The Endogenous Tryptophan Metabolite and NAD\textsuperscript{+} Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress
Felix Sahm, Iris Oezen, Christiane A. Opitz, Bernhard Radlwimmer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemin, Wolfgang Wick, and Michael Platten

Précis: A downstream catabolite of the tryptophan degradation pathway of IDO- and TDO-dependent immune escape, which is elevated in the majority of human cancers, is found to be a key element in their therapeutic resistance, with implications to improve treatment.

Hypoxia Triggers Hedgehog-Mediated Tumor–Stromal Interactions in Pancreatic Cancer

Précis: These findings provide evidence for a novel molecular mechanism that explains the high levels of hypoxia and desmoplasia that contribute to therapy resistance in pancreatic cancer.

Single Copies of Mutant \textit{KRAS} and Mutant \textit{PIK3CA} Cooperate in Immortalized Human Epithelial Cells to Induce Tumor Formation

Précis: These findings suggest a paradigm that helps to explain how a single mutant \textit{KRAS} allele can cooperate with mutant \textit{PIK3CA} to impart a transformed phenotype.
Prevention and Epidemiology

Colorectal Cancer Risk Associated with Hormone Use Varies by Expression of Estrogen Receptor-β

Anja Rudolph, Csaba Toth, Michael Hoffmeister, Wilfried Roth, Esther Herpel, Peter Schirmacher, Hermann Brenner, and Jenny Chang-Claude

Précis: Expression of estrogen receptor β, the predominant estrogen receptor in colon tissue, appears to be involved in the reduction of colorectal cancer risk that may arise with use of oral contraceptives or menopausal hormone therapy.

Therapeutics, Targets, and Chemical Biology

Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGFR2, Is Mediated by Neurophilin 1

Ling Zhang, Graham C. Parry, and Eugene G. Levin

Précis: Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.

Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer

Irina V. Kovtun, John C. Cherille, Stephen J. Murphy, Sarah H. Johnson, Shabnam Zarei, Farhad Kosari, William R. Sukov, R. Jeffrey Karnes, and George Vasmatzis

Précis: This work has important clinical implications because it demonstrates that changes associated with aggressive tumor behavior can be identified prior to the morphologic changes characteristic of aggressive prostate cancer.

Collagen Prolyl Hydroxylases Are Essential for Breast Cancer Metastasis

Daniele M. Gilkes, Pallavi Chaturvedi, Saumendra Baipai, Carmen C. Wong, Hong Wei, Stephen Pitcairn, Maimon E. Hubbi, Denis Wirtz, and Greg L. Semenza

Précis: Although collagen prolyl hydroxylases have been implicated broadly in cancer pathophysiology, their precise contributions have not been well understood; an important gap in knowledge addressed by this study.

Interleukin-1β Promotes Skeletal Colonization and Progression of Metastatic Prostate Cancer Cells with Neuroendocrine Features

Qingxin Liu, Mike R. Russell, Kristina Shahriri, Daniele L. Jernigan, Mercedes L. Lioni, Fernando U. Garcia, and Alessandro Fatatis

Précis: The identification of IL-1β as an important mediator of metastasis in prostate cancer should prompt immediate testing of anti-IL-1β strategies to treat advanced disease.

Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake

Marlous Arjaans, Thijs H. Oude Munnink, Sjoukje F. Oosting, Anton G.T. Terwisscha van Scheltinga, Jourik A. Gietema, Erik T. Garbacik, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Lou, Lei Lx, Hui Deng, Jing Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

Précis: These findings identify a little-studied microRNA the epigenetic downregulation of which strongly affects clinical outcomes and malignant cell behaviors in small-cell lung cancer.

PF1-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains

Sarah Picard, David Da Costa, Angeliki Thanasopoulos, Panagis Filippakopoulos, Paul V. Fish, Martinophilp, Oleg Fedorov, Paul Brennan, Mark E. Bunnage, Dafydd R. Owen, James E. Bradner, Philippe Taniere, Brendan O’Sullivan, Susanne Müller, Juerg Schwaller, Tatjana Stankovic, and Stefan Knapp

Précis: This study suggests that it may be possible to target an important transcriptional regulatory domain that has been implicated in a broad number of aggressive blood cancers, as a generalizable therapeutic approach.

Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3356</td>
<td><strong>Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis</strong></td>
<td>Thomas O'Hare, Christopher A. Eide, Anupriya Agarwal, Lauren T. Adrian, Matthew S. Zabriskie, Ryan J. MacKenzie, Dorian H. LaTocha, Kara J. Johnson, Huihong You, Jenny Luo, Steven M. Riddle, Bryan D. Marks, Kurt W. Vogel, Dennis R. Koop, John Appar, Jeffrey W. Tyner, Michael W. Deininger, and Brian J. Druker</td>
</tr>
<tr>
<td>3371</td>
<td><strong>Simultaneous Targeting of Tumor Antigens and the Tumor Vasculature Using T Lymphocyte Transfer Synergizes to Induce Regression of Established Tumors in Mice</strong></td>
<td>Dhanalakshmi Chinnasamy, Eric Tran, Zhiya Yu, Richard A. Morgan, Nicholas P. Restifo, and Steven A. Rosenberg</td>
</tr>
<tr>
<td>3393</td>
<td><strong>Regulation of FANCD2 by the mTOR Pathway Contributes to the Resistance of Cancer Cells to DNA Double-Strand Breaks</strong></td>
<td>Changxian Shen, Duane Oswald, Doris Phelp, Hakan Cam, Christopher E. Pelloski, Qishen Pang, and Peter J. Houghton</td>
</tr>
<tr>
<td>3402</td>
<td><strong>Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1</strong></td>
<td>Bo Cen, Sandeep Mahajan, Wenzhang Wang, and Andrew S. Kraft</td>
</tr>
<tr>
<td>3412</td>
<td><strong>CIP4 Controls CCL19-Driven Cell Steering and Chemotaxis in Chronic Lymphocytic Leukemia</strong></td>
<td>Gema Malat-Engra, Julien Vaude, Loïc Ysebaert, Manon Farcé, Fanny Lafouresse, Guy Laurent, Frédérique Gaits-Iacovoni, Giorgio Scita, and Loïc Dupré</td>
</tr>
<tr>
<td>3425</td>
<td><strong>miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL-6-Mediated Paracrine Effects in Head and Neck Cancer</strong></td>
<td>Cheng-Chia Yu, Lo-Lin Tsai, Mong-Lien Wang, Chuan-Hang Yu, Wen-Liang Lo, Yun-Ching Chang, Guang-Yuh Chiou, Ming-Tung Chou, and Shih-Hwa Chiu</td>
</tr>
<tr>
<td>3441</td>
<td><strong>Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations</strong></td>
<td>Richard L. Price, Jeun Song, Katherine Bingmer, Tae Hyong Kim, Ji-Yeon Yi, Michal O. Nowicki, Xiaoqiu Mo, Todd Holon, Eric Murran, Christopher Alvarez-Breckenridge, Soledad Fernandez, Balveen Kaur, Andreana Rivera, Michael Oglesbee, Charles Cook, E. Antonio Chiocca, and Chang-Hyuk Kwon</td>
</tr>
<tr>
<td>3451</td>
<td><strong>Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence</strong></td>
<td>Hang Cui, Yahui Kong, Mei Xu, and Hong Zhang</td>
</tr>
</tbody>
</table>
Dual Role of the Antioxidant Enzyme Peroxiredoxin 6 in Skin Carcinogenesis

Frank Rolfs, Marcel Huber, Florian Gruber, Friederike Böhm, Herbert J. Pfister, Valery N. Bochkov, Erwin Tschachler, Reinhard Dummer, Daniel Hohl, Matthias Schäfer, and Sabine Werner

Précis: Antioxidant functions do not contribute exclusively to tumor suppression, as widely believed, but can also promote tumor development depending on the stage of the disease.

Growth of Triple-Negative Breast Cancer Cells Relies upon Coordinate Autocrine Expression of the Proinflammatory Cytokines IL-6 and IL-8


Précis: Findings offer a preclinical proof of principle to improve therapy of triple-negative breast cancer, a particularly aggressive disease subtype lacking effective mechanism-based interventions.

ABOUT THE COVER

In gliomas, constitutive metabolism of the essential amino acid tryptophan leads to the accumulation of the tryptophan metabolite quinolinic acid. Quinolinic acid is used by tumor cells to generate NAD⁺, thus contributing to the resistance towards radiotherapy and chemotherapy by replenishing depleted intracellular NAD pools. Using Western blot analyses and immunohistochemistry, it was found that the key enzyme leading to accumulation of quinolinic acid, 3-hydroxyanthranilate oxygenate (3-HAO), is expressed by tumor-infiltrating monocytes. Thus, infiltrating monocytes contribute to resistance to cytotoxic therapies in malignant gliomas. For details, see article by Sahm and colleagues on page 3225.