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**MICROENVIRONMENT AND IMMUNOLOGY**

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**Oncogene-Driven Intrinsic Inflammation Induces Leukocyte Production of Tumor Necrosis Factor That Critically Contributes to Mammary Carcinogenesis**
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**Receptor Tyrosine Kinase Signaling Favors a Protumorigenic State in Breast Cancer Cells by Inhibiting the Adaptive Immune Response**

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

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**Optical Detection of Buccal Epithelial Nanoarchitectural Alterations in Patients Harboring Lung Cancer: Implications for Screening**

**Précis**: A genetic algorithm and an agent-based mathematical model that can predict cancer vaccine activity reveal critical issues in vaccine design.
### Selective Depletion of Foxp3<sup>+</sup> Regulatory T Cells Improves Effective Therapeutic Vaccination against Established Melanoma

Katjana Klages, Christian T. Mayer, Katharina Lahl, Christoph Loddenkemper, Michele W.L. Teng, Shin Foong Ngiow, Mark J. Smyth, Alf Hamann, Jochen Huehn, and Tim Sparwasser

Précis: First study to show that depleting FoxP3<sup>+</sup> T regulatory cells along with vaccination can trigger regression of established melanomas.

### Conditional Regulatory T-Cell Depletion Releases Adaptive Immunity Preventing Carcinogenesis and Suppressing Established Tumor Growth

Michele W.L. Teng, Shin Foong Ngiow, Bianca von Scheidt, Nicole McLaughlin, Tim Sparwasser, and Mark J. Smyth

Précis: First demonstration that established spontaneous and experimental tumors can regress following specific, complete, and delayed regulatory T-cell depletion.

### Protein Kinase D1 Suppresses Epithelial-to-Mesenchymal Transition through Phosphorylation of Snail

Cheng Du, Chunyou Zhang, Sazzad Hassan, Md. Helal Uddin Biswas, and K.C. Balaji

Précis: Factors that regulate the epithelial-mesenchymal transition in cancer are of great importance given the common role of this program in driving invasion and metastasis.

### eIF2α Kinase PKR Modulates the Hypoxic Response by Stat3-Dependent Transcriptional Suppression of HIF-1α

Andreas I. Papadakis, Efrosyni Paraskeva, Philippios Peidis, Hala Muaddi, Suiyang Li, Leda Raptis, Kostas Pantopoulos, George Simos, and Antonis E. Koromilas

Précis: Findings reveal a novel tumor suppressor function of the eIF2α kinase PKR that acts through the control of Stat3 rather than eIF2α.

### H3K9 Histone Methyltransferase G9a Promotes Lung Cancer Invasion and Metastasis by Silencing the Cell Adhesion Molecule Ep-CAM

Min-Wei Chen, Kuo-Tai Hua, Hsin-Jung Kao, Chia-Chun Chü, Lin-Hung Wei, Gunmar Johnsson, Shine-Gwo Shiah, Pui-Sheng Chen, Yung-Ming Jeng, Tsu-Yao Cheng, Tsung-Ching Lai, Jeng-Shou Chang, Yi-Hua Jan, Ming-Hsien Chien, Chih-Jen Yang, Ming-Shyan Huang, Michael Hsiao, and Min-Liang Kuo

Précis: First study to show that depleting Foxp3<sup>+</sup> T regulatory cells along with vaccination can trigger regression of established melanomas.

### microRNA Signature and Expression of Dicer and Drosha Can Predict Prognosis and Delineate Risk Groups in Neuroblastoma


Précis: This first study of the microRNA processing enzyme Dicer/Drosha in neuroblastoma establishes the value of combining micro RNA signature and Dicer/Drosha in classification and prognostication of neuroblastoma.

### Fibroblast Growth Factor Receptor 4 Regulates Tumor Invasion by Coupling Fibroblast Growth Factor Signaling to Extracellular Matrix Degradation


Précis: Findings define a key new regulatory mechanism of epithelial-to-mesenchymal transition that involves an FGF receptor isoform previously linked to tumor progression.

### HER-2 Signaling, Acquisition of Growth Factor Independence, and Regulation of Biological Networks Associated with Cell Transformation

Aliccia Bollig-Fischer, Michele Dziubinski, Alaina Boyer, Ramsi Haddad, Craig N. Giroux, and Stephen P. Ethier

Précis: Findings suggest that mutational-activated and ligand-activated forms of growth factor receptors regulate distinct transcription programs that differentially affect motility, stress response, and stem cell properties.
MicroRNA Mediates DNA Demethylation Events Triggered by Retinoic Acid during Neuroblastoma Cell Differentiation
Sudipto Das, Niamh Foley, Kenneth Bryan, Karen M. Watters, Isabella Bray, Derek M. Murphy, Patrick G. Buckley, and Raymond L. Stallings

Précis: Findings establish a significant role for microRNA function in the mechanism by which tumor growth is blocked by retinoic acid, widely used to treat certain pediatric and adult tumors.

The RB-E2F1 Pathway Regulates Autophagy
Hong Jiang, Vanesa Martin, Candelaria Gomez-Manzano, David G. Johnson, Marta Alonso, Erin White, Jing Xu, Timothy J. McDonnell, Naoki Shinojima, and Juan Fueyo

Précis: Findings provide a mechanistic explanation for the relevance of RB status in cancer development and its resistance to therapies.

Ratio of miR-196s to HOXC8 Messenger RNA Correlates with Breast Cancer Cell Migration and Metastasis
Yong Li, Maoxiang Zhang, Huijun Chen, Zheng Dong, Vadivel Ganapathy, Muthusamy Thangaraju, and Shuang Huang

Précis: Findings define an miRNA family in metastasis suppression and suggest its use in predicting breast cancer metastatic capability.

RasGRP3 Contributes to Formation and Maintenance of the Prostate Cancer Phenotype
Dazhi Yang, Noemi Kedei, Luowei Li, Juan Tao, Julia F. Velasquez, Aleksandra M. Michalowski, Balázs I. Tóth, Rita Marincsák, Attila Varga, Tamás Biró, Stuart H. Yuspa, and Peter M. Blumberg

Précis: Findings define an important signaling element upstream of Ras in metastatic prostate cancer, which may constitute a novel therapeutic target for treatment of androgen-independent disease.

Nucleotide Excision Repair Gene Expression after Cisplatin Treatment in Melanoma
Nikola A. Bowden, Katie A. Ashton, Kelly A. Avery-Kiejda, Xu Dong Zhang, Peter Hersey, and Rodney J. Scott

Précis: Defects in the ability of melanoma cells to recognize certain types of DNA damage may underlie the clinical resistance of melanoma to cisplatin treatment.

Dietary Fish Oil Alters T Lymphocyte Cell Populations and Exacerbates Disease in a Mouse Model of Inflammatory Colitis

Précis: Findings that fish oil enriched with DHA can promote colitis and colon adenocarcinoma in mice indicate that supplements for clinical benefit should be approached with caution, particularly in individuals with chronic inflammatory conditions such as inflammatory bowel diseases.

Keratinocyte-Specific Stat3 Heterozygosity Impairs Development of Skin Tumors in Human Papillomavirus 8 Transgenic Mice
Marco De Andrea, Massimo Rittà, Manuela M. Landini, Cinzia Borigina, Michele Mondini, Florian Kern, Karin Ehrenreiter, Manuela Baccarini, Gian Paolo Marcuzzi, Sigur Smola, Herbert Pfister, Santo Landolfo, and Marisa Garigli

Précis: Findings offer the first direct evidence of a critical role for STAT3 in epithelial cancers induced by human papillomaviruses of the genus β.

Expression of the Transcriptional Repressor Gfi-1 Is Regulated by C/EBPα and Is Involved in Its Proliferation and Colony Formation–Inhibitory Effects in p210BCR/ABL-Expressing Cells
Maria Rosa Lidonnici, Alessandra Audia, Angela Rachele Soliera, Marco Prisco, Giovanna Ferrari-Amorotti, Todd Waldron, Nick Donato, Ying Zhang, Robert V. Martinez, Tessa L. Holyoake, and Bruno Calabretta

Précis: Identification of the mechanisms responsible for the growth suppressive effects of C/EBPα is essential for development of therapeutic strategies based on transcription factor activation.
Synergistic Chemosensitivity of Triple-Negative Breast Cancer Cell Lines to Poly(ADP-Ribose) Polymerase Inhibition, Gemcitabine, and Cisplatin
Kedar Hastak, Elizabeth Alli, and James M. Ford

Précis: Findings address the clinical challenge faced by women with “triple-negative” breast cancers which lack hormone receptors or HER2 amplification, an aggressive disease presently without effective treatment options.

Apatinib (YN968D1) Reverses Multidrug Resistance by Inhibiting the Efflux Function of Multiple ATP-Binding Cassette Transporters
Yan-jun Mi, Yong-ju Liang, Hong-bing Huang, Hong-yun Zhao, Chung-Pu Wu, Fang Wang, Li-yang Tao, Chuan-zhao Zhang, Chun-Ling Dai, Amit K. Tiwari, Xiao-xu Ma, Kenneth Kin Wah To, Suresh V. Ambudkar, Zhe-Sheng Chen, and Li-wu Fu

Précis: A tyrosine kinase inhibitor in clinical trials is found to also inhibit multidrug resistance, perhaps expanding its clinical applications in combination with conventional chemotherapeutic drugs.

Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer
Meng-Lei Zhu, Craig M. Horbinski, Mark Garzotto, David Z. Qian, Tomasz M. Beer, and Natasha Kyprianou

Précis: The therapeutic effects of taxanes in castration-resistant prostate cancers are linked to their effects on androgen signaling.

Role of LIM and SH3 Protein 1 (LASP1) in the Metastatic Dissemination of Medulloblastoma
Christopher Traenka, Marc Remke, Andrey Korshunov, Sebastian Bender, Thomas Hielscher, Paul A. Northcott, Hendrik Witt, Marina Ryzhova, Jörg Felsberg, Axel Benner, Stephanie Riester, Wolfram Scheurlen, Thomas G. P. Grunewald, Andreas von Deimling, Andreas E. Kulozik, Guido Reifenberger, Michael D. Taylor, Peter Lichter, Elke Butt, and Stefan M. Pfister

Précis: Findings define and functionally characterize an independent prognostic biomarker involved in the most common malignant brain tumor of childhood.

Aberrant Silencing of Cancer-Related Genes by CpG Hypermethylation Occurs Independently of Their Spatial Organization in the Nucleus

Précis: Extensive chromatin changes at promoters in cancer cells appear to occur locally without preference for nuclear position or repositioning.

Cell Surface Tetraspanin CD9 Mediates Chemosensitivity in Small Cell Lung Cancer
Satoshi Kohno, Takashi Kijima, Yasushdi Otani, Masahide Mori, Toshiyuki Minami, Ryo Takahashi, Izumi Nagatomo, Yoshito Takeda, Hiroshi Kida, Shota Goya, Mitsuhiro Yoshida, Toru Kumagai, Isao Tachibana, Soichiro Yokota, and Ichiro Kawase

Précis: Findings rationalize antibody attack of a cell surface tetraspanin to reverse drug resistance in highly aggressive small cell lung cancers, which tend to relapse rapidly in resistant forms after initial therapy.

A Novel, Selective, and Efficacious Nanomolar Pyridopyrazinone Inhibitor of V600EBRAF
Steven Whittaker, Delphine Ménard, Ruth Kirk, Lesley Ogilvie, Douglas Hedley, Alfonso Zambon, Filipa Lopes, Natasha Preece, Helen Mann, Sareena Rana, Maryou Lambros, Jorge S. Reis-Filho, Richard Marais, and Caroline J. Springer

Précis: A novel orally bioavailable drug selectively inhibits oncogenic mutants of the BRAF kinase thus eliciting major therapeutic responses in melanomas where BRAF mutations are common.

Contextual Synthetic Lethality of Cancer Cell Kill Based on the Tumor Microenvironment
Norman Chan, Isabel M. Pires, Zuzana Bencokova, Carla Coackley, Kaisa R. Luoto, Nirnay Bhogal, Minalini Lakshman, Ponnari Gottipati, F. Javier Oliver, Thomas Hellday, Ester M. Hammond, and Robert G. Bristow

Précis: Findings broaden the potential application of small molecule inhibitors of the DNA repair polymerase PARP-1, which are currently in clinical trials.
**Genome-wide Analysis of Novel Splice Variants Induced by Topoisomerase I Poisoning Shows Preferential Occurrence in Genes Encoding Splicing Factors**

Stéphanie Solier, Jennifer Barb, Barry R. Zeeberg, Sudhir Varma, Mike C. Ryan, Kurt W. Kohn, John N. Weinstein, Peter J. Munson, and Yves Pommier

Précis: Findings explain the abnormal splicing of a large number of genes in response to the generation of topoisomerase I cleavage complexes trapped by certain DNA damaging drugs.

**Activity of the Novel Dual Phosphatidylinositol 3-Kinase/Mammalian Target of Rapamycin Inhibitor NVP-BEZ235 Against T-Cell Acute Lymphoblastic Leukemia**

Francesca Chiarini, Cecilia Grimaldi, Francesca Ricci, Pier Luigi Tazzari, Camilla Evangelisti, Andrea Ognibene, Michela Battistelli, Elisabetta Falciere, Fraia Melchionda, Andrea Pession, Pasqualepaolo Pagliaro, James A. McCubrey, and Alberto M. Martelli

Précis: Preclinical proof of concept study indicates that a novel orally available dual inhibitor of PI3K and mTOR may be a highly effective therapeutic to treat T-cell acute lymphoblastic leukemia.

**Aerobic Glycolysis Suppresses p53 Activity to Provide Selective Protection from Apoptosis upon Loss of Growth Signals or Inhibition of BCR-Abl**

Emily F. Mason, Yuxing Zhao, Pankuri Goraksha-Hicks, Jonathan L. Coloff, Hugh Gannon, Stephen N. Jones, and Jeffrey C. Rathmell

Précis: This study demonstrates the role of cell metabolism in sensitivity to targeted therapy and suggests that metabolic manipulations may enhance the efficacy of the tyrosine kinase inhibitor Gleevec.

**De novo Lipogenesis Protects Cancer Cells from Free Radicals and Chemotherapeutics by Promoting Membrane Lipid Saturation**

Evelien Rysman, Koen Brusselmans, Katryn Scheys, Leen Timmermans, Rita Derua, Sebastian Munck, Paul P. Van Veldhoven, David Waltregny, Veerle W. Daniëls, Jelle Machiels, Frank Vanderhoydonc, Karine Smans, Etienne Waelkens, Guido Verhoeven, and Johannes V. Swinnen

Précis: De novo fatty acid synthesis promotes membrane lipid saturation and helps cancer cells to survive both carcinogenic and therapeutic insults.

**hsa-miR-191 Is a Candidate Oncogene Target for Hepatocellular Carcinoma Therapy**

Eran Elyakim, Elinat Sitbon, Alexander Faerman, Sarit Tabak, Eve Montia, Liron Belanis, Avital Dov, Eric G. Marcusson, C. Frank Bennett, Ayelet Chajut, Dalia Cohen, and Noga Yerushalmi

Précis: Findings offer preclinical proof of concept for a rational strategy to improve treatment of liver cancer, a deadly disease that is particularly common in the Far East.

**Prostate Cancer Radiosensitization through Poly(ADP-Ribose) Polymerase-1 Hyperactivation**

Ying Dong, Erik A. Bey, Long-Shan Li, Wareef Kabbani, Jingsheng Yan, Xian-Jin Xie, Jer-Tsong Hsieh, Jimming Gao, and David A. Boothman

Précis: Findings prompt clinical evaluation of β-lapachone (Arq501) as a radiosensitizer in prostate cancer, based on definition of a targeting strategy that exploits overexpression of oxidoreductase NQO1 and hyperactivation of PARP-1.

**Epithelial-to-Mesenchymal Transition Promotes Tubulin Detyrosination and Microtubules that Enhance Endothelial Engagement**

Rebecca A. Whipple, Michael A. Matrone, Edward H. Cho, Eric M. Balzer, Michele I. Vitolo, Jennifer R. Yoon, Olga B. Ioffe, Kimberly C. Tuttle, Jing Yang, and Stuart S. Martin

Précis: Findings elucidate microtubule alterations that prime invasive tumor cells for metastatic reattachment after they have entered the bloodstream.

**De novo Lipogenesis Protects Cancer Cells from Free Radicals and Chemotherapeutics by Promoting Membrane Lipid Saturation**

Evelien Rysman, Koen Brusselmans, Katryn Scheys, Leen Timmermans, Rita Derua, Sebastian Munck, Paul P. Van Veldhoven, David Waltregny, Veerle W. Daniëls, Jelle Machiels, Frank Vanderhoydonc, Karine Smans, Etienne Waelkens, Guido Verhoeven, and Johannes V. Swinnen

Précis: De novo fatty acid synthesis promotes membrane lipid saturation and helps cancer cells to survive both carcinogenic and therapeutic insults.
Chemotrap-1: An Engineered Soluble Receptor That Blocks Chemokine-Induced Migration of Metastatic Cancer Cells In vivo
Silvia Lanati, Darryl R. Dunn, Myriam Roussigné, Maxine S. Emmett, Virginie Carriere, Denis Jullien, Jessica Budge, Justin Fryer, Monique Erard, Françoise Cailler, Jean-Phillipe Girard, and David O. Bates

Précis: Study describes a tractable strategy to treat systemic cancers by sequestering a chemokine known to drive metastasis.

Cyclin D2–Cyclin-Dependent Kinase 4/6 Is Required for Efficient Proliferation and Tumorigenesis following Apc Loss
Alicia M. Cole, Kevin Myant, Karen R. Reed, Rachel A. Ridgway, Dimitris Athineos, Gis R. Van den Brink, Vanesa Muncan, Hans Clevers, Alan R. Clarke, Peter Sicinski, and Owen J. Sansom

Précis: Apc loss is the key initiating event in colorectal cancer and thus finding target genes that are required for the phenotypes of Apc loss is vital.

Carcinoembryonic Antigen Interacts with TGF-β Receptor and Inhibits TGF-β Signaling in Colorectal Cancers
Ying Li, Hong Cao, Zhongxian Jiao, Suresh B. Pakala, Divijendra Natha Sirigiri, Wenpin Li, Rakesh Kumar, and Lopa Mishra

Précis: A common clinical marker of cancer progression may also represent a potential therapeutic target, thereby serving as a theranostic molecule.

Unique DNA Methylation Patterns Distinguish Noninvasive and Invasive Urothelial Cancers and Establish an Epigenetic Field Defect in Premalignant Tissue
Erika M. Wolff, Yoshitomo Chihara, Fei Pan, Daniel J. Weisenberger, Kimberly D. Siegmund, Kokichi Sugano, Kiyotaka Kawashima, Peter W. Laird, Peter A. Jones, and Gangning Liang

Précis: Findings offer compelling evidence that noninvasive and invasive bladder tumors arise via distinct epigenetic pathways.

Impact of Stromal Sensitivity on Radiation Response of Tumors Implanted in SCID Hosts Revisited
Mónica García-Barros, Tin Hwe Thin, Jerry Maj, Carlos Cordon-Cardo, Adriana Haimovitz-Friedman, Zvi Fuks, and Richard Kolesnik

Précis: DNA damage-mediated endothelial clonogenic lethality plays a mandatory role in the complex pathophysiologic mechanism of tumor cure by SDRT, and provides an explanation for the wild-type SDRT responses reported in tumors implanted in SCID mice.

Secreted and Membrane-Bound Isoforms of Protease ADAM9 Have Opposing Effects on Breast Cancer Cell Migration
Jessica L. Fry and Alex Toker

Précis: Ignored for many years, changes in alternate splicing patterns in cancer cells are now increasingly recognized as critical determinants of modifier functions that affect malignant progression.

Silencing of Thrombospondin-1 Is Critical for Myc-Induced Metastatic Phenotypes in Medulloblastoma
Limei Zhou, Daniel Picard, Young-Shin Ra, Meihua Li, Paul A. Northcott, Yaqi Hu, Duncan Stearns, Cynthia Hawkins, Michael D. Taylor, James Rutka, Sandy D. Der, and Annie Huang

Précis: Study offers proof of concept for an effective therapeutic strategy to treat medulloblastoma, a common pediatric brain cancer where more effective treatments are greatly needed.

Vascular Endothelial Growth Factor Receptor-1 Signaling Promotes Mobilization of Macrophage Lineage Cells from Bone Marrow and Stimulates Solid Tumor Growth
Masashi Muramatsu, Seiji Yamamoto, Tsuyoshi Osawa, and Masahumi Shibuya

Précis: VEGF signaling in bone marrow–derived macrophages recruited to tumors constitutes a significant part of the contribution of VEGF to tumor progression, beyond the direct effects on tumor angiogenesis.

Modulation of Gene Expression and Tumor Cell Growth by Redox Modification of STAT3
Li Li, Shing-hu Cheung, Emma L. Evans, and Peter E. Shaw

Précis: Findings indicate that STAT3 is subject to redox control that influences its ability to promote breast cancer cell proliferation and resistance to oxidative stress.
The Myc–miR-17–92 Axis Blunts TGFβ Signaling and Production of Multiple TGFβ-Dependent Antiangiogenic Factors
Michael Dew, Jamie L. Fox, Stacy Hultine, Prema Sundaram, Wenge Wang, Yingqiu Y. Liu, Emma Furth, Gregory H. Enders, Wafik El-Deiry, Janell M. Schelter, Michele A. Cleary, and Andrei Thomas-Tikhonenko

Précis: Results elucidate a microRNA- and TGFβ-dependent mechanism through which c-Myc acts to control tumor angiogenesis.

8247 Intraprostatic Steroidogenic Enzymes – Letter
Elahe Mostaghel, Peter S. Nelson, Colleen Nelson, and R. Bruce Montgomery

8249 Intraprostatic Steroidogenic Enzymes – Response
Johannes Hofland, Wytske M. van Weerden, Guido Jenster, Fritz H. Schröder, and Frank H. de Jong

Correction: The Epidermal Growth Factor Receptor Antibody Cetuximab Induces Autophagy in Cancer Cells by Downregulating HIF-1α and Bcl-2 and Activating the Beclin 1/hVps34 Complex

Correction: The ITK-SYK Oncogene Induces a T-Cell Lymphoproliferative Disease in Mice Mimicking Human Disease

LETTERS TO THE EDITOR

ABOUT THE COVER

Tubulin-based microtentacles facilitate epithelial-endothelial attachment. Confocal imaging of human mammary epithelial cells (HMLE) transfected with GFP-Membrane (green) engaging a confluent monolayer of mCherry-labeled (red) human bone endothelial cells. Top, angle, and side views show that HMLE cells remain rounded without observable microtentacles (left vertical panel set). HMLE cells that have undergone an epithelial-to-mesenchymal transition via stable Twist expression display microtentacles, which increase endothelial cell attachment (right vertical panel set). For details, see the article by Whipple et al. on page 8127 of this issue.
Cancer Research

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Cancer Res 2010;70:7735-8251.

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