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**PREVENTION AND EPIDEMIOLOGY**

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Précis: Findings offer the first epidemiological evidence for the role of two important adipokines in the early stage of colorectal tumorigenesis, distinct from their involvement in insulin resistance.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Essential Requirement for PP2A Inhibition by the Oncogenic Receptor c-KIT Suggests PP2A Reactivation as a Strategy to Treat c-KIT+ Cancers
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Précis: Findings suggest activation of an anti-oncogenic protein phosphatase as a strategy to treat drug-resistant cancers driven by the c-KIT oncogene.

Halogenated Benzimidazole Carboxamides Target Integrin α₄β₁ on T-Cell and B-Cell Lymphomas
Richard D. Carpenter, Arutselvan Natarajan, Edmond Y. Lau, Mirela Andrei, Danielle M. Solano, Felice C. Lightstone, Sally J. DeNardo, Kit S. Lam, and Mark J. Kurth

Précis: Novel molecular tools are described to improve structural understanding of an integrin target that may be useful to broadly attack lymphomas.

PTEN Loss Compromises Homologous Recombination Repair in Astrocytes: Implications for Glioblastoma Therapy with Temozolomide or Poly(ADP-Ribose) Polymerase Inhibitors
Brian McEllin, Cristel V. Camacho, Bipasha Mukherjee, Brandon Hahm, Nozumi Tomimatsu, Robert M. Bachoo, and Sandeep Burma

Précis: Findings establish a mechanistic rationale to treat PTEN-deficient tumors with PARP inhibitors presently in clinical development, possibly expanding the scope of their application beyond merely BRCA1/2-deficient tumors.
RG7204 (PLX4032), a Selective BRAFV600E Inhibitor, Displays Potent Antitumor Activity in Preclinical Melanoma Models
Hong Yang, Brian Higgins, Kenneth Kolinsky, Kathryn Packman, Zenaida Go, Raman Iyer, Stanley Kolis, Sylvia Zhao, Richard Lee, Joseph F. Grippo, Kathleen Schostack, Mary Ellen Simcox, David Heimbrook, Gideon Bollag, and Fei Su

Precis: Striking first report of the preclinical efficacy of a mutant Raf kinase-specific inhibitor augurs promise for its ongoing clinical development.

TUMOR AND STEM CELL BIOLOGY

The Polycomb Group Protein Bmi-1 Is Essential for the Growth of Multiple Myeloma Cells
Zainab Jagani, Dmitri Wiederschain, Alice Loo, Dan He, Rebecca Mosher, Paul Fordjour, John Monahan, Michael Morrissey, Yun-Mae Yao, Christoph Lengauer, Markus Warmuth, William R. Sellers, and Marion Dorsch

Precis: An oncogenic Polycomb group protein found to be a critical driver in multiple myelomas, one of the most deadly blood cancers.

Effects of Ionizing Radiation on Self-Renewal and Pluripotency of Human Embryonic Stem Cells
Kitchener D. Wilson, Ning Sun, Mei Huang, Wendy Y. Zhang, Andrew S. Lee, Zongjin Li, Shan X. Wang, and Joseph C. Wu

Precis: Human embryonic stem cells maintain their tumorigenic potential even after significant ionizing radiation exposures.

A Mouse Model of Melanoma Driven by Oncogenic KRAS
Carla Milagre, Nathalie Dhomen, Felipe C. Geyer, Robert Hayward, Maryou Lambros, Jorge S. Reis-Filho, and Richard Marais

Precis: Mouse model findings offer evidence that KRAS activation may be a founder event in melanoma.

Shedding of RANKL by Tumor-Associated MT1-MMP Activates Src-Dependent Prostate Cancer Cell Migration
Aaron L. Sabbota, Hyeong-Reh Choi Kim, Xiaoning Zhe, Rafael Fridman, R. Daniel Bonfil, and Michael L. Cher

Precis: Findings establish a mechanism of prostate cancer cell invasion that is enhanced by a protease-directed autocrine loop amenable to therapeutic attack.

Extracellular Protease ADAMTS9 Suppresses Esophageal and Nasopharyngeal Carcinoma Tumor Formation by Inhibiting Angiogenesis

Precis: Tumor suppressive effects of an extracellular protease implicated in aerodigestive cancers are mediated by anti-angiogenic effects.

Frequent Attenuation of the WWOX Tumor Suppressor in Osteosarcoma Is Associated with Increased Tumorigenicity and Aberrant RUNX2 Expression
Kyle C. Kurek, Sara Del Mare, Zaidoun Salah, Suhaib Abdeen, Hussain Sadiq, Suk-hee Lee, Eugenio Gaudio, Nicola Zanesi, Kevin B. Jones, Barry DeYoung, Gail Amir, Mark Gebhardt, Matthew Warman, Gary S. Stein, Janet L. Stein, Jane B. Lian, and Rami I. Aqeilan

Precis: Findings establish the pathobiological significance of a suspected tumor suppressor in human osteosarcoma, a very aggressive bone cancer, with potential prognostic and therapeutic implications.

Compensatory Upregulation of Tyrosine Kinase Etk/BMX in Response to Androgen Deprivation Promotes Castration-Resistant Growth of Prostate Cancer Cells
Bojie Dai, Hege Chen, Shengjie Guo, Xi Yang, Douglas E. Linn, Feng Sun, Wei Li, Zhiyong Guo, Kexin Xu, Oekyung Kim, Xiangtian Kong, Jonathan Melamed, Shaopeng Qiu, Hegang Chen, and Yun Qiu

Precis: Findings identify a compensatory mechanism activated in prostate after androgen ablation, apparently contributing to androgen resistance.

Inhibition of the Sodium-Potassium-Chloride Cotransporter Isoform-1 Reduces Glioma Invasion
Brian R. Haas and Harald Sontheimer

Precis: Findings rationalize an immediate opportunity to reposition a drug presently used for non-cancer indications as a treatment for primary brain tumors.
**Exchange Protein Directly Activated by Cyclic AMP Increases Melanoma Cell Migration by a Ca²⁺-Dependent Mechanism**
Erdene Baljinnyam, Mariana S. De Lorenzo, Lai-Hua Xie, Mizuka Iwatsubo, Suzie Chen, James S. Goydos, Martha C. Nowycky, and Kousaku Iwatsubo

*Précis:* A novel mechanism is described for invasive migration of melanoma cells, suggesting new routes to attack metastatic disease.

**Atoh1 Inhibits Neuronal Differentiation and Collaborates with Gli1 to Generate Medulloblastoma-Initiating Cells**
Olivier Ayrault, Haotian Zhao, Frederique Zindy, Chunxu Qu, Charles J. Sherr, and Martine F. Roussel

*Précis:* Findings define two transcription factors that are sufficient to transform a neuronal progenitor into a tumor-initiating cell in the common childhood brain tumor medulloblastoma.

**Alternatively Spliced RAGEv1 Inhibits Tumorigenesis through Suppression of JNK Signaling**
Anastasia Z. Kalea, Fiona See, Evis Harja, Maria Arriero, Ann Marie Schmidt, and Barry I. Hudson

*Précis:* Findings define a mechanism through which a novel theranostic biomarker in cancer may be used to suppress malignant disease.

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**ABOUT THE COVER**

RG7204 (PLX4032) is a small molecule inhibitor that selectively blocks the activity of oncogenic BRAF<sup>V600E</sup> kinase. The BRAF<sup>V600E</sup> mutation is common in several human cancers, with especially high prevalence in melanoma. In the present study, Yang and colleagues describe the effect of RG7204 on tumor cells. RG7204 suppresses ERK activation and cellular proliferation in tumor cells with BRAF<sup>V600E</sup> but not in cells expressing only wild-type BRAF. Significantly, RG7204 treatment caused partial or complete tumor regressions and improved survival of animals bearing BRAF<sup>V600E</sup> tumors, demonstrating potent antitumor activity. These preclinical efficacy data generated in several melanoma xenograft models have foreshadowed the clinical results observed in a multi-center Phase I trial that has been enriched with metastatic melanoma patients testing positive for the BRAF<sup>V600E</sup> mutation. For details, see the article by Yang and colleagues on page 5518 of this issue.