

CANCER RESEARCH

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CANCER RESEARCH HIGHLIGHTS

1633 **Mdm2 and MdmX: Partners in p53 Destruction**
James J. Manfredi

See related article by Yang et al., *Cancer Res* 2021;81:898–909

1635 **A Complementary Strategy to Mitigate Radiation-Induced Cognitive Decline**
Navyateja Korimerla and Daniel R. Wahl

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1637 **Beyond Stamp Collecting: Evolutionary and Functional Genomics Advance Our Understanding of Cancer Biology**

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GENOME AND EPIGENOME

1639 **Cancer-Associated Fibroblasts Promote Aggressive Gastric Cancer Phenotypes via Heat Shock Factor 1-Mediated Secretion of Extracellular Vesicles**

Nil Grunberg, Meirav Pevsner-Fischer, Tal Goshen-Lago, Judith Diment, Yaniv Stein, Hagar Lavon, Shimrit Mayer, Oshrat Levi-Galibov, Gil Friedman, Yifat Ofir-Birin, Li-Jyun Syu, Cristina Migliore, Eyal Shimoni, Salomon M. Stemmer, Baruch Brenner, Andrzej A. Dlugosz, David Lyden, Neta Regev-Rudzki, Irit Ben-Aharon, and Ruth Scherz-Shouval

This study shows how HSF1 regulates a stromal transcriptional program associated with aggressive gastric cancer and identifies multiple proteins within this program as candidates for therapeutic intervention.

1654 **Cancer-Specific Targeting of Taurine-Upregulated Gene 1 Enhances the Effects of Chemotherapy in Pancreatic Cancer**

Yoshihiko Tasaki, Miho Suzuki, Keisuke Katsushima, Keiko Shinjo, Kenta Iijima, Yoshiteru Murofushi, Aya Naiki-Ito, Kazuki Hayashi, Chenjie Qiu, Akiko Takahashi, Yoko Tanaka, Tokuichi Kawaguchi, Minoru Sugawara, Tomoya Kataoka, Mitsuru Naito, Kanjiro Miyata, Kazunori Kataoka, Tetsuo Noda, Wentao Gao, Hiromi Kataoka, Satoru Takahashi, Kazunori Kimura, and Yutaka Kondo

Targeting *TUG1* coupled with a cancer-specific drug delivery system effectively modulates 5-FU catabolism in *TUG1*-overexpressing PDAC cells, thus contributing to a new combinatorial strategy for cancer treatment.

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- 1667 Germline and Somatic Genetic Variants in the p53 Pathway Interact to Affect Cancer Risk, Progression, and Drug Response**
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These results offer evidence of how cancer susceptibility SNPs can interact with cancer driver genes to affect cancer progression and present novel therapeutic targets.
- 1681 Multiomics Characterization of Low-Grade Serous Ovarian Carcinoma Identifies Potential Biomarkers of MEK Inhibitor Sensitivity and Therapeutic Vulnerability**
Raunak Shrestha, Marta Llauro Fernandez, Amy Dawson, Joshua Hoenisch, Stanislav Volik, Yen-Yi Lin, Shawn Anderson, Hannah Kim, Anne M. Haegert, Shane Colborne, Nelson K.Y. Wong, Brian McConeghy, Robert H. Bell, Sonal Brahmabhatt, Cheng-Han Lee, Gabriel E. DiMattia, Stephane Le Bihan, Gregg B. Morin, Colin C. Collins, and Mark S. Carey
These findings highlight the utility of global multiomics to characterize LGSOC cell lines as research models, to determine biomarkers of MEKi resistance, and to identify potential novel therapeutic targets.
- 1695 A Large-Scale Association Study Detects Novel Rare Variants, Risk Genes, Functional Elements, and Polygenic Architecture of Prostate Cancer Susceptibility**
Nima C. Emami, Taylor B. Cavazos, Sara R. Rashkin, Clinton L. Cario, Rebecca E. Graff, Caroline G. Tai, Joel A. Mefford, Linda Kachuri, Eunice Wan, Simon Wong, David Aaronson, Joseph Presti, Laurel A. Habel, Jun Shan, Dilrini K. Ranatunga, Chun R. Chao, Nirupa R. Ghai, Eric Jorgenson, Lori C. Sakoda, Mark N. Kvale, Pui-Yan Kwok, Catherine Schaefer, Neil Risch, Thomas J. Hoffmann, Stephen K. Van Den Eeden, and John S. Witte
This study maps the biological relationships between diverse risk factors for prostate cancer, integrating different functional datasets to interpret and model genome-wide data from over 200,000 men with and without prostate cancer.
See related commentary, p. 1637
- METABOLISM AND CHEMICAL BIOLOGY**
- 1704 ELOVL5 Is a Critical and Targetable Fatty Acid Elongase in Prostate Cancer**
Margaret M. Centenera, Julia S. Scott, Jelle Machiels, Zeyad D. Nassar, Deanna C. Miller, Irene Zinonos, Jonas Dehairs, Ingrid J.G. Burvenich, Giorgia Zadra, Paolo M. Chetta, Clyde Bango, Emma Evergren, Natalie K. Ryan, Joanna L. Gillis, Chui Yan Mah, Terence Tieu, Adrienne R. Hanson, Ryan Carelli, Katarzyna Bloch, Vasilios Panagopoulos, Etienne Waelkens, Rita Derua, Elizabeth D. Williams, Andreas Evdokiou, Anna Cifuentes-Rius, Nicolas H. Voelcker, Ian G. Mills, Wayne D. Tilley, Andrew M. Scott, Massimo Loda, Luke A. Selth, Johannes V. Swinnen, and Lisa M. Butler
This study identifies phospholipid elongation as a new metabolic target of androgen action that is critical for prostate tumor metastasis.
- MOLECULAR CELL BIOLOGY**
- 1719 CKAP2L Promotes Non-Small Cell Lung Cancer Progression through Regulation of Transcription Elongation**
Tiziana Monteverde, Sudhakar Sahoo, Manuela La Montagna, Peter Magee, Lei Shi, Dave Lee, Robert Sellers, Alexander R. Baker, Hui Sun Leong, Matteo Fassan, and Michela Garofalo
These findings demonstrate the oncogenic function of CKAP2L through regulation of transcription elongation and suggest that targeting CKAP2L could enhance therapeutic response in patients with NSCLC.
- 1732 Glia-Selective Deletion of Complement C1q Prevents Radiation-Induced Cognitive Deficits and Neuroinflammation**
Mineh Markarian, Robert P. Krattli Jr, Jabra D. Baddour, Leila Alikhani, Erich Giedzinski, Manal T. Usmani, Anshu Agrawal, Janet E. Baulch, Andrea J. Tenner, and Munjal M. Acharya
Clinically-relevant radiotherapy induces aberrant complement activation, leading to brain injury. Microglia-selective genetic deletion of CNS complement C1q ameliorates radiation-induced cognitive impairments, synaptic loss, and neuroinflammation, highlighting the potential for C1q as a novel therapeutic target.
See related commentary, p. 1635
- 1745 PINK1-Mediated Inhibition of EGFR Dimerization and Activation Impedes EGFR-Driven Lung Tumorigenesis**
Emily Pei-Ying Lin, Bo-Tsang Huang, Wei-Yun Lai, Yi-Ting Tseng, Shuenn-Chen Yang, Hao-Cheng Kuo, and Pan-Chyr Yang
This study identifies PINK1 as a critical tumor suppressor that impedes EGFR dimerization and highlights PINK1-CTD as a potential therapeutic agent in EGFR-driven lung cancer.

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- 1758** **RINT1 Regulates SUMOylation and the DNA Damage Response to Preserve Cellular Homeostasis in Pancreatic Cancer**
Frank Arnold, Johann Gout, Heike Wiese, Stephanie E. Weissinger, Elodie Roger, Lukas Perkhof, Karolin Walter, Jeanette Scheible, Caterina Prelli Bozzo, André Lechel, Thomas J. Ettrich, Ninel Azoitei, Li Hao, Axel Fürstberger, Ewa K. Kaminska, Konstantin M.J. Sparrer, Volker Rasche, Sebastian Wiese, Hans A. Kestler, Peter Möller, Thomas Seufferlein, Pierre-Olivier Frappart, and Alexander Kleger
These findings provide new insights into the aggressive behavior of PDAC, showing that RINT1 directly correlates with survival in patients with PDAC by disturbing the SUMOylation process, a crucial modification in carcinogenesis.
- TUMOR BIOLOGY AND IMMUNOLOGY**
- 1775** **Cooperative Targeting of Immunotherapy-Resistant Melanoma and Lung Cancer by an AXL-Targeting Antibody-Drug Conjugate and Immune Checkpoint Blockade**
Julia Boshuizen, Nora Pencheva, Oscar Krijgsman, Daniela D'Empaire Altimari, Patricia Garrido Castro, Beaunelle de Bruijn, Maarten A. Ligtenberg, Elke Gresnigt-Van den Heuvel, David W. Vredevoogd, Ji-Ying Song, Nils Visser, Georgi Apriamashvili, Maarten L. Janmaat, Theo S. Plantinga, Patrick Franken, Mischa Houtkamp, Andreas Lingnau, Maria Jure-Kunkel, and Daniel S. Peeper
These findings show that targeting AXL-positive tumor fractions with an antibody-drug conjugate enhances anti-tumor immunity in several humanized tumor models of melanoma and lung cancer.
- 1788** **Serial Stimulation of Invariant Natural Killer T Cells with Covalently Stabilized Bispecific T-cell Engagers Generates Antitumor Immunity While Avoiding Anergy**
Shalu Sharma Kharkwal, Christopher T. Johndrow, Natacha Veerapen, Himanshu Kharkwal, Noemi A. Saavedra-Avila, Leandro J. Carreño, Samantha Rothberg, Jinghang Zhang, Scott J. Garforth, Peter J. Jarvis, Lianjun Zhang, Alena Donda, Amareeta K. Besra, Liam R. Cox, Steven C. Almo, Alan Howell, Elizabeth E. Evans, Maurice Zauderer, Gurdyal S. Besra, and Steven A. Porcelli
Covalently stabilized conjugates that engage the antigen receptors of iNKT cells and target a tumor antigen activate potent antitumor immunity without induction of anergy or depletion of the responding iNKT cells.
- 1802** **Pan-Cancer Analysis of Ligand-Receptor Cross-talk in the Tumor Microenvironment**
Umesh Ghoshdastider, Neha Rohatgi, Marjan Mojtavabi Naeini, Probhonjon Baruah, Egor Revkov, Yu Amanda Guo, Simone Rizzetto, Angeline M.L. Wong, Sundar Solai, Tin T. Nguyen, Joe Poh Sheng Yeong, Javed Iqbal, Puay Hoon Tan, Balram Chowbay, Ramanuj Dasgupta, and Anders J. Skanderup
This study provides deconvoluted bulk tumor transcriptomes across multiple cancer types to infer cross-talk in the tumor microenvironment.
- 1813** **Evasion of Innate Immunity Contributes to Small Cell Lung Cancer Progression and Metastasis**
A C
Mingrui Zhu, Yi Huang, Matthew E. Bender, Luc Girard, Rahul Kollipara, Buse Eglencen-Polat, Yujiro Naito, Trisha K. Savage, Kenneth E. Huffman, Shohei Koyama, Atsushi Kumanogoh, John D. Minna, Jane E. Johnson, and Esra A. Akbay
This study discovers in SCLC and neuroblastoma impairment of an inherent mechanism of recognition of tumor cells by innate immunity and proposes that this mechanism can be reactivated to promote immune surveillance.
- 1827** **Survivin Expression Is Differentially Regulated by a Selective Cross-talk between RBM38 and miRNAs let-7b or miR-203a**
Christopher A. Lucchesi, Jin Zhang, Buyong Ma, Ruth Nussinov, and Xinbin Chen
These findings show that RBM38 exerts opposing effects on survivin expression via two miRNAs, and disruption of the RBM38-AGO2 complex by an eight-amino acid peptide sensitizes tumor spheroids to survivin inhibitor YM155.
- CONVERGENCE AND TECHNOLOGIES**
- 1840** **Pan-Cancer Drivers Are Recurrent Transcriptional Regulatory Heterogeneities in Early-Stage Luminal Breast Cancer**
Shambhavi Singh, Matthew D. Sutcliffe, Kathy Repich, Kristen A. Atkins, Jennifer A. Harvey, and Kevin A. Janes
Profiling intratumor heterogeneity of luminal breast carcinoma cells identifies a recurrent set of genes, suggesting sporadic activation of pathways known to drive other types of cancer.
See related articles, p. 1853 and p. 1868
- 1853** **Fragmentation of Small-Cell Lung Cancer Regulatory States in Heterotypic Microenvironments**
Dylan L. Schaff, Shambhavi Singh, Kee-Beom Kim, Matthew D. Sutcliffe, Kwon-Sik Park, and Kevin A. Janes
These findings demonstrate that the single-cell regulatory heterogeneity of small-cell lung cancer becomes increasingly elaborate in the liver, a common metastatic site for the disease.
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1868 Premalignant Oligodendrocyte Precursor Cells Stall in a Heterogeneous State of Replication Stress Prior to Gliomagenesis

Matthew D. Sutcliffe, Rui P. Galvao, Lixin Wang, Jungeun Kim, Lauren K. Rosenfeld, Shambhavi Singh, Hui Zong, and Kevin A. Janes

Profiling premalignant cell states in a mouse model of glioma uncovers regulatory heterogeneity in glioma cells-of-origin and defines a state of replication stress that precedes tumor initiation.

See related articles, p. 1840 and p. 1853

1909 Delta-Like Ligand–Notch1 Signaling Is Selectively Modulated by HPV16 E6 to Promote Squamous Cell Proliferation and Correlates with Cervical Cancer Prognosis

Maryam Khelil, Heather Griffin, Maaiké C.G. Bleeker, Renske D.M. Steenbergen, Ke Zheng, Taylor Saunders-Wood, Sanne Samuels, Jossie Rotman, Wim Vos, Brendy E. van den Akker, Renée X. de Menezes, Gemma G. Kenter, John Doorbar, and Ekaterina S. Jordanova

This study investigates cervical cancer cell-of-origin populations and describes a DLL-Notch1 phenotype that is associated with disease prognosis and that might help identify cells that are susceptible to HPV-induced carcinogenesis.

TRANSLATIONAL SCIENCE

1883 The Hydroxyquinoline Analogue YUM70 Inhibits GRP78 to Induce ER Stress–Mediated Apoptosis in Pancreatic Cancer

AC Soma Samanta, Suhui Yang, Bikash Debnath, Ding Xue, Yuting Kuang, Kavya Ramkumar, Amy S. Lee, Mats Ljungman, and Nouri Neamati

This study identifies a novel ER stress inducer that binds GRP78 and inhibits pancreatic cancer cell growth *in vitro* and *in vivo*, demonstrating its potential as a therapeutic agent for pancreatic cancer.

1896 MYCN-Amplified Neuroblastoma Is Addicted to Iron and Vulnerable to Inhibition of the System Xc⁻/Glutathione Axis

Konstantinos V. Floros, JinYang Cai, Sheeba Jacob, Richard Kurupi, Carter K. Fairchild, Mayuri Shende, Colin M. Coon, Krista M. Powell, Benjamin R. Belvin, Bin Hu, Madhavi Puchalapalli, Sivapriya Ramamoorthy, Kimberly Swift, Janina P. Lewis, Mikhail G. Dozmorov, John Glod, Jennifer E. Koblinski, Sosipatros A. Boikos, and Anthony C. Faber

The study shows how MYCN increases intracellular iron levels and subsequent GSH pathway activity and demonstrates the antitumor activity of FDA-approved SAS and auranofin in patient-derived xenograft models of MYCN-amplified neuroblastoma.

CORRECTION

1922 Local Targeting of NAD⁺ Salvage Pathway Alters the Immune Tumor Microenvironment and Enhances Checkpoint Immunotherapy in Glioblastoma

Ming Li, Ameya R. Kirtane, Juri Kiyokawa, Hiroaki Nagashima, Aaron Lopes, Zain A. Tirmizi, Christine K. Lee, Giovanni Traverso, Daniel P. Cahill, and Hiroaki Wakimoto

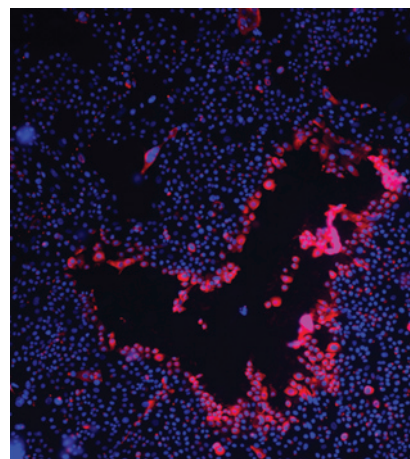
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ABOUT THE COVER

Immunofluorescent staining of DLL4 in a keratinocyte cell line, NIKS, highlights the high expression of this Notch1 ligand in migratory and proliferative cells of the leading edge of large monolayer gaps. This DLL4 phenotype is inherent to reserve cells in the normal, HPV-uninfected cervix, and HPV16 E6 expression sustains Notch1 ligand expression, likely facilitating a more durable skewing of squamous cell fate. Cervical tumors that show high DLL4 expression are associated with worse disease prognosis. For details, see Khelil and colleagues on page 1909.



Cancer Research

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