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Cancer Research

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MICROENVIRONMENT AND IMMUNOLOGY

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- Précis:* Findings reveal an intriguing mechanism through which tumor-associated neutrophils present in the tumor microenvironment can trigger an antigen-specific cytolytic T-cell response against the malignant cells present there.

- 3163 | **Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Immunomodulatory Antibodies**
Inge Verbrugge, Jim Hagekyriakou, Leslie L. Sharp, Mara Galli, Alison West, Nicole M. McLaughlin, H el ene Duret, Hideo Yagita, Ricky W. Johnstone, Mark J. Smyth, and Nicole M. Haynes
- Précis:* Findings show how systemically delivered monoclonal antibodies that can concomitantly stimulate antitumor immunity and degrade tumoral immunosuppression can act as powerful adjuvants to improve the efficacy of cancer radiotherapy, with immediate translational potential as immunoradiotherapy.

- 3175 | **CXCL10 Promotes Osteolytic Bone Metastasis by Enhancing Cancer Outgrowth and Osteoclastogenesis**
Jong-Ho Lee, Ha-Neui Kim, Kyung-Ok Kim, Won Jong Jin, Seungbok Lee, Hong-Hee Kim, Hyunil Ha, and Zang Hee Lee
- Précis:* Findings advance understanding of the microenvironmental contributions in the bone that permit the development of osteolytic bone metastasis, with implications for treatment of this common aspect of malignant progression in some common cancers.

3187 **Loss of Fibroblast HIF-1 α Accelerates Tumorigenesis**

Jung-whan Kim, Colin Evans, Alexander Weidemann, Norihiko Takeda, Yun Sok Lee, Christian Stockmann, Cristina Branco-Price, Filip Brandberg, Gustavo Leone, Michael C. Ostrowski, and Randall S. Johnson

Précis: The unexpected finding that HIF-1 α can exert tumor-suppressive effects in cancer-associated fibroblasts contrasts radically with the protumorigenic effects of this factor in cancer cells themselves, with potential implications for manipulation of this important pathway for therapeutic benefit.

3196 **Combination Therapy with HSP90 Inhibitor 17-DMAG Reconditions the Tumor Microenvironment to Improve Recruitment of Therapeutic T cells**

Aparna Rao, Jennifer L. Taylor, Nina Chi-Sabins, Mayumi Kawabe, William E. Gooding, and Walter J. Storkus

Précis: Used in combinational studies for immunochemotherapy, a chaperone small-molecule inhibitor might generally heighten antitumor responses mediated by specific CD8-positive T cells.

3228 **MEK Inhibition Leads to PI3K/AKT Activation by Relieving a Negative Feedback on ERBB Receptors**

Alexa B. Turke, Youngchul Song, Carlotta Costa, Rebecca Cook, Carlos L. Arteaga, John M. Asara, and Jeffrey A. Engelman

Précis: Findings suggest that, by unleashing ERBB/PI3K/AKT signaling in cancer cells, MEK inhibitors might have complex effects on cancer pathophysiology, with implications for clinical trial design.

3238 **DEDD Interacts with PI3KC3 to Activate Autophagy and Attenuate Epithelial–Mesenchymal Transition in Human Breast Cancer**

Qi Lv, Wei Wang, Jianfei Xue, Fang Hua, Rong Mu, Heng Lin, Jun Yan, Xiaoxi Lv, Xiaoguang Chen, and Zhuo-Wei Hu

Précis: A key effector molecule for cell death signaling receptors activates autophagy but also attenuates epithelial–mesenchymal transition, placing it at an important intersection to modify metabolic and metastatic pathways in cancer.

3251 **Chk2 Phosphorylation of Survivin- Δ Ex3 Contributes to a DNA Damage–Sensing Checkpoint in Cancer**

Alessia Lopergolo, Michele Tavecchio, Sofia Lisanti, Jagadish C. Ghosh, Takehiko Dohi, Alice Favarsani, Valentina Vaira, Silvano Bosari, Nobuhiko Tanigawa, Domenico Delia, Andrew V. Kossenkov, Louise C. Showe, and Dario C. Altieri

Précis: This study identifies a novel role of the checkpoint kinase Chk2 in controlling sensing of double-strand DNA breaks in tumor cells.

3260 **Oncogenic PI3K Mutations Lead to NF- κ B–Dependent Cytokine Expression following Growth Factor Deprivation**

Jessica E. Hutti, Adam D. Pfefferle, Sean C. Russell, Mayukh Sircar, Charles M. Perou, and Albert S. Baldwin

Précis: This important study furthers a deepening trend in the field by enhancing our understanding of how the most common mutations in cancer not only exert autonomous effects in cancer cells but also powerfully influence the local tumor microenvironment to support the outgrowth of these cells.

3270 **TMEM16A Induces MAPK and Contributes Directly to Tumorigenesis and Cancer Progression**

Umamaheswar Duvvuri, Daniel J. Shiwerski, Dong Xiao, Carol Bertrand, Xin Huang, Robert S. Edinger, Jason R. Rock, Brian D. Harfe, Brian J. Henson, Karl Kunzelmann, Rainer Schreiber, Raja S. Seethala, Ann Marie Egloff, Xing Chen, Vivian W. Lui, Jennifer R. Grandis, and Susanne M. Gollin

Précis: A calcium-activated chloride channel is shown to promote tumorigenesis in head and neck cancers via signaling through the Ras/Raf/MEK pathway and therefore may represent a novel therapeutic target.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3207 **Induction of the RNA Regulator LIN28A Is Required for the Growth and Pathogenesis of RESTless Breast Tumors**

Kearney T.W. Gunsalus, Matthew P. Wagoner, Kassondra Meyer, Wyatt B. Potter, Barry Schoenike, Soyoung Kim, Caroline M. Alexander, Andreas Friedl, and Avtar Roopra

Précis: This study offers pivotal mechanistic insights into how the loss of a transcriptional repressor that occurs frequently in breast cancer leads to an increase in tumor growth.

3217 **Histone Lysine Methyltransferase SETD8 Promotes Carcinogenesis by Deregulating PCNA Expression**

Masashi Takawa, Hyun-Soo Cho, Shinya Hayami, Gouji Toyokawa, Masaharu Kogure, Yuka Yamane, Yukiko Iwai, Kazuhiro Maejima, Koji Ueda, Akiko Masuda, Naoshi Dohmae, Helen I. Field, Tatsuhiko Tsunoda, Takaaki Kobayashi, Takayuki Akasu, Masanori Sugiyama, Shin-ichi Ohnuma, Yutaka Atomi, Bruce A.J. Ponder, Yusuke Nakamura, and Ryuji Hamamoto

Précis: By revealing a specific mechanism of epigenetic regulation of a central cell-cycle regulator implicated in many cancers, this study establishes a lysine methylation pathway as a potential target for generalized cancer treatment.

PREVENTION AND EPIDEMIOLOGY

- 3282 **Increased Caffeine Intake Is Associated with Reduced Risk of Basal Cell Carcinoma of the Skin**
Fengju Song, Abrar A. Qureshi, and Jiali Han

Précis: This prospective analysis shows an inverse association between caffeine intake and the risk of basal cell carcinoma in 2 large national cohorts.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 3290 **Cancer Cell Secretion of the DAMP Protein HMGB1 Supports Progression in Malignant Mesothelioma**
Sandro Jube, Zeyana S. Rivera, Marco E. Bianchi, Amy Powers, Ena Wang, Ian Pagano, Harvey I. Pass, Giovanni Gaudino, Michele Carbone, and Haining Yang

Précis: This study offers a preclinical proof-of-principle that therapies aimed at blocking HMGB1-driven inflammation may be beneficial to patients with mesothelioma, especially at early stages of tumor growth.

- 3302 **Combined EGFR/MET or EGFR/HSP90 Inhibition Is Effective in the Treatment of Lung Cancers Codriven by Mutant EGFR Containing T790M and MET**
Lu Xu, Eiki Kikuchi, Chunxiao Xu, Hiromichi Ebi, Dalia Ercan, Katherine A. Cheng, Robert Padera, Jeffrey A. Engelman, Pasi A. Jänne, Geoffrey I. Shapiro, Takeshi Shimamura, and Kwok-Kin Wong

Précis: Using a bistransgenic murine lung cancer model, this study offers preclinical proof-of-principle that combination therapies targeting EGFR and MET overcome tyrosine kinase inhibitor resistance in non-small cell lung cancer.

- 3312 **Identification of Anaplastic Lymphoma Kinase as a Potential Therapeutic Target in Ovarian Cancer**
Hong Ren, Zhi-Ping Tan, Xin Zhu, Katherine Crosby, Herbert Haack, Jian-Min Ren, Sean Beausoleil, Albrecht Moritz, Gregory Innocenti, John Rush, Yi Zhang, Xin-Min Zhou, Ting-Lei Gu, Yi-Feng Yang, and Michael J. Comb

Précis: Findings suggest the use of ALK kinase inhibitors now in clinical development as potential agents for treatment of some patients with serous ovarian carcinoma or stromal sarcoma.

- 3324 **Antibody Targeting of Cell-Bound MUC1 SEA Domain Kills Tumor Cells**

Edward Pichinuk, Itai Benhar, Oded Jacobi, Michael Chalik, Lotem Weiss, Ravit Ziv, Carolyn Sympson, Amolkumar Karwa, Nechama I. Smorodinsky, Daniel B. Rubinstein, and Daniel H. Wreschner

Précis: Findings explore the development of a universal class of anticancer antibodies, showing high-affinity binding and potent killing of cancer and cancer stem cells that highly express a common cancer antigen.

- 3337 **Glucose-Regulated Protein 78 Controls Cross-talk between Apoptosis and Autophagy to Determine Antiestrogen Responsiveness**

Katherine L. Cook, Ayesha N. Shajahan, Anni Wärrri, Lu Jin, Leena A. Hilakivi-Clarke, and Robert Clarke

Précis: Expression of an endoplasmic reticulum-located chaperone protein is shown to play a role in the development of acquired antiestrogen resistance, suggesting that the unfolded protein response may be an adaptation to stress in estrogen receptor-positive breast cancer.

- 3350 **Sensitivity of Glioblastomas to Clinically Available MEK Inhibitors Is Defined by Neurofibromin 1 Deficiency**

Wendy L. See, I-Li Tan, Joydeep Mukherjee, Theodore Nicolaides, and Russell O. Pieper

Précis: This study offers immediate implications for stratification of brain cancer patients who might be treated with MEK inhibitors.

- 3360 **The Nedd8-Activating Enzyme Inhibitor MLN4924 Induces Autophagy and Apoptosis to Suppress Liver Cancer Cell Growth**

Zhongguang Luo, Guangyang Yu, Hyuk Woo Lee, Lihui Li, Lingyan Wang, Dongqin Yang, Yongfu Pan, Chan Ding, Jing Qian, Lijun Wu, Yiwei Chu, Jing Yi, Xiangdong Wang, Yi Sun, Lak Shin Jeong, Jie Liu, and Lijun Jia

Précis: Findings offer preclinical evidence for therapeutic efficacy of a first-in-class neddylation inhibitor to treat liver cancer and provide a mechanistic rationale for its combination with an autophagy inhibitor.

3372 **Acquired Resistance to Tamoxifen Is Associated with Loss of the Type I Insulin-like Growth Factor Receptor: Implications for Breast Cancer Treatment**

Dedra H. Fagan, Ryan R. Uselman, Deepali Sachdev, and Douglas Yee

Précis: Findings in a preclinical breast cancer model of tamoxifen resistance may explain the reason for the lack of clinical benefit observed in trials that combine anti-IGF1 receptor and antiestrogen therapies.

3405 **PTEN and NF1 Inactivation in Schwann Cells Produces a Severe Phenotype in the Peripheral Nervous System That Promotes the Development and Malignant Progression of Peripheral Nerve Sheath Tumors**

Vincent W. Keng, Eric P. Rahrmann, Adrienne L. Watson, Barbara R. Tschida, Christopher L. Moertel, Walter J. Jessen, Tilat A. Rizvi, Margaret H. Collins, Nancy Ratner, and David A. Largaespada

Précis: This study establishes a mouse model that can rapidly recapitulate the histologies associated with onset of human neurofibromas and their malignant progression to high-grade malignant nerve tumors, based on genetic mutations that are relevant to the human tumor setting.

TUMOR AND STEM CELL BIOLOGY

3381 **Definition of Genetic Events Directing the Development of Distinct Types of Brain Tumors from Postnatal Neural Stem/Progenitor Cells**

Falk Hertwig, Katharina Meyer, Sebastian Braun, Sara Ek, Rainer Spang, Cosima V. Pfenninger, Isabella Artner, Gaëlle Prost, Xinbin Chen, Jaclyn A. Biegel, Alexander R. Judkins, Elisabet Englund, and Ulrike A. Nuber

Précis: This study reveals that, within malignant brain tumors derived from a common precursor cell pool, the temporal order of genetic events that accumulate is a critical determinant of the histopathologic phenotype that emerges.

3393 **Distinct microRNA Expression Profiles in Prostate Cancer Stem/Progenitor Cells and Tumor-Suppressive Functions of let-7**

Can Liu, Kevin Kelnar, Alexander V. Vlassov, David Brown, Junchen Wang, and Dean G. Tang

Précis: microRNA expression profiling performed in prostate cancer stem/progenitor cells identifies a relatively small signature of functionally significant tumor-suppressive genes in the control of prostate cancer stem cell activity.

3414 **CD44s Regulates the TGF- β -Mediated Mesenchymal Phenotype and Is Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma**

Kosuke Mima, Hirohisa Okabe, Takatsugu Ishimoto, Hiromitsu Hayashi, Shigeki Nakagawa, Hideyuki Kuroki, Masayuki Watanabe, Toru Beppu, Mayumi Tamada, Osamu Nagano, Hideyuki Saya, and Hideo Baba

Précis: The so-called standard isoform of a stem cell marker plays a crucial role in mesenchymal phenotypes associated with progression of hepatocellular carcinoma, with implications for therapeutic targeting of this deadly disease.

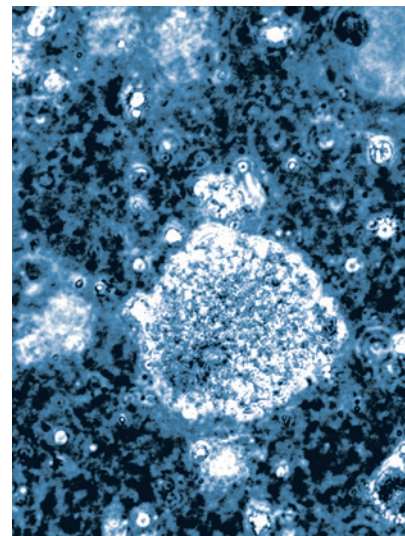
3424 **FRMD4A Upregulation in Human Squamous Cell Carcinoma Promotes Tumor Growth and Metastasis and Is Associated with Poor Prognosis**

Stephen J. Goldie, Klaas W. Mulder, David Wei-Min Tan, Scott K. Lyons, Andrew H. Sims, and Fiona M. Watt

Précis: A candidate stem cell marker implicated in epithelial polarization is found to be a key regulator of metastatic growth in head and neck cancers, with implications for therapeutic targeting of this aggressive and increasingly common disease.

ABOUT THE COVER

Malignant mesothelioma cells secrete the damage-associated molecular pattern protein HMGB1 that promotes tumor progression and sustains the malignant phenotype. HMGB1-secreting mesothelioma cells are addicted to HMGB1, and their anchorage independent growth is impaired by the antagonist BoxA or by a HMGB1 specific monoclonal antibody (mAb), or by a mAb against HMGB1 receptor RAGE, as indicated by the reduced number and size of colonies, compared to controls. For details, see article by Jube et al. on page 3290 of this issue.



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