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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  

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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  

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

### Integrated Systems and Technologies

**SIRT1 Pathway Dysregulation in the Smoke-Exposed Airway Epithelium and Lung Tumor Tissue**  
Jennifer Beane, Luis Cheng, Raffaella Soldi, Xiaohui Zhang, Gang Liu, Christina Anderli, Marc E. Lenburg, Avrum Spira, and Andrea H. Bild  

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

**Metabolic Associations of Reduced Proliferation and Oxidative Stress in Advanced Breast Cancer**  
Livnat Jerby, Lior Wolf, Carsten Denkert, Gideon Y. Stein, Mika Hilvo, Matej Oresic, Tamar Geiger, and Eytan Ruppin  

**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.**
### MICROENVIRONMENT AND IMMUNOLOGY

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**Precise:** 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.

**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.

**Precis:** A systematic comparison of 2 common polymorphic forms of FGFR3 reveals a higher risk of developing aggressive colorectal cancer for carriers of the FOGFR3Arg allele, potentially offering a simple prognostic marker in this setting.

**Precis:** 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.

**Precis:** 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.

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**Precis:** Findings reveal a new mechanism for controlling EGFR signaling in cancer cells through clustering and endocytosis of the receptor Neuregulin-1, which highlights its identification as a rational therapeutic target for cancer treatment.
An Integrated Genomic Screen Identifies LDHB as an Essential Gene for Triple-Negative Breast Cancer
Mark L. McCleland, Adam S. Adler, Yonglei Shang, Thomas Hunsaker, Tom Truong, David Peterson, Eric Torres, Li Li, Benjamin Haley, Jean-Philippe Stephan, Marcia Belvin, Georgia Hatzivassiliou, Elizabeth M. Blackwood, Laura Corson, Marie Evangelista, Jiping 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 O. Schmid, Meng Dong, Silke Haubiss, Godeshard Friedel, Sahine Bodt, Andreas Grabner, German Ott, Thomas E. Mudter, 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
Berendice Aguilar, Inho Choi, Dongwon Choi, Hee Kyoung Chung, Sunju Lee, JaeHyuk Yoo, Yong Suk Lee, Yong Sun Maeng, Ha Neul Lee, EunKyung Park, Kyu Eui Kim, Nam Yoon 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 the 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 Steroyl CoA Desaturase 1 Activity to Promote Bladder Tumor Growth
Xiangnan Du, Qian-Rena Wang, Emily Chan, Mark Merchant, JinFeng 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. Plichta, 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 Matsuoi, 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 Esrich, 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 RhoGAP 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.
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**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**TUMOR AND STEM CELL BIOLOGY**
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

PengXu 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 malignant transformed epithelial cells.

Oncostatin M Modulates the Mesenchymal–Epithelial Transition of Lung Adenocarcinoma Cells by a Mesenchymal Stem Cell-Mediated Paracrine Effect

Mong-Lien Wang, Chih-Ming Pan, Shih-Hwa Chiuo, Wen-Hsin Chen, Hsiang-Yi Chang, Oscar Kuang-Sheng Lee, Han-Sui Hsu, and Cheng-Wen Wu

Précis: A molecule secreted by mesenchymal stem cells attracted to tumors is found to exert an anticancer effect in lung cancer, with potential implications for cancer therapy.

Gliomagenesis Arising from Pten- and Ink4a/Arf-Deficient Neural Progenitor Cells Is Mediated by the p53-Fbxw7/Cdc4 Pathway, Which Controls c-Myc

Hong Sug Kim, Kevin Woolard, 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.
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