

BREAKING INSIGHTS

- 843** Highlights from Recent Cancer Literature


PERSPECTIVE

- 845** Perspective on Circulating Tumor Cell Clusters: Why It Takes a Village to Metastasize
Mario Giuliano, Anum Shaikh, Hin Ching Lo, Grazia Arpino, Sabino De Placido, Xiang H. Zhang, Massimo Cristofanilli, Rachel Schiff, and Meghana V. Trivedi

GENOME AND EPIGENOME

- 853** Single-Cell RNA-seq Reveals a Subpopulation of Prostate Cancer Cells with Enhanced Cell-Cycle-Related Transcription and Attenuated Androgen Response
Aaron M. Horning, Yao Wang, Che-Kuang Lin, Anna D. Louie, Rohit R. Jadhav, Chia-Nung Hung, Chiou-Miin Wang, Chun-Lin Lin, Nameer B. Kirma, Michael A. Liss, Addanki P. Kumar, LuZhe Sun, Zhijie Liu, Wei-Ting Chao, Qianben Wang, Victor X. Jin, Chun-Liang Chen, and Tim H.-M. Huang
Significance: Illustrating the challenge in treating cancers with targeted drugs, which by selecting for drug resistance can drive metastatic progression, this study characterized the plasticity and heterogeneity of prostate cancer cells with regard to androgen dependence, defining the character or minor subpopulations of androgen-independent cells that are poised for clonal selection after androgen-deprivation therapy.
- 865** Integrated Molecular Characterization of the Lethal Pediatric Cancer Pancreatoblastoma
Tomoya Isobe, Masafumi Seki, Kenichi Yoshida, Masahiro Sekiguchi, Yusuke Shiozawa, Yuichi Shiraishi, Shunsuke Kimura, Misa Yoshida, Yoshikage Inoue, Akira Yokoyama, Nobuyuki Kakiuchi, Hiromichi Suzuki, Keisuke Kataoka, Yusuke Sato, Tomoko Kawai, Kenichi Chiba, Hiroko Tanaka, Teppei Shimamura, Motohiro Kato, Akihiro Iguchi, Asahito Hama, Tomoaki Taguchi, Masaharu Akiyama, Junya Fujimura, Akiko Inoue, Tsuyoshi Ito, Takao Deguchi, Chikako Kiyotani, Tomoko Iehara, Hajime Hosoi, Akira Oka, Masashi Sanada, Yukichi Tanaka, Kenichiro Hata, Satoru Miyano, Seishi Ogawa, and Junko Takita
Significance: Molecular genetic analysis of a rare untreatable pediatric tumor reveals Wnt/IGF2 aberrations and features of early pancreas progenitor-like cells, suggesting cellular origins and rational strategies for therapeutic targeting.

METABOLISM AND CHEMICAL BIOLOGY

- 877** LNMICC Promotes Nodal Metastasis of Cervical Cancer by Reprogramming Fatty Acid Metabolism
 Chunliang Shang, Wei Wang, Yuandong Liao, Yili Chen, Tianyu Liu, Qiqiao Du, Jiaming Huang, Yanchun Liang, Junxiu Liu, Yunhe Zhao, Luyan Guo, Zheng Hu, and Shuzhong Yao
Significance: These results establish the role of a novel long noncoding RNA in lymph node metastasis, with implications as a candidate prognostic biomarker and therapeutic target in cervical cancer.

MOLECULAR CELL BIOLOGY

- 891** Oncogenic RAS-Induced Perinuclear Signaling Complexes Requiring KSR1 Regulate Signal Transmission to Downstream Targets
Sandip K. Basu, Sook Lee, Jacqueline Salotti, Srikanta Basu, Krisada Sakchaisri, Zhen Xiao, Vijay Walia, Christopher J. Westlake, Deborah K. Morrison, and Peter F. Johnson
Significance: In addressing the long-standing question of the difference between normal and oncogenic RAS pathway signaling, this study shows that oncogenic RAS specifically triggers constitutive endocytosis-dependent movement of effector kinases to a perinuclear region, thereby creating connections to unique downstream targets such as the core prosenescence and the inflammatory regulatory transcription factor C/EBP β .

TUMOR BIOLOGY AND IMMUNOLOGY


- 909** LIF Drives Neural Remodeling in Pancreatic Cancer and Offers a New Candidate Biomarker
 Christian Bressy, Sophie Lac, Jérémy Nigri, Julie Leca, Julie Roques, Marie-Noëlle Lavaut, Véronique Secq, Fabienne Guillaumond, Thi-Thien Bui, Daniel Pietrasz, Samuel Granjeaud, Jean-Baptiste Bachet, Mehdi Ouassi, Juan Iovanna, Sophie Vasseur, and Richard Tomasini
Significance: This study suggests a target to limit neural remodeling in pancreatic cancer, which contributes to poorer quality of life and heightened metastatic progression in patients.

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922 Amplification of Oncolytic Vaccinia Virus Widespread Tumor Cell Killing by Sunitinib through Multiple Mechanisms

Minah Kim, Maximilian Nitschké, Barbara Sennino, Patrizia Murer, Brian J. Schriver, Alexander Bell, Aishwarya Subramanian, Corry E. McDonald, Jiahu Wang, Howard Cha, Marie-Claude Bourgeois-Daigneault, David H. Kirn, John C. Bell, Naomi De Silva, Caroline J. Breitbach, and Donald M. McDonald

Significance: These findings reveal multiple unrecognized features of the antitumor properties of oncolytic vaccinia viruses, all of which can be amplified by the multitargeted kinase inhibitor sunitinib.

938 LSD1 Stimulates Cancer-Associated Fibroblasts to Drive Notch3-Dependent Self-Renewal of Liver Cancer Stem-like Cells

Chungang Liu, Limei Liu, Xuejiao Chen, Jiamin Cheng, Heng Zhang, Chengcheng Zhang, Juanjuan Shan, Junjie Shen, and Cheng Qian

Significance: These seminal findings illuminate a complex pathway in the tissue microenvironment of liver cancer, which is responsible for orchestrating the self-renewal of stem-like cancer cells, with potential implications to improve therapy and limit relapses.

950 Tenascin-C Promotes Tumor Cell Migration and Metastasis through Integrin $\alpha9\beta1$ -Mediated YAP Inhibition

Zhen Sun, Anja Schwenzer, Tristan Rupp, Devadarssen Murdamoothoo, Rolando Vegliante, Olivier Lefebvre, Annick Klein, Thomas Hussenet, and Gertraud Orend

Significance: These results illuminate how the extracellular matrix glycoprotein tenascin-C in the tumor microenvironment promotes invasive migration and metastatic progression by employing integrin $\alpha9\beta1$, abolishing actin stress fiber formation, and inhibiting YAP and its target gene expression, with potential implications for cancer prognosis and therapy.

962 Nkx2-2as Suppression Contributes to the Pathogenesis of Sonic Hedgehog Medulloblastoma



Yimeng Zhang, Ting Wang, Shan Wang, Yanlu Xiong, Rui Zhang, Xiang Zhang, Jing Zhao, An-Gang Yang, Lei Wang, and Lintao Jia

Significance: These findings illuminate the role of noncoding RNAs in Hedgehog signaling and an interplay between the Hedgehog and Hippo pathways in medulloblastoma pathogenesis.

974 Coactivation of Estrogen Receptor and IKK β Induces a Dormant Metastatic Phenotype in ER-Positive Breast Cancer

Lamiaa El-Shennawy, Oleksii Dubrovskiy, Irida Kastrati, Jeanne M. Danes, Yiqun Zhang, Herbert E. Whiteley, Chad J. Creighton, and Jonna Frasor

Significance: The canonical NF κ B pathway promotes expansion of stem/basal-like cells and a dormant, metastatic phenotype in ER⁺ breast cancer cells.

985 Adaptive and Reversible Resistance to Kras Inhibition in Pancreatic Cancer Cells



Pan-Yu Chen, Mandar Deepak Muzumdar, Kimberly Judith Dorans, Rebecca Robbins, Arjun Bhutkar, Amanda del Rosario, Philipp Mertins, Jana Qiao, Anette Claudia Schafer, Frank Gertler, Steven Carr, and Tyler Jacks

Significance: These results call into question the degree to which pancreatic cancers are addicted to KRAS by illustrating adaptive nongenetic and nontranscriptional mechanisms of resistance to Kras blockade, with implications for the development of KRAS inhibitors for PDAC treatment.

1003 A2AR Adenosine Signaling Suppresses Natural Killer Cell Maturation in the Tumor Microenvironment

Arabella Young, Shin Foong Ngiow, Yulong Gao, Ann-Marie Patch, Deborah S. Barkauskas, Meriem Messaoudene, Gene Lin, Jerome D. Coudert, Kimberley A. Stannard, Laurence Zitvogel, Mariapia A. Degli-Esposti, Eric Vivier, Nicola Waddell, Joel Linden, Nicholas D. Huntington, Fernando Souza-Fonseca-Guimaraes, and Mark J. Smyth

Significance: Ablating adenosine signaling is found to promote natural killer cell maturation and antitumor immunity and reduce tumor growth.

TRANSLATIONAL SCIENCE

1017 miR-204-5p and miR-211-5p Contribute to BRAF Inhibitor Resistance in Melanoma

Marta Díaz-Martínez, Lucía Benito-Jardón, Lola Alonso, Lisa Koetz-Ploch, Eva Hernando, and Joaquin Teixidó

Significance: Identification of miRNAs that enable resistance to BRAF inhibitors in melanoma suggests a mechanism-based strategy to limit resistance and to improve clinical outcomes.

1031 NKG2D-Based CAR T Cells and Radiotherapy Exert Synergistic Efficacy in Glioblastoma

Tobias Weiss, Michael Weller, Matthias Guckenberger, Charles L. Sentman, and Patrick Roth

Significance: These findings provide evidence for synergy of conventional anticancer therapy and CAR T cells and heralds future studies for other treatment combinations.

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- 1044** ER Stress Signaling Promotes the Survival of Cancer "Persister Cells" Tolerant to EGFR Tyrosine Kinase Inhibitors
Hideki Terai, Shunsuke Kitajima, Danielle S. Potter, Yusuke Matsui, Laura Gutierrez Quiceno, Ting Chen, Tae-jung Kim, Maria Rusan, Tran C. Thai, Federica Piccioni, Katherine A. Donovan, Nicholas Kwiatkowski, Kunihiko Hinohara, Guo Wei, Nathanael S. Gray, Eric S. Fischer, Kwok-Kin Wong, Teppei Shimamura, Anthony Letai, Peter S. Hammerman, and David A. Barbie

Significance: These findings reveal a novel function of the recently described *ufmylation* pathway, an ER stress survival signaling in drug-tolerant persister cells, which has important biological and therapeutic implications.

- 1058** Downregulating Neuropilin-2 Triggers a Novel Mechanism Enabling EGFR-Dependent Resistance to Oncogene-Targeted Therapies
Sabrina Rizzolio, Chiara Battistini, Gabriella Cagnoni, Maria Apicella, Viviana Vella, Silvia Giordano, and Luca Tamagnone

Significance: These important findings identify the cell surface molecule *Nrp2* as the pivotal switch of a novel, actionable pathway driving EGFR upregulation and resistance to oncogene-targeted therapies.

- 1069** A20 Regulates the DNA Damage Response and Mediates Tumor Cell Resistance to DNA-Damaging Therapy
Chuanzhen Yang, Weicheng Zang, Zefang Tang, Yapeng Ji, Ruidan Xu, Yongfeng Yang, Aiping Luo, Bin Hu, Zemin Zhang, Zhihua Liu, and Xiaofeng Zheng

Significance: This study identifies the ubiquitin-editing enzyme A20 as a key factor in mediating cancer cell resistance to DNA-damaging therapy, with implications for blocking its function to leverage the efficacy of chemotherapy and radiotherapy.

- 1083**  Inhibition of Translesion DNA Synthesis as a Novel Therapeutic Strategy to Treat Brain Cancer
Jung-Suk Choi, Casey Seol Kim, and Anthony Berdis

Significance: Combinatorial treatment of glioblastoma with temozolomide and a novel artificial nucleoside that inhibits replication of damaged DNA can safely enhance therapeutic responses.

- 1097** Targeting CDK6 and BCL2 Exploits the "MYB Addiction" of Ph⁺ Acute Lymphoblastic Leukemia

Marco De Dominicis, Patrizia Porazzi, Angela Rachele Soliera, Samanta A. Mariani, Sankar Addya, Paolo Fortina, Luke F. Peterson, Orietta Spinelli, Alessandro Rambaldi, Giovanni Martinelli, Anna Ferrari, Ilaria Iacobucci, and Bruno Calabretta

Significance: MYB blockade can suppress Philadelphia chromosome-positive leukemia in mice, suggesting that this therapeutic strategy may be useful in patients who develop resistance to imatinib and other TKIs used to treat this disease.

- 1110** Comprehensive Mutation and Copy Number Profiling in Archived Circulating Breast Cancer Tumor Cells Documents Heterogeneous Resistance Mechanisms

Costanza Paoletti, Andi K. Cani, Jose M. Larios, Daniel H. Hovelson, Kimberly Aung, Elizabeth P. Darga, Emily M. Cannell, Paul J. Baratta, Chia-Jen Liu, David Chu, Maryam Yazdani, Allen R. Blevins, Valeria Sero, Nahomi Tokudome, Dafydd G. Thomas, Christina Gersch, Anne F. Schott, Yi-Mi Wu, Robert Lonigro, Dan R. Robinson, Arul M. Chinnaiyan, Farideh Z. Bischoff, Michael D. Johnson, Ben H. Park, Daniel F. Hayes, James M. Rae, and Scott A. Tomlins

Significance: These findings demonstrate the complementary nature of genomic profiling from paired tissue metastasis and circulating tumor cells from patients with metastatic breast cancer.

CORRECTIONS

- 1123** Correction: Regulatory Aspects of Optical Methods and Exogenous Targets for Cancer Detection

- 1124** Correction: Integrating Models to Quantify Environment-Mediated Drug Resistance

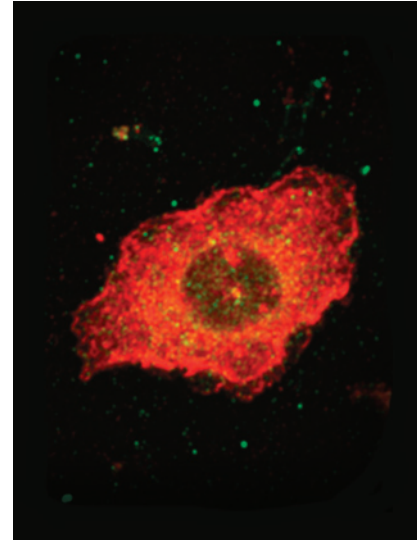
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ABOUT THE COVER

Immunofluorescence imaging of CK2 α and Rab11 in human A549 lung adenocarcinoma cells treated with the endocytosis inhibitor, Dynasore. Visualization of KSR1, p-ERK, CK2 α , and other RAS pathway proteins revealed their perinuclear cytoplasmic localization in tumor cells. These "perinuclear signaling complexes" (PSC) are induced upon RAS pathway activation, reside on perinuclear endosomes, and can be disrupted by endocytosis inhibitors. PSCs appear to be a defining feature of most or all cancer cells and regulate RAS signal transmission to downstream targets. For details, see article by Basu and colleagues on page 891.



Cancer Research

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