

## Drug Resistance

**Major finding:** *ESR1*, the gene encoding estrogen receptor (ER)  $\alpha$ , is mutated in hormone-resistant breast cancer.

**Concept:** Ligand-binding domain mutations lead to constitutive ER $\alpha$  activity and reduce hormonal therapy efficacy.

**Impact:** Patients with *ESR1* mutations may respond to alternate therapies that target ER signaling.

### ESR1 MUTATIONS ARE RECURRENT IN HORMONE-RESISTANT BREAST CANCER

Hormone therapy, an inclusive term for drugs that inhibit estrogen receptor (ER) signaling or block estrogen production, is initially effective in the approximately 70% of patients with breast cancer who have ER-positive tumors, but many patients develop resistance after long-term drug exposure. Toy and colleagues performed sequencing and copy number analysis of commonly mutated genes in tumors from patients with metastatic ER-positive breast cancer who progressed while on hormone therapy to identify potential resistance mechanisms, and Robinson and colleagues performed whole-exome sequencing of patients with hormone-resistant metastatic ER-positive breast cancer enrolled in a clinical sequencing program to identify actionable mutations for personalized therapy. Remarkably, both groups identified recurrent mutations affecting the ligand-binding domain of estrogen receptor 1 (*ESR1*), the gene encoding ER $\alpha$ , that were not observed in unselected or untreated populations. These ER $\alpha$  mutants had markedly increased transcriptional activity in the absence of ligand and promoted hormone-independent tumor growth after estrogen deprivation *in vivo*. Consistent with these findings, structural analyses indicated that the mutant proteins adopted a con-

formation similar to agonist-bound wild-type ER $\alpha$  regardless of the presence of ligand. ER antagonists such as tamoxifen or fulvestrant were still effective against the ligand-binding domain ER $\alpha$  mutants, but Toy and colleagues noted that the mutant proteins retained a significant amount of residual activity and required higher drug doses than wild-type ER $\alpha$  for full inhibition. Although studies of larger cohorts of patients with ER-positive breast cancer before and after hormone therapy will be needed to determine the frequency of acquired *ESR1* mutations, these studies implicate mutations in the ligand-binding domain of ER $\alpha$  as a potential hormone therapy resistance mechanism and suggest that patients with activating *ESR1* mutations may benefit from more potent or selective ER antagonists or alternate therapies that target ER signaling. ■

Toy W, Shen Y, Won H, Green B, Sakr RA, Will M, et al. *ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet* 2013;45:1439–45.

Robinson DR, Wu YM, Vats P, Su F, Lonigro RJ, Cao X, et al. *Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet* 2013;45:1446–51.

## Signaling

**Major finding:**  $\alpha$ -Catenin is part of the APC destruction complex and regulates  $\beta$ -catenin-dependent transcription.

**Clinical relevance:**  $\alpha$ -Catenin binds to the catenin inhibitory domain of APC, which is often deleted in colon cancer.

**Impact:**  $\alpha$ -Catenin may play a broader role in the regulation of WNT/ $\beta$ -catenin signaling than previously realized.

### $\beta$ -CATENIN IS TARGETED TO THE APC DESTRUCTION COMPLEX BY $\alpha$ -CATENIN

Somatic mutations of the adenomatous polyposis coli (*APC*) tumor suppressor gene are found in the majority of colon cancers and usually result in truncation of the APC protein. Inactivation of APC, which normally binds  $\beta$ -catenin and cooperates with other proteins in a destruction complex to promote  $\beta$ -catenin proteolysis, promotes tumorigenesis due to aberrant  $\beta$ -catenin stabilization and activation of WNT/ $\beta$ -catenin target genes. Paradoxically, mutant APC proteins often lack the catenin inhibitory domain (CID), which is required for proteasomal degradation of  $\beta$ -catenin, but  $\beta$ -catenin does not interact with the CID. Choi and colleagues performed a proteomic analysis of APC-interacting proteins and detected  $\alpha$ -catenin, which is known to link the actin cytoskeleton to adhesion complexes and interact with  $\beta$ -catenin at cell-cell adherens junctions. Unexpectedly,  $\alpha$ -catenin was found to bind the APC CID and was required for not only the interaction between  $\beta$ -catenin and APC but also the ubiquitination and proteolysis of  $\beta$ -catenin. Phosphorylation of  $\alpha$ -catenin on tyrosine 117, which frequently occurs in transformed cells, significantly inhibited  $\alpha$ -catenin binding to APC, suggesting



that  $\alpha$ -catenin phosphorylation may be a common way in which cancer cells upregulate  $\beta$ -catenin activity and raising the possibility that targeting kinases upstream of  $\alpha$ -catenin may have the added benefit of promoting  $\beta$ -catenin destruction. In response to WNT signal,  $\beta$ -catenin recruits  $\alpha$ -catenin to WNT/ $\beta$ -catenin target gene promoters.  $\alpha$ -Catenin then recruits APC, and the two proteins cooperate to repress transcription by recruiting lysine-specific demethylase 1, reducing histone H3 lysine 4 methylation, and promoting  $\beta$ -catenin release at WNT/ $\beta$ -catenin target genes. Collectively, these findings indicate that  $\alpha$ -catenin plays a central role in the regulation of  $\beta$ -catenin stability and WNT/ $\beta$ -catenin target gene regulation as part of the APC destruction complex and suggests that APC mutations or  $\alpha$ -catenin phosphorylation promote  $\beta$ -catenin stability and transcriptional activity by disrupting the interaction between APC and  $\alpha$ -catenin. ■

Choi SH, Estarás C, Moresco JJ, Yates JR 3rd, Jones KA.  *$\alpha$ -Catenin interacts with APC to regulate  $\beta$ -catenin proteolysis and transcriptional repression of Wnt target genes. Genes Dev* 2013;24:2473–88.