Targeted Therapy

Major finding: Coinhibition of CHK1 and MK2 synergistically stimulates apoptosis in *KRAS*-mutant cancer cells.

Concept: *KRAS*- and *BRAF*-mutant tumors exhibit genotoxic stress that induces tonic activation of CHK1 and MK2.

Impact: Combined inhibition of CHK1 and MK2 may provide a clinical benefit in *KRAS*- or *BRAF*-driven cancers.

DUAL CHECKPOINT ABROGATION IS SYNERGISTIC IN *KRAS*-MUTANT CANCER

In response to genotoxic stress, the DNA damage response, which is governed primarily by the ATM–CHK2, ATR–CHK1, and p38–MK2 (also known as MAPKAPK2) checkpoint effector pathways, becomes activated in order to slow cell-cycle progression and allow time for DNA repair. The CHK1 and MK2 pathways converge on inhibition of cell division cycle 25 (CDC25)–mediated activation of cyclin-dependent kinases, prompting Dietlein and colleagues to hypothesize that simultaneous small-molecule inhibition of CHK1 and MK2 may synergistically silence the DNA damage checkpoint. To systematically characterize combinatorial drug–inhibitor relationships, 96 cancer cell lines were screened with various concentrations of the CHK1 inhibitor PF477736 and the MK2 inhibitor PF3644022, and PreCISE (predictor of chemical inhibitor synergistic effects) software was used to calculate synergism scores based on GI_{50} drug curves. Synergistic effects between PF477736 and PF3644022 were observed in 33 of 96 cell lines and were correlated with mutations in the *KRAS* or *BRAF* oncogenes or deletion of the tumor suppressor gene *CDKN2A*. Combined CHK1/MK2 inhibition prevented CDC25B phosphorylation, promoted apoptosis, and reduced long-term survival specifically in *KRAS*-, *BRAF*- or *CDKN2A*-altered cell lines, but had little effect in nonsynergistic lines or as single agents. Mechanistically, *KRAS*-driven cells were characterized by tonic activation of CHK1 and MK2, indicative of oncogene-induced genotoxic stress, and cotreatment with PF477736 and PF3644022 enhanced DNA damage and triggered mitotic catastrophe in synergistic cell lines. Combined CHK1/MK2 inhibition suppressed *KRAS*-mutant tumor growth *in vivo* and extended overall survival in mice. Furthermore, human *KRAS*-mutant tumors exhibited chronic activation of CHK1 and MK2, and patient-derived *KRAS*- or *BRAF*-mutant cancer cells displayed exquisite sensitivity to combined CHK1/MK2 inhibition *ex vivo*. Together, these results suggest that *KRAS*- and *BRAF*-mediated oncogenic stress confers dependency on the CHK1/MK2 checkpoint and provide a rationale for combinatorial inhibition of CHK1 and MK2 as a therapeutic strategy in *KRAS*- or *BRAF*-driven tumors. ■

Dietlein F, Kalb B, Jokic M, Noll EM, Strong A, Tharun L, et al. A synergistic interaction between Chk1 and MK2 inhibitors in KRAS*-mutant cancer. Cell 2015;162:146–59.*

Lung Cancer

Major finding: SCLC is characterized by oncogenic *TP73* rearrangements and inactivating mutations in NOTCH genes.

Concept: Comprehensive analysis revealed complex rearrangements and universal *TP53* and *RB1* inactivation.

Impact: Rare mutations in kinase genes suggest potential therapeutic targets in individual patients.

GENOMIC PROFILING IDENTIFIES RECURRENT GENETIC ALTERATIONS IN SCLC

Patients with small cell lung cancer (SCLC) initially respond to chemotherapy, the most common treatment strategy for SCLC, but inevitably experience lethal recurrence, demonstrating the need to discover new therapeutic targets in SCLC. Past whole-exome sequencing efforts have identified only a few recurrent mutations in SCLC. To identify the complex genomic rearrangements that contribute to SCLC pathogenesis, George, Lim, and colleagues performed whole-genome sequencing (WGS) of 110 human SCLC tumors, as well as transcriptome and copy-number analysis of a subset of these tumors and WGS or whole-exome sequencing of 8 SCLC tumors from mice carrying conditional alleles for *Trp53*, *Rb1*, and *Rbl2*. This comprehensive analysis identified biallelic inactivation of *TP53* and *RB1* via missense mutations or complex genomic translocations in all but two human SCLCs, a frequency higher than that previously reported. In addition, two tumors with wild-type *RB1* were affected by chromothripsis and exhibited overexpression of cyclin D1, suggesting that *RB1* inactivation in SCLC can result via an alternative mechanism. WGS also revealed rare mutations in kinase genes, such as *BRAF* and *PIK3CA*, which suggest that individual patients may benefit from targeted therapies. *TP73* was altered in 13% of human SCLCs by somatic mutations or genomic rearrangements, the latter resulting in oncogenic N-terminally truncated *TP73* transcript variants, including p73Δex2/3, which have been shown to exert a dominant-negative effect on *TP53*. Furthermore, inactivating genomic alterations in NOTCH family genes were identified in 25% of human SCLC tumors. Activation of NOTCH signaling reduced the number of SCLC tumors and increased survival in a *Trp53;Rb1;Rbl2*–deficient mouse model of SCLC and abolished neuroendocrine gene expression in SCLC cell lines. Together, these results show that universal inactivation of *TP53* and *RB1* is required for SCLC pathogenesis, identify NOTCH genes as tumor suppressors and regulators of neuroendocrine differentiation in SCLC, and suggest new therapeutic targets for SCLC. ■

George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47–53.