Cancer Research

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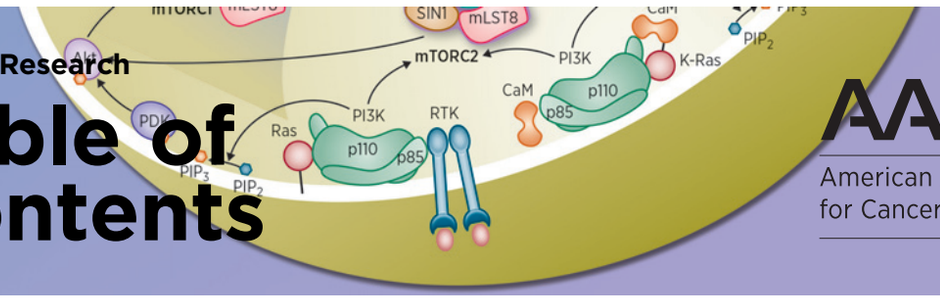

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BREAKING INSIGHTS

585 Highlights from Recent Cancer Literature

REVIEWS

587 Evidence for the ISG15-Specific Deubiquitinase USP18 as an Antineoplastic Target
Lisa Maria Mustachio, Yun Lu, Masanori Kawakami, Jason Roszik, Sarah J. Freemantle, Xi Liu, and Ethan Dmitrovsky

593 Oncogenic Ras Isoforms Signaling Specificity at the Membrane
Ruth Nussinov, Chung-Jung Tsai, and Hyunbum Jang

603 T-type Ca^{2+} Channels: T for Targetable
Marta C. Sallán, Anna Visa, Soni Shaikh, Mireia Nàger, Judit Herreros, and Carles Cantí

PRIORITY REPORT

610 T-Cell Densities in Brain Metastases Are Associated with Patient Survival Times and Diffusion Tensor MRI Changes
Rasheed Zakaria, Angela Platt-Higgins, Nitika Rathi, Mark Radon, Sumit Das, Kumar Das, Maneesh Bhojak, Andrew Brodbelt, Emmanuel Chavredakis, Michael D. Jenkinson, and Philip S. Rudland

Significance: *These findings show that white matter tract integrity is degraded in areas where T-cell infiltration is highest, providing a noninvasive method to identify immunologically active microenvironments in secondary brain tumors.*

GENOME AND EPIGENOME

617 Mutational Mechanisms That Activate Wnt Signaling and Predict Outcomes in Colorectal Cancer Patients
William Hankey, Michael A. McIlhatton, Kenechi Ebede, Brian Kennedy, Baris Hancioglu, Jie Zhang, Guy N. Brock, Kun Huang, and Joanna Groden

Significance: *These findings suggest that colon adenomas driven by APC mutations are distinct from those driven by WNT gain-of-function mutations, with implications for identifying at-risk patients with advanced disease based on gene expression patterns.*

631 Genomic and Epigenomic Signatures in Ovarian Cancer Associated with Resensitization to Platinum Drugs
Fang Fang, Horacio Cardenas, Hao Huang, Guanglong Jiang, Susan M. Perkins, Chi Zhang, Harold N. Keer, Yunlong Liu, Kenneth P. Nephew, and Daniela Matei

Significance: *Epigenomic targeting may improve therapeutic outcomes in platinum-resistant and recurrent ovarian cancer in part by effects on DNA repair and antitumor immune responses.*

MOLECULAR CELL BIOLOGY

645 SIRT6 Is a Target of Regulation by UBE3A That Contributes to Liver Tumorigenesis in an ANXA2-Dependent Manner
Saishruti Kohli, Abhishek Bhardwaj, Richa Kumari, and Sanjeev Das

Significance: *These findings provide mechanistic insights into regulation of the tumor suppressive sirtuin SIRT6 and its implications for the development of hepatocellular carcinoma.*

TUMOR BIOLOGY AND IMMUNOLOGY

659 Radiotherapy-Activated Cancer-Associated Fibroblasts Promote Tumor Progression through Paracrine IGF1R Activation
Joke Tommelein, Elly De Vlieghere, Laurine Verset, Elodie Melsens, Justine Leenders, Benedicte Descamps, Annelies Debucquoy, Christian Vanhove, Patrick Pauwels, Christian P. Gespach, Anne Vral, Astrid De Boeck, Karin Haustermans, Pascal de Tullio, Wim Ceelen, Pieter Demetter, Tom Boterberg, Marc Bracke, and Olivier De Wever

Significance: *These findings reveal that paracrine IGF1/IGF1R signaling promotes colorectal cancer progression, establishing a preclinical rationale to target this activation loop.*

671 Tamoxifen Resistance in Breast Cancer Is Regulated by the EZH2–ERα–GREB1 Transcriptional Axis
Yanming Wu, Zhao Zhang, Mauro E. Cenciarini, Cecilia J. Proietti, Matias Amasino, Tao Hong, Mei Yang, Yiji Liao, Huai-Chin Chiang, Virginia G. Kaklamani, Rinath Jeselsohn, Ratna K. Vadlamudi, Tim Hui-Ming Huang, Rong Li, Carmine De Angelis, Xiaoyong Fu, Patricia V. Elizalde, Rachel Schiff, Myles Brown, and Kexin Xu

Significance: *This study suggests a new strategy to overcome endocrine resistance in metastatic breast cancer by targeting a particular epigenetic program defined within.*

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685 **Deletion of Neuropilin 1 from Microglia or Bone Marrow–Derived Macrophages Slows Glioma Progression**
Jeremy Tetsuo Miyauchi, Michael D. Caponegro, Danling Chen, Matthew K. Choi, Melvin Li, and Stella E. Tsirka

Significance: *This study highlights the proangiogenic receptor neuropilin 1 in macrophages and microglial cells in gliomas as a pivotal modifier of tumor neovascularization and immunosuppression, strengthening emerging evidence of the functional coordination of these two fundamental traits of cancer.*

695 **Tumor-Associated Fatigue in Cancer Patients Develops Independently of IL1 Signaling**
Aaron J. Grossberg, Elisabeth G. Vichaya, Diana L. Christian, Jessica M. Molkentine, Daniel W. Vermeer, Phillip S. Gross, Paola D. Vermeer, John H. Lee, and Robert Dantzer

Significance: *These findings challenge the current understanding of fatigue in cancer patients, the most common and debilitating sequela associated with malignancy.*

TRANSLATIONAL SCIENCE

706 **Small-Molecule Inhibition of PD-1 Transcription Is an Effective Alternative to Antibody Blockade in Cancer Therapy**
Alison Taylor, David Rothstein, and Christopher E. Rudd

Significance: *These findings show how GSK-3 inhibitors that downregulate PD-1 expression can enhance $CD8^+$ T-cell function in cancer therapy to a similar degree as PD-1 blocking antibodies, offering a next-generation approach in the design of immunotherapeutic approaches for cancer management.*

718 **Oncolytic Virotherapy Blockade by Microglia and Macrophages Requires STAT1/3**
Zahid M. Delwar, Yvonne Kuo, Yan H. Wen, Paul S. Rennie, and William Jia

Significance: *These findings suggest a strategy to enhance the therapeutic efficacy of oncolytic virotherapy in glioblastoma.*

731 **VEGFR2–Mediated Reprogramming of Mitochondrial Metabolism Regulates the Sensitivity of Acute Myeloid Leukemia to Chemotherapy**
Sandrina Nóbrega-Pereira, Francisco Caíado, Tânia Carvalho, Inês Matias, Gonçalo Graça, Luís G. Gonçalves, Bruno Silva-Santos, Haakan Norell, and Sérgio Dias

Significance: *These findings reveal a mitochondrial metabolic vulnerability that might be exploited to kill chemotherapy-resistant acute myeloid leukemia cells.*

742 **Synthetic Lethality of PARP Inhibitors in Combination with MYC Blockade Is Independent of BRCA Status in Triple-Negative Breast Cancer**
Jason. P.W. Carey, Cansu Karakas, Tuyen Bui, Xian Chen, Smruthi Vijayaraghavan, Yang Zhao, Jing Wang, Keith Mikule, Jennifer K. Litton, Kelly K. Hunt, and Khandan Keyomarsi

Significance: *Dual targeting of MYC-regulated homologous recombination and PARP-mediated DNA repair yields potent synthetic lethality in triple-negative breast tumors and other aggressive tumors characterized by MYC overexpression.*

758 **Improved Tumor Penetration and Single-Cell Targeting of Antibody–Drug Conjugates Increases Anticancer Efficacy and Host Survival**
Cornelius Cilliers, Bruna Menezes, Ian Nessler, Jennifer Linderman, and Greg M. Thurber

Significance: *This study shows how lowering the drug-to-antibody ratio during treatment can improve the intratumoral distribution of a antibody-drug conjugate, with implications for improving the efficacy of this class of cancer drugs.*

769 **Transcription Factor Activities Enhance Markers of Drug Sensitivity in Cancer**
Luz Garcia-Alonso, Francesco Iorio, Angela Matchan, Nuno Fonseca, Patricia Jaaks, Gareth Peat, Miguel Pignatelli, Fiammetta Falcone, Cyril H. Benes, Ian Dunham, Graham Bignell, Simon S. McDade, Mathew J. Garnett, and Julio Saez-Rodriguez

Significance: *Systematic analysis of transcriptional dysregulation in cancer cell lines and patient tumor specimens offers a publicly searchable foundation to discover new opportunities to refine personalized cancer therapies.*

781 ***CDKN2A/p16*** **Deletion in Head and Neck Cancer Cells Is Associated with CDK2 Activation, Replication Stress, and Vulnerability to CHK1 Inhibition**
Mayur A. Gadhikar, Jiexin Zhang, Li Shen, Xiayu Rao, Jing Wang, Mei Zhao, Nene N. Kalu, Faye M. Johnson, Lauren A. Byers, John Heymach, Walter N. Hittelman, Durga Udayakumar, Raj K. Pandita, Tej K. Pandita, Curtis R. Pickering, Abena B. Redwood, Helen Piwnica-Worms, Katharina Schlacher, Mitchell J. Frederick, and Jeffrey N. Myers

Significance: *These results suggest a biomarker-driven strategy for selecting HNSCC patients who may benefit the most from therapy with CHK inhibitors.*

798 **Aptamer-Conjugated Extracellular Nanovesicles for Targeted Drug Delivery**
Yuan Wan, Lixue Wang, Chuandong Zhu, Qin Zheng, Guoxiang Wang, Jinlong Tong, Yuan Fang, Yiqiu Xia, Gong Cheng, Xia He, and Si-Yang Zheng

Significance: *A new and rapid method for production of drug-targeting nanovesicles has implications for cancer treatment by chimeric antigen receptor T cells and other therapies.*

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809 **IDO Immune Status after Chemoradiation May Predict Survival in Lung Cancer Patients**
Weili Wang, Lei Huang, Jian-Yue Jin, Shruti Jolly, Yong Zang, Huanmei Wu, Li Yan, Wenhu Pi, Lang Li, Andrew L. Mellor, and Feng-Ming (Spring) Kong

Significance: *Radiotherapy appears to influence systemic IDO activity and to exert a significant impact on metastatic risk and overall survival, with possible implications for defining a biomarker to optimize radiation dose in patients to improve outcomes.*

817 **Peripheral Neuropathy Induced by Microtubule-Targeted Chemotherapies: Insights into Acute Injury and Long-term Recovery**
Krystyna M. Wozniak, James J. Vornov, Ying Wu, Ying Liu, Valentina A. Carozzi, Virginia Rodriguez-Menendez, Elisa Ballarini, Paola Alberti, Eleonora Pozzi, Sara Semperboni, Brett M. Cook, Bruce A. Littlefield, Kenichi Nomoto, Krista Condon, Sean Eckley, Christopher DesJardins, Leslie Wilson, Mary A. Jordan, Stuart C. Feinstein, Guido Cavaletti, Michael Polydefkis, and Barbara S. Slusher

Significance: *This detailed preclinical study of the long-term effects of widely used antitubulin cancer drugs on the peripheral nervous system may help guide clinical evaluations to improve personalized care in limiting neurotoxicity in cancer survivors.*

CONVERGENCE AND TECHNOLOGIES

830 **Modeling the Subclonal Evolution of Cancer Cell Populations**
Diego Chowell, James Napier, Rohan Gupta, Karen S. Anderson, Carlo C. Maley, and Melissa A. Wilson Sayres

Significance: *The model presented in this paper addresses tumor heterogeneity by framing expectations for the number of resistant subclones in a tumor, with implications for future studies of the evolution of therapeutic resistance.*

CORRECTIONS

840 **Correction: Extracellular Matrix Receptor Expression in Subtypes of Lung Adenocarcinoma Potentiates Outgrowth of Micrometastases**

841 **Correction: Morphoproteomic Characterization of Lung Squamous Cell Carcinoma Fragmentation, a Histological Marker of Increased Tumor Invasiveness**

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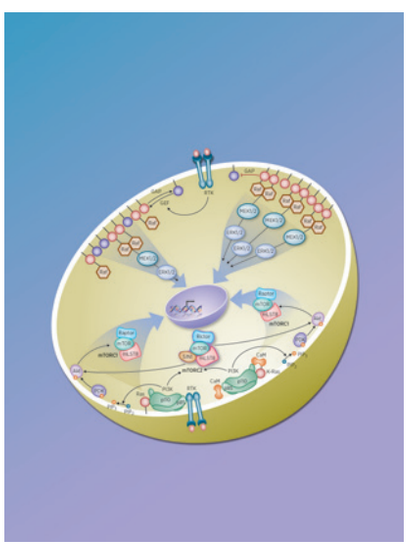
ABOUT THE COVER

Membrane-anchored wild-type and mutant Ras form dimers (or nanoclusters). Dimerization (or nanoclustering) is required for Raf's dimerization, activation, and Raf/MEK/ERK (MAPK) signaling (top part of the figure). By contrast, Ras dimerization (nanoclustering) is not required for PI3Kα activation, because PI3Kα essentially acts as a single unit (bottom part of the figure). Wild-type Ras activation of PI3Kα is helped by the phosphorylated C-terminal motif of RTK, which releases the autoinhibition of the p110 subunit by the p85 subunit. In the absence of RTK signaling, phosphorylated calmodulin helps oncogenic KRas. Because only KRas binds calmodulin, only KRas can fully activate PI3Kα/Akt signaling. Full activation of both MAPK and PI3Kα/Akt proliferative pathways by oncogenic KRas4B, but not by HRas or NRas, may help explain why the KRas4B isoform is especially highly populated in certain cancers. For details, see article by Nussinov and colleagues on page 593.



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