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#### MOLECULAR AND CELLULAR PATHOBIOLOGY

**4504** Elevated Expression of the C-Type Lectin CD93 in the Glioblastoma Vasculature Regulates Cytoskeletal Rearrangements That Enhance Vessel Function and Reduce Host Survival
Elise Langenkamp, Lei Zhang, Roberta Lugano, Hua Huang, Tamador Elsir Abu Elhassan, Maria Georganaki, Wesam Bazzar, Johan Lööf, George Trendelenburg, Magnus Essand, Fredrik Pontén, Anja Smits, and Anna Dimberg

**Précis:** The C-type lectin CD93 enhances tumor vascular function by regulating endothelial migration, adhesion, and cytoskeletal rearrangements, and its expression in human glioblastoma vasculature correlates with poor survival outcome.

**4517** Tetraspanin CD81 Promotes Tumor Growth and Metastasis by Modulating the Functions of T Regulatory and Myeloid-Derived Suppressor Cells
Felipe Vences-Catalán, Ranjani Rajapaksa, Minu K. Srivastava, Aurelien Marabelle, Chiung-Chi Kuo, Ronald Levy, and Shoshana Levy

**Précis:** These findings demonstrate that the cell surface tetraspanin CD81, which is widely expressed in cancer, can contribute to immune escape by attenuating the immunosuppressive activity of innate and adaptive cells, which drive malignant progression.

#### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**4527** Cytosolic TMEM88 Promotes Invasion and Metastasis in Lung Cancer Cells by Binding DVL5
Xiupeng Zhang, Xinmiao Yu, Guiyang Jiang, Yuan Miao, Liang Wang, Yong Zhang, Yang Liu, Chunjue Fan, Xuyong Lin, Qianze Dong, Qiang Han, Huanyu Zhao, Yong Han, Xu Han, Xuezhu Rong, Shuting Ding, Endi Wang, and Enhua Wang

**Précis:** This study reveals the biological roles of TMEM88 with different localization in NSCLC in vivo and in vitro and provides a new potential target for the therapy of lung cancer patients.

**4538** The PKC/NF-κB Signaling Pathway Induces APOBEC3B Expression in Multiple Human Cancers
Brandon Leonard, Jennifer L. McCann, Gabriel J. Starrett, Leah Kosyakovsky, Elizabeth M. Luengas, Amy M. Molan, Michael B. Burns, Rebecca M. McDougell, Peter J. Parker, William L. Brown, and Reuben S. Harris

**Précis:** By revealing how a DNA mutator factor is upregulated in many human cancers, where it may contribute to pathogenesis and progression, this provocative study suggests new uses for PKC and NF-κB inhibitors in the neoadjuvant setting to decrease risks of acquired drug resistance and metastasis.

**4548** c-Myc Alterations Confer Therapeutic Response and Acquired Resistance to c-Met Inhibitors in MET-Addicted Cancers
Aijun Shen, Lai Wang, Min Huang, Jingya Sun, Yi Chen, Yan-Yan Shen, Xinying Yang, Xin Wang, Jian Ding, and Meiyu Geng

**Précis:** These findings suggest the idea that alterations to the transcription factor c-Myc confer a generalized mechanism of therapeutic resistance to inhibitors of upstream acting kinases, based on studies of acquired resistance to c-Met kinase inhibitors.

**4550** Targeting the MDM2/MDM4 Interaction Interface as a Promising Approach for p53 Reactivation Therapy
Marsha Pellegrino, Francesca Mancini, Rossella Lucà, Alice Coletti, Nicola Giacchì, Isabella Manni, Ivan Artis, Fulvio Florenzano, Emanuela Teveroni, Marianna Buttarelli, Laura Fici, Rossella Brandi, Tiziana Bruno, Maurizio Fanciulli, Sara D’Onofrio, Giulia Piaggio, Roberto Pellicciari, Alfredo Pontecorvi, Jean Christophe Marine, Antonio Macchiariulo, and Fabiola Moretti

**Précis:** A novel strategy to reactivate p53 for therapeutic purposes offers increased specificity and potential more limited toxicity, compared to other approaches that have been examined.

**4573** Activation Status of the Pregnane X Receptor Influences Vemurafenib Availability in Humanized Mouse Models
A. Kenneth MacLeod, Lesley A. McLaughlin, Colin J. Henderson, and C. Roland Wolf

**Précis:** These findings show how absorption and metabolism of the melanoma drug vemurafenib influence its systemic availability, elucidating mechanisms potentially underlying therapeutic response, drug resistance, and consequences of multi-drug interactions.
Cancer Stem Cell Marker Phenotypes Are Reversible and Functionally Homogeneous in a Preclinical Model of Pancreatic Cancer

Joseph S. Dosch, Elizabeth K. Ziemke, Amrith Shettigar, Alnawaz Rehemtulla, and Judith S. Sebolt-Leopold

Précis: These findings suggest that cancer stem cell markers are reversible, with isolated cell subpopulations equally tumorigenic and sensitive to chemotherapy in a mouse model of pancreatic cancer, challenging hierarchically organized models for understanding how cancer stem-like cells contribute to cancer pathogenicity and progression.

Heterochromatin Protein HP1γ Promotes Colorectal Cancer Progression and Is Regulated by miR-30a

Ming Liu, Feifei Huang, Dan Zhang, Junyi Ju, Xiao-Bin Wu, Ying Wang, Yadong Wang, Yupeng Wu, Min Nie, Zhuchen Li, Chi Ma, Xi Chen, Jin-Yong Zhou, Remxiang Tan, Bo-Lin Yang, Ke Zen, Chen-Yu Zhang, Yu-Gen Chen, and Quan Zhao

Précis: This study identifies a new epigenetic regulatory axis that controls the development of colorectal cancer, with implications for its prognosis and therapy.

Breast Cancer Cells Respond Differentially to Modulation of TGFβ2 Signaling after Exposure to Chemotherapy or Hypoxia


Précis: These findings provide mechanistic insight into how chemotherapy-resistant cell populations emerge and also illustrate the inherent flaws in any treatment strategy that does not address tumor heterogeneity as driven by genetic and epigenetic factors in tumor cells and their tissue microenvironment.

PI3K–mTORC2 but not PI3K–mTORC1 Regulates Transcription of HIF2A/EPAS1 and Vascularization in Neuroblastoma

Sofie Mohlin, Arash Hamidian, Kristoffer von Stedingk, Esther Bridges, Caroline Wigerup, Daniel Bexell, and Sven Pahlman

Précis: This study elucidates expression control mechanisms for HIF-2, a central regulator of cellular responses to hypoxia that is less understood than HIF-1, with practical implications in suggesting how to better target aggressive neuroblastomas, where HIF-2 tends to be selectively overexpressed.

Transmission of a Mouse Model of Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System through Combined Deletion of Snf5 and p53

Jessica M.Y. Ng, Daniel Martinez, Eric D. Marsh, Zhe Zhang, Eric Rappaport, Mariarita Santi, and Tom Curran

Précis: These findings offer insight into the development of oligodenodcytes, a connective tissue cell in the central nervous system, and address the lack of preclinical models for a rare pediatric rhabdoid tumor arising from precursors of that cell lineage, known as atypical teratoid/rhabdoid tumors (AT/RT).

A Systematic Analysis Reveals Heterogeneous Changes in the Endocytic Activities of Cancer Cells

Sarah R. Elkin, Nawal Bendris, Carlos R. Reis, Yunyun Zhou, Yang Xie, Kenneth E. Huffman, John D. Minna, and Sandra L. Schmid

Précis: Endocytotic alterations in cancer cells, which affect cell surface expression patterns, have a major influence on cancer phenotypes, highlighting broad-based opportunities to control cancer by modulating endocytic dynamics.

A TDO2-AhR Signaling Axis Facilitates Anoikis Resistance and Metastasis in Triple-Negative Breast Cancer

Nicholas C. D’Amato, Thomas J. Rogers, Michael A. Gordon, Lisa I. Greene, Dawn R. Cochrane, Nicole S. Spoelstra, Travis C. Nemkov, Angelo D’Alessandro, Kirk C. Hansen, and Jennifer K. Richer

Précis: Seminal findings deepen the evidence of a role for tryptophan catabolism in metastasis, intensifying interest in clinical development of small molecule inhibitors of tryptophan catabolic enzymes already at the forefront of the immunotherapy revolution as key mediators of immune escape.

Retraction: Meeting Report: Inaugural Chemotherapy-Induced Peripheral Neuropathy Symposium, Santa Barbara, CA, February 2015

Nicholas C. D’Amato, Thomas J. Rogers, Michael A. Gordon, Lisa I. Greene, Dawn R. Cochrane, Nicole S. Spoelstra, Travis C. Nemkov, Angelo D’Alessandro, Kirk C. Hansen, and Jennifer K. Richer

Précis: Seminal findings deepen the evidence of a role for tryptophan catabolism in metastasis, intensifying interest in clinical development of small molecule inhibitors of tryptophan catabolic enzymes already at the forefront of the immunotherapy revolution as key mediators of immune escape.
ABOUT THE COVER

Lung metastases from an orthotopic syngeneic breast cancer (left, wild type; right, knockout) are shown. The study found that metastases are highly reduced in CD81-deficient mice. Immune suppressor cells, T-regulatory (Treg) cells, and myeloid-derived suppressor cells were impaired in these knockout mice. Wild-type Tregs restored the metastatic phenotype in the knockout animals. For details, see article by Vences-Catalán and colleagues on page 4517.