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Carla Boccaccio and Paolo M. Comoglio

3200  Vesicle Trafficking and RNA Transfer Add Complexity and Connectivity to Cell–Cell Communication
Charles T. Roberts Jr and Peter Kurre

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

3206  Application of Raman Spectroscopy to Identify Microcalcifications and Underlying Breast Lesions at Stereotactic Core Needle Biopsy
Ishan Barman, Narahara Chari Dingari, Anushree Saha, Sasha McGee, Luis H. Galindo, Wendy Liu, Donna Plecha, Nina Klein, Ramachandra Rao Dasari, and Maryann Fitzmaurice

Precis: These findings illustrate a powerful noninvasive spectroscopic approach to detect microcalcifications and other cancer-associated lesions that offers real-time feedback to radiologists during biopsy procedures and thus could reduce nondiagnostic and false-negative biopsies.

3216  Manganese-Enhanced MRI Reveals Early-Phase Radiation-Induced Cell Alterations In Vivo
Shigeyschi Saito, Sumitaka Hasegawa, Aiko Sekita, Rumiana Bakalova, Takako Furukawa, Kenya Murase, Tsuneo Saka, and Ichio Aoki

Precis: This study reports a noninvasive method to monitor cell-cycle alterations in tumors based on manganese uptake and MRI offering a potentially useful tool for longitudinal studies to optimize radiotherapy.

**MICROENVIRONMENT AND IMMUNOLOGY**

3225  The Endogenous Tryptophan Metabolite and NAD+ 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. Guillemim, Wolfgang Wick, and Michael Platten

Precis: 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.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

3235  Hypoxia Triggers Hedgehog-Mediated Tumor–Stromal Interactions in Pancreatic Cancer

Precis: 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.

3248  Single Copies of Mutant KRAS and Mutant PIK3CA Cooperate in Immortalized Human Epithelial Cells to Induce Tumor Formation

Precis: These findings suggest a paradigm that helps to explain how a single mutant KRAS allele can cooperate with mutant PIK3CA to impart a transformed phenotype.
Dachshund Binds p53 to Block the Growth of Lung Adenocarcinoma Cells
Ke Chen, Kongming Wu, Xiaoxin Cai, Wei Zhang, Jie Zhou, Jing Wang, Adam Ertel, Zhiping Li, Hallgeir Rui, Andrew Quong, Michael P. Lisanti, Aydin Tozeren, Ceylan Tanes, Sankar Addyka, Michael Gormley, Chenguang Wang, Steven B. McMahon, and Richard G. Pestell
Précis: This report identifies a modifier of EGFR signaling and stem cell function as an important new regulator of p53 in the most common type of lung cancer.

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 Bajpai, 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 Shahriari, Daniëlle M. 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.

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

DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer
Jianzhong Cao, Yongmei Song, Nan Bi, Jie Shen, Wenyang Liu, Jing Fan, Guogui Sun, Tong Tong, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Lai, Lei L.Z., Hui Deng, Jingteng Cheng, Jingde Zhu, Luhuai 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.

PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains
Sarah Picard, David Da Costa, Angeliki Thanasopoulos, Panagis Filippakopoulos, Paul V. Fish, Martin Philpott, 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.

Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake
Précis: Bevacizumab treatment decreases tumor uptake of antibodies by vessel normalization, and this should be taken into account in the design of clinical trials that combine bevacizumab with other antibodies.

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.
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**TUMOR AND STEM CELL BIOLOGY**

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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.