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**INTEGRATED SYSTEMS AND TECHNOLOGIES**

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**PRÉCIS:**

**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, Sherleen 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, Soutiana 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 Sceney, Christophe Paget, Christina S.F. Wong, Helene Duret, Jürg Tschopp, Andreas Möller, and Mark J. Smyth

Precis: 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

Precis: 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, Dedeepta Vaka, Purvesh Khatri, Olivier Gevaert, Ron Chen, Yanlyn Zheng, Anna K. Gillespie, Nicole Clarke, Yue Xu, Joseph Shrager, Choung D. Hoang, Sylvia Plevritis, Atul J. Butte, and E. Alejandro Sweet-Cordero

Precis: 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 Zigel, 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

Precis: 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 Gaughhler, Stefan Stattner, Josef Karner, Martin Klöpflinger, Friedrich Wirba, Andrea Reti, Balazs Hegedus, Andreas Baierl, Bettina Grasl-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian

Precis: A systematic comparison of 2 common polymorphic forms of FGFR4 reveals a higher risk of developing aggressive colorectal cancer for carriers of the FGFR4∗ 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

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.

5790 Aryl Hydrocarbon Receptor-Induced Adrenomedullin Mediates Cigarette Smoke Carcinogenicity in Humans and Mice
Sergio Portal-Nzánz, Uma T. Shankavaram, Mahadev Rao, Nicole Datrice, Scott Atay, Marta Aparicio, Kevin A. Camphausen, Pedro M. Fernández-Salgueiro, Han Chung, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cutiltta, and Enrique Zudaire

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.

5801 Neuropilin-1–Dependent Regulation of EGF-Receptor Signaling
Sandra Bizzolto, Noa Rabinowicz, Elena Railero, Letizia Lanzetti, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone

Precis: 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.
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

Précis: 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 Matsuo, Hisanori Uehara, Tsurenaru Miki, Yusuke Nakamura, Hiro-omi Kanayama, and Toyomasa Katagiri

Précis: 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

Précis: 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

Précis: 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 p15\(^{INK4b}\) and p16\(^{INK4a}\), Leading to Neoplastic Transformation and Poor Prognosis in Human Cancer
Xiaoalan Qian, Marian E. Durkin, Dunrui Wang, Brajendra K. Tripathi, Lyra Olson, Xu-Yu Yang, William C. Vass, Nicholas C. Popescu, and Douglas R. Lowy

Précis: 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.
Hedgehog Signaling Blockade Delays Hepatocarcinogenesis Induced by Hepatitis B Virus X Protein
Alla Arzumanyan, Vaishnavi Sambandam, Marcia M. Clayton, Steve S. Choi, Guanhua Xie, Anna Mae Diehl, Dae-Yeul Yu, and Mark A. Feitelson
Précis: Hedgehog signaling is emerging as a major driver in the development and progression of liver cancer.

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 Schlomer, Maureen Baran, Sergei 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.

Genetic Screening for Synthetic Lethal Partners of Polynucleotide Kinase/Phosphatase: Potential for Targeting SHP-1–Depleted Cancers
Todd R. Mereniuk, Robert A. Maranchuk, Anja Schindler, Jonathan Penner-Chea, Gary K. Freschiamp, Samar Hegazy, Raymond Lai, Edan Foley, and Michael Weinfeld
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.

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 platinum drugs remains a major goal in the oncology clinic, given the large and diverse number of cancers that use these chemotherapeutic agents in treatment.

Brachytherapy Using Injectable Seeds That Are Self-Assembled from GeneticallyEncoded 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.

Gene Screening for Synthetic Lethal Partners of Polynucleotide Kinase/Phosphatase: Potential for Targeting SHP-1–Depleted Cancers
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The V-ATPase-Inhibitor Archazolid Abrogates Tumor Metastasis via Inhibition of Endocytic Activation of the Rho-GTPase Rac1
Romina M. Wiedmann, Karin V. Schwarzenberg, Andrea Palamidesi, 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.

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OTX2 Represses Myogenic and Neuronal Differentiation in Medulloblastoma Cells
Ren-Yuan Bai, Verena Staedlke, 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

PengXue 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.

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 Chiou, 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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