN1: active intracellular NOTCH1, TCR: T-cell receptor.

signaling are highly prevalent in ETP-ALL leukemias and can also be found in typical T-ALL.[*1] Analysis of preclinical models support that inhibition of the JAK-STAT signaling pathway induce significant antileukemic effects in T-ALL and enhance the effect of glucocorticoid therapy[12] (Fig. 1). In this context, and most notably, the JAK-STAT inhibition can be effective not only in tumors harboring JAK-STAT activating mutations, but also in leukemias with enhanced sensitivity to pathway activation following stimulation with IL-7 as is the case of most ETP-ALL tumors.[12]

Tysosine kinase inhibitors in T-ALL

Tyrosine kinase fusion oncogenes are rarely found in T-ALL, yet they offer a unique opportunity for therapeutic targeting. The *NUP214-ABL1* oncogene present in 5% of T-ALL cases and less frequent *ABL1* gene fusions *EML1-ABL1* and *ETV6-ABL1* result in constitutive and oncogenic activation of ABL1 signaling, which can be blocked with small molecule tyrosine kinase inhibitors[*1] and these agents have shown clinical benefit in some cases.[13–15]

NT5C2 mutations in relapsed T-ALL

Relapsed T-ALL is genetically heterogeneous and frequently emerges via selection of ancestral populations via branched clonal evolution. Relapse-associated mutations in the cytosolic nucleotidase 2 gene (*NT5C2*) drive resistance to 6-mercaptopurine.[*16] *NT5C2* mutations can be found in 20% of T-ALL relapses with one hotspot allele *NT5C2* p.R367Q accounting for almost 90% of cases.[*16,17] Relapse-associated *NT5C2* mutations are gain of function alleles with increased nucleotidase activity and induce 6-MP resistance by facilitating the clearance of cytotoxic 6-MP-derived metabolites generated by the salvage pathway of purine biosynthesis.[*16,17]

The role of immunotherapy in T-ALL

Chimeric antigen receptor (CAR) T cells targeting T-cell antigens would kill each other. This barrier for product generation can be bypassed via CRISPR knockout of the T-cell antigen as demonstrated by the effective generation of CAR T cells with specificity against CD7.[18] A second strategy is the development of CAR T cells selectively targeting cells expressing a TCRB containing the C1 constant chain.[*19] The *TCRB* gene locus contains 2 alternatively sequences for the constant C region (C1 and C2) and the normal T-cell pool contains a mix of TCRB C1 and TCRB C2-expressing cells. Anti-TCRBC CAR T cells that specifically target TCRBC1 preserve the TCRBC2+ lymphocyte pool, and much of the immune repertoire with it, but effectively kills TCRBC1+ normal and malignant T-cells[*19] (Fig. 1). Finally, antibodies against CD3 can induce strong TCR signals in TCR+ T-ALLs, which triggers negative-selection-like programmed cell death.[20]

Future perspectives

The identification of druggable oncogenic driver genes and pathways offers new opportunities for therapeutic intervention in

clinical trials testing the safety and efficacy of new targeted drugs and immunotherapies in the treatment of T-ALL.

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