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Cancer Research

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- 2418 | **Epithelial-to-Mesenchymal Transition and Autophagy Induction in Breast Carcinoma Promote Escape from T-cell-Mediated Lysis**
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- Précis:* This seminal study shows how the acquisition of EMT and autophagy in cancers promotes their ability to escape T-cell immunity, revealing new mechanistic perspectives on how immune escape and metastatic progression are linked.

- 2428 | **EGFR-TKI Resistance Due to *BIM* Polymorphism Can Be Circumvented in Combination with HDAC Inhibition**
Takayuki Nakagawa, Shinji Takeuchi, Tadaaki Yamada, Hiromichi Ebi, Takako Sano, Shigeki Nanjo, Daisuke Ishikawa, Mitsuo Sato, Yoshinori Hasegawa, Yoshitaka Sekido, and Seiji Yano

Précis: This study unravels the mechanistic basis for EGFR inhibitor resistance in patients who harbor a common *BIM* polymorphism that prevents *BIM* induction needed for a robust drug response and shows how to restore sensitivity by epigenetic reprogramming with an HDAC inhibitor.

CLINICAL STUDIES

- 2435 | **Higher Frequencies of GARP⁺CTLA-4⁺Foxp3⁺ T Regulatory Cells and Myeloid-Derived Suppressor Cells in Hepatocellular Carcinoma Patients Are Associated with Impaired T-Cell Functionality**
Suresh Kalathil, Amit A. Lugade, Austin Miller, Renuka Iyer, and Yasmin Thanavala

Précis: This is one of the first studies to confirm the expectation that multiple immunosuppressive phenotypes are present in patients with advanced cancer, with results that also greatly encourage testing of combinatorial approaches to degrade these phenotypes in this most challenging population as a rational strategy of immunotherapy.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2445 | **Automated Tracking of Nanoparticle-labeled Melanoma Cells Improves the Predictive Power of a Brain Metastasis Model**
Terje Sundstrøm, Inderjit Daphu, Ingvild Wendelbo, Erlend Hodneland, Arvid Lundervold, Heike Immervoll, Kai Ove Skaftnesmo, Michal Babic, Pavla Jendelova, Eva Sykova, Morten Lund-Johansen, Rolf Bjerkvig, and Frits Thorsen

Précis: This study describes a model that can improve upon the predictive elements derived from preclinical studies of brain metastasis, perhaps ultimately helping reduce the number of clinical trials that fail to show patient benefit.

MICROENVIRONMENT AND IMMUNOLOGY

- 2457 **Selective Blockade of Matrix Metalloprotease-14 with a Monoclonal Antibody Abrogates Invasion, Angiogenesis, and Tumor Growth in Ovarian Cancer**
Rajani Kaimal, Raid Aljumaily, Sarah L. Tressel, Rutika V. Pradhan, Lidija Covic, Athan Kuliopulos, Corrine Zarwan, Young B. Kim, Sheida Sharifi, and Anika Agarwal
Précis: Targeting MMP-14 with a monoclonal antibody may be important for antiangiogenic therapy not only in ovarian cancer but also in other solid tumors.
- 2468 **Interleukin 21–Induced Granzyme B–Expressing B Cells Infiltrate Tumors and Regulate T Cells**
Stefanie Lindner, Karen Dahlke, Kai Sontheimer, Magdalena Hagn, Christof Kaltenmeier, Thomas F.E. Barth, Thamara Beyer, Frank Reister, Dorit Fabricius, Ramin Lotfi, Oleg Lunov, G. Ulrich Nienhaus, Thomas Simmet, Rolf Kreienberg, Peter Möller, Hubert Schrezenmeier, and Bernd Jahrsdörfer
Précis: This potentially seminal study establishes the existence and control of human B-regulatory cells in the tumor microenvironment, which under the control of IL-21 may contribute significantly to Treg-dependent mechanisms of local immune escape.
- 2480 **Chemotherapy Alters Monocyte Differentiation to Favor Generation of Cancer-Supporting M2 Macrophages in the Tumor Microenvironment**
Eveline M. Dijkgraaf, Moniek Heusinkveld, Bart Tummers, Lisa T.C. Vogelpoel, Renske Goedemans, Veena Jha, Johan W.R. Nortier, Marij J.P. Welters, Judith R. Kroep, and Sjoerd H. van der Burg
Précis: Chemotherapy-induced activation of the NFκB pathway reinforces immune suppression in tumor microenvironments where prostaglandin E2 and IL-6 are being produced, suggesting combination strategies with inhibitors of COX-2 or IL-6 signaling to improve chemotherapeutic efficacy.
- 2493 **Chemotherapy Acts as an Adjuvant to Convert the Tumor Microenvironment into a Highly Permissive State for Vaccination-Induced Antitumor Immunity**
Tae Heung Kang, Chih-Ping Mao, Sung Yong Lee, Alexander Chen, Ji-Hyun Lee, Tae Woo Kim, Ronald D. Alvarez, Richard B.S. Roden, Drew Pardoll, Chien-Fu Hung, and T.-C. Wu
Précis: Immunotherapy that simply combines cytotoxic chemotherapy with local vaccination with tumor antigens should be explored carefully, given its potential to markedly improve outcomes.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 2505 **Thyroid Hormone Regulation of miR-21 Enhances Migration and Invasion of Hepatoma**
Ya-Hui Huang, Yang-Hsiang Lin, Hsiang-Cheng Chi, Chen-Hsin Liao, Chia-Jung Liao, Sheng-Ming Wu, Cheng-Yi Chen, Yi-Hsin Tseng, Chung-Ying Tsai, Sheng-Yen Lin, Yu-Ting Hung, Chih-Jen Wang, Crystal D. Lin, and Kwang-Huei Lin
Précis: Mechanistic findings reveal how the thyroid hormone can drive the growth and invasion of liver cancer cells by directly regulating an oncogenic microRNA that mediates the hormone's procancerous effects.
- 2518 **SRC Signaling Is Crucial in the Growth of Synovial Sarcoma Cells**
Sebastian Michels, Marcel Trautmann, Elisabeth Sievers, Dagmar Kindler, Sebastian Huss, Marcus Renner, Nicolaus Friedrichs, Jutta Kirfel, Susanne Steiner, Elmar Endl, Peter Wurst, Lukas Heukamp, Roland Penzel, Olle Larsson, Akira Kawai, Shinya Tanaka, Hiroshi Sonobe, Peter Schirmacher, Gunhild Mechttersheimer, Eva Wardelmann, Reinhard Büttner, and Wolfgang Hartmann
Précis: SRC activation is a critical signaling component of synovial sarcomas and represents a promising therapeutic target in this disease setting.
- 2529 **PARI Overexpression Promotes Genomic Instability and Pancreatic Tumorigenesis**
Kevin W. O'Connor, Donniphat Dejsuphong, Eunmi Park, Claudia M. Nicolae, Alec C. Kimmelman, Alan D. D'Andrea, and George-Lucian Moldovan
Précis: This study offers preclinical proof-of-concept for a novel element in the homologous recombination pathway of DNA repair widely elevated in pancreatic cancer as a candidate therapeutic target to treat this deadly disease.
- 2540 **Inhibition of SRC Corrects GM-CSF Hypersensitivity That Underlies Juvenile Myelomonocytic Leukemia**
Severa Bunda, Michelle W. Kang, Stephanie S. Sybingco, Julie Weng, Helene Favre, Danielle H. Shin, Meredith S. Irwin, Mignon L. Loh, and Michael Ohh
Précis: This study identifies Src as the critical oncogenic driver and potential druggable target of juvenile myelomonocytic leukemia, an aggressive myeloid malignancy without an effective cure.

2551 **Endocrine Fibroblast Growth Factor FGF19 Promotes Prostate Cancer Progression**

Shu Feng, Olga Dakhova, Chad J. Creighton, and Michael Ittmann

Précis: Expression of an endocrine FGF in prostate cancers is found to promote tumor progression, suggesting it may offer a novel therapeutic target.

2563 **CYP24A1 and CYP27B1 Polymorphisms Modulate Vitamin D Metabolism in Colon Cancer Cells**

Elizabeth T. Jacobs, Chad Van Pelt, Ryan E. Forster, Wasiq Zaidi, Elizabeth A. Hibler, Michael A. Galligan, Mark R. Haussler, and Peter W. Jurutka

Précis: These results illustrate how naturally occurring genetic variations in vitamin D metabolic pathways may influence the risk of colon cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2574 **Characterization of Torin2, an ATP-Competitive Inhibitor of mTOR, ATM, and ATR**

Qingsong Liu, Chunxiao Xu, Sivapriya Kirubakaran, Xin Zhang, Wooyoung Hur, Yan Liu, Nicholas P. Kwiatkowski, Jinhua Wang, Kenneth D. Westover, Peng Gao, Dalia Ercan, Mario Niepel, Carson C. Thoreen, Seong A. Kang, Matthew P. Patricelli, Yuchuan Wang, Tanya Tupper, Abigail Altabel, Hidemasa Kawamura, Kathryn D. Held, Danny M. Chou, Stephen J. Elledge, Pasi A. Janne, Kwok-Kin Wong, David M. Sabatini, and Nathanael S. Gray

Précis: An mTOR inhibitor with superior pharmacologic properties in vivo is found to inhibit PIKK family kinases involved in DNA damage signaling and to cooperate strongly with MEK kinase inhibition in killing mouse and human cancer cells.

2587 **MDM2 Small-Molecule Antagonist RG7112 Activates p53 Signaling and Regresses Human Tumors in Preclinical Cancer Models**

Christian Tovar, Bradford Graves, Kathryn Packman, Zoran Filipovic, Brian Higgins Mingxuan Xia, Christine Tardell, Rosario Garrido, Edmund Lee, Kenneth Kolinsky, Kwong-Him To, Michael Linn, Frank Podlaski, Peter Wovkulich, Binh Vu, and Lyubomir T. Vassilev

Précis: The first p53 activator to reach clinical trials is shown in preclinical testing to shrink human tumors, offering a proof-of-concept for eradication of tumors with wild-type forms of this tumor suppressor.

2598 **Ex Vivo Expansion of Highly Cytotoxic Human NK Cells by Cocultivation with Irradiated Tumor Cells for Adoptive Immunotherapy**

Seon Ah Lim, Tae-Jin Kim, Jung Eun Lee, Chung Hee Sonn, Kwanghee Kim, Jiyoung Kim, Jong Gwon Choi, Il-Kyu Choi, Chae-Ok Yun, Jae-Hong Kim, Cassian Yee, Vinay Kumar, and Kyung-Mi Lee

Précis: This article shows how to activate and expand human NK cells, providing the basis for a straightforward strategy to expand a highly cytotoxic effector cell population that may help treat advanced cancers refractory to conventional therapy.

2608 **Ex Vivo Activation of CD56⁺ Immune Cells That Eradicate Neuroblastoma**

Piya Rujkijyanont, Wing Keung Chan, Paul W. Eldridge, Timothy Lockey, Martha Holladay, Barbara Rooney, Andrew M. Davidoff, Wing Leung, and Queenie Vong

Précis: These results show a clinically expedient strategy to generate activated NK cells that are highly cytotoxic to neuroblastoma with minimal risk of GvHD.

2619 **scFv-Based "Grababody" as a General Strategy to Improve Recruitment of Immune Effector Cells to Antibody-Targeted Tumors**

Zheng Cai, Ting Fu, Yasuhiro Nagai, Lian Lam, Marla Yee, Zhiqiang Zhu, and Hongtao Zhang

Précis: A novel recombinant molecule combining the specificity of an antibody variable chain with the IgG binding domain facilitates the ability to enable tumor specific killing by endogenous immune effector cells.

TUMOR AND STEM CELL BIOLOGY

2628 **AMPK Activation by Oncogenesis Is Required to Maintain Cancer Cell Proliferation in Astrocytic Tumors**

Marcos Ríos, Marc Foretz, Benoit Viollet, Angel Prieto, Máximo Fraga, Jose A. Costoya, and Rosa Señaris

Précis: Whether AMPK is essential or not for cancer cell proliferation has been somewhat controversial, but this preclinical study offers a clear rationale for its further exploration as a therapeutic target in brain cancers.

2639 **Rhythmic Control of the ARF-MDM2 Pathway by ATF4 Underlies Circadian Accumulation of p53 in Malignant Cells**

Michiko Horiguchi, Satoru Koyanagi, Ahmed M. Hamdan, Keisuke Kakimoto, Naoya Matsunaga, Chikamasa Yamashita, and Shigehiro Ohdo

Précis: Circadian rhythms that determine the accumulation of p53 in malignant cells explain how temporal changes in their chemosensitivity can result, with potential implications for increasing therapeutic efficacy by optimizing the time of drug administration in patients.

2650 **Menin Epigenetically Represses Hedgehog Signaling in MEN1 Tumor Syndrome**

Buddha Gurung, Zijie Feng, Daniel V. Iwamoto, Austin Thiel, Guanghui Jin, Chen-Min Fan, Jessica M.Y. Ng, Tom Curran, and Xianxin Hua

Précis: Mechanistic results suggest a way to treat parathyroid, pituitary, pancreatic, and other tumors that characterize the MEN1 syndrome, offering a unified treatment approach.

2659 **Hepatocyte Growth Factor Activator Inhibitor Type 1 Is a Suppressor of Intestinal Tumorigenesis**

Shinri Hoshiko, Makiko Kawaguchi, Tsuyoshi Fukushima, Yukihiro Haruyama, Kenji Yorita, Hiroyuki Tanaka, Motoharu Seiki, Haruhiko Inatsu, Kazuo Kitamura, and Hiroaki Kataoka

Précis: A membrane-associated tumor suppressor in the intestinal tract is defined that may stimulate novel therapeutic approaches to prevent progression of benign colon tumors.

2671 **Inherited Variation in miR-290 Expression Suppresses Breast Cancer Progression by Targeting the Metastasis Susceptibility Gene *Arid4b***

Natalie Goldberger, Renard C. Walker, Chang Hee Kim, Scott Winter, and Kent W. Hunter

Précis: This is the first study to show that inherited differences in microRNA expression can modify susceptibility to metastatic progression in breast cancer.

2682 **CD44-Positive Cancer Stem Cells Expressing Cellular Prion Protein Contribute to Metastatic Capacity in Colorectal Cancer**

Lei Du, Guanhua Rao, Hongyi Wang, Baowei Li, Weili Tian, Jiantao Cui, Leya He, Brian Laffin, Xiuyun Tian, Chunyi Hao, Hongmin Liu, Xin Sun, Yushan Zhu, Dean G. Tang, Maryam Mehrpour, Youyong Lu, and Quan Chen

Précis: Prions may be functional markers of a highly metastatic subpopulation of cancer stem cells in colorectal cancer, where they might be targeted to treat metastatic disease.

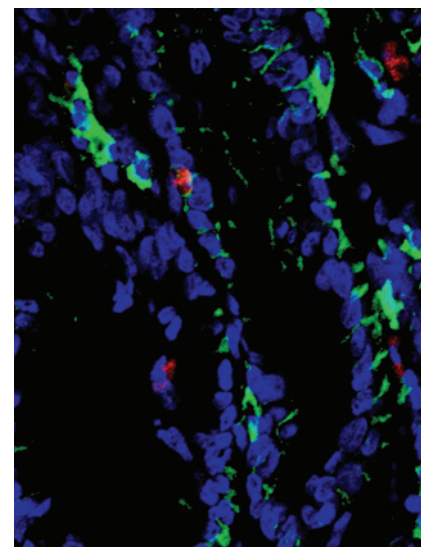
2695 **Regulation of Lung Cancer Metastasis by Klf4-Numb-like Signaling**

Valentina Vaira, Alice Favarsani, Nina M. Martin, David S. Garlick, Stefano Ferrero, Mario Nosotti, Joseph L. Kissil, Silvano Bosari, and Dario C. Altieri

Précis: These findings uncover a novel signaling network centered on the polarity protein Numb-like, which dually promotes abnormal cell motility needed for metastasis along with the persistence of cancer-initiating, stem-like cells that reduce overall survival in lung cancer.

ABOUT THE COVER

Cancer stem cells are implicated in tumor metastasis although the exact mechanisms remain poorly understood. The expression of cellular prion protein (PrPc), a highly conserved glycoprotein that has the same protein sequence as the scrapie prion protein, is positively correlated with an increased risk of metastasis in colorectal cancer. By double immunofluorescence staining of CD44 (green) and PrPc (red), CD44⁺PrPc⁺ cells were detected in the cryosections of colorectal cancers. PrPc⁺CD44⁺ colorectal cancer stem cells displayed high liver metastatic capability. For details, see article by Du and colleagues on page 2682.



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