BRENNING ADVANCES

3191 Highlights from Recent Cancer Literature

REVIEWS

3193 The MET Oncogene in Glioblastoma Stem Cells: Implications as a Diagnostic Marker and a Therapeutic Target
Carla Roccacino 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

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

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 Radlhammer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemin, Wolfgang Wick, and Michael Platten

3225 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

3235 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
Grace M. Wang, Hong Yuen Wong, Hiroyuki Konishi, Brian G. Blair, Abde M. Abukhdeir, John P. Gustin, D. Marc Rosen, Samuel Ray Denmeade, Danijela Jelovac, Sarah Crossmann, Rory L. Cochran, Sivasundaram Karnan, Yuko Konishi, Akimobu Ota, Yoshitaka Hosokawa, Pedram Argani, Josh Lauring, and Ben Ho Park

3248 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 Addya, 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, Shahram 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 Gregg 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 Shahririan, Danielle L. Jernigan, Mercedes I. 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.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGF2, 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.

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 Luo, 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.

PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains
Sarah Picard, David Da Costa, Angeliki Thanasopoulou, Panagis Filipakopoulos, 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.
Regulation of FANCD2 by the mTOR
Hedgehog Signaling Alters Reliance on Simultaneous Targeting of Tumor Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1

Precise: This study provides a rationale to improve the efficacy of AKT inhibitors for cancer therapy.

CIP4 Controls CCL19-Driven Cell Steering and Chemotaxis in Chronic Lymphocytic Leukemia

Precise: This study offers proof of principle for using antiangiogenic drugs to enhance the efficacy of adoptive T-cell therapies for cancer treatment.

miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL-6–Mediated Paracrine Effects in Head and Neck Cancer

Precise: This study provides important new mechanistic insights into how leukemia cells migrate, with potentially important implications for understanding how to block invasive growth by these cells.

Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations

Precise: A virus that infects a large proportion of humans is linked for the first time to formation of brain tumors in a mouse model.

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Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence

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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 NAD³⁺, 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.