**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.

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**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.

**impact:**


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

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**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.

Lorlatinib Is Active in ROS1-Positive Non–Small Cell Lung Cancer


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