Lung Cancer

Major Finding: The CLIP1–LTK fusion drives advanced non–small cell lung cancer (NSCLC) and represents a therapeutic target.

Concept: Constitutive activation of the LTK kinase by the CLIP1–LTK fusion increases tumor growth.

Impact: Targeting of this fusion using lorlatinib represents a potential therapy for NSCLC.

THE CLIP1–LTK FUSION IS AN ONCOGENIC DRIVER OF NSCLC

Although targeted therapy against known oncogenic drivers has improved outcomes for patients with non–small cell lung cancer (NSCLC), those with unknown oncogenic drivers lack therapeutic options. To address this, Izumi, Matsumoto, and colleagues applied whole-transcriptome sequencing of NSCLC samples with no known oncogenic drivers obtained from the lung cancer genome screening platform LC-SCRUM-Asia. In-frame fusion transcripts of the microtubule plus-end-tracking protein *CLIP1* and the receptor tyrosine kinase *LTK* were uncovered. Notably, all three patients with NSCLC that harbored the *CLIP1–LTK* fusion were negative for other known oncogenic drivers, suggesting that these drivers are mutually exclusive. As multiple coiled coil domains were predicted to be present in CLIP1 upstream of the LTK domain, it was hypothesized that these domains allowed protein dimerization and constitutive activation of LTK kinase. Mouse embryonic fibroblasts transfected with the CLIP1–LTK fusion were found to have more robust phosphorylation of LTK than cells transfected with wild-type LTK. Additionally, cells transfected with the CLIP1–LTK fusion exhibited larger colonies than cells with wild-type LTK or EGFR overexpression *in vitro*, demonstrating that CLIP1–LTK has transforming activity. Furthermore, only mouse xenografts with cells transduced with the CLIP1–LTK fusion formed tumors, whereas mice injected with cells overexpressing LTK did not. Lorlatinib, an inhibitor originally for ALK tyrosine kinases, was also effective in blocking LTK phosphorylation, inhibiting CLIP1–LTK-induced cell viability and growth, as well as inhibiting tumor growth of CLIP1–LTK cell injected into mice. The patient positive for the *CLIP1–LTK* fusion also received lorlatinib as an LTK-targeted therapy, and the 2- and 5-month follow-up CT images showed rapid and significant reduction of both primary and metastatic tumors. Overall, this study highlights the *CLIP1–LTK* fusion as a novel oncogenic driver of NSCLC and demonstrates lorlatinib as a potential therapy for patients with NSCLC who harbor this fusion. ■

Izumi H, Matsumoto S, Liu J, Tanaka K, Mori S, Hayashi K, et al. The CLIP1-LTK fusion is an oncogenic driver in non-small-cell lung cancer. Nature 2021;600:319–23.

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Immunotherapy

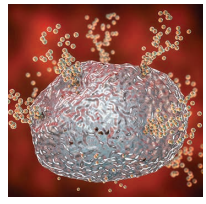
Major Finding: H1 antihistamines were associated with improved clinical outcome of immunotherapy treatments.

Concept: Histamine receptor H1 increases the cell membrane expression of the T-cell inhibitory receptor VISTA.

Impact: H1 antihistamines may potentially be used as an adjuvant treatment to improve immunotherapy response.

HIGH EXPRESSION OF HISTAMINE RECEPTOR, HRH1, REDUCES IMMUNOTHERAPY RESPONSE

Patient response to immune checkpoint blockade (ICB) remains variable. To investigate what may affect a patient's response to this type of therapy, Li, Xiao, and colleagues conducted a retrospective analysis on the effect of the top 40 charted pharmaceutical drugs patients were taking while on ICB therapy and their influence on ICB response. The only drug found to be significantly correlated with better survival, outside of aspirin, which is known to reduce the immunotherapy death rate in mice, were antihistamines specific for histamine receptor H1 (HRH1). This was observed in patients with melanoma and lung cancer taking ICB treatments but was not observed in patients only on chemotherapy, indicating tumor cells were not being directly targeted. Further analysis revealed that high HRH1 expression correlated with the dysfunction of T cells as well as poor survival in triple-negative breast cancer (TNBC) and lung adenocarcinoma with a strong trend in melanoma. Additionally, tumors with high HRH1 expression demonstrated resistance to immunotherapy and had shorter overall survival. Investigation into the specific expression pattern of HRH1 revealed low expression on tumor cells but high expression on M2 immunosuppressive macrophages, with histamine, the ligand for HRH1, also being highly expressed



in the blood of patients with TNBC and colon cancer. Antitumor immunity was restored upon HRH1 inhibition through polarization of macrophages back to an M1 phenotype and reduction of macrophage-mediated T-cell suppression. The effect of macrophage HRH1 on T-cell suppression was found to be mediated mostly by modulation of the inhibitory receptor, VISTA, expression on the cell membrane through alterations to Ca^{2+} release. Inhibition of HRH1 along with ICB treatment increased therapy response in multiple tumor models. Lastly, allergic responses led to significantly worse outcomes in both murine tumor models and retrospective patient analyses, and patients with high levels of plasma histamine had worse response to ICB compared to those with low levels of histamine. Thus, this study indicates the role that histamine or preexisting allergies play in ICB response and suggests the combinatorial use of H1 antihistamines to improve immunotherapy outcomes. ■

Li H, Xiao Y, Li Q, Yao J, Yuan X, Zhang Y, et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. Cancer Cell 2022;40:36–52.e9.

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