BREAKING ADVANCES

1671 Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

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PRIORITY REPORTS

1690 Notch4 Signaling Induces a Mesenchymal–Epithelial–like Transition in Melanoma Cells to Suppress Malignant Behaviors
Ehsan Bonyadi Rad, Heinz Hamerlincl, Christian Wels, Ulrich Popper, Dinoot Ravindran Menon, Heimo Breiteneder, Melitta Kitzvoegerer, Christine Hafner, Meinhard Herly, Helmut Bergler, and Helmut Schaider

1698 A Preclinical Model of Chronic Alcohol Consumption Reveals Increased Metastatic Seeding of Colon Cancer Cells in the Liver
Hwi-Jin Im, Hyrongs-Cheeg Kim, Jin-Seok Lee, Hyo-Seon Kim, Jung-Hyo Cho, Il-Joo Jo, Sung-Joo Park, and Chang-Gue Son

INTEGRATED SYSTEMS AND TECHNOLOGIES

1705 The Cancer Stem Cell Fraction in Hierarchically Organized Tumors Can Be Estimated Using Mathematical Modeling and Patient-Specific Treatment Trajectories
Benjamin Werner, Jacob G. Scott, Andrea Sotoriva, Alexander R. A. Anderson, Arne Traulsen, and Philipp M. Altrock

1714 Genomic Landscape of Somatic Alterations in Esophageal Squamous Cell Carcinoma and Gastric Cancer
Nan Hu, Mitsutaka Kadota, Huainian Liu, Christian C. A. Abnet, Hu Su, Hailong Wu, Neal D. Freedman, Howard H. Yang, Chaoyu Wang, Chunhua Yan, Lemin Wang, Sheryl Gere, Amy Hutchinson, Guanghong Song, Yuan Wang, Ting Ding, You-Lin Qiao, Jill Koshiol, Sanford M. Dawsey, Carol Giffen, Alisa M. Goldstein, Philip R. Taylor, and Maxwell P. Lee

1724 Distinct Subtypes of Gastric Cancer Defined by Molecular Characterization Include Novel Mutational Signatures with Prognostic Capability
Xiangchun Li, William K.K. Wu, Rui Xing, Sunny H. Wong, Yuexin Liu, Xiaodong Fang, Yanlin Zhang, Mengyao Wang, Jiagian Lin, Lin Li, Yong Zhou, Senwei Tang, Shaoliang Peng, Kunlong Qiu, Longyun Chen, Reixin Chen, Huanming Yang, Wei Zhang, Matthew T.V. Chan, Youyong Lu, Joseph J.Y. Sung, and Jun Yu

1733 An Atlas of the Human Kinome Reveals the Mutational Landscape Underlying Dysregulated Phosphorylation Cascades in Cancer
Aleksandra Olow, Zhongzhong Chen, R. Hannes Niedner, Denise M. Wolf, Christina Yau, Aleksandr Pankov, Evelyn Pet Rong Lee, Lamorna Brown-Swigart, Laura J. van ’t Veen, and Jean-Philippe Coupé

Précis: By curating a large number of public databases, this study created a large map of human kinase circuits that can be globally interrogated to identify mutated signaling nodes in cancers and to select actionable targets for therapy.
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#### MICROENVIRONMENT AND IMMUNOLOGY

**1746**  
Calreticulin Expression in Human Non–Small Cell Lung Cancers Correlates with Increased Accumulation of Antitumor Immune Cells and Favorable Prognosis  
Jitka Fuchkova, Etienne Becht, Kristina Iribaren, Jeremy Goc, Romain Remark, Diane Damotte, Marco Alfano, Priyanka Devi, Jerome Biton, Claire Germain, Audrey Lupo, Wolf Herve Fridman, Marie-Caroline Dieu-Nosjean, Guido Kroemer, Catherine Sautès-Fridman, and Isabelle Cremers  
Précis: These findings highlight the potential for calreticulin, a potent “eat-me” signal on cancer cells that triggers antitumor immune responses, to serve as a clinical prognostic biomarker in patients with non-small cell lung cancer.

**1757**  
TGFβ Signaling Intersects with CD103 Integrin Signaling to Promote T-Lymphocyte Accumulation and Antitumor Activity in the Lung Tumor Microenvironment  
Marie Boutet, Ludienne Gauthier, Marine Leclerc, Gwendoline Gros, Vincent de Montpreville, Nathalie Théret, Emmanuel Donnadieu, and Fathia Mami-Chouaib  
Précis: New mechanistic insights into the antitumorigenic role of TGFβ reveal its participation in inside-out integrin signaling to promote the recruitment and activity of T lymphocytes in the tumor microenvironment.

**1770**  
Exosomes Derived from Hypoxic Oral Squamous Cell Carcinoma Cells Deliver miR-21 to Normoxic Cells to Elicit a Prometastatic Phenotype  
Guiquan Zhu, Wei Wang, Xiaoxia Li, Jin Chen, Kun Liu, Chunhua Li, and Ling Li, Chao Li, Shaoxin Wang, Zhaohui Wang, Jian Jiang, Hao Li, Yang Jia, Gang Zhang, and Xueqin Liu  
Précis: Tumor cells in hypoxic regions may remotely educate cells in oxygen-rich regions to invasively invade local tissue by secreting exosomes, which deliver proinvasive miRNAs to the recipient cells.

**1781**  
Chromogranin A Is Preferentially Cleaved into Proangiogenic Peptides in the Bone Marrow of Multiple Myeloma Patients  
Mimma Bianco, Anna Maria Gasparri, Barbara Colombo, Flavio Curnis, Stefania Girlanda, Maurilio Ponzoni, Maria Teresa Sabrina Bertilacci, Arianna Calcino, Angelina Sacchi, Elisabetta Ferrero, Marina Ferrarini, Marta Chesi, P. Leif Bergsagel, Matteo Bellone, Giovanni Tonon, Fabio Ciceri, Magda Marcacci, Federico Caligaris-Cappio, and Angelo Corti  
Précis: Angiogenesis during multiple myeloma appears to be regulated by bone marrow–derived signals that alter the balance of circulating anti- and proangiogenic chromogranin A polypeptides, with potential prognostic and therapeutic implications for patients with this hematological malignancy.

**1792**  
Basophil Recruitment into Tumor-Draining Lymph Nodes Correlates with Th2 Inflammation and Reduced Survival in Pancreatic Cancer Patients  
Lucia De Monte, Sonja Wörmann, Emanuela Brunetto, Silvia Heltai, Gilda Magliacane, Michele Reni, Anna Maria Paganoni, Helios Recalde, Anna Mondino, Massimo Falconi, Francesca Aleotti, Gianpaolo Balzano, Hana Algül, Claudio Doglioni, and Maria Pia Protti  
Précis: These findings suggest a new strategy to attack pancreatic cancers by undermining basophil-mediated signals in the tumor microenvironment that drive pathogenic inflammation and poor patient outcomes.

#### MOLECULAR AND CELLULAR PATHOBIOLOGY

**1814**  
Mutational Landscape and Antiproliferative Functions of ELF Transcription Factors in Human Cancer  
Précis: This study reveals that ELF transcription factors are inactivated frequently in a wide range of human cancers, where they can function as tumor suppressors.

**1825**  
The Ephrin-A1/EPHA2 Signaling Axis Regulates Glutamine Metabolism in HER2-Positive Breast Cancer  
Victoria M. Youngblood, Laura C. Kim, Deanna N. Edwards, Yoonha Hwang, Pranav R. Santapuram, Steven M. Stidivist, Pengcheng Lu, Fei Ye, Dana M. Brantley-Sieders, and Jian Chen  
Précis: This study highlights a potential opportunity to therapeutically target glutamine-dependent cells that support tumor growth.
Small-Molecule Inhibition of the Histone Lysine Demethylase KDM1A Suppresses the Growth of Multiple Acute Myeloid Leukemia Subtypes
John P. McGrath, Kaylyn E. Williamson, Srividya Balasubramanian, Shubho Odate, Shilpi Arosa, Charlie Hatton, Thomas M. Edwards, Thomas O’Brien, Steven Magnusson, David Stokoe, Danette L. Daniels, Barbara M. Bryant, and Patrick Trojer
Précis: Multiple AML subtypes appear to rely critically on a particular lysine-specific demethylase, especially subtypes harboring RUNX1-RUNX1T1 translocations, rendering these aggressive blood tumors highly sensitive to therapeutic eradication by pharmacological inhibitors of this enzyme.

TUMOR AND STEM CELL BIOLOGY

1989

Small-Molecule Prodigiosin Restores p53 Tumor Suppressor Activity in Chemoresistant Colorectal Cancer Stem Cells via c-Jun-Mediated ΔNp73 Inhibition and p73 Activation
Vanun V. Prabhu, Bo Hong, Joshua E. Allen, Shengliang Zhang, Amriti R. Lulla, David T. Dicker, and Wafik S. El-Deiry
Précis: These findings illuminate the mechanism underlying the antitumor effects of the small molecule prodigiosin in colorectal cancer stem cells, offering a preclinical rationale for the clinical study of p73-activating approaches to treat refractory and recurrent colorectal cancers.

2000

Aspirin Suppresses the Acquisition of Chemoresistance in Breast Cancer by Disrupting an NFκB–IL6 Signaling Axis Responsible for the Generation of Cancer Stem Cells
Shilpi Saha, Shrvanti Mukherjee, Poulanmi Khan, Kirti Kajal, Minakshi Mazumdar, Argha Mann, Sanhita Mukherjee, Sunanda De, Debarshi Jana, Dipendra K. Sarkar, and Tanya Das
Précis: These results suggest that aggressive recurrence of breast cancer after chemotherapy might be suppressed in part with aspirin, which appears to disrupt the de novo generation of chemoresistant cancer stem-like cells.

2013

Combined Treatment with Epigenetic, Differentiating, and Chemotherapeutic Agents Cooperatively Targets Tumor-Initiating Cells in Triple-Negative Breast Cancer
Vanessa F. Merino, Nguyen Nguyen, Kideok Jin, Helen Sadik, Sooweng Cho, Preethi Korangath, Liangfeng Han, Yolanda M.N. Foster, Xian C. Zhou, Zhe Zhang, Roisin M. Connolly, Yered Stearns, Syed Z. Ali, Christina Adams, Qian Chen, Duoja Pan, David L. Huso, Peter Ordentlich, Angela Brodie, and Saraswati Sukumar
Précis: The combined effects of HDAC inhibition, retinoid-induced cell differentiation, and chemotherapy appear to target tumor-initiating cells and trigger regressions in triple-negative breast cancer, with implications for overcoming disease recurrence due to residual cancer stem-like cell populations.
LETTERS TO THE EDITOR

2050  REG3β Plays a Key Role in IL17RA Protumoral Effect—Letter
Qing Li, Jun-Li Liu, and Zu-Hua Gao

2051  REG3β Plays a Key Role in IL17RA Protumoral Effect—Response
Celine Loncle, Laia Bonjoch, Emma Folch-Puy, Maria Belen Lopez-Millan, Sophie Lac, Maria Inés Molejon, Eduardo Chuluyan, Pierre Cordelier, Pierre Dubus, Gwen Lomberk, Raul Urrutia, Daniel Closa, and Juan I. Iovanna

CORRECTION

2052  Correction: Lupeol Suppresses Cisplatin-Induced Nuclear Factor-κB Activation in Head and Neck Squamous Cell Carcinoma and Inhibits Local Invasion and Nodal Metastasis in an Orthotopic Nude Mouse Model

ABOUT THE COVER

Accumulating evidence suggests a major role for cancer stem cells (CSC) in chemoresistance. An interplay between breast CSCs and non-CSCs involving NFκB/IL6 paracrine loop was decoded as the mechanism responsible for expansion of invasive, chemoresistant CSC population in patients suffering from disease relapse after chemotherapy. The image shows immunostaining for NFκB (brown), a pivotal inflammatory regulator, in primary tumors of patients with breast cancer that acquired aggressive phenotype following chemotherapy. Prior treatment with aspirin suppressed acquisition of chemoresistance by perturbing NFκB nuclear translocation in pre-existing CSCs. Thus, combining aspirin and chemotherapy may offer a new treatment strategy to improve recurrence-free survival of breast cancer patients. For details, see article by Saha and colleagues on page 2000.