Role for Stromal Heterogeneity in Prostate Tumorigenesis

Marina A. Kiskowski, Roger S. Jackson, Jheelam Banerjee, Xiaohong Li, Minchul Kang, Juan M. Iturregui, Omar E. Franco, Simon W. Hayward, and Neil A. Bhowmick

Précis: Heterogeneity of stromal TGF-β responsiveness supports cooperative intrastromal signaling and prostate adenocarcinoma progression.

Functional Synergies yet Distinct Modulators Affected by Genetic Alterations in Common Human Cancers

Marina Bessarabova, Olga Pustovalova, Weiwei Shi, Tatiana Serebiyinskaya, Alex Ishkin, Kornelia Polyak, Victor E. Velculescu, Tatiana Nikolskaya, and Yuri Nikolsky

Précis: This genetic bioinformatics study reports the development of a cancer model offering a unified perspective on the complex signaling and regulatory networks that comprise different human cancers.

Endoglin Regulates Cancer–Stromal Cell Interactions in Prostate Tumors

Diana Romero, Christine O’Neill, Aleksandra Terzic, Liangru Contois, Kira Young, Barbara A. Conley, Raymond C. Bergan, Peter C. Brooks, and Calvin P.H. Vary

Précis: Findings show how a TGF-β accessory receptor being explored as a therapeutic target acts to support the viability of cancer-associated fibroblasts in the tumor microenvironment, which are key drivers of angiogenesis and growth.

Expression of Id-1 Is Regulated by MCAM/MUC18: A Missing Link in Melanoma Progression

Maya Zigler, Gabriel J. Villares, Andrey S. Dobroff, Hua Wang, Li Huang, Russell B. Brauer, Takaafumi Kamiya, Vladislava O. Melnikova, Renduo Song, Ran Friedman, Rhoda M. Alani, and Menashe Bar-Eli

Précis: Mechanistic findings reveal how an important cell adhesion molecule melanoma regulates metastatic progression.
Tumor-Evoked Regulatory B Cells Promote Breast Cancer Metastasis by Converting Resting CD4⁺ T Cells to T-Regulatory Cells

Précis: Findings indicate that tumor-evoked regulatory B cells are crucial for lung metastasis, acting to convert resting T cells to regulatory T cells that promote immune escape in the target tissue.

Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies

Précis: Findings reveal that addition of IL-21 to culture provides an extrinsic reprogramming signal to generate effective T-cell immunotherapy.

Unraveling Cancer Chemoimmunotherapy Mechanisms by Gene and Protein Expression Profiling of Responses to Cyclophosphamide

Précis: Rapidly growing interest in combined regimens of chemoimmunotherapy is based upon emerging evidence that the efficacy of certain chemotherapeutic agents relies upon coordinate immune stimulatory effects.

Anti-TIM3 Antibody Promotes T Cell IFN-γ-Mediated Antitumor Immunity and Suppresses Established Tumors

Précis: The first antibody targeting investigations for a little studied T-cell co-inhibitory receptor establish single agent activity and mechanism of action in multiple preclinical mouse models of cancer and primary carcinogenesis.
**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

3590 | Bel-2 Inhibits Nuclear Homologous Recombination by Localizing BRCA1 to the Endomembranes
Corentin Laulier, Aurélie Barascu, Josée Guirouillh-Barbat, Géaëlle Pennarun, Catherine Le Chalony, François Chevalier, Gaëlle Palerme, Pascale Bertrand, Jean Marc Verbavatz, and Bernard S. Lopez

**Précis:** Findings suggest a new tumor suppressor function and new mode of regulation for BRCA1, with general implications for understanding the role of homologous recombination in the maintenance of genome stability.

3603 | Deciphering the Molecular Events Necessary for Synergistic Tumor Cell Apoptosis Mediated by the Histone Deacetylase Inhibitor Vorinostat and the BH3 Mimetic ABT-737
Adrian P. Wiegmans, Amber E. Alsop, Michael Bots, Leonie A. Cluse, Steven P. Williams, Kellie-Marie Banks, Rachael Balli, Clare L. Scott, Anna Frenzel, Andreas Villunger, and Ricky W. Johnstone

**Précis:** An extensive analysis of the basis for cancer cell death synergy between two important new classes of molecular targeted therapies stimulates interest in evaluation of their clinical combination.

3616 | Epigenetic Silencing of MicroRNA-203 Dysregulates ABL1 Expression and Drives Helicobacter-Associated Gastric Lymphomagenesis
Vanessa J. Craig, Sergio B. Cogliatti, Hubert Rehauer, Thomas Wiendisch, and Anne Müller

**Précis:** Progression of H. pylori-associated gastritis to gastric MALT lymphoma is epigenetically regulated by promoter methylation of a microRNA that regulates the ABL oncogene.

3625 | Following Cytochrome c Release, Autophagy Is Inhibited during Chemotherapy-Induced Apoptosis by Caspase 8–Mediated Cleavage of Beclin 1
Hua Li, Peng Wang, Quanhong Sun, Wen-Xing Ding, Xiao-Ming Yin, Robert W. Sobol, Donna B. Stolz, Jian Yu, and Lin Zhang

**Précis:** This study provides direct evidence that cleavage of Beclin 1 by caspases functions as a critical switch for turning off autophagy for effective killing of cancer cells.

3635 | The Dual EGFR/HER2 Inhibitor Lapatinib Synergistically Enhances the Antitumor Activity of the Histone Deacetylase Inhibitor Panobinostat in Colorectal Cancer Models
Melissa J. LaBonte, Peter M. Wilson, Will Fazzone, Jared Russell, Stan G. Louie, Anthony El-Khoueiry, Heinz-Josef Lenz, and Robert D. Ladner

**Précis:** Findings provide a preclinical rationale to combine HDAC inhibitors with EGFR and HER2-targeted therapies in clinical trials seeking to improve colorectal cancer treatment.

3649 | Contribution of Abcc10 (Mrp7) to In Vivo Paclitaxel Resistance as Assessed in Abcc10−/− Mice

**Précis:** This is the first study to define an ATP-binding transporter other than P-glycoprotein that mediates cytotoxic sensitivity to taxanes.

3658 | STAT3 Mediates Resistance to MEK Inhibitor through MicroRNA miR-17
Bingbing Dai, Jieru Meng, Michael Peyton, Luc Girard, William G. Bornmann, Lin Ji, John D. Minna, Bingliang Fang, and Jack A. Roth

**Précis:** This study suggests strategies to overcome resistance to MEK kinase inhibitors which are presently being evaluated in clinical trials.

3669 | Differential Expression of S6K2 Dictates Tissue-Specific Requirement for S6K1 in Mediating Aberrant mTORC1 Signaling and Tumorigenesis
Caterina Nardella, Andrea Lunardi, Giuseppe Fedele, John G. Clohessy, Andrea Alimonti, Sara C. Kozma, George Thomas, Massimo Loda, and Pier Paolo Pandolfi

**Précis:** Findings suggest clinical evaluation of S6 kinase inhibitors in a subset of adrenal gland tumors lacking the tumor suppressor PTEN.
Effects of Carbon Ion Beam on Putative Colon Cancer Stem Cells and Its Comparison with X-rays
Xing Cui, Kazuhiko Oonishi, Hirohiko Tsujii, Takeshi Yasuda, Yoshitaka Matsumoto, Yoshiya Furusawa, Makoto Akashi, Tadashi Kamada, and Ryuichi Okayasu

Précis: This is the first study to show that carbon ion beam therapy may have advantages over photon beam therapy in targeting cancer stem-like cells for destruction.

ΔNp63 Versatilely Regulates a Broad NF-κB Gene Program and Promotes Squamous Epithelial Proliferation, Migration, and Inflammation
Xinping Yang, Hai Lu, Bin Yan, Rose-Anne Romano, Yansong Bian, Jay Friedman, Praveen Duggal, Clint Allen, Ryan Chuang, Reza Ehsanian, Han Si, Satrajit Sinha, Carter Van Waes, and Zhong Chen

Précis: Mechanistic findings reveal how the interaction of two key epidermal regulatory transcription factors orchestrate inflammatory changes characteristic of injury and malignant transformation.

Does the Hepatitis B Antigen HBx Promote the Appearance of Liver Cancer Stem Cells?
Alla Arzumanyan, Tiffany Friedman, Irene O.L. Ng, Marcia M. Clayton, Zhaorui Lian, and Mark A. Feitelson

Précis: This work establishes a link between chronic HBV infection and liver cancer by showing that the virus oncoprotein, HBx, promotes the appearance of "stemness" markers.

Correction: Oncogenic Synergy between ErbB1, Nucleolin, and Mutant Ras

ABOUT THE COVER
Breast cancer induces the generation of regulatory B cells (tBregs) from resting B cells. As a result, tBregs convert T cells into Tregs which infiltrate CCL17/CCL22-expressing lungs to protect metastasizing cancer cells from NK cells. For details, see the article by Olkhanud and colleagues on page 3505 of this issue.
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