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T.O. Nielsen, N.M. Poulin, and M. Ladanyi

Biallelic Mutations in BRCA1 Cause a New Fanconi Anemia Subtype

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Précis: Deleterious biallelic BRCA1 mutations predispose to a Fanconi anemia-like disorder characterized by developmental abnormalities and breast and ovarian cancer susceptibility.

PI3′-Kinase Inhibition Forestalls the Onset of MEK1/2 Inhibitor Resistance in BRAF-Mutated Melanoma

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M.M. Deuker, V. Marsh Durban, W.A. Phillips, and M. McMahon

Précis: Treatment with PI3K inhibitors enhances the depth of response to MEK1/2 inhibition and delays the development of drug-resistant tumors in BRAF-mutated melanoma mouse models.

Research Articles

Linking Tumor Mutations to Drug Responses via a Quantitative Chemical–Genetic Interaction Map

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Précis: Isogenic cell lines can be used to systematically map direct relationships between genetic alterations and drug responses and identify actionable interactions.
Aberrant Glycosylation Promotes Lung Cancer Metastasis through Adhesion to Galectins in the Metastatic Niche ........................................... 168
N.E. Reticker-Flynn and S.N. Bhatia
Précis: Changes in glycosyltransferase activity in lung cancer cells enhance surface presentation of the carbohydrate ligand T-antigen and potentiate metastasis via increased binding to tumor-mobilized galectin-3+ leukocytes.
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NOTCH Decoys That Selectively Block DLL/NOTCH or JAG/NOTCH Disrupt Angiogenesis by Unique Mechanisms to Inhibit Tumor Growth ...................... 182
Précis: Specific inhibition of JAG- or DLL-mediated NOTCH signaling using synthetic NOTCH1 decoys inhibits tumor angiogenesis via distinct mechanisms.
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Promotion of Colorectal Cancer Invasion and Metastasis through Activation of NOTCH–DAB1–ABL–RHOGEF Protein TRIO ................. 198
M. Sonoshita, Y. Itatani, F. Kakizaki, K. Sakimura, T. Terashima, Y. Katsuyama, Y. Sakai, and M.M. Taketo
Précis: NOTCH–DAB1 signaling promotes colon cancer cell invasion and progression by stimulating ABL-mediated phosphorylation of the RHOGEF TRIO at tyrosine residue 2681.
See commentary, p. 115

Reticker-Flynn and Bhatia found that tumor-derived IL6 induced CD11b+ galectin-3+ leukocyte mobilization from the bone marrow in a mouse model of lung adenocarcinoma. Metastatic cell lines and human non–small cell lung cancer samples exhibited increased surface presentation of the galectin-3 ligand, Thomsen-Friedenreich Antigen (T-Antigen). Elevated T-Antigen surface presentation was mediated by altered expression of the glycosyltransferases C2GnT2 and St6GalNAc4, which prevented T-Antigen glycan elongation. Restoration of T-Antigen glycan chain elongation decreased T-Antigen presentation, reduced tumor-cell galectin-3 binding, and inhibited experimental metastases in vivo. These results indicate that aberrant glycosyltransferase activities play a critical role in the early metastatic niche to promote metastatic progression of lung tumors. For details, please see the article by Reticker-Flynn and Bhatia on page 168.

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