**PERSPECTIVES**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1049</td>
<td>Chemoprevention Meets Glucose Control</td>
<td>Jeffrey A. Engelman and Lewis C. Cantley</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>See article p. 1066</em></td>
</tr>
<tr>
<td>1053</td>
<td>DNA Methylation Markers for Prostate Cancer with a Stem Cell Twist</td>
<td>Carmen Jeronimo and Manel Esteller</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>See article p. 1084</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>See article p. 1093</em></td>
</tr>
</tbody>
</table>

**REVIEW**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1060</td>
<td>Metformin and Other Biguanides in Oncology: Advancing the Research Agenda</td>
<td>Michael Pollak</td>
</tr>
</tbody>
</table>

**RESEARCH ARTICLES**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1066</td>
<td>Metformin Prevents Tobacco Carcinogen–Induced Lung Tumorigenesis</td>
<td>Regan M. Memmott, Jose R. Mercado, Colleen R. Maier, Shigeru Kawabata, Stephen D. Fox, and Phillip A. Dennis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>See perspective p. 1049</em></td>
</tr>
<tr>
<td>1077</td>
<td>Metformin Suppresses Colorectal Aberrant Crypt Foci in a Short-term Clinical Trial</td>
<td>Kunihiro Hosono, Hiroki Endo, Hirokazu Takahashi, Michiko Sugiyama, Eiji Sakai, Takashi Uchiyama, Kaori Suzuki, Hiroshi Iida, Yasunari Sakamoto, Kyoko Yoneda, Tomoko Koido, Chikako Tokoro, Yasunobu Abe, Masahiko Inamori, Hitoshi Nakagama, and Atsushi Nakajima</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>See perspective p. 1049</em></td>
</tr>
</tbody>
</table>

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**Global Reactivation of Epigenetically Silenced Genes in Prostate Cancer**

Iliya 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 Padvya, Joan Phelan, Silvia Spivakovsky, Helen Yoo Bowne, Judith D. Goldberg, Linda Rontzksy, 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**


**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
White Tea Extract Induces Apoptosis in Non–Small Cell Lung Cancer Cells: the Role of Peroxisome Proliferator–Activated Receptor-γ and 15-Lipoxygenases

1132


Vascular Endothelial Growth Factor Receptor 2–Targeted Chemoprevention of Murine Lung Tumors

1141

Vijaya Karoor, Mysan Le, Daniel Merrick, Edward C. Dempsey, and York E. Miller

A Dominant-Negative c-jun Mutant Inhibits Lung Carcinogenesis in Mice

1148

Jay W. Tichelaar, Ying Yan, Qing Tan, Yian Wang, Richard D. Estensen, Matthew R. Young, Nancy H. Colburn, Hulian Yin, Colleen Goodin, Marshall W. Anderson, and Ming You

Synthetic Progestins Differentially Promote or Prevent 7,12-Dimethylbenz(a)anthracene–Induced Mammary Tumors in Sprague-Dawley Rats

1157

Indira Benakanakere, Cynthia Besch-Williford, Candace E. Carroll, and Salman M. HYder

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

1168


Genome-Wide Catalogue of Chromosomal Aberrations in Barrett’s Esophagus and Esophageal Adenocarcinoma: A High-Density Single Nucleotide Polymorphism Array Analysis

1176

Jian Gu, Jaffer A. Ajani, Ernest T. Hawk, Yuanqing Ye, Jeffrey H. Lee, Manoop S. Bhutani, Wayne L. Hofstetter, Stephen G. Swisher, Kenneth K. Wang, and Xifeng Wu

Molecular Alterations Associated with Sulindac-Resistant Colorectal Tumors in APCΔmin/+ Mice

1187

Emily J. Greenspan, Frank C. Nichols, and Daniel W. Rosenberg

Enhanced Induction of Mucin-Depleted Foci in Estrogen Receptor β Knockout Mice

1198

Diana Saleiro, Genoveva Murillo, 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

1205

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.