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- 15** New Perspectives, Opportunities, and Challenges
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Leah J. Wilson, Adam Linley, Dean E. Hammond,
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- 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^{R132H}-
Induced Metabolic Liabilities
Matthew S. Waitkus, Christopher J. Pirozzi, Casey J. Moure,
Bill H. Diplas, Landon J. Hansen, Austin B. Carpenter,
Rui Yang, Zhaohui Wang, Brian O. Ingram, Edward D. Karoly,
Robert P. Mohny, Ivan Spasojevic, Roger E. McLendon,
Henry S. Friedman, Yiping He, Darell D. Bigner, and Hai Yan
- Significance:* These findings show that the homonid-specific brain enzyme GDH2 may be essential to mitigate metabolic liabilities created by IDH1 mutations in glioma, with possible implications to leverage its therapeutic management by IDH1 inhibitors.

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 Yun
- 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 DANCER
Promotes Cancer in Part by Reducing
p21 Levels
Yunqi Lu, Zhongyi Hu, Lingegowda S. Mangala,
Zachary E. Stine, Xiaowen Hu, Dahai Jiang, Yan Xiang,
Youyou Zhang, Sunila Pradeep, Cristian Rodriguez-Aguayo,
Gabriel Lopez-Berestein, Angelo M. DeMarzo, Anil K. Sood,
Lin Zhang, and Chi V. Dang
- 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. Bence,
Heather M. Wilson, and Mirela Delibegović
- 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** TGF β Promotes Genomic Instability after
Loss of RUNX3
Vaidehi Krishnan, Yu Lin Chong, Tuan Zea Tan,
Madhura Kulkarni, Muhammad Bakhait Bin Rahmat,
Lavina Sierra Tay, Haresh Sankar, Doorgesh S. Jokhun,
Amudha Ganesan, Linda Shyue Huey Chuang,
Dominic C. Voon, GV Shivashankar, Jean-Paul Thiery, and
Yoshiaki Ito
- Significance:* RUNX3 inactivation in cancer removes an antioxidant barrier against DNA double strand breaks induced by TGF β expressed in the tumor microenvironment.

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TUMOR BIOLOGY AND IMMUNOLOGY

103 An Akt3 Splice Variant Lacking the Serine 472 Phosphorylation Site Promotes Apoptosis and Suppresses Mammary Tumorigenesis

Kimita Suyama, Jiahong Yao, Huizhi Liang, Outhiriaradjou Benard, Olivier D. Loudig, Dulguun Amgalan, Wendy M. McKimpson, Greg R. Phillips, Jeffrey Segall, Yihong Wang, Susan Fineberg, Larry Norton, Richard N. Kitsis, and Rachel B. Hazan

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

Fernando P. Canale, María C. Ramello, Nicolás Núñez, Cintia L. Araujo Furlan, Sabrina N. Bossio, Melisa Gorosito Serrán, Jimena Tosello Boari, Andrés del Castillo, Marta Ledesma, Christine Sedlik, Eliane Piaggio, Adriana Gruppi, Eva V. Acosta Rodríguez, and Carolina L. Montes

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 Rosnagl, Hiba Ghura, Christopher Groth, Eva Altrock, Franz Jakob, Sarah Schott, Pauline Wimberger, Theresa Link, Jan Dominik Kuhlmann, Arnulf Stenzl, Jörg Hennenlotter, Tilmann Todenhöfer, Markus Rojewski, Karen Bieback, and Inaam A. Nakchbandi

Significance: These findings establish an inverse relationship between a subpopulation of mesenchymal stromal cells and cancer cells in the bone marrow.

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

Jeff W. Kwak, Jennifer Laskowski, Howard Y. Li, Maria V. McSharry, Trisha R. Sippel, Bonnie L. Bullock, Amber M. Johnson, Joanna M. Poczobutt, Alexander J. Neuwelt, Stephen P. Malkoski, Mary C. Weiser-Evans, John D. Lambris, Eric T. Clambey, Joshua M. Thurman, and Raphael A. Nemenoff

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

Carolin Blattner, Viktor Fleming, Rebekka Weber, Bianca Himmelhan, Peter Altevogt, Christoffer Gebhardt, Torsten J. Schulze, Hila Razon, Elias Hawila, Gizi Wildbaum, Jochen Utikal, Nathan Karin, and Viktor Umansky

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 Coordinately Regulate Urothelial Cancer Stem-like Cells

Akira Ooki, Maria Del Carmen Rodriguez Pena, Luigi Marchionni, Wikum Dinalankara, Asma Begum, Noah M. Hahn, Christopher J. VandenBussche, Zeshaan A. Rasheed, 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 Protumoral IL17A-Producing $\gamma\delta$ T Cells in Breast Cancer

Emmanuel C. Patin, Daphnée Souillard, Sébastien Fleury, Maya Hassane, David Dombrowicz, Christelle Faveeuw, François Trottein, and Christophe Paget

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

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205 MUC1-C Induces PD-L1 and Immune Evasion in Triple-Negative Breast Cancer

Takahiro Maeda, Masayuki Hiraki, Caining Jin, Hasan Rajabi, Ashujit Tagde, Maroof Alam, Audrey Bouillez, Xiufeng Hu, Yozo Suzuki, Masaaki Miyo, Tsuyoshi Hata, Kunihiro Hinohara, and Donald Kufe

Significance: These findings show how upregulation of the transmembrane mucin MUC1 contributes to immune escape in an aggressive form of breast cancer, with potential implications for a novel immunotherapeutic approach.

216 miR-519d Promotes Melanoma Progression by Downregulating EphA4

Kuo-Tai Hua, Jin-Bong Hong, Yi-Shuan Sheen, Hsin-Yi Huang, Yi-Ling Huang, Jau-Shiuh Chen, and Yi-Hua Liao

Significance: These results suggest a significant role for miR-519d in determining expression of a pivotal cell adhesion molecule that may impact risks of malignant progression in many cancers.

230 Evidence for Kaposi Sarcoma Originating from Mesenchymal Stem Cell through KSHV-induced Mesenchymal-to-Endothelial Transition

Yuqing Li, Canrong Zhong, Dawei Liu, Wenjing Yu, Weikang Chen, Yan Wang, Songtao Shi, and Yan Yuan

Significance: These findings indicate that Kaposi sarcomas, which arise frequently in AIDS patients, originate from neural crest-derived mesenchymal stem cells, with possible implications for improving the clinical treatment of this malignancy.

246 Small-Molecule Inhibition of Axl Targets Tumor Immune Suppression and Enhances Chemotherapy in Pancreatic Cancer



Kathleen F. Ludwig, Wenting Du, Noah B. Sorrelle, Katarzyna Wnuk-Lipinska, Mary Topalovski, Jason E. Toombs, Victoria H. Cruz, Shinichi Yabuuchi, N.V. Rajeshkumar, Anirban Maitra, James B. Lorens, and Rolf A. Brekken

Significance: These results establish a preclinical mechanistic rationale for the clinical development of AXL inhibitors to improve the treatment of PDAC patients.

TRANSLATIONAL SCIENCE

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



Elizabeth A. Reap, Carter M. Suryadevara, Kristen A. Batich, Luis Sanchez-Perez, Gary E. Archer, Robert J. Schmittling, Pamela K. Norberg, James E. Herndon II, Patrick Healy, Kendra L. Congdon, Patrick C. Gedeon, Olivia C. Campbell, Adam M. Swartz, Katherine A. Riccione, John S. Yi, Mohammed K. Hossain-Ibrahim, Anirudh Saraswathula, Smita K. Nair, Anastasie M. Dunn-Pirio, Taylor M. Broome, Kent J. Weinhold, Annick Desjardins, Gordana Vlahovic, Roger E. McLendon, Allan H. Friedman, Henry S. Friedman, Darell D. Bigner, Peter E. Fecci, Duane A. Mitchell, and John H. Sampson

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, Jinliang 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.

278 Rapid Intraoperative Diagnosis of Pediatric Brain Tumors Using Stimulated Raman Histology

Todd C. Hollon, Spencer Lewis, Balaji Pandian, Yashar S. Niknafs, Mia R. Garrard, Hugh Garton, Cormac O. Maher, Kathryn McFadden, Matija Snuderl, Andrew P. Lieberman, Karin Muraszko, Sandra Camelo-Piragua, and Daniel A. Orringer

Significance: A new imaging method simplifies diagnosis and informs decision making during pediatric brain tumor surgery.

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 Niranjana 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.

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POPULATION AND PREVENTION SCIENCE

302 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, Grethe S. Tell, Despoina Theofylaktopoulos, Ruth C. Travis, Marie-Christine Boutron-Ruault, Agnès Fournier, Gianluca Severi, Marina Kvaskoff, Heiner Boeing, Manuela M. Bergmann, Renée T. Fortner, Rudolf Kaaks, Antonia Trichopoulos, Anastasia Kotanidou, Pagona Lagiou, Domenico Palli, Sabina Sieri, Salvatore Panico, H. Bas Bueno-de-Mesquita, Petra H. Peeters, Kjell Grankvist, Mikael Johansson, Antonio Agudo, Jose Ramon Quiros Garcia, Nerea Larranaga, Maria-Jose Sanchez, Maria Dolores Chirlaque, Eva Ardanaz, 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

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

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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.

