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The FGFR4-G388R Single-Nucleotide Polymorphism Alters Pancreatic Neuroendocrine Tumor Progression and Response to mTOR Inhibition Therapy

Stefano Serra, Lei Zheng, Manal Hassan, Alexandria T. Phan, Linda J. Woodhouse, James C. Yao, Sherreen Ezzat, and Sylvia L. Asa

**Précis:** A coding SNP in the FGFR4 gene correlates with progression status in pancreatic neuroendocrine tumors and also with the response to everolimus, an mTOR inhibitor of therapeutic interest in this setting, potentially offering a simple stratification marker.

DNA Methylation Biomarkers Offer Improved Diagnostic Efficiency in Lung Cancer

Georgios Nikolaidis, Olaide Y. Raji, Soultana Markopoulou, John R. Gosney, Julie Bryan, Chris Warburton, Martin Walshaw, John Sheard, John K. Field, and Triantafillos Liloglou

**Précis:** Determination of a simple DNA methylation signature in cells obtained from bronchial washings may improve the accuracy of clinical diagnoses of lung cancer.

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SIRT1 Pathway Dysregulation in the Smoke-Exposed Airway Epithelium and Lung Tumor Tissue

Jennifer Beane, Luis Cheng, Raffaella Soldi, Xiaohui Zhang, Gang Liu, Christina Anderliud, Marc E. Lemburg, Avrum Spira, and Andrea H. Bild

**Précis:** This study presents the first genome-scale study of the metabolism of breast cancer, providing new system-level insights into the metabolic progression of different subsets of this disease.

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Clinicopathological Features of Homologous Recombination–Deficient Epithelial Ovarian Cancers: Sensitivity to PARP Inhibitors, Platinum, and Survival


**Précis:** Defects in DNA repair mediated by the homologous recombination machinery define a subset of ovarian cancers that are sensitive to PARP inhibitors and that have favorable survival outcomes when cotreated with platinum chemotherapy.

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DNA Methylation Biomarkers Offer Improved Diagnostic Efficiency in Lung Cancer

Georgios Nikolaidis, Olaide Y. Raji, Soultana Markopoulou, John R. Gosney, Julie Bryan, Chris Warburton, Martin Walshaw, John Sheard, John K. Field, and Triantafillos Liloglou

**Précis:** Determination of a simple DNA methylation signature in cells obtained from bronchial washings may improve the accuracy of clinical diagnoses of lung cancer.
**Microenvironment and Immunology**

5721  
**NLRP3 Suppresses NK Cell–Mediated Responses to Carcinogen-Induced Tumors and Metastases**  
Melvyn T. Chow, Jaclyn Sceneay, Christophe Paget, Christina S.F. Wong, Helene Duret, Jürg Tschopp, Andreas Möller, and Mark J. Smyth  
**Précis:** Findings reveal a proinflammatory pathway that suppresses cancer-controlling NK cells along with a class of suppressor myeloid cells that actually promotes the anticancer activity of NK cells.

5733  
**Endoneurial Macrophages Induce Perineural Invasion of Pancreatic Cancer Cells by Secretion of GDNF and Activation of RET Tyrosine Kinase Receptor**  
Oren Cavel, Olga Shomron, Ayelet Shabtay, Joseph Vital, Leonor Trejo-Leider, Noam Weizman, Yakov Krelin, Yuman Fong, Richard J. Wong, Moran Amit, and Ziv Gil  
**Précis:** A paracrine response between pancreatic adenocarcinoma cells and macrophages that rove nerve tracks appears to orchestrate nerve invasion by localized tumors, a type of invasion that occurs in various types of encapsulated glandular tumors.

5744  
**Cross-Species Functional Analysis of Cancer-Associated Fibroblasts Identifies a Critical Role for CLCF1 and IL6 in Non–Small Cell Lung Cancer In Vivo**  
Silvestre Vicent, Leanne C. Sayles, Dedeepya Vaka, Purvesh Khatri, Olivier Gevaert, Ron Chen, Yanyan Zheng, Anna K. Gillespie, Nicole Clarke, Yue Xu, Joseph Shrager, Richard J. Wong, Moran Amit, and Ziv Gil  
**Précis:** A cross-species approach identifies 2 IL-6 family members as key contributors to paracrine signaling between cancer cells and cancer-associated fibroblasts in lung adenocarcinoma.

5757  
**Galectin-3 Contributes to Melanoma Growth and Metastasis via Regulation of NFAT1 and Autotaxin**  
Russell R. Braeuer, Maya Zigler, Takafumi Kamiya, Andrey S. Dobroff, Li Huang, Woonyoung Choi, David J. McConkey, Einav Shoshan, Aaron K. Mobley, Renduo Song, Avraham Raz, and Menashe Bar-Eli  
**Précis:** This study elucidates a new mechanism by which galectin-3 contributes to tumor growth and metastasis by regulating the expression of protumorigenic genes, such as autotaxin.

**Molecular and Cellular Pathobiology**

5767  
**Differential Effects of Polymorphic Alleles of FGFR4 on Colon Cancer Growth and Metastasis**  
Christine Heinzel, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gaughghofer, Stefan Stattner, Josef Karam, Martin Klimpfinger, Friedrich Wiba, Andrea Reti, Balazs Hegedus, Andreas Baierl, Bettina Grasl-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian  
**Précis:** A systematic comparison of 2 common polymorphic forms of FGFR4 reveals a higher risk of developing aggressive colorectal cancer for carriers of the FGFR4<sup>arg</sup> allele, potentially offering a simple prognostic marker in this setting.

5778  
**Prohibitin Attenuates Colitis-Associated Tumorigenesis in Mice by Modulating p53 and STAT3 Apoptotic Responses**  
**Précis:** Reduced levels of a mitochondrial protein during chronic intestinal inflammation may be an underlying factor promoting colitis-associated cancer by acting to modulate epithelial cell apoptosis.

5790  
**Aryl Hydrocarbon Receptor-Induced Adrenomedullin Mediates Cigarette Smoke Carcinogenicity in Humans and Mice**  
Sergio Portal-Nuñez, Uma T. Shankavaram, Mahadev Rao, Nicole Datrice, Scott Atay, Marta Aparicio, Kevin A. Camphausen, Pedro M. Fernández-Salguero, Han Chung, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cuttitta, and Enrique Zudaire  
**Précis:** Findings suggest that lung cancers arising in smokers may be susceptible to treatment with therapeutics that target a proinflammatory oncogenic pathway known to mediate tumor-immune cell crosstalk, angiogenesis, and metastasis.

5801  
**Neuropilin-1–Dependent Regulation of EGF-Receptor Signaling**  
Sabrina Bizzolo, Noa Rabinowicz, Elena Rainero, Letizia Lanzetti, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone  
**Précis:** Findings reveal a new mechanism for controlling EGFR signaling in cancer cells through clustering and endocytosis of the receptor Neuropilin-1, which highlights its identification as a rational therapeutic target for cancer treatment.
A Journal of the American Association for Cancer Research v www.aacrjournals.org

An Integrated Genomic Screen Identifies LDHB as an Essential Gene for Triple-Negative Breast Cancer
Mark L. McClendon, Adam S. Adler, Yonglei Shang, Thomas Hunssaker, Tom Truong, David Peterson, Eric Torres, Li Li, Benjamin Haley, Jean-Philippe Stephan, Marcia Belvin, Georgia Hatzivassiliou, Elizabeth M. Blackwood, Laura Corson, Marie Evangelista, Jipping Zha, and Ron Firestein

Precise: While the glycolytic regulator lactate dehydrogenase has been studied previously in breast cancer, this study offers an incisive advance by defining a crucial specific role for a particular isoform of this enzyme in a breast cancer subtype with few therapeutic options.

Cancer Cells Cue the p53 Response of Cancer-Associated Fibroblasts to Cisplatin
Jens G. Schmid, Meng Dong, Silke Haubeiss, Godehard Friedel, Sahine Bode, Andreas Grabner, German Ott, Thomas E. Mürder, Moshe Oren, Walter E. Aulitzky, and Heiko van der Kuip

Precise: Within the tumor microenvironment, the p53 response of cancer cell determines the p53 response within adjacent cancer-associated fibroblasts, illustrative of the master-slave relationship that cancer cells enforce on their neighboring cells.

Lymphatic Reprogramming by Kaposi Sarcoma Herpes Virus Promotes the Oncogenic Activity of the Virus-Encoded G-protein–Coupled Receptor
Berencie Aguilar, Inho Choi, Dongwon Choi, Hee Kyoung Chung, Sunju Lee, JaeHyouk Yoo, Yong Suk Lee, Yong Sun Maeng, Ha Neul Lee, Eunkyung Park, Kyu Eui Kim, Nam Youn Kim, Jae Myung Baik, Jae U. Jung, Chester J. Koh, and Young-Kwon Hong

Precise: Findings resolve long-standing questions about the pathological impact of the ability of Kaposi's sarcoma herpes virus to reprogram the tumor microenvironment, explaining why this process favors formation of Kaposi's sarcoma, which are the most common forms of cancer in HIV patients.

FGFR3 Stimulates Stearoyl CoA Desaturase 1 Activity to Promote Bladder Tumor Growth
Xiangnan Du, Qian-Rena Wang, Emily Chan, Mark Merchant, Jinping Liu, Dorothy French, Avi Ashkenazi, and Jing Qing

Precise: Findings reveal a previously unrecognized role for the FGF receptor FGFR3 in regulating lipid metabolism to maintain tumor growth and survival.

Basal but not Luminal Mammary Epithelial Cells Require PI3K/mTOR Signaling for Ras-Driven Overgrowth
Kristin A. Plchta, Jessica L. Mathers, Shelley A. Gestl, Adam B. Glick, and Edward J. Gunther

Precise: Oncogenic Ras uses distinct effector pathways to drive dysregulated proliferation of the cells derived from different layers of a stratified epithelium.

DDX31 Regulates the p53-HDM2 Pathway and rRNA Gene Transcription through Its Interaction with NPM1 in Renal Cell Carcinomas
Tomoya Fukawa, Masaya Ono, Taisuke Matsuou, Hisanori Uehara, Tsuneharu Miki, Yusuke Nakamura, Hiro-omi Kanayama, and Toyomasa Katagiri

Precise: Findings offer potentially seminal insights into the origins of renal cell cancer, addressing long standing questions about how sporadic forms of this cancer develop.

The Metabolomic Signature of Malignant Glioma Reflects Accelerated Anabolic Metabolism
Prakash Chinnaiyan, Elizabeth Kensicki, Gregory Bloom, Antony Prabhu, Bhaswati Sarcar, Soumen Kahali, Steven Eschrich, Xiaotao Qu, Peter Forsyth, and Robert Gillies

Precise: Global metabolomic analysis identifies key features underlying the aggressive phenotype of malignant glioma, providing novel strategies for therapeutic intervention.

Identification of FoxM1/Bub1b Signaling Pathway as a Required Component for Growth and Survival of Rhabdomyosarcoma
Xiaolin Wan, Choh Yeung, Su Young Kim, Joseph G. Dolan, Vu N. Ngo, Sandra Burkett, Javed Khan, Louis M. Staudt, and Lee J. Helman

Precise: Dysregulation of a mitotic checkpoint signaling pathway has a critical role in the growth of pediatric tumors, defining direct interactions between the oncogenic transcription factor, FoxM1, and the key mitotic checkpoint protein, Bub1B.

Inactivation of the Dlc1 Gene Cooperates with Downregulation of p15INK4b and p16INK4a, Leading to Neoplastic Transformation and Poor Prognosis in Human Cancer
Xiaolan Qian, Marian E. Durkin, Dunrui Wang, Brajendra K. Tripathi, Lyra Olson, Xu-Yu Yang, William C. Vass, Nicholas C. Popescu, and Douglas R. Lowy

Precise: Diminished expression of a RhGAP tumor suppressor along with the Cdk inhibitors p15 and p16 drives cell transformation in mouse cells and confers poor prognosis in clinical cases of lung and colon cancer.
**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**5921**

**Temporal Molecular and Biological Assessment of an Erlotinib-Resistant Lung Adenocarcinoma Model Reveals Markers of Tumor Progression and Treatment Response**

Zoe Weaver, Simone DiFilippantonio, Julian Carretero, Philip L. Martin, Rajaa El Meskini, Anthony J. Iacovelli, Michelle Gumprecht, Alan Kulaga, Theresa Guerin, Jerome Scholmer, Maureen Baran, Sergio Kozlov, Thomas McCann, Salvador Mena, Fatima Al-Shahrour, Danny Alexander, Kwok-Kin Wong, and Terry Van Dyke

*Précis:* This study illustrates the importance of longitudinal therapeutic studies in preclinical assessment of drug principles by offering in vivo evidence that tyrosine kinase inhibitors can exert a strong, unexpected impact on specific metabolic controls.

**5934**

**Genetic Screening for Synthetic Lethal Partners of Polynucleotide Kinase/Phosphatase: Potential for Targeting SHP-1-Depleted Cancers**


*Précis:* This paper elucidates a synthetic lethal combination of target inactivation events that can increase levels of DNA damage that escape repair, suggesting an effective killing paradigm to exploit therapeutically.

**5945**

**Cisplatin Sensitivity Mediated by WEE1 and CHK1 Is Mediated by miR-155 and the miR-15 Family**

Lynn M. Pouliot, Yu-Chi Chen, Jennifer Bai, Rajarshi Guha, Scott E. Martin, Michael M. Gottesman, and Matthew D. Hall

*Précis:* Defeating acquired resistance to platin drugs remains a major goal in the oncology clinic, given the large and diverse number of cancers that use these chemotherapeutic agents in treatment.

**5956**

**Brachytherapy Using Injectable Seeds That Are Self-Assembled from Genetically Encoded Polypeptides In Situ**

Wenge Liu, Jonathan McDaniel, Xinghai Li, Daisuke Asai, Felipe Garcia Quiroz, Jeffery Schaal, Ji Sun Park, Michael Zalutsky, and Ashutosh Chilkoti

*Précis:* A novel injectable modality that can self-assemble a polypeptide-based radionuclide seed at tumor sites could radically improve treatment of prostate cancers that are presently treated by brachytherapy, an invasive radiotherapeutic procedure.

**5966**

**p21-Activated Kinase 1 Is Required for Efficient Tumor Formation and Progression in a Ras-Mediated Skin Cancer Model**

Hoi Yee Chow, Adrian M. Jubb, Jennifer N. Koch, Zahara M. Jaffer, Dina Stepanova, David A. Campbell, Sergio G. Duron, Marie O’Farrell, Kathy Q. Cai, Andres J.P. Klein-Szanto, J. Silvio Gutkind, Klaus P. Hoeflich, and Jonathan Chernoff

*Précis:* Findings offer preclinical proof-of-concept for a functionally pleiotropic kinase as a therapeutic target in KRAS-driven tumors, illustrating a key mechanism for its action through signaling by Erk but not Akt.

**5976**

**The V-ATPase-Inhibitor Archazolid Abrogates Tumor Metastasis via Inhibition of Endocytic Activation of the Rho-GTPase Rac1**

Ramina M. Wiedmann, Karin V. Schwarzenberg, Andrea Palamidessi, Laura Schreiner, Rebekka Kubisch, Johanna Liebl, Christina Schempp, Dirk Trauner, Gyorgy Vereb, Stefan Zahler, Ernst Wagner, Rolf Müller, Giorgio Scita, and Angelika M. Vollmar

*Précis:* Findings reveal insights into how a vacular proton pump drives tumor dissemination and metastasis, with implications for how to apply therapeutics that can target this pump.

**TUMOR AND STEM CELL BIOLOGY**

**5988**

**OTX2 Represses Myogenic and Neuronal Differentiation in Medulloblastoma Cells**

Ren-Yuan Bai, Verena Staedtke, Hart G. Lidov, Charles G. Eberhart, and Gregory J. Riggins

*Précis:* Findings may hold the key to understanding the etiology of medullo-myeloblastoma, a subtype of the common pediatric brain tumor medulloblastoma that is marked by the presence of differentiated muscle cells.
Rat Mcs1b Is Concordant to the Genome-Wide Association-Identified Breast Cancer Risk Locus at Human 5q11.2 and MIER3 Is a Candidate Cancer Susceptibility Gene
Aaron D. denDekker, Xin Xu, M. Derek Vaughn, Aaron H. Puckett, Louis L. Gardner, Courtney J. Lambring, Lucas Deschenes, and David J. Samuelson

Précis: Genetic studies in the rat suggest a good candidate for a breast cancer susceptibility gene that has been mapped previously to human chromosome 5q11.2.

A Synthetic Matrix with Independently Tunable Biochemistry and Mechanical Properties to Study Epithelial Morphogenesis and EMT in a Lung Adenocarcinoma Model
Bartley J. Gill, Don L. Gibbons, Laila C. Roudsari, Jennifer E. Saik, Zain H. Rizvi, Jonathon D. Roybal, Jonathan M. Kurie, and Jennifer L. West

Précis: Findings illuminate the extracellular cues that influence epithelial morphogenesis by showing how a synthetic ECM mimetic can affect metastatic properties.

Rab25 Is a Tumor Suppressor Gene with Antiangiogenic and Anti-Invasive Activities in Esophageal Squamous Cell Carcinoma
Man Tong, Kwok Wah Chan, Jessie Y.J. Bao, Kai Yau Wong, Jin-Na Chen, Pak Shing Kwan, Kwan Ho Tang, Li Fu, Yan-Ru Qin, Si Lok, Xin-Yuan Guan, and Stephanie Ma

Précis: This study advances progress in the acute need for identifying biomarkers that can assist the diagnosis, prognosis, and treatment of esophageal cancer, a deadly disease with a rising incidence.

Loss of SNAIL Regulated miR-128-2 on Chromosome 3p22.3 Targets Multiple Stem Cell Factors to Promote Transformation of Mammary Epithelial Cells
Peng-Xu Qian, Arindam Banerjee, Zheng-Sheng Wu, Xiao Zhang, Hong Wang, Vijay Pandey, Wei-Jie Zhang, Xue-Fei Lv, Sheng Tan, Peter E. Lobie, and Tao Zhu

Précis: Results elucidate a signaling axis that drives mesenchymal character and stem cell-like traits in malignantly transformed epithelial cells.

Glomagenesis Arising from Pten- and Ink4a/Arf-Deficient Neural Progenitor Cells Is Mediated by the p53-Fbw7/Cdc4 Pathway, Which Controls c-Myc
Hong Sug Kim, Kevin Woodard, Chen Lai, Peter O. Bauer, Dragan Maric, Hua Song, Aiguo Li, Svetlana Kotliarova, Wei Zhang, and Howard A. Fine

Précis: A sophisticated genetically engineered mouse model confirms that p53 mutations contribute to formation of aggressive brain tumors by supporting c-Myc overexpression but also by protecting cells against c-Myc-induced apoptosis.

ABOUT THE COVER

Perineural invasion of cancer cells is found in most patients with pancreatic adenocarcinoma and is common in other tumors as well. Immunohistochemical analysis of specimens excised from patients with pancreatic cancer showed a significant increase in the number of endoneurial macrophages around nerves invaded by cancer. Using animal models and time-lapse analysis, we noticed that these endoneurial macrophages facilitated cancer cells dissociation from tumors and the formation of cell clusters that migrated in a unidirectional fashion along the nerve toward the ganglion. The study identified a paracrine response between endoneurial macrophages and cancer cells, which orchestrates the formation of nerve invasion. For details, see article by Cavel and colleagues on page 5733.