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Précis: A mouse model allowing inducible inhibition of autophagy in autochthonous PDAC shows that blocking autophagy suppresses tumor growth by direct effects on tumor cells and by increasing intratumor macrophages.
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An RNA-Based Digital Circulating Tumor Cell Signature Is Predictive of Drug Response and Early Dissemination in Prostate Cancer ............... 288
Précis: Digital quantification of circulating tumor cell RNA may allow for noninvasive disease monitoring in patients with prostate cancer, predicting early dissemination in localized cancer and abiraterone response in metastatic disease.
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Deconstruction of a Metastatic Tumor Microenvironment Reveals a Common Matrix Response in Human Cancers .................. 304
Précis: Integrated molecular, cellular, and biochemical analyses of ovarian cancer at different stages of metastasis characterized the evolution of metastatic ovarian cancer within the metastatic microenvironment.
MYC Drives a Subset of High-Risk Pediatric Neuroblastomas and Is Activated through Mechanisms Including Enhancer Hijacking and Focal Enhancer Amplification .......... 320


Précis: A transgenic zebrafish model shows that MYC can drive neuroblastomagenesis, and MYC is upregulated via enhancer amplification or enhancer hijacking in a subset of high-risk neuroblastomas.

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


Précis: Anchored multiplex PCR identified intergenic gene fusions in 14% of patients with advanced HR+ breast cancer and their association with poor outcomes and drug resistance, suggesting the potential for therapeutic targeting. See commentary, p. 272 See article, p. 354

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. See commentary, p. 272 See article, p. 336

ON THE COVER

Matissek, 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 Matissek, Onozato, Sun, and colleagues on page 336.