

Lung Cancer

Major finding: Combined ALK and IGF1R blockade synergistically inhibits ALK fusion-positive lung cancer growth.

Mechanism: IGF1R signaling via IRS1 sustains downstream signaling and promotes ALK inhibitor resistance.

Impact: Cotargeting IGF1R and ALK may be an effective therapeutic approach for ALK fusion-positive lung cancer.

IGF1R SIGNALING IS A THERAPEUTIC TARGET IN ALK FUSION-POSITIVE LUNG CANCER

Patients with lung cancer harboring fusions in the anaplastic lymphoma receptor tyrosine kinase (*ALK*) gene exhibit prolonged progression-free survival following treatment with the ALK tyrosine kinase inhibitor (TKI) crizotinib, but inevitably develop resistance. However, the mechanisms of resistance to ALK inhibition are not fully understood. Lovly and colleagues describe a patient with *ALK* fusion-positive (*ALK*⁺) lung cancer who had an exceptional response to insulin-like growth factor 1 receptor (IGF1R) inhibition, suggesting potential crosstalk between IGF1R and ALK. Treatment of *ALK*⁺ TKI-sensitive lung cancer cell lines with the combination of crizotinib and IGF1R inhibitors resulted in a synergistic decrease in cell proliferation, enhanced apoptosis, and reduced phosphorylation of downstream effectors compared with crizotinib alone. Conversely, the addition of IGF1 promoted crizotinib resistance by inducing IGF1R phosphorylation, indicating that IGF1R signaling may compensate for reduced ALK signaling during crizotinib therapy. Insulin receptor substrate 1 (IRS1), an adaptor protein for IGF1R, also interacted with and functioned as an adaptor protein for ALK, and IRS1 depletion increased



the sensitivity of *ALK*⁺ cells to crizotinib. In addition, ALK TKI-resistant lung cancer cells displayed enhanced IGF1R activation compared with isogenic ALK TKI-sensitive cells, and patient tumor samples showed increased IGF1R and IRS1 levels at the time of crizotinib resistance, validating the relationship between IGF1R and ALK *in vivo*. Inhibition of IGF1R or knockdown of IRS1 partially restored the sensitivity of ALK TKI-resistant cells to ALK inhibition. Furthermore, LDK-378 (ceritinib), a second-generation ALK inhibitor that has shown activity in patients who progressed on crizotinib, more potently inhibited *ALK*⁺ xenograft growth than crizotinib and also inhibited IGF1-induced phosphorylation of IGF1R *in vitro*, suggesting that this agent may function by blocking both ALK and IGF1R. These results identify cooperative effects of ALK and IGF1R inhibitors in *ALK*⁺ lung cancer and suggest that this combination treatment may limit or overcome resistance to ALK inhibitor therapy. ■

Lovly CM, McDonald NT, Chen H, Ortiz-Cuaran S, Heukamp LC, Yan Y, et al. Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer. *Nat Med* 2014;20:1027–34.

Drug Discovery

Major finding: Small molecules that selectively bind RAL-GDP inhibit RAL activity and suppress tumor growth.

Approach: Structure-based screening identified allosteric inhibitors that block RAL effector binding.

Impact: RAL-targeting molecules provide useful research tools and new avenues for cancer therapeutics.

SMALL MOLECULES INHIBIT THE RAS-LIKE SMALL GTPASES RALA AND RALB

Activating RAS mutations are found in over one-third of human tumors; however, efforts to directly target oncogenic RAS by inhibiting its posttranslational modifications have thus far been unsuccessful. An alternative approach is the development of inhibitors targeting signaling pathways downstream of RAS, including the RAS-like small GTPases RALA and RALB, which have been implicated in the proliferation, survival, and metastasis of several human cancers. Yan and colleagues performed a structure-based virtual screen to identify small molecules that selectively bind to a site within RALA-GDP that is proximal to, but independent of, the guanine nucleotide binding pocket. Of the 88 candidate compounds, three small molecules suppressed RALA activity in human bladder cancer cells, as measured by a decrease in RALA binding to its effector protein RAL-binding protein 1, without affecting the interaction of RALA with GTP or GDP. In addition, these three compounds, RBC6, RBC8, and RBC10, reduced RAL-driven cell spreading of murine

embryonic fibroblasts. Nuclear magnetic resonance spectroscopy revealed that RBC8 and an RBC8 derivative, BQU57, were selective for this allosteric site in the GDP-bound form of RAL, supporting the notion that these compounds lock RAL in an inactive state. Treatment with RBC8 or BQU57 impaired the anchorage-independent growth of human lung cancer cell lines and suppressed the growth of human lung cancer xenografts *in vivo* in a dose-dependent manner, similar to the effects of concomitant knockdown of *RALA* and *RALB*. These antitumor effects were mediated via specific inhibition of *RALA* and *RALB* activation, but not RAS or RHOA activity. These first-generation small-molecule RAL inhibitors provide a new tool for the study of RAL signaling and a potential therapeutic strategy for RAL-driven cancers. ■

Yan C, Liu D, Li L, Wempe ME, Guin S, Khanna M, et al. Discovery and characterization of small molecules that target the GTPase RAL. *Nature* 2014 Sep 14 [Epub ahead of print].