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Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor–Positive Breast Cancer ................. 336


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Identifying and Targeting Sporadic Oncogenic Genetic Aberrations in Mouse Models of Triple-Negative Breast Cancer ................. 354


Précis: Combined whole-exome and RNA sequencing discovers diverse mutations that activate MAPK or PI3K signaling in mouse models of triple-negative breast cancer, suggesting potential therapeutic targets.

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ON THE COVER

Matissese, Onozato, Sun, and colleagues used anchored multiplex PCR to find gene rearrangements that might drive tumorigenesis in 173 patients with advanced hormone receptor–positive (HR+) breast cancer. Intergenic fusions were identified in 14% of patients, including ESR1–associated fusions in 8 patients, and AKT3, NOTCH1, PRKCA, and BRAF fusions each in 2 patients. Overexpressing PIK3CA, RAF1, or AKT3 kinase fusions activated mTORC1 signaling and induced oncogenic deregulation of breast epithelial cells in three-dimensional cultures, and RPS6KC1–AKT3 fusion accelerated tumor growth in vivo. These tumors were resistant to estrogen withdrawal, but could be resensitized by CDK4/6 inhibition. Moreover, fusion-positive tumors were linked to shorter overall survival in patients with HR+ breast cancer. Collectively, these findings indicate that intergenic fusions can drive tumorigenesis and drug resistance in HR+ breast cancer, suggesting potential therapeutic targets. For details, please see the article by Matissese, Onozato, Sun, and colleagues on page 336.