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

1104  UV Radiation Inhibits 15-Hydroxyprostaglandin Dehydrogenase Levels in Human Skin: Evidence of Transcriptional Suppression

RESEARCH ARTICLES

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, Hiroki Endo, Hirokazu Takahashi, Michiko Sugiyama, Eiji Sakai, Takashi Uchiyama, Kaori Suzuki, Hirosi Iida, Yasunari Sakamoto, Kyoko Yoneda, Tomoko Koide, Chikako Tokoro, Yasunobu Abe, Masahiko Inamori, Hitoshi Nakagama, and Atsushi Nakajima

1124  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 Siderousy, Francisco Bermudez, Germain Jean-Charles, Thomas McCaffrey, Tapan Padhya, Joan Phelan, Silvia Spivakovskiy, Helen Yoo Bowne, Judith D. Goldberg, Linda Rolnitzky, Miriam Robbins, A. Ross Kerr, David Sirois, and Joseph A. Califano
See perspective p. 1056

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, Yewseoek Suh, Chenelle R. Heren, Mohammad Saleem, Imtiaz A. Siddiqui, and Hasan Mukhtar

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1141</td>
<td>Vascular Endothelial Growth Factor Receptor 2–Targeted Chemoprevention of Murine Lung Tumors</td>
<td>Vijaya Karoor, Mysan Le, Daniel Merrick, Edward C. Dempsey, and Yorke E. Miller</td>
</tr>
<tr>
<td>1148</td>
<td>A Dominant-Negative c-jun Mutant Inhibits Lung Carcinogenesis in Mice</td>
<td>Jay W. Tichelaar, Yang Tan, Qing Tan, Yian Wang, Richard D. Estensen, Matthew R. Young, Nancy H. Colburn, Huiyan Yin, Colleen Goodin, Marshall W. Anderson, and Ming You</td>
</tr>
<tr>
<td>1157</td>
<td>Synthetic Progestins Differentially Promote or Prevent 7,12-Dimethylbenz(a)anthracene–Induced Mammary Tumors in Sprague-Dawley Rats</td>
<td>Indira Benakanekere, Cynthia Besch-Williford, Candace E. Carroll, and Salman M. Hyde</td>
</tr>
<tr>
<td>1187</td>
<td>Molecular Alterations Associated with Sulindac-Resistant Colon Tumors in ApCΔmin/+ Mice</td>
<td>Emily J. Greenspan, Frank C. Nichols, and Daniel W. Rosenberg</td>
</tr>
<tr>
<td>1198</td>
<td>Enhanced Induction of Mucin-Depleted Foci in Estrogen Receptor β Knockout Mice</td>
<td>Diana Saleiro, Genoveva Murillo, Dennis B. Lubahn, Levy Kopelovich, Kenneth S. Korach, and Rajendra G. Mehta</td>
</tr>
<tr>
<td>1205</td>
<td>Mitochondrial DNA Mutation in Normal Margins and Tumors of Recurrent Head and Neck Squamous Cell Carcinoma Patients</td>
<td>Santanu Dasgupta, Rachel Koch, William H. Westra, Joseph A. Califano, Patrick K. Ha, David Sidransky, and Wayne M. Koch</td>
</tr>
</tbody>
</table>

**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.