Leukemia

Major Finding: Coactivation of STAT5 and ERK suppressed transformation in B-cell acute lymphoblastic leukemia.

Concept: STAT5- or ERK-activating genetic lesions were common but nearly mutually exclusive in this cancer.

Impact: Reactivating a suppressed oncogenic pathway may synergize with inhibition of the primary driver.

THE ONCOGENES *STAT5* AND *ERK* HAVE OPPOSING ROLES IN LEUKEMOGENESIS

In B-cell acute lymphoblastic leukemia (B-ALL) and other cancers, transformation of normal cells into malignant cells generally requires the accumulation of multiple genetic aberrations. In an analysis of 1,148 B-ALL cases, Chan and colleagues found that STAT5- or ERK-activating genetic lesions were common, occurring in 31.4% or 33.6% of cases, respectively; however, only 3% of cases had concurrent STAT5 and ERK activation, a much lower percentage than expected by chance. Consistent with this, in B-ALL patient-derived xenografts, STAT5 phosphorylation and ERK phosphorylation were inversely related. Further, intermittent treatment of Philadelphia chromosome–positive B-ALL cells with the tyrosine kinase inhibitor ponatinib (which reduces STAT5 signaling) until the development of resistance resulted in a switch from dependence on STAT5 signaling to ERK signaling and sensitivity to the MEK1/2 inhibitor trametinib. Activating genetic lesions affecting STAT5 or ERK were correlated with pro-B-cell or pre-B-cell phenotypes, respectively, and the transition from a pro-B-cell to a pre-B-cell phenotype in mouse bone marrow was associated with activation of the master transcription factor BCL6 (normally upregulated by ERK and downregulated by STAT5) and suppression of the master transcription factor MYC (normally upregulated by STAT5 and downregulated by ERK). Further investigation showed that STAT5 and ERK played opposing roles in leukemogenesis; for example, activation of STAT5 or ERK alone increased colony formation and cell proliferation, but activation of both pathways suppressed colony formation and cell proliferation. Additionally, genetic ablation of the STAT5 pathway in ERK-driven B-ALL cells or the ERK pathway in STAT5-driven B-ALL cells increased colony formation *in vitro* and reduced the time to leukemia initiation *in vivo*. These results suggested that reactivation of a suppressed oncogenic pathway may synergize with inhibition of the primary oncogenic driver, an idea supported by *in vitro* and *in vivo* experiments. Together, this work provides a new perspective on the roles of oncogenes in B-ALL and implies that a new treatment paradigm based on exploiting these opposing functions may be worth investigating further. ■

Chan LN, Murakami MA, Robinson ME, Caeser R, Sadras T, Lee J, et al. Signalling input from divergent pathways subverts B cell transformation. Nature 2020;583:845–51.

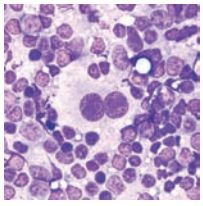
Clinical Trials

Major Finding: CD30-directed CAR T cells were safe and produced a 62% overall response rate in Hodgkin lymphoma.

Concept: In this phase I/II trial, responses were better (72%) with fludarabine-containing lymphodepletion.

Impact: This CAR T-cell therapy, perhaps with immune-checkpoint blockade, is worth investigating further.

CD30-TARGETED CAR T CELLS SHOW PROMISE IN PRETREATED HODGKIN LYMPHOMA



For the approximately 15% of patients with Hodgkin lymphoma who exhibit primary refractory or relapsed disease, currently available treatment options have efficacy that is lower than desired and can produce substantial treatment-related adverse events. Based on the fact that CD30 is ubiquitously expressed by the malignant cells of Hodgkin lymphoma and on evidence that this cell-surface receptor is therapeutically targetable, Ramos and colleagues initiated a phase I/II clinical trial of CD30-directed chimeric antigen receptor (CAR) T-cell therapy in 41 patients with $CD30^+$ relapsed or refractory Hodgkin lymphoma who had received at least two prior lines of therapy (range 2–23). Patients were pretreated with lymphodepleting agents including bendamustine alone, bendamustine plus fludarabine, or cyclophosphamide plus fludarabine. Among the 32 patients who received a fludarabine-containing lymphodepletion regimen, the overall response rate was 72%, including 59% with complete responses. The overall response rate among all 37 patients whose disease was evaluable for response was slightly lower, at 62%, with 51% being complete responses, reflecting the 0% overall response rate among the patients who received lymphodepletion with bendamustine alone. Among the patients who attained complete responses, five remained in complete remission after more than one year (range 15–25 months) following initial response assessment. With regard to safety, there were no dose-limiting toxicities, all instances of cytokine release syndrome were grade 1, and no neurotoxicity was observed, but grade 3 or higher hematologic adverse events were common. One notable toxicity was skin rash, which was observed in 48% of patients and may be attributable to CD30 expression by skin keratinocytes; however, the rashes observed were largely asymptomatic and transient. The favorable safety profile and preliminary evidence of efficacy of CD30-targeted CAR T-cell therapy in Hodgkin lymphoma supports continued investigation of this treatment, potentially in combination with immune-checkpoint blockade given that these CAR T cells have been shown to express PD-1. ■

Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. Jour Clin Oncol 2020 Jul 23 [Epub ahead of print].