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 lung cancer, occurred early in tumor development. Importantly, patients who experienced tumor relapse displayed an increased proportion of clonal mutations in primary tumors, suggesting that subclonal mutations may represent a biomarker and driver of tumor recurrence. Consistent with these findings, de Bruin and colleagues detected significant intratumor heterogeneity and evidence of branched tumor evolution in NSCLC using whole-exome and/or whole-genome sequencing of 25 spatially distinct regions from seven stage IB–IIIB tumors. Importantly, however, in addition to clonal driver mutations occurring early in tumor evolution, this analysis also identified the presence of subclonal cancer driver mutations and late-stage copy-number alterations, challenging the notion that a single biopsy is sufficient to define all tractable oncogenic events. In addition, temporal analysis of genomic instability in tumors from former smokers suggested a prolonged latency period between genome-doubling and detection of clinical disease. Furthermore, analysis of point mutations by both groups revealed a global shift in the mutational landscape and diversity in genomic instability processes over time, with a decrease in smoking-associated mutations in late tumors and an increase in subclonal C>T and C>G mutations associated with APOBEC cytidine deaminase activity. Together, these results emphasize that deep sequencing efforts of multiple tumors will likely be required to accurately assess intratumor heterogeneity, identify subclonal oncogenic drivers, and predict patient relapse in NSCLC.


NEUROBLASTOMA

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.

ERK5 Is a Potential Therapeutic Target in ALK-Positive Neuroblastoma

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