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**EDITORIAL**

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Mark J. Suto

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7. KRAS Oncogenic Signaling Extends beyond Cancer Cells to Orchestrate the Microenvironment
Patrícia Dias Carvalho, Carlos F. Guimarães, Ana P. Cardoso, Susana Mendonça, Ângela M Costa, Maria J. Oliveira, and Sérgio Velho

15. New Perspectives, Opportunities, and Challenges in Exploring the Human Protein Kinome
Leah J. Wilson, Adam Linley, Dean E. Hammond, Fiona E. Hood, Judy M. Coulson, David J. MacEwan, Sarah J. Ross, Joseph R. Slupsky, Paul D. Smith, Patrick A. Eyers, and Ian A. Prior

30. Pleiotropic Roles for ZEB1 in Cancer
Julie Caramel, Maud Ligier, and Alain Puisieux

**METABOLISM AND CHEMICAL BIOLOGY**

36. Adaptive Evolution of the GDH2 Allosteric Domain Promotes Gliomagenesis by Resolving IDH1 substitutions. Induced Metabolic Liabilities
Matthew S. Waitkus, Christopher J. Pirozzi, Casey J. Moure, Bill H. Diplas, Landon J. Hansen, Austin B. Carpenter, Rui Yang, Zhao-Hui Wang, Brian O. Ingrazia, Edward D. Karoly, Robert P. Moloney, Ivan Spasojevic, Roger E. McLendon, Henry S. Friedman, Yiping He, Darell D. Bigner, and Hai Yan

**MOLECULAR CELL BIOLOGY**

51. CBX8 Exhibits Oncogenic Activity via AKT/β-Catenin Activation in Hepatocellular Carcinoma
Chris Zhiyi Zhang, Shi-Lu Chen, Chun-Hua Wang, Yang-Fan He, Xia Yang, Dan Xie, and Jing-Ping Yung

Significance: Elucidation of a key new element of the β-catenin signaling pathway in liver cancer may suggest new therapeutic targets.

64. MYC Targeted Long Noncoding RNA DANCR Promotes Cancer in Part by Reducing p21 Levels

Significance: These findings expand knowledge of how MYC drives cancer cell proliferation by identifying an oncogenic long noncoding RNA that is widely overexpressed in human cancers.

75. Deficiency in Protein Tyrosine Phosphatase PTP1B Shortens Lifespan and Leads to Development of Acute Leukemia
Samantha Le Sommer, Nicola Morrice, Martina Pesaresi, Dawn Thompson, Mark A. Vickers, Graeme I. Murray, Nimesh Mody, Benjamin G. Neel, Kendra K. Rence, Heather M. Wilson, and Mitjda Delilbegovic

Significance: This study defines a tumor suppressor function for the protein tyrosine phosphatase PTP1B in myeloid lineage cells, with evidence that its genetic inactivation in mice is sufficient to drive acute myeloid leukemia.

88. TGFβ Promotes Genomic Instability after Loss of RUNX3

Significance: RUNX3 inactivation in cancer removes an antioxidant barrier against DNA double strand breaks induced by TGFβ expressed in the tumor microenvironment.
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TUMOR BIOLOGY AND IMMUNOLOGY

103 An Akt3 Splice Variant Lacking the Serine Phosphorylation Site Promotes Apoptosis and Suppresses Mammary Tumorigenesis

Significance: These results illuminate an unexpected function for an endogenously expressed Akt isoform in promoting apoptosis, underscoring the likelihood that different Akt isoforms exert distinct functions in human cancer.

115 CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8 T Cells

Significance: The tumor microenvironment elicits a subset of functionally exhausted CD8 T cells by creating conditions that induce cell surface expression of CD39, an immunosuppressive molecule that can be therapeutically targeted to restore effector T-cell function.

129 A Subpopulation of Stromal Cells Controls Cancer Cell Homing to the Bone Marrow
Stephanie Rossnagl, Habiba Ghura, Christopher Groth, Eva Altrnoch, Franz Jakob, Sarah Schott, Pauline Wimberger, Theresa Link, Jan Dominik Kuhlmann, Arnulf Stenzl, Pauline Wimberger, Theresa Link, Evan Piaggio, Adriana Gruppi, Eva V. Acosta Rodríguez, Hans Joachim BNike, Maria del Carmen Rodriguez-Pena, Luigi Marchionni, Wikum Dinajankara, Asma Begum, Noah M. Hahn, Christopher J. VandenBussche, Zeshaan A. Rashed, Shifeng Mao, George J. Netto, David Sidransky, and Mohammad O. Hoque

Significance: These findings validate the importance of the CCR5/CCR5 ligand axis not only for MDSC recruitment but also for further activation of their immunosuppressive functions in the tumor microenvironment, with potentially broad therapeutic implications, given existing clinically available inhibitors of this axis.

143 Complement Activation via a C3a Receptor Pathway Alters CD4 T Lymphocytes and Mediates Lung Cancer Progression

Significance: This provocative study suggests that inhibiting complement activation may heighten immunotherapeutic responses in lung cancer, offering findings with immediate implications, given the existing clinical availability of complement antagonists.

157 CCR5 Myeloid-Derived Suppressor Cells Are Enriched and Activated in Melanoma Lesions

Significance: These findings validate the importance of the CCR5/CCR5 ligand axis not only for MDSC recruitment but also for further activation of their immunosuppressive functions in the tumor microenvironment, with potentially broad therapeutic implications, given existing clinically available inhibitors of this axis.

168 YAP1 and COX2 Coordinatey Regulate Urothelial Cancer Stem-like Cells
Akira Ooki, Maria Del Carmen Rodriguez Pena, Luigi Marchionni, Wikum Dinajankara, Asma Begum, Noah M. Hahn, Christopher J. VandenBussche, Zeshaan A. Rashed, Shifeng Mao, George J. Netto, David Sidransky, and Mohammad O. Hoque

Significance: These findings offer a preclinical rationale to target the COX2 and YAP1 pathways concurrently with systemic chemotherapy to improve the clinical management of UCB, based on evidence that these two pathways expand cancer stem-like cell populations that mediate resistance to chemotherapy.

182 Interleukin-27 Exerts Its Antitumor Effects by Promoting Differentiation of Hematopoietic Stem Cells to M1 Macrophages
Yukino Chiba, Izuru Mizoguchi, Junichi Furusawa, Hideaki Hasegawa, Mio Ohashi, Mingli Xu, Toshiyuki Owaki, and Takayuki Yoshimoto

Significance: These findings show how the interleukin IL27 exerts potent antitumor activity by enhancing the generation of myeloid progenitor cells that can differentiate into antitumorigenic M1 macrophages.

195 Type I IFN Receptor Signaling Controls IL7-Dependent Accumulation and Activity of Promutual IL17A-Producing γδT Cells in Breast Cancer
Emmanuel C. Patin, Daphnee Soulard, Sébastien Fleury, Maya Hassane, David Dombrovicz, Christelle Faveeau, François Trottstein, and Christophe Paget

Significance: Tumor-derived IL7 can represent a therapeutic target to prevent accumulation of immune cells endowed with potent protumoral activities.
TRANSLATIONAL SCIENCE

256 Dendritic Cells Enhance Polyfunctionality of Adoptively Transferred T Cells That Target Cytomegalovirus in Glioblastoma

Significance: A randomized pilot trial in patients with GBM implicates polyfunctional T-cell responses as a biomarker for effective antitumor immunotherapy.

265 A Potent, Metabolically Stable Tubulin Inhibitor Targets the Colchicine Binding Site and Overcomes Taxane Resistance
Kinsie E. Arnst, Yuxi Wang, Dong-Jin Hwang, Yi Xue, Terry Costello, David Hamilton, Qiang Chen, Jiniang Yang, Frank Park, James T. Dalton, Duane D. Miller, and Wei Li

Significance: These findings offer preclinical proof of concept for the continued development of DJ101 as a next-generation antitubulin drug for cancer therapy.

CONVERGENCE AND TECHNOLOGIES

290 ConsensusDriver Improves upon Individual Algorithms for Predicting Driver Alterations in Different Cancer Types and Individual Patients
Denis Bertrand, Sibyl Drissler, Burton K. Chia, Jia Yu Koh, Chenhao Li, Chayaporn Suphavilai, Iain Beehuat Tan, and Niranjan Nagarajan

Significance: These findings assess state-of-the-art cancer driver prediction methods and develop a new and improved consensus-based approach for use in precision oncology.
Results from the European Prospective Investigation into Cancer and Nutrition Link Vitamin B6 Catabolism and Lung Cancer Risk

Hui Zuo, Per M. Ueland, Øivind Midttun, Stein E. Vollset, Geethe S. Tell, Despoina Theofylaktopoulou, Ruth C. Travis, Marie-Christine Boutron-Ruault, Agnès Fournier, Gianluca Severi, Marina Kvaskoff, Heiner Boeing, Manuela M. Bergmann, Renée T. Fortner, Rudolf Kaelble, Antonia Trichopoulou, Anastasia Kotanidou, Pagona Lagiou, Domenico Palli, Sabina Sieri, Salvatore Panico, H. Bas Bueno-de-Mesquita, Petra H. Peeters, Kjell Granloevist, Mikael Johansson, Antonio Agudo, Jose Ramon Quiros Garcia, Nerea Larranaga, Maria-Jose Sanchez, Maria Dolores Chirlaque, Eva Andanaz, Shu-Chun Chuang, Valentina Gallo, Paul Brennan, Mattias Johansson, and Arve Ulvik

Significance: This large cohort study firmly establishes an association between an index of vitamin B6 levels with lung cancer risk.

Correction: Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer

ABOUT THE COVER

Kinases are master regulators of cell signaling networks that are frequently dysregulated in cancer, and members of the kinome family have been successfully targeted for therapeutic benefit. In this figure, the activity, cellular requirement, disease association, availability of protein structures and drugs, and research publications associated with each of the 535 members of the human protein kinome are displayed. It highlights how most research attention has been focused on relatively small subsets of the kinome. In the associated resource-based review, the authors discuss their current understanding of the human protein kinome, highlight emerging and overlooked areas, and describe key aspects of kinase signaling biology and some of the challenges associated with treating perturbed kinase networks in patients. For details, see article by Wilson and colleagues on page 15.