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Real-Time Imaging Reveals Local, Transient Vascular Permeability, and Tumor Cell Intravasation Stimulated by TIE2hi Macrophage–Derived VEGFA .......... 932

Précis: Hyperpermeability of tumor vasculature is dynamic and restricted to the Tumor MicroEnvironment of Metastasis (TMEM).

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HOXB7 Is an ERα Cofactor in the Activation of HER2 and Multiple ER Target Genes Leading to Endocrine Resistance .......... 944

Précis: HOXB7 is upregulated by MYC-mediated suppression of miR-196a and enhances expression of ER target genes in tamoxifen-resistant breast cancer cells.

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Combined EGFR/MEK Inhibition Prevents the Emergence of Resistance in EGFR-Mutant Lung Cancer ................................................................. 960
Précis: Acquired resistance to EGFR inhibitors can be prevented with dual EGFR and MEK inhibition, which results in prolonged ERK1/2 inhibition and increased apoptosis in EGFR-mutant NSCLC.

Synthetic Lethal Approaches Exploiting DNA Damage in Aggressive Myeloma .................. 972
Précis: Upregulation of MYC in multiple myeloma cells drives DNA damage via replicative stress and ROS induction, and confers sensitivity to ATR inhibitors and small-molecule inducers of ROS.

Mass Cytometric Functional Profiling of Acute Myeloid Leukemia Defines Cell-Cycle and Immunophenotypic Properties That Correlate with Known Responses to Therapy ................. 988
G.K. Behbehani, N. Samusik, Z.B. Bjornson, W.J. Fantl, B.C. Medeiros, and G.P. Nolan
Précis: High-dimensional analysis of patient-derived AML cells using mass cytometry identifies changes in immunophenotypic patterns and cell-cycle kinetics that are predictive of AML subtype and chemotherapeutic response.

See commentary, p. 912

ON THE COVER Tricker, Xu, and colleagues found that combined treatment with the mutant EGFR-selective inhibitor WZ4002 and the MEK inhibitor trametinib delayed the development of acquired resistance in EGFR inhibitor-naïve and EGFR

T790M-positive lung cancer cells. WZ4002/trametinib treatment prevented ERK1/2 reactivation and increased apoptosis. Combination treatment was also significantly more effective than WZ4002 alone in suppressing tumor regrowth in xenograft models and a genetically engineered mouse model of EGFR

T790M-mutant lung cancer. Although EGFR and ERK inhibition were maintained in the majority of WZ4002/trametinib-resistant tumor nodules, both AKT and S6 were frequently reactivated, and the addition of an mTOR inhibitor restored WZ4002/trametinib sensitivity in vitro and in vivo. These results highlight the potential clinical utility of initial cotargeting of EGFR and MEK to prevent the emergence of acquired resistance in EGFR-mutant lung cancer. For details, please see the article by Tricker, Xu, and colleagues on page 960.