RESEARCH WATCH

Tumor Heterogeneity

**Major finding:** NSCLC is characterized by branched evolution and pronounced intratumor genomic heterogeneity.

**Approach:** Next-generation sequencing revealed subclonal diversification and diverse mutational processes.

**Impact:** Intratumor heterogeneity is likely to pose a challenge for therapeutic strategies in NSCLC.

MULTIREGION SEQUENCING IDENTIFIES INTRATUMOR HETEROGENEITY IN NSCLC

Targeting of oncogenic drivers in non-small cell lung cancer (NSCLC) represents an attractive therapeutic strategy; however, early genomic characterization of these tumors suggests that intratumor heterogeneity may present a challenge to effective treatment. Zhang and colleagues assessed the extent of genomic diversity in NSCLC by performing whole-exome sequencing on 48 regions from 11 lung adenocarcinomas, primarily consisting of stage I disease. Although the majority of mutations were detected in all tumor regions, evidence for intratumor heterogeneity was also observed in each tumor. Phylogenetic analysis revealed that mutations in MYCN, which is commonly amplified and copy-number altered in NSCLC, are associated with poor prognosis. ALK-driven activation of MYCN in neuroblastoma cell lines and that ERK5 activation targets. Umapathy and colleagues found that ALK stimulated MYCN expression and potentially overcome crizotinib resistance in patients with ALK-positive neuroblastoma.

**Mechanism:** ALK-driven activation of ERK5 via PI3K/AKT and MEKK3 is required for MYCN transcription.

**Impact:** ERK5 blockade may enhance the efficacy of the ALK inhibitor crizotinib in ALK-positive neuroblastoma.

Neuroblastoma

**Major finding:** ERK5 promotes ALK-induced transcription of MYCN and enhances neuroblastoma cell proliferation.

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ERK5 IS A POTENTIAL THERAPEUTIC TARGET IN ALK-POSITIVE NEUROBLASTOMA

Anaplastic lymphoma kinase (ALK) has been implicated as an oncogenic driver in pediatric neuroblastoma and is frequently activated by amplification and gain-of-function mutations. However, results from phase I trials have suggested that, in contrast to other tumor types such as non-small cell lung cancer, single-agent therapy with the ALK inhibitor crizotinib is not effective in pediatric patients with ALK-positive neuroblastoma, underscoring the need to identify additional therapeutic targets. Umapathy and colleagues found that ALK stimulated phosphorylation of the kinase ERK5 (also known as MAPK7) in ALK-positive neuroblastoma cell lines and that ERK5 activation was necessary for ALK-induced transcription of the oncogene MYCN, which is commonly amplified in neuroblastoma and is associated with poor prognosis. ALK-driven activation of ERK5 was mediated by PI3K-AKT signaling and downstream phosphorylation of the ERK5 activator MEKK3 (also known as MAP3K3), and treatment with crizotinib or PI3K pathway inhibitors diminished the levels of phosphorylated ERK5 in the nucleus and reduced NMYC expression in neuroblastoma cells. Single-agent treatment with the ERK5 inhibitor XMD8-92 impaired the proliferation of ALK-positive, MYCN-amplified neuroblastoma cell lines in vitro, indicating that ERK5 may be a potential therapeutic target. Furthermore, combined treatment with crizotinib and XMD8-92 synergistically decreased neuroblastoma cell growth, suggesting that ERK5 blockade may enhance the efficacy of crizotinib in ALK-positive neuroblastoma. Consistent with this idea, dual inhibition of ALK and ERK5 more effectively inhibited the growth of ALK-positive xenograft tumors in vivo compared with single-agent treatment and resulted in reduced expression of NMYC in tumors. These findings suggest that concomitant ALK and ERK5 inhibition may represent an effective therapeutic strategy to suppress oncogenic MYCN expression and potentially overcome crizotinib resistance in patients with ALK-positive neuroblastoma.

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Multiregion Sequencing Identifies Intratumor Heterogeneity in NSCLC

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