Ovarian Cancer

Major finding: Somatic *DICER1* hot-spot mutations occur in 29% of nonepithelial ovarian cancers.

Mechanism: *DICER1* RNase IIIb domain mutations impair miRNA but not miRNA* strand cleavage.

Impact: Residual *DICER1* function may be oncogenic in specific cellular contexts.

DICER1 MUTATIONS IN NONEPITHELIAL OVARIAN CANCERS MAY BE ONCOGENIC

Sex cord–stromal tumors and germ cell tumors are rare nonepithelial variants of ovarian cancer for which the pathogenesis is poorly understood. Heravi-Moussavi and colleagues performed whole-exome and whole-transcriptome sequencing of 14 nonepithelial ovarian tumors and identified 4 heterozygous nonsynonymous missense mutations in the microRNA (miRNA) processing gene *DICER1*. Because these mutations were closely clustered in a hot spot encompassing the metal-binding residues of the DICER1 RNase IIIb domain, the authors sequenced this region in a validation set of 102 additional nonepithelial ovarian cancers. *DICER1* hot-spot mutations were identified in 30 of these tumors, with the vast majority occurring in Sertoli-Leydig cell tumors, a subtype of ovarian sex cord–stromal tumors. In total, 60% of the Sertoli-Leydig cell tumors included in the validation set harbored a *DICER1* mutation. The authors performed *in vitro* RNA cleavage assays to determine the effect of these hot-spot mutations on DICER1 activity and showed that these mutants had severely impaired RNase IIIb activity that affected cleavage of the miRNA targeting strand. However, the mutants displayed normal RNase IIIa–mediated cleavage of the imperfectly complementary miRNA* strand and tumors with hot-spot mutations were positive for DICER1 expression and had normal levels of mature and processed miRNA, suggesting that these were not loss-of-function mutations. Instead, the recurrent, focal nature of the *DICER1* mutations and incomplete loss of DICER1 enzymatic activity observed in nonepithelial ovarian tumors indicate that, in certain cell types, aberrant miRNA processing may be oncogenic. The cell type–specific nature of these mutations is particularly interesting given that epithelial ovarian cancers rarely harbor *DICER1* mutations and often exhibit decreased *DICER1* expression. Further research is needed to determine which aspects of DICER1 functional impairment drive tumorigenesis and whether these mutations are present in other cancer types. ■

Heravi-Moussavi A, Anglesio MS, Cheng SW, Senz J, Yang W, Prentice L, et al. Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. N Engl J Med 2012;366:234–42.

Breast Cancer

Major finding: Unique ER-binding site acquisition is associated with poor outcome in ER-positive tumors.

Mechanism: The plasticity of ER binding may be mediated by the pioneer factor FOXA1.

Impact: Resistance to hormone therapies is not caused by loss of ER binding to DNA.

ESTROGEN RECEPTOR BINDING PROFILES PREDICT BREAST CANCER OUTCOME

Estrogen receptor α (ER) is overexpressed in the majority of breast cancers, but the relationship between ER-binding activity and prognosis is unclear because genome-wide binding studies have been restricted to breast cancer cell lines. Ross-Innes and colleagues performed ER chromatin immunoprecipitation and high-throughput sequencing (ChIP-seq) in a panel of primary ER-positive and ER-negative breast cancers with known outcomes and identified a core set of binding sites that were present in 75% of all ER-positive tumors regardless of outcome, indicating that ER still binds to chromatin in tumors that are resistant to hormone therapy. Interestingly, in normal human mammary glands and liver samples, relatively few ER-binding events were observed, and almost no overlap was seen between individuals, indicating that distinct genomic loci are recurrently occupied by ER in breast cancers. Differential binding analysis further identified ER-binding events that were enriched in poor-outcome tumors, and expression of the genes within 20 kilobases of these regulatory sites could predict clinical outcome of ER-positive tumors. Binding motifs for the pioneer factor FOXA1, which was highly expressed in ER-positive metastases, were enriched in the poor-outcome ER-binding events, suggesting that FOXA1 mediates changes in ER binding during cancer progression. This possibility was supported by the observation that over half of mitogen-induced changes in ER occupancy *in vitro* occurred at FOXA1-bound sites. Together, these findings reveal the dynamic nature of ER binding and suggest that changes in ER occupancy contribute to the aggressiveness of breast cancer. ■

Ross-Innes CS, Stark R, Teschendorff AE, Holmes KA, Ali HR, Dunning MJ, et al. Differential oestrogen receptor binding is associated with clinical outcome in breast cancer. Nature 2012; 481:389–93.