Oncogenes

Major Finding: The histone acetyltransferase EP300 regulates TCF3–HLF, which promotes acute lymphoblastic leukemia.

Concept: In TCF3–HLF$^+$ patient-derived xenograft models, an EP300 inhibitor stalled leukemogenesis.

Impact: This study provides insight into TCF3–HLF-driven leukemia and identifies a potential vulnerability.

THE LEUKEMIA-DRIVING FUSION PROTEIN TCF3–HLF IS REGULATED BY EP300

The chimeric transcription factor TCF3–HLF characterizes a subtype of acute lymphoblastic leukemia (ALL) that is highly recalcitrant to treatment. In a study of this cancer-driving fusion protein, Huang, Mouttet, Warnatz, and colleagues first verified that TCF3–HLF is required for disease maintenance in an ALL cell line, a finding they confirmed in two patient-derived xenograft (PDX) mouse models of ALL. Further experiments in an ALL cell line implied that the presence of TCF3–HLF may interfere with transcriptional programs that ordinarily drive lymphoid differentiation and may also increase *MYC* RNA and MYC protein levels, promoting a stem-like state. In the ALL cells, TCF3–HLF predominantly occupied active enhancers, particularly superenhancers, and notably appeared to target a superenhancer cluster ~2 Mb downstream of *MYC*. Chromosome-conformation capture coupled with qPCR in the ALL cell line and the PDX models revealed that TCF3–HLF was required for spatial interactions between the *MYC* promoter and a pair of superenhancers occupied by the fusion protein. TCF3–HLF colocalized with the proto-oncoprotein ERG on chromatin in ALL cells, including at the previously noted *MYC* superenhancer, and loss of TCF3–HLF abolished ERG binding at all tested loci, whereas loss of ERG only moderately interfered with TCF3–HLF binding at the same sites, hinting that TCF3–HLF may act as a pioneer transcription factor in this context. Interactome profiling of TCF3–HLF in ALL cells uncovered interactions between the fusion protein and several other transcription factors; of note, there was evidence for interactions between TCF3–HLF and the histone acetyltransferase EP300 as well as some proteins implicated in leukemias and other cancers. In the PDX models, treatment with the EP300 inhibitor A-485 substantially reduced *TCF3–HLF* RNA levels, decreased the expression of genes activated by TCF3–HLF, and stalled leukemogenesis. Together, these results provide a detailed characterization of TCF3–HLF$^+$ ALL and identify EP300 as a potentially targetable vulnerability in this fatal subtype of leukemia. ■

Huang Y, Mouttet B, Warnatz HJ, Risch T, Rietmann F, Frommelt F, et al. The leukemogenic TCF3-HLF complex rewires enhancers driving cellular identity and self-renewal conferring EP300 vulnerability. Cancer Cell 2019;36:630–44.e9.

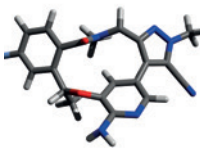
Clinical Trials

Major Finding: In a phase I/II trial, lorlatinib was safe and effective in *ROS1*-positive non–small cell lung cancer.

Concept: The drug was most effective in TKI-naïve patients, who had an objective response rate of 62%.

Impact: Proceding to larger, controlled trials, perhaps especially in TKI-naïve patients, is justified.

LORLATINIB IS ACTIVE IN *ROS1*-POSITIVE NON–SMALL CELL LUNG CANCER



In approximately 1% to 2% of patients with non–small cell lung cancer (NSCLC), chromosomal rearrangements of the *ROS1* locus (encoding the tyrosine kinase ROS1) are present. These patients may respond to ALK tyrosine kinase inhibitors (TKI), such as crizotinib, but most develop resistance. In a multicenter, open-label, single-arm, phase I/II clinical trial, Shaw and colleagues tested the safety and efficacy of the third-generation oral TKI lorlatinib in 69 patients with advanced, *ROS1*-positive NSCLC. Among the participants, 21 (30%) were TKI-naïve, 40 (58%) had previously been administered crizotinib, and 8 (12%) had previously received other TKIs. Overall, 28 patients (41%) had objective responses. The most favorable response rate was seen in the 21 TKI-naïve patients, among whom 13 patients (62%) had objective responses, including two patients (10%) who experienced complete responses and 11 patients (52%) who experienced partial responses. Further, five of the 11 patients (45%) in the TKI-naïve group who had brain metastases at baseline experienced objective responses, whereas eight of the 10 patients (80%) in the TKI-naïve group who did not have brain metastases at baseline experienced objective responses. Consistent with lorlatinib's ability to cross the blood–brain barrier, seven of the 11 patients (64%) in the TKI-naïve group who had brain metastases at baseline experienced intracranial objective responses. Among all 21 TKI-naïve patients, the median duration of response was 25.3 months. Of all 69 patients, 66 (96%) experienced at least one treatment-related adverse effect (most commonly hypercholesterolemia, hypertriglyceridemia, or edema), with serious treatment-related adverse effects occurring in five patients (7%). One patient (1%) permanently discontinued treatment due to adverse effects; however, no deaths deemed to be due to treatment occurred. Some limitations of the study include its small size and single-arm design. Although recruitment of *ROS1*-positive patients for future trials of lorlatinib may be challenging due to the small patient population, this trial indicates that further study of the drug is warranted, perhaps especially in TKI-naïve patients. ■

Shaw AT, Solomon BJ, Chiari R, Riely GJ, Besse B, Soo RA, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol 2019;20:1691–701.