PERSPECTIVES

1049 Chemoprevention Meets Glucose Control
Jeffrey A. Engelman and Lewis C. Cantley
See article p. 1066

1053 DNA Methylation Markers for Prostate Cancer with a Stem Cell Twist
Carmen Jerónimo and Manel Esteller
See article p. 1084

1056 Screening for Oral Premalignancy and Cancer: What Platform and Which Biomarkers?
Mark W. Lingen
See article p. 1093

REVIEW

1060 Metformin and Other Biguanides in Oncology: Advancing the Research Agenda
Michael Pollak

1066 Metformin Prevents Tobacco Carcinogen–Induced Lung Tumorigenesis
Regan M. Memmott, Jose R. Mercado, Colleen R. Maier, Shigeru Kawabata, Stephen D. Fox, and Phillip A. Dennis
See perspective p. 1049

1077 Metformin Suppresses Colorectal Aberrant Crypt Foci in a Short-term Clinical Trial
Kunihiro Hosono, Hiromi Endo, Hirokazu Takahashi, Michiko Sugiyama, Eiji Sakai, Takashi Uchiyama, Koeri Suzuki, Hiroshi Iida, Yasunari Sakamoto, Kyoko Yoneda, Tomoko Koide, Chikako Tokoro, Yasunobu Abe, Masahiko Inamori, Hitoshi Nakagama, and Atsushi Nakajima

GLOBAL REACTIVATION OF EPIGENETICALLY SILENCED GENES IN PROSTATE CANCER
Ilsya Ibragimova,
Inmaculada Ibáñez de Cáceres,
Amanda M. Hoffman, Anna Potapova,
Essel Dulaimi, Tahseen Al-Saleem,
Gary R. Hudes, Michael F. Ochs,
and Paul Cairns
See perspective p. 1053

ENDOTHELIN RECEPTOR TYPE B GENE PROMOTER HYPERMETHYLATION IN SALIVARY RINSES IS INDEPENDENTLY ASSOCIATED WITH RISK OF ORAL CAVITY CANCER AND PREMALIGNANCY
Kavita Malhotra Pattani, Zhe Zhang,
Semra Demokan, Chad Glazer,
Myriam Loyo, Steven Goodman,
David Sidransky, Francisco Bermudez,
Germain Jean-Charles, Thomas McCaffrey,
Tapan Padhya, Joan Phelan,
Silvia Spivakovsky, Helen Yoo Bowne,
Judith D. Goldberg, Linda Rolnitzky,
Miriam Robbins, A. Ross Kerr, David Sirois,
and Joseph A. Califano
See perspective p. 1056

UV RADIATION INHIBITS 15-HYDROXYPROSTAGLANDIN DEHYDROGENASE LEVELS IN HUMAN SKIN: EVIDENCE OF TRANSCRIPTIONAL SUPPRESSION
Benjamin L. Judson, Akira Miyaki,
Vikram D. Kekatpure, Baoheng Du,
Patricia Gilleau-deaud, Mary Sullivan-Whalen,
Arash Mohebati, Sudhir Nair, Jay O. Boyle,
Richard D. Granstein, Kotha Subbaramaiah,
James G. Krueger, and Andrew J. Dannenberg

DISRUPTION OF ANDROGEN AND ESTROGEN RECEPTOR ACTIVITY IN PROSTATE CANCER BY A NOVEL DIETARY DITERPENE CARNOSOL: IMPLICATIONS FOR CHEMOPREVENTION
Jeremy J. Johnson, Deeba N. Syed,
Yewseok Suh, Chenelle R. Heren,
Mohammad Saleem, Imtiaz A. Siddiqui,
and Hasan Mukhtar

LOW-CARBOHYDRATE DIETS AND PROSTATE CANCER: HOW LOW IS “LOW ENOUGH”?*
Elizabeth M. Masko, Jean A. Thomas II,
Jodi A. Antonelli, Jessica C. Lloyd,
Tameika E. Phillips, Susan H. Poulton,
Mark W. Dewhirst, Salvatore V. Pizzo,
and Stephen J. Freedland
1132 White Tea Extract Induces Apoptosis in Non–Small Cell Lung Cancer Cells: the Role of Peroxisome Proliferator-Activated Receptor-γ and 15-Lipoxygenases

1141 Vascular Endothelial Growth Factor Receptor 2–Targeted Chemoprevention of Murine Lung Tumors
Vijaya Karoor, Mysan Le, Daniel Merrick, Edward C. Dempsey, and Yorke E. Miller

1148 A Dominant-Negative c-jun Mutant Inhibits Lung Carcinogenesis in Mice
Jay W. Tichelaar, Ying Yan, Qing Tan, Yian Wang, Richard D. Estensen, Matthew R. Young, Nancy H. Colburn, Hulan Yin, Colleen Goodin, Marshall W. Anderson, and Ming You

1157 Synthetic Progestins Differentially Promote or Prevent 7,12-Dimethylbenz(a)anthracene–Induced Mammary Tumors in Sprague-Dawley Rats
Indira Benakanere, Cynthia Besch-Williford, Candace E. Carroll, and Salman M. Hyde

1168 Resveratrol Modulates Drug- and Carcinogen-Metabolizing Enzymes in a Healthy Volunteer Study

1176 Genome-Wide Catalogue of Chromosomal Aberrations in Barrett’s Esophagus and Esophageal Adenocarcinoma: A High-Density Single Nucleotide Polymorphism Array Analysis
Jian Gu, Jaffer A. Ajani, Ernest T. Hawk, Yuanqing Ye, Jeffrey L. Lee, Manooop S. Bhutani, Wayne L. Hofstetter, Stephen G. Swisher, Kenneth K. Wang, and Xinfeng Wu

Molecular Alterations Associated with Sulindac-Resistant Colon Tumors in Apc(din+) Mice
Emily J. Greenspan, Frank C. Nichols, and Daniel W. Rosenberg

Enhanced Induction of Mucin-Depleted Foci in Estrogen Receptor β Knockout Mice
Diana Saleiro, Genoveva Muriio, Dennis B. Lubahn, Levy Kopelovich, Kenneth S. Korach, and Rajendra G. Mehta

Mitochondrial DNA Mutation in Normal Margins and Tumors of Recurrent Head and Neck Squamous Cell Carcinoma Patients
Santanu Dasgupta, Rachel Koch, William H. Westra, Joseph A. Califano, Patrick K. Ha, David Sidransky, and Wayne M. Koch

ABOUT THE COVER

The diagram reflects potential and known effects of the diabetes drug metformin (one of the most commonly used drugs in the world) on important molecular pathways of carcinogenesis in cells. The mammalian target of rapamycin (mTOR) exists in TOR complex 1 (TORC1) and TORC2. TORC1 controls cell growth through phosphorylating p70 S6 kinase (p70S6K) and 4E-binding protein 1 (4EBP1). Various inputs of TORC1 regulation appear to directly affect the TSC1–TSC2 complex, which controls activation of the Ras homologue enriched in brain (RHEB) protein that directly activates TORC1. Growth factor signaling (through phosphatidylinositol 3-kinase [PI3K]/Akt and extracellular signal-regulated kinase [ERK]/ribosomal S6 kinase [Rsk] signaling) and energy homeostasis (through AMP-activated protein kinase [AMPK]) directly phosphorylate TSC2. In vivo, metformin downregulates TORC1 possibly via both AMPK-dependent mechanisms and AMPK-independent mechanisms (dotted blue line from “Energy stress”) or via its effect of decreasing levels of circulating insulin and insulin-like growth factor (IGF), which decreases activation of the IGF-1 receptor (IGF-1R)/insulin receptor (IR), leading in turn to suppression of PI3K and Ras signaling. See articles by Memmott et al. (beginning on page 1066), Hosono et al. (beginning on page 1077), Pollak (beginning on page 1060), and Engelman and Cantley (beginning on page 1049) for more information.