Colorectal Cancer

Major finding: Germline variants of *POLD1* and *POLE* predispose to colorectal adenomas and carcinomas.

Concept: DNA polymerase δ and ε proofreading domain mutations impair correction of mispaired bases.

Impact: Individuals with an unexplained history of colorectal neoplasia may harbor *POLE* or *POLD1* mutations.

GERMLINE DNA POLYMERASE MUTATIONS INCREASE CANCER SUSCEPTIBILITY

Germline mutations in at least 10 genes have been implicated in familial colorectal cancer predisposition syndromes, but some individuals with a family history of multiple benign colorectal adenomas or early-onset colorectal cancer do not have mutations in known cancer predisposition genes. To uncover additional risk variants, Palles and colleagues used linkage analysis to identify shared genomic regions among affected individuals within single families and searched for nonsilent coding variants within these regions. Analysis of one family identified a heterozygous germline mutation in *POLE*, which encodes the catalytic subunit of DNA polymerase ε, the enzyme responsible for synthesis and proofreading of the leading strand during DNA replication. This variant, which results in an amino acid substitution in the active site of the exonuclease domain that mediates proofreading, was identified in 12 additional unrelated individuals with a family history of colorectal tumors within a large validation set but was not identified in any control subjects. A similar analysis of another family identified a heterozygous mutation in *POLD1* affecting the exonuclease domain of DNA polymerase δ, the enzyme that mediates lagging strand synthesis and proofreading. *POLD1* mutation carriers were also prone to endometrial cancer, as is the case in patients with Lynch syndrome. The affected POLD1 and POLE residues are highly conserved, and the equivalent mutations led to a mutator phenotype in *Schizosaccharomyces cerevisiae* caused by increased base substitution arising from impaired exonuclease activity. Mapping of these mutations onto the structure of yeast DNA polymerase suggested that both likely induce detrimental exonuclease active site conformational changes. Consistent with these findings, *POLD1*- and *POLE*-mutant tumors were microsatellite stable but had an increased rate of base substitution mutations. POLD1 and POLE mutations should therefore be considered in patients with an unexplained history of multiple colorectal adenomas or early-onset cancers. ■

Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet 2012 Dec 23 [Epub ahead of print].

Targeted Therapy

Major finding: BCL-XL and MEK inhibition cooperate to induce regression of *KRAS*-mutant cancer models.

Mechanism: BH3 mimetics free BIM from BCL-XL–mediated suppression following MEK inhibition.

Impact: Pairing cytostatic targeted therapies with proapoptotic agents may improve clinical responses.

COMBINED MEK AND BCL-XL INHIBITION KILLS *KRAS*-MUTANT CELLS

Activating mutations in *KRAS* are among the most common genetic events in human cancers. Strategies to treat *KRAS*-mutant cancers are urgently needed because KRAS remains an intractable drug target. Preclinical studies have indicated that inhibition of MEK, a key KRAS effector, potently suppresses proliferation of *KRAS*-mutant cancer cells, but these cytostatic effects have not translated into clinical responses in patients with *KRAS*-mutant tumors. Based on the premise that the complexity of KRAS signaling may require simultaneous targeting of more than one effector pathway, Corcoran and colleagues screened a small hairpin RNA (shRNA) library targeting druggable genes for those that cooperated with selumetinib and other MEK inhibitors to selectively reduce the viability of *KRAS*-mutant cell lines. The top scoring gene was *BCL2L1*, encoding the antiapoptotic BH3 family member BCL-XL. The combination of selumetinib and navitoclax, a clinically available BH3 mimetic that inhibits the prosurvival function of BCL-XL by blocking its ability to bind and sequester proapoptotic proteins, had a significantly greater effect on proliferation and survival of *KRAS*-mutant cell lines than either agent did alone. Levels of the proapoptotic protein BIM increased in response to selumetinib, along with a proportional increase in the amount of BCL-XL bound to BIM, suggesting that suppression of prosurvival molecules such as BCL-XL can induce cell death in response to selumetinib by freeing BIM from inhibition. Indeed, navitoclax completely blocked the interaction between BIM and BCL-XL in selumetinib-treated cells, and combined use of selumetinib and navitoclax induced significant tumor regression in KRAS-driven mouse cancer models. Together, these findings suggest that combined inhibition of BCL-XL and MEK may be effective in *KRAS*-mutant cancers and underscore the therapeutic potential of augmenting the effects of targeted therapies with potentiators of apoptosis. ■

Corcoran RB, Cheng KA, Hata AN, Faber AC, Ebi H, Coffee EM, et al. Synthetic lethal interaction of combined BCL-XL and MEK inhibition promotes tumor regressions in KRAS mutant cancer models. Cancer Cell 2013;23:121–8.