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## July 1, 2017 • Volume 77 • Number 13

### BREAKING ADVANCES

3381 Highlights from Recent Cancer Literature

### OBITUARY

3383 Enrico Mihich, MD: In Memoriam (1928–2016)  
Margaret Foti and Youcef M. Rustum

### MEETING REPORT

3386 Obstacles, Opportunities and Priorities for Advancing Metastatic Breast Cancer Research  
Margaret Flowers, Stephanie Birkey Reffey, Shirley A. Mertz, and Marc Hurlbert for the Metastatic Breast Cancer Alliance

### MOLECULAR AND CELLULAR PATHOBIOLOGY

3391 Cyclin D1 Restrains Oncogene-Induced Autophagy by Regulating the AMPK–LKB1 Signaling Axis  
Précis: These findings suggest how AMPK activation by cyclin D1 may couple cell proliferation to energy homeostasis.

3406 VHL Inactivation in Precancerous Kidney Cells Induces an Inflammatory Response via ER Stress–Activated IRE1α Signaling  
Chan-Yen Kuo, Chih-Hung Lin, and Tien Hsu  
Précis: A tumor suppressor gene mutation in normal epithelial cells can induce inflammatory response via ER stress signaling, thus providing a potential early cancer prevention strategy via modulation of metabolic stress.

### TUMOR AND STEM CELL BIOLOGY

3417 Novel Androgen Receptor Coregulator GRHL2 Exerts Both Oncogenic and Antimetastatic Functions in Prostate Cancer  
Précis: These results show how a grainyhead-like transcription factor enhances androgen receptor expression and activity, driving proliferation of prostate cancer cells, but it also acts differentially to limit their metastatic capacity.

3431 Distinct Roles of HES1 in Normal Stem Cells and Tumor Stem-like Cells of the Intestine  
Norihiro Goto, Taro Ueo, Akihisa Fukuda, Kenji Kawada, Yoshiharu Sakai, Hiroyuki Miyoshi, Makoto Mark Takeo, Tsutomu Chiba, and Hiroshi Seno  
Précis: These results show how a stem cell transcription factor plays a different role in cancer stem-like cells, where its disruption leads to tumor regression without perturbing normal stem cell homeostasis, thereby validating it as a cancer therapeutic target.

3455 Androgen Receptor Supports an Anchorage-Independent, Cancer Stem Cell-like Population in Triple-Negative Breast Cancer  
Valerie N. Barton, Jessica L. Christenson, Michael A. Gordon, Lisa I. Greene, Thomas J. Rogers, Kiel Butterfield, Beatrice Babbs, Nicole S. Spoelstra, Nicholas C. D’Amato, Anthony Elias, and Jennifer K. Richer  
Précis: These mechanistic studies demonstrate that androgen receptor–targeting therapies may empower chemotherapy in triple-negative breast cancers by targeting drug-resistant cancer stem-like cells.
Mismatch Repair Proteins Initiate Epigenetic Alterations during Inflammation-Driven Tumorigenesis
Ashley R. Maiuri, Michael Peng, Shruthi Sriramkumar, Caitlin M. Kamplain, Christina E. DeStefano Shields, Cynthia L. Sears, and Heather M. O'Hagan

Precis: MSH2 is required for recruitment of epigenetic proteins to damaged chromatin and for DNA hypermethylation-mediated alterations in inflammation-induced tumors.

Targetable T-type Calcium Channels Drive Glioblastoma
Ying Zhang, Nichola Cruickshanks, Fang Yuan, Baomin Wang, Mary Pahuski, Julia Wulfkuhle, Isela Gallagher, Alexander F. Koeppel, Sarah Hatéf, Christopher Papanicolas, Ji Won Lee, Liam J. Simpson, and Roger Abounader

Precis: This potentially seminal study provides a preclinical proof of concept for repurposing the FDA-approved drug mibebradil as a mechanism-based treatment for deadly glioblastomas.

Monitoring Tumor Response to Antivascular Therapy Using Non-Contrast Intravoxel Incoherent Motion Diffusion-Weighted MRI
Changzheng Shi, Dexiang Liu, Zeyu Xiao, Dong Zhang, Guanshu Liu, Guanshu Liu, Hanwei Chen, and Liangping Luo

Precis: These findings highlight advantages of a novel noninvasive imaging technique that can be used to predict efficacy of antivascular therapies, without the need for contrast media.

Engineering and Functional Characterization of Fusion Genes Identifies Novel Oncogenic Drivers of Cancer

Precis: High-throughput construction of fusion genes often found in tumors facilitates more rapid functional tests to select optimal therapies directed against these genes.

Inhibition of Mitochondrial Matrix Chaperones and Antiapoptotic Bcl-2 Family Proteins Empower Antitumor Therapeutic Responses
Georg Karpel-Massler, Chiaki Tsuge Ishida, Elena Bianchetti, Chang Shu, Rolando Perez-Lorenzo, Basil Horst, Matei Banu, Kevin A. Roth, Jeffrey N. Bruce, Peter Canoll, Dario C. Altieri, and Markus D. Siegelin

Precis: This study offers a preclinical proof of concept for the combination of BH3 mimetic drugs and mitochondrial chaperone inhibitors as an effective therapeutic strategy for better management of drug-resistant tumors.

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Targeting FBW7 as a Strategy to Overcome Resistance to Targeted Therapy in Non–Small Cell Lung Cancer
Mingxiang Ye, Yong Zhang, Xinxin Zhang, Jianbin Zhang, Pengyu Jing, Lit Lu, Nan Li, Xia Li, Libo Yao, Jian Zhang, and Jian Zhang

Precis: FBW7 downregulations stabilize the antiapoptotic BCL-2 family member MCL-1, unveiling a new mechanism of resistance to targeted therapeutics in the most common form of lung cancer.

Immune-Related Gene Expression Profiling After PD-1 Blockade in Non–Small Cell Lung Carcinoma, Head and Neck Squamous Cell Carcinoma, and Melanoma
Aleix Prat, Alejandro Navarro, Laia Paré, Noemí Reguart, Patricia Galván, Tomás Pascual, Alex Martínez, Paolo Nucifora, Laura Corcuera, Llucia Alos, Nuria Parés, Susana Cedrés, Cheng Fan, Joel S. Parker, Lydia Gaba, Iván Victoria, Nuria Vílora, Ana Vivancos, Ana Arance, and Enriqueta Felip

Precis: These results argue that a pre-existing stable adaptive immune response is sufficient to predict a clinical outcome, regardless of the type of cancer or a PD-1 therapeutic antibody administered to patients.

EGFR Mediates Responses to Small-Molecule Drugs Targeting Oncogenic Fusion Kinases
Aria Vaishnavi, Laura Schubert, Uwe Rix, Lindsay A. Marek, Anh T. Le, Stephen B. Keysar, Magdalena J. Glogowska, Matthew A. Smith, Severine Kako, Natalia I. Sumi, Kurtis D. Davies, Kathryn E. Ware, Marielle Varella-Garcia, Eric B. Haura, Antonio Jimeno, Lynn E. Heasley, Dara L. Aisner, and Robert C. Doebele

Precis: These findings show how previously unknown EGFR signaling mechanisms confer a critical survival mechanism to enable evasion from oncogene-specific inhibitors, providing a rationale to cotarget EGFR to reduce risks of developing drug resistance.
MICROENVIRONMENT AND IMMUNOLOGY

3577  Chimeric PD-1:28 Receptor Upgrades Low-Avidity T cells and Restores Effector Function of Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy
Ramona Schlenker, Luis Felipe Olguín-Contreras, Matthias Leisegang, Julia Schnappinger, Anja Disovic, Svenja Rühland, Peter J. Nelson, Heinrich Leonhardt, Hartmann Harz, Susanne Wilde, Dolores J. Schendel, Wolfgang Uckert, Gerald Willimsky, and Elfriede Noessner
Précis: This study illustrates a method to empower adoptive T-cell therapies by engineering higher avidities that can improve effector function without sacrificing specificity.

3591  Epstein–Barr Virus-Induced VEGF and GM-CSF Drive Nasopharyngeal Carcinoma Metastasis via Recruitment and Activation of Macrophages
Di Huang, Shi-Jian Song, Zi-Zhao Wu, Wei Wu, Xiu-Ying Cui, Jiewen Chen, Lin Ding, Jia-Yi Zeng, Xu-Cheng Su, Yan Nie, Jianing Chen, Di Huang, Yandan Yao, Jiewen Chen, Lin Ding, Jia-Yi Zeng, Shicheng Su, Xue Chao, Fengxi Su, Herui Yao, Hai Hu, and Erwei Song
Précis: These findings define a feed-forward loop between virally infected nasopharyngeal cancer cells and macrophages and show how metastatic potential can evolve concurrently with virus-induced chronic inflammation.

3605  Tumor-Associated Macrophages Promote Malignant Progression of Breast Phyllodes Tumors by Inducing Myofibroblast Differentiation
Yan Nie, Jianing Chen, Di Huang, Yandan Yao, Jiewen Chen, Lin Ding, Jia-Yi Zeng, Shicheng Su, Xue Chao, Fengxi Su, Herui Yao, Hai Hu, and Erwei Song
Précis: In establishing how tumor-associated macrophages drive myofibroblast differentiation and malignant progression of a type of stromal breast tumor, this study uncovers a series of potential therapeutic targets for its treatment.

3619  STING Activation Reverses Lymphoma-Mediated Resistance to Antibody Immunotherapy
Leh N. Dahal, Lang Dou, Khiyam Hussain, Rena Liu, Alexander Earley, Kerry L. Cox, Salome Murinello, Ian Tracy, Francesco Forconi, Andrew J. Steele, Patrick J. Duriez, Diego Gomez-Nicola, Jessica L. Teeling, Martin J. Glennie, Mark S. Cragg, and Stephen A. Beers
Précis: These findings suggest that STING agonists can empower monoclonal antibody therapies by reprogramming tumor-associated macrophages and curbing locoregional immunosuppression in the tumor microenvironment.

3632  Deletion of Lactate Dehydrogenase-A in Myeloid Cells Triggers Antitumor Immunity
Pankaj Seth, Eva Csizmadia, Andreas Hedblom, Marta Vuerich, Han Xie, Maillin Li, Maria Serena Longhi, and Barbara Wegiel
Précis: Lactate dehydrogenase-A in the tumor microenvironment is a key determinant of immune responses against cancer and as such may provide a therapeutic target to blunt locoregional immune escape in tumors.

3644  Sarcoma Eradication by Doxorubicin and Targeted TNF Relies upon CD8+ T-cell Recognition of a Retroviral Antigen
Philipp Probst, Janine Kopp, Annette Oxenius, Mario P. Colombo, Danilo Ritz, Tim Fugmann, and Dario Neri
Précis: These findings offer evidence that retroviral genes contribute to tumoral immune surveillance through a process that can be improved by treatment with a TNF derivative and the chemotherapeutic drug doxorubicin.

3655  CXCL1 Is Critical for Premetastatic Niche Formation and Metastasis in Colorectal Cancer
Dingzhi Wang, Haiyan Sun, Jie Wei, Bo Cen, and Raymond N. DuBois
Précis: These findings show how VEGFA induces production of the neutrophil chemotractant CXCL1 in primary tumor macrophages, driving myeloid-derived suppressor cells to generate a premetastatic niche that enables later metastasis.

3666  Landscape of Combination Immunotherapy and Targeted Therapy to Improve Cancer Management
Leandro M. Colli, Mitchell J. Machiela, Han Zhang, Timothy A. Myers, Lea Jessop, Olivier Delattre, Kai Yu, and Stephen J. Chanock
Précis: A survey of genomic profiles from public databases indicate that 8.9% of solid tumor patients could benefit from combinations of immunotherapy and targeted therapy, an approach that might significantly impact overall patient survival.
Expansion of Tumor-Infiltrating CD8+ T cells Expressing PD-1 Improves the Efficacy of Adoptive T-cell Therapy

Précis: The antitumor activity of adoptive T-cell therapy is limited by low rates of ex vivo expansion of the highly differentiated PD-1+ CD8 TIL population, which is responsible for the majority of tumor cell recognition in bulk CD8 TIL.

Persistent Immune Stimulation Exacerbates Genetically Driven Myeloproliferative Disorders via Stromal Remodeling
Claudio Tripodo, Alessia Burocchi, Pier Paolo Piccaluga, Claudia Chiodoni, Paola Portararo, Barbara Cappetti, Laura Botti, Alessandro Gulino, Alessandro Isidori, Arcangelo Liso, Giusepppe Visani, Maria Paola Martelli, Brunangelo Falini, Pier Paolo Pandolfi, Mario P. Colombo, and Sabina Sangaletti

Précis: Formation of neutrophil extracellular traps (NET) composed of DNA-protein complexes in the bone marrow tissue microenvironment stimulates the expansion of myeloid precursor cells, which support a certain class of human leukemias.

PREVENTION AND EPIDEMIOLOGY

Beta-Blocker Drug Use and Survival among Patients with Pancreatic Adenocarcinoma
Ruzan Udumyan, Scott Montgomery, Fang Fang, Henrik Almroth, Unnur Valdimarsdottir, Anders Ekborn, Karin E. Smedby, and Katja Fall

Précis: These results suggest the repositioning of beta-blocker drugs, which are used widely to control hypertension and cardiac arrhythmias, to improve the survival of pancreatic cancer patients.

Assessment of Breast Cancer Risk Factors Reveals Subtype Heterogeneity
Johanna Holm, Louise Eriksson, Alexander Ploner, Mikael Eriksson, Mattias Rantalainen, Jingmei Li, Per Hall, and Kamila Czene

Précis: Breast cancer risk factors differ by molecular subtype, supporting distinct etiologies and offering implications for prevention studies, which rely on modeling risk prediction.

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RETraction

Retraction: Molecular Mechanism of MART-1+/A*0201+ Human Melanoma Resistance to Specific CTL-Killing Despite Functional Tumor–CTL Interaction

CORRECTIONS

Correction: Rescue of p53 Function by Small-Molecule RITA in Cervical Carcinoma by Blocking E6-Mediated Degradation

Correction: Epigenetic Switch between SOX2 and SOX9 Regulates Cancer Cell Plasticity

Correction: Genetic Disruption of the Multifunctional CD98/LAT1 Complex Demonstrates the Key Role of Essential Amino Acid Transport in the Control of mTORC1 and Tumor Growth

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ABOUT THE COVER

Immunometabolism is emerging as a critical determinant of cancer pathophysiology. A balance between tumor promotion and elimination is dependent on the state of functional polarization of macrophage populations within the tumor microenvironment. Lactic acid generated by lactate dehydrogenase-A is a key metabolite that facilitates the immunosuppressive tumor microenvironment. Deletion of lactate dehydrogenase-A in myeloid cells restores the immunocompetent tumor microenvironment by reversing macrophage phenotype and antitumor immunity. Immunofluorescence staining revealed an increased number of infiltrating inducible nitric oxide synthase-positive (red) and M1-skewed F4.80-positive (green) macrophages in K-Ras tumors after deletion of lactate dehydrogenase-A. For details, see article by Seth and colleagues on page 3632.
2017;77:3381-3721.

Cancer Res 2017;77:3381-3721.

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