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581 Immunotherapy with PI3K Inhibitor and Toll-Like Receptor Agonist Induces IFN-γ IL-17 Polyfunctional T Cells That Mediate Rejection of Murine Tumors

**Précis:** Findings suggest important uses for PI3K inhibitors in heightening responses to cancer immunotherapy and immunochemotherapy regimens that use TLR ligands.

592 IFNβ Produced by TLR4-Activated Tumor Cells Is Involved in Improving the Antitumoral Immune Response
Nicolás Gonzalo Núñez, Virginia Andreani, Maria Inés Crespo, David Andrés Nocera, Maria Laura Breser, Gabriel Morón, Lien Dejager, Claude Libert, Virginia Rivero, and Mariana Maccioni

**Précis:** Immune regulatory Toll-like receptors on cancer cells are active, and when stimulated by Toll-like receptor ligands, can block tumor growth due to the induction of self-limiting IFN responses by the cancer cells.

### MOLECULAR AND CELLULAR PATHOBIOLOGY

604 S100A7 Enhances Mammary Tumorigenesis through Upregulation of Inflammatory Pathways
Mohd W. Nasser, Zahida Qamri, Yadwinder S. Deol, Janani Ravi, Catherine A. Powell, Prashant Trikha, Reto A. Schwendener, Xue-Feng Bai, Konstantin Shilo, Xianghong Zou, Gustavo Leone, Ronald Wolf, Stuart H. Yuspa, and Ramesh K. Ganju

**Précis:** A novel mouse model of breast cancer shows how a factor implicated in tissue inflammation can enhance growth and metastasis by activating proinflammatory pathways which recruit tumor-associated macrophages.

616 Common Structural and Epigenetic Changes in the Genome of Castration-Resistant Prostate Cancer

**Précis:** Findings reveal insights into how prostate cancers develop resistance to androgen deprivation therapy, still the leading challenge to treating advanced disease.

626 Sef Downregulation by Ras Causes MEK1/2 to Become Aberrantly Nuclear Localized Leading to Polyploidy and Neoplastic Transformation
Stéphanie Duhamel, Josée Hébert, Louis Gaboury, Amélie Bouchard, Ronald Simon, Guido Sauter, Mark Basik, and Sylvain Meloche

**Précis:** Findings show how controlling the nuclear localization of MEK makes vital contributions to the acquisition of chromosomal instability and to malignant progression.
Monoallelic Expression Determines Oncogenic Progression and Outcome in Benign and Malignant Brain Tumors

Erin J. Walker, Cindy Zhang, Pedro Castelo-Branco, Cynthia Hawkins, Wes Wilson, Nataliya Zhukova, Noa Alon, Ana Novokmet, Berivan Baskin, Peter Ray, Christiane Knobbe, Peter Dirks, Michael D. Taylor, Sidney Croul, David Malkin, and Uri Tabori

Précis: Monoallelic expression is a frequent event in brain tumors that is both gene- and tumor-specific and associated with tumor progression and aggressiveness.

Classifying Human Brain Tumors by Lipid Imaging with Mass Spectrometry


Précis: Rapid point-of-care methods of diagnosis offer the capability to optimize decision making during surgical operations and to improve planning for suitable adjuvant therapy postoperatively.

A Novel FoxM1-Caveolin Signaling Pathway Promotes Pancreatic Cancer Invasion and Metastasis

Chen Huang, Zhengjin Qiu, Liwei Wang, Zhihai Peng, Zhiliang Jia, Craig D. Logsdon, Xiangdong Le, Daoyan Wei, Suyun Huang, and Keping Xie

Précis: Findings reveal a core modifier pathway of metastasis in human cancer by defining a central transcriptional regulator of metastasis as a regulator of a master organizer of membrane lipid rafts that modifies many oncogenic signals.

Nucleotide Excision Repair Factor XPC Enhances DNA Damage–Induced Apoptosis by Downregulating the Antiapoptotic Short Isoform of Caspase-2

Qi-En Wang, Chunhua Han, Bo Zhang, Kanaga Sabapathy, and Altaf A. Wani

Précis: This article defining a new function for a DNA repair protein is important because it establishes a general mechanistic strategy to resuscitate a cell death pathway in p53-deficient tumor cells that may resensitize them to many existing chemotherapeutic agents that act by inducing DNA damage.

Prevalent Serum Antibody Is Not a Marker of Immune Protection against Acquisition of Oncogenic HPV16 in Men


Précis: There appear to be differences in the way that men and women react to prior HPV exposure, such that the presence of HPV serum antibodies offers a suitable marker to predict immune protection against future genital infections in women, but not in men.

Mitochondrial DNA Sequence Variation and Risk of Pancreatic Cancer

Ernest T. Lam, Paige M. Bracci, Elizabeth A. Holly, Catherine Chu, Annie Poon, Eunice Wan, Krystal White, Pui-Yan Kwok, Ludmila Pawlikowska, and Gregory J. Tranah

Précis: The interface between cancer genetics and metabolomics may benefit from this advance in understanding how variations in mitochondrial DNA sequence, which vary more widely than the nuclear genome, may precisely influence cancer risk.

Urinary Estrogens and Estrogen Metabolites and Subsequent Risk of Breast Cancer among Premenopausal Women

A. Heather Eliassen, Donna Spiegelman, Xia Xu, Larry K. Keefer, Timothy D. Veenstra, Robert L. Barbieri, Walter C. Willett, Susan E. Hankinson, and Regina G. Ziegler

Précis: This large study counterintuitively suggests that premenopausal women with higher levels of certain urinary estrogens may be at considerably lower risks of susceptibility to later breast cancers.

Genetic Determinants for Promoter Hypermethylation in the Lungs of Smokers: A Candidate Gene-Based Study

Shuguang Leng, Christine A. Stidley, Yushi Liu, Christopher K. Edlund, Randall P. Willink, Younghun Han, Maria Teresa Landi, Michael Thun, Maria A. Picchi, Shannon E. Bruse, Richard E. Crowell, David Van Den Berg, Neil E. Caporaso, Christopher L. Amos, Jill M. Siegfried, Yohannes Tesfaigzi, Frank D. Gilliland, and Steven A. Belinsky

Précis: Genetic determinants of promoter hypermethylation in lung cells from smokers can be combined with clinical and somatic markers to improve risk assessment models for lung cancer.
THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Metronomic Dosing of BH3 Mimetic Small Molecule Yields Robust Antiangiogenic and Antitumor Effects
Atsushi Imai, Benjamin D. Zeitlin, Fernanda Visioli, Zhihong Dong, Zhaoceng Zhang, Sudha Krishnamurthy, Emily Light, Frank Worden, Shaomeng Wang, and Jacques E. Nor

Précis: The efficacy of targeted drugs that disrupt the function of certain Bcl-2 family proteins might be increased by continuous low-dose administration with the benefit of decreased side effects.

Sphingosine-1-Phosphate Produced by Sphingosine Kinase 1 Promotes Breast Cancer Progression by Stimulating Angiogenesis and Lymphangiogenesis
Masayuki Nagahashi, Subramaniam Ramachandran, Eugene Y. Kim, Jeremy C. Allegood, Omar M. Rashid, Akimitsu Yamada, Renping Zhao, Sheldon Müllstien, Huiping Zhou, Sarah Spiegel, and Kazuaki Takabe

Précis: A generalized therapy that targets both arms of the angiogenic process that supplies blood to tumors and drains metastatic cells from them may be achieved by inhibiting production of a critical bioactive lipid mediator, as illustrated in this preclinical breast cancer study.

A Pharmacologic Inhibitor of the Protease Taspase1 Effectively Inhibits Breast and Brain Tumor Growth

Précis: Findings offer a preclinical demonstration of the selective antitumor properties for small molecule inhibitors of a protein threonine endopeptidase implicated in initiating and maintaining cancer pathophysiology.

Targeting Protein Synthesis in a Myc/mTOR-Driven Model of Anorexia-Cachexia Syndrome Delays Its Onset and Prolongs Survival
Francis Robert, John R. Mills, Aouad Ageron, Dantong Wang, Sergio DiMarco, Regina Cencic, Michel L. Tremblay, Imed Eddine Gallouzi, Siegfried Hekimi, Simon S. Wing, and Jerry Pelletier

Précis: A unique preclinical model is described that can address cachexic syndromes in cancer, which cause a great deal of suffering in patients but have garnered little attention as yet from basic researchers.

Identification of Molecular Vulnerabilities in Human Multiple Myeloma Cells by RNA Interference Lethality Screening of the Druggable Genome
Rodger E. Tiedemann, Yuan Xiao Zhu, Jessica Schmidt, Chang Xin Shi, Chris Sereduk, Hongwei Yin, Spyro Mousses, and A. Keith Stewart

Précis: Genome-scale siRNA screening and gene expression profiling identify new potential therapeutic targets to treat aggressive multiple myeloma.

Antitumor Activity of BRAF Inhibitor Vemurafenib in Preclinical Models of BRAF-Mutant Colorectal Cancer
Hong Yang, Brian Higgins, Kenneth Kolinsky, Kathryn Packman, William D. Bradley, Richard J. Lee, Kathleen Schostack, Mary Ellen Simcox, Scott Kopetz, David Heimbrook, Brian Lestini, Gideon Bollag, and Fei Su

Précis: This study offers a preclinical proof of principle for the BRAF inhibitor vemurafenib in combination with other standard chemotherapeutics or targeted agents as an effective modality for colorectal cancer treatment.
Monofunctional Platinum–DNA Adducts Are Strong Inhibitors of Transcription and Substrates for Nucleotide Excision Repair in Live Mammalian Cells
Guangyu Zhu, MyatNoeZin Myint, Wee Han Ang, Lina Song, and Stephen J. Lippard

Précis: Platinum complexes that form monofunctional adducts on targeted DNA may be more potent than the most widely used platinum anticancer drug, cisplatin.

TUMOR AND STEM CELL BIOLOGY

801 Targeting Quiescent Tumor Cells via Oxygen and IGF-I Supplementation
Alastair H. Kyle, Jennifer H.E. Baker, and Andrew I. Minchinton

Précis: Traditional cytotoxic chemotherapies work best against cycling cells, but against the majority of noncycling cells in tumors, strategies to augment their much weaker effects might greatly increase patient responses and survival.

810 SMYD3 Promotes Cancer Invasion by Epigenetic Upregulation of the Metalloproteinase MMP-9
Alicia M. Cock-Rada, Souhila Medjkane, Natacha Janski, Nadhir Yousfi, Martine Perichon, Marie Chaussepied, Johanna Chluba, Gordon Langsley, and Jonathan B. Weitzman

Précis: Results identify the SMYD3 histone methyltransferase as an important new regulator of MMP9, an extracellular matrix protease that is a key regulator of metastatic cancer progression.

LETTERS TO THE EDITOR

821 Tumor-Initiating Cells in Childhood Neuroblastoma—Letter
Sofie Mohlin, Alexander Pietras, Caroline Wigerup, Ingrid Øra, Michael Anding, Kenneth Nilsson, Tor Olofsson, David Gisselsson, and Sven Pahlman

823 Tumor-Initiating Cells in Childhood Neuroblastoma—Response
Loen M. Hansford and David R. Kaplan

CORRECTIONS

825 Correction: Tumor Cells Secrete Galectin-1 to Enhance Endothelial Cell Activity

826 Correction: Decreased Lymphangiogenesis and Lymph Node Metastasis by mTOR Inhibition in Head and Neck Cancer

827 Correction: Hypoxia Induces Escape from Innate Immunity in Cancer Cells via Increased Expression of ADAM10: Role of Nitric Oxide

ABOUT THE COVER

Human hS100A7/psoriasin has been shown to be highly expressed in invasive breast tumors and is associated with increased inflammatory cell infiltrates. Using a novel transgenic mouse model, we have shown that overexpression of mS100a7a15, the murine homolog of hS100A7/psoriasin, enhances breast tumor growth by activating proinflammatory and metastatic pathways through recruitment of tumor-associated macrophages. The figure demonstrates ductal hyperplasia in mammary epithelial cells in mS100a7a15 overexpressing mice, as detected by hematoxylin and eosin staining. For details, see the article by Nasser and colleagues on page 604 of this issue.

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