Drug Resistance

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

Concept: Ligand-binding domain mutations lead to constitutive ERα 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 ERα, that were not observed in unselected or untreated populations. These ERα 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 conformation similar to agonist-bound wild-type ERα regardless of the presence of ligand. ER antagonists such as tamoxifen or fulvestrant were still effective against the ligand-binding domain ERα 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 ERα 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 ERα 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: α-Catenin is part of the APC destruction complex and regulates β-catenin–dependent transcription.

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

Impact: α-Catenin may play a broader role in the regulation of WNT/β-catenin signaling than previously realized.

β-CATENIN IS TARGETED TO THE APC DESTRUCTION COMPLEX BY α-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 β-catenin and cooperates with other proteins in a destruction complex to promote β-catenin proteolysis, promotes tumorigenesis due to aberrant β-catenin stabilization and activation of WNT/β-catenin target genes. Paradoxically, mutant APC proteins often lack the catenin inhibitory domain (CID), which is required for proteasomal degradation of β-catenin, but β-catenin does not interact with the CID. Choi and colleagues performed a proteomic analysis of APC-interacting proteins and detected α-catenin, which is known to link the actin cytoskeleton to adhesion complexes and interact with β-catenin at cell–cell adherens junctions. Unexpectedly, α-catenin was found to bind the APC CID and was required for not only the interaction between β-catenin and APC but also the ubiquitination and proteolysis of β-catenin. Phosphorylation of α-catenin on tyrosine 117, which frequently occurs in transformed cells, significantly inhibited α-catenin binding to APC, suggesting that α-catenin phosphorylation may be a common way in which cancer cells upregulate β-catenin activity and raising the possibility that targeting kinases upstream of α-catenin may have the added benefit of promoting β-catenin destruction. In response to WNT signal, β-catenin recruits α-catenin to WNT/β-catenin target gene promoters. α-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 β-catenin release at WNT/β-catenin target genes. Collectively, these findings indicate that α-catenin plays a central role in the regulation of β-catenin stability and WNT/β-catenin target gene regulation as part of the APC destruction complex and suggests that APC mutations or α-catenin phosphorylation promote β-catenin stability and transcriptional activity by disrupting the interaction between APC and α-catenin. ■

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