Metformin Decreases the Dose of Chemotherapy for Prolonging Tumor Remission in Mouse Xenografts Involving Multiple Cancer Cell Types

Dimitrios Ilipoulos, Heather A. Hirsch, and Kevin Struhl

 précis: Preclinical findings suggest that combining the diabetes drug metformin with standard chemotherapy prolongs remission in multiple contexts, and may allow chemotherapy doses to be lowered in patients.

 CLINICAL STUDIES

Ribbonucleotide Reductase Small Subunit M2B Prognoses Better Survival in Colorectal Cancer

Xi Yong Liu, Lily Lai, Xiaochen Wang, Lijun Xue, Sofia Leora, Jun Wu, Shuya Hu, Keqiang Zhang, Mei-Ling Kuo, Lun Zhou, Hang Zhang, Yafan Wang, Yan Wang, Bingsen Zhou, Rebecca A. Nelson, Shu Zhang, Suzhan Zhang, Peiguo Chu, and Yun Yen

 précis: This study defines a simple immunohistochemical marker the presence of which strongly prognoses better survival outcomes in colorectal cancer patients.

MICROENVIRONMENT AND IMMUNOLOGY

Adjuvant Combination and Antigen Targeting as a Strategy to Induce Polyfunctional and High-Avidity T-Cell Responses against Poorly Immunogenic Tumors

Fernando Aranda, Diana Llopiz, Nancy Diaz-Valdés, José Ignacio Riezu-Boj, Jaimie Beznar, Marta Ruiz, Marta Martínez, Maia Durantez, Cristina Mansilla, Jesús Prieto, Juan José Lasarte, Francisco Borras-Cuesta, and Pablo Sarobe

 précis: Findings show how enhancing innate immunity with multiple adjuvant combination and improving T cell responses by targeted antigen strategies can elicit an effective immunotherapeutic response against poorly immunogenic tumors.
Aurora A is a Repressed Effector Target of the Chromatin Remodeling Protein INI1/hSNF5 Required for Rhabdoid Tumor Cell Survival

SeungJae Lee, Velasco Cimica, Nandini Ramachandra, David Zaggag, and Ganjam V. Kalpana

Précis: High expression of the mitotic kinase Aurora A may underlie the aggressive behavior of rhabdoid tumors and findings suggest that targeting Aurora A may offer a rational therapeutic strategy to inhibit these tumors.

Novel Theranostic Opportunities Offered by Characterization of Altered Membrane Lipid Metabolism in Breast Cancer Progression


Précis: This is the first study to describe the global changes in lipids that occur during breast cancer progression, highlighting new candidate prognostic markers and therapeutic targets in this important metabolic arena.

mTORC1 and mTORC2 Regulate EMT, Motility, and Metastasis of Colorectal Cancer via RhoA and Rac1 Signaling Pathways

Pat Gulhati, Kanika A. Bowen, Jianyu Liu, Payton D. Stevens, Piotr G. Rychahou, Min Chen, Eun Y. Lee, Heidi L. Weiss, Kathleen L. O’Connor, Tianyan Gao, and B. Mark Evers

Précis: mTOR kinases regulate cell proliferation and survival but new connections to metastasis revealed here for the first time offer a mechanistic rationale for certain uses of dual mTOR inhibitors in settings of advanced cancer.

FOXO1 Inhibits Runx2 Transcriptional Activity and Prostate Cancer Cell Migration and Invasion

Haijun Zhang, Yunqian Pan, Li Zheng, Chungyoul Choe, Bruce Lindgren, Eric D. Jensen, Jennifer J. Westendorf, Liang Cheng, and Haojie Huang

Précis: Mechanistic findings suggest a basis for understanding how prostate cancers metastasize to bone, a major site for disease progression in many patients.

The IL-8–Regulated Chemokine Receptor CXCR7 Stimulates EGFR Signaling to Promote Prostate Cancer Growth

Rajendra Kumar Singh and Bal L. Lokeshwar

Précis: Findings suggest that pro-inflammatory cytokine IL-8, which is elevated in the microenvironment of many tumors, may stimulate tumor cell growth in part through increasing expression of a chemokine receptor that colocalizes with EGFR and activates EGFR signaling.

Association of Specific Genotypes in Metastatic Suppressor HTPAP with Tumor Metastasis and Clinical Prognosis in Hepatocellular Carcinoma

Ning Ben, Jin-Cai Wu, Qiong-Zhu Dong, Hai-Jing Sun, Hu-Liang Jia, Guo-Cai Li, Bing-Sheng Sun, Chan Dai, Jiong Shi, Jin-Wang Wei, Yuan-Yuan Sheng, Hai-Jun Zhou, Qing-Hai Ye, and Lun-Xiu Qin

Précis: Findings identify an HTPAP genotype and associated gene expression pattern that favors metastasis progression and that could be used to predict tumor metastasis and prognosis in HCC patients.

Large-scale Exploration of Gene–Gene Interactions in Prostate Cancer Using a Multistage Genome-wide Association Study

Julia Ciampa, Meredith Yeager, Laufey Amundadottir, Kevin Jacobs, Peter Kraft, Charles Chung, Sholom Wacholder, Kai Yu, William Wheeler, Michael J. Thun, W. Ryan Divers, Susan Gapstur, Demetrius Albanes, Jarmo Virtamo, Stephanie Weinstein, Edward Giovannucci, Walter C. Willett, Geraldine Cancel-Tassin, Olivier Cussenot, Antoine Valeri, David Hunter, Robert Hoover, Giles Thomas, Stephen Chanock, and Nilanjan Chatterjee

Précis: A large genome-wide study that incorporated modern analytic methods highlights some provocative genetic interactions with established susceptibility loci that may help elucidate roots of prostate cancer susceptibility.
A Simple Approach to Cancer Therapy Afforded by Multivalent Pseudopeptides That Target Cell-Surface Nucleoproteins

Damien Destouches, Nicolas Page, Yamina Hamma-Kourbali, Valérie Machi, Olivier Chaloin, Sophie Frechault, Charalampos Birmpas, Panagiotis Katsoris, Julien Beyrath, Patricia Albanese, Marie Maurer, Gilles Carpentier, Jean-Marc Strub, Alain Van Dorselaer, Sylviane Muller, Dominique Bagnard, Jean Paul Briand, and José Courti

Précis: This interesting study defines a non-cytotoxic molecule that can efficiently localize to tumors, exert an antiangiogenesis activity, and selectively induce cancer cell death.

Inhibition of HIF Prolyl Hydroxylase-2 Blocks Tumor Growth in Mice through the Antiproliferative Activity of TGFβ

Anne Klotzsche-von Ameln, Antje Muschter, Soulafa Mamlouk, Joanna Kalucka, Ina Prade, Kristin Franke, Maryam Rezaei, David M. Poitz, Georg Breier, and Ben Wielockx

Précis: Mechanistic findings deepen understanding of the anti-proliferative effects of TGFβ, offering new insights into the interaction of several crucial growth signaling pathways and suggesting possible therapeutic targets.

Polo-Like Kinase Plk2 Is an Epigenetic Determinant of Chemosensitivity and Clinical Outcomes in Ovarian Cancer


Précis: Findings define a mitotic kinase as a key determinant of drug resistance in epithelial ovarian cancer, with important implications for improving the management of this often deadly disease.

High-Throughput RNAi Screening Reveals Novel Regulators of Telomerase

Maria Antonietta Cerone, Darren J Burgess, Cristina Naceur-Lombardelli, Christopher J. Lord, and Alan Ashworth

Précis: Findings point to ERK8 and other kinases that modulate telomerase activity as candidate therapeutic targets to disrupt telomere maintenance in cancer.
**TUMOR AND STEM CELL BIOLOGY**

3377  
**Cdk2 is Required for Breast Cancer Mediated by the Low Molecular Weight Isoform of Cyclin E**  
Said Akli, Carolyn S. Van Pelt, Tuyen Bui, Laurent Meijer, and Khandan Keyomarsi  

*Précis:* Findings establish a requirement for Cdk2 in LMW-cyclin E mediated mammary tumorigenesis, arguing that human breast tumors overexpressing LMW-cyclin E are prime candidates for anti-Cdk2 therapy.

3387  
**A Developmental Taxonomy of Glioblastoma Defined and Maintained by MicroRNAs**  
Tae-Min Kim, Wei Huang, Richard Park, Peter J. Park, and Mark D. Johnson  

*Précis:* Findings suggest the existence of at least five distinct forms of glioblastoma that each relate to distinct stages of neural stem cell differentiation, providing an expanded framework to understand disease pathogenesis in a human neurodevelopmental context.

3400  
**Phosphoglucose Isomerase/Autocrine Motility Factor Mediates Epithelial-Mesenchymal Transition Regulated by miR-200 in Breast Cancer Cells**  
Aamir Ahmad, Amro Aboukameel, Dejuan Kong, Zhiwei Wang, Seema Sethi, Wei Chen, Fazlul H. Sarkar, and Avraham Raz  

*Précis:* Findings define a microRNA signaling node that links an important pathway of epithelial-mesenchyme transition to cell metabolism and survival pathways with pivotal roles in cancer.

3410  
**ID4 Imparts Chemoresistance and Cancer Stemness to Glioma Cells by Derepressing miR-9*–Mediated Suppression of SOX2**  
Hye-Min Jeon, Young-Woo Sohn, Se-Young Oh, Sung-Hak Kim, Samuel Beck, Soonhag Kim, and Hyunggee Kim  

*Précis:* This study connects key regulators of stem cell properties and chemotherapeutic drug resistance in brain cancer, with potential implications for improving treatment.

3422  
**BRCA1 Counteracts Progesterone Action by Ubiquitination Leading to Progesterone Receptor Degradation and Epigenetic Silencing of Target Promoters**  
Verónica Calvo and Miguel Beato  

*Précis:* The findings of this important study may help explain why host mutations in the BRCA1 tumor suppressor exert a tissue specificity in preferentially elevating the risk of breast cancer.

**CORRECTIONS**

3432  
**Correction: Cytokine Receptor CXCR4 Mediates Estrogen-Independent Tumorigenesis, Metastasis, and Resistance to Endocrine Therapy in Human Breast Cancer**

3433  
**Correction: Genome-Wide Analysis of Alternative Splicing in Medulloblastoma Identifies Splicing Patterns Characteristic of Normal Cerebellar Development**
ABOUT THE COVER

Several recent studies have demonstrated the involvement of cell-surface nucleolin in angiogenesis and tumor growth. In this study, we addressed the following questions:

Does N6L (or Nucant), a synthetic ligand of cell-surface nucleolin (nM range), block angiogenesis and tumor growth? What are its mechanisms of action, its bio-distribution and finally does it target other cell surface nucleolin partner proteins?

The key findings of this study are that:

- N6L inhibits anchorage-dependent and independent growth of several tumor cell lines and blocked angiogenesis
- N6L inhibit, in vivo tumor growth in a number of mouse subcutaneous human xenograft models
- N6L bio-distribution studies indicate that N6L rapidly localizes selectively in tumor tissue (see cover figure)
- N6L is a pro-apoptotic molecule, as demonstrated by in vivo as well as in vitro experiments
- Pull-down experiments and mass-spectrometry analysis have confirmed that nucleophosmin is a partner for nucleolin and also a target (nM range) for N6L.

ImmuPharma group is currently developing N6L in Phase I/IIa clinical trials before initiating full efficacy studies in various indications as identified during this series of experiments. We believe that these findings pave the way for a novel approach of cancer treatment. For details, see the article by Destouches and colleagues on page 3296 of this issue.