Oncogenic Isocitrate Dehydrogenase Mutations: Mechanisms, Models, and Clinical Opportunities .................. 730
R.A. Cairns and T.W. Mak

Discovery of a Novel ERK Inhibitor with Activity in Models of Acquired Resistance to BRAF and MEK Inhibitors .................. 742

Précis: An ERK1/2 inhibitor with properties of both type I and type II kinase inhibitors suppresses MAPK signaling and proliferation in BRAF and MEK inhibitor-resistant cancer cells. See commentary, p. 719

Inhibition of Ron Kinase Blocks Conversion of Micrometastases to Overt Metastases by Boosting Antitumor Immunity .................. 751
H. Eyob, H.A. Ekiz, Y.S. DeRose, S.E. Waltz, M.A. Williams, and A.L. Welm

Précis: The receptor tyrosine kinase RON suppresses antitumor immune responses to promote metastatic outgrowth and is a potential therapeutic target to inhibit metastasis.

Frequent Mutation of the PI3K Pathway in Head and Neck Cancer Defines Predictive Biomarkers .................. 761

Précis: PI3K pathway mutations are found in 30.5% of head and neck squamous cell carcinomas and may indicate sensitivity to PI3K inhibitors. See commentary, p. 722
Integrative Genomic Characterization of Oral Squamous Cell Carcinoma Identifies Frequent Somatic Drivers


Précis: Gene expression, copy number, methylation, and mutation analyses implicate Notch deregulation in oral squamous cell carcinoma and identify potentially actionable events.

See commentary, p. 722

Diacylglycerol Kinase α Is a Critical Signaling Node and Novel Therapeutic Target in Glioblastoma and Other Cancers


Précis: Inhibition of diacylglycerol kinase α downregulates oncogenic pathways including HIF-1α and mTOR and is selectively toxic to glioblastoma and other cancer cells.

See commentary, p. 726

ZNF365 Promotes Stability of Fragile Sites and Telomeres


Précis: ZNF365 is a p53-inducible gene product that maintains genomic stability by preventing recombination of defective telomere ends and common fragile site abnormalities.

Selective Estrogen Receptor Modulators and Pharmacogenomic Variation in ZNF423 Regulation of BRCA1 Expression: Individualized Breast Cancer Prevention


Précis: SNPs related to ZNF423 and CTSO are associated with breast cancer risk during SERM therapy, and these genes promote estrogen-dependent induction of BRCA1 transcription in an SNP-dependent fashion.

See commentary, p. 728

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ON THE COVER

Head and neck squamous cell carcinomas (HNSCC) are a genetically heterogeneous group of cancers with a poor survival rate. Lui and colleagues evaluated the mutation frequency of mitogenic pathways in HNSCCs and found that 30.5% of tumors harbored PI3K pathay mutations. Patient-derived tumorgrafts with hotspot and noncanonical PIK3CA mutations were highly sensitive to PI3K inhibitors. Pickering and colleagues performed integrated genomic analyses of oral squamous cell carcinomas (OSCC), a particularly lethal, poorly characterized HNSCC subtype. The Notch pathway was deregulated in 66% of OSCCs, and inactivation of NOTCH1 was shown to drive OSCC growth. Common inactivating mutations of FAT1 and CASP8 were also identified. Together, these findings provide insight into the etiology of HNSCC and identify potential therapeutic targets. For details, please see the article by Lui and colleagues on page 761 and the article by Pickering and colleagues on page 770.