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3255 Endothelial Thermotolerance Impairs Nanoparticle Transport in Tumors
Alexander F. Bagley, Ruth Scherz-Shouval, Peter A. Galie, Angela Q. Zhang, Jeffrey Wyckoff, Luke Whitesell, Christopher S. Chen, Susan Lindquist, and Sangutea N. Bhattacharya

Précis: Nanomaterials that assist the delivery of therapeutics into solid tumors are desired, but molecular adaptations in the tumor endothelium may counteract these effects, with direct consequences for therapeutic efficacy.
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**MICROENVIRONMENT AND IMMUNOLOGY**

3268 Tumors Escape CD4⁺ T-cell–Mediated Immunosurveillance by Impairing the Ability of Infiltrating Macrophages to Indirectly Present Tumor Antigens

Andress Aune Tveita, Fredrik Schjesvold, Ole Audun Haabeth, Marte Fauskanger, and Bjarne Bogen

Précis: Tumors appear to escape immunity in part by indirectly blocking the ability of roving macrophages to present tumor antigens to the immune system, a finding that may be relevant to optimizing T-cell immunotherapies for cancer.

3279 Rapamycin Impairs Antitumor CD8⁺ T-cell Responses and Vaccine-Induced Tumor Eradication

Nada Chaouli, Catherine Fayolle, Belinda Desruess, Marine Oberkampf, Alexandre Tang, Daniel Ladant, and Claude Leclerc

Précis: The essential role of mTOR for antitumor T-cell functions implicated in immunotherapy and the immune-stimulating effects of radiotherapy and chemotherapy needed for effective therapeutic responses point to a fatal flaw in the rationale to develop mTOR inhibitors as cancer therapy.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

3292 Activation-Induced Cytidine Deaminase Contributes to Pancreatic Tumorigenesis by Inducing Tumor-Related Gene Mutations

Yugo Sawai, Yuzo Kodama, Takahiro Shimizu, Yuji Ota, Takahisa Maruno, Yuji Eso, Akira Kurita, Masahiro Shioi, Yoshishita Tsuji, Norimitsu Uza, Yuko Matsumoto, Toshihiko Masui, Shinji Lemoto, Hiroyuki Marusawa, and Tsutomu Chiba

Précis: Transgenic mice that express the cytosine deaminase AID develop precancerous pancreatic lesions without the apparent involvement of oncogenes, offering a unique mouse model of pancreatic cancer to analyze mutations involved in later stages of pancreatic carcinogenesis.

3302 ITGBl1 Is a Runx2 Transcriptional Target and Promotes Breast Cancer Bone Metastasis by Activating the TGFβ Signaling Pathway

Xiao-Qing Li, Xin Dua, Dong-Mei Li, Peng-Zaoh Kong, Yan Sun, Pei-Fang Liu, Qing-Shan Wang, and Yu-Mei Feng

Précis: This study identifies a critical function for a little studied integrin β-like molecule in bone metastasis of breast cancer, a dismal feature of advanced disease that is presently untreatable, with implications for clinical biomarker and therapeutic targeting studies.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

3314 Pharmacological Ascorbate Radio sensitizes Pancreatic Cancer


Précis: These striking findings offer a preclinical proof of concept for the parenteral delivery of pharmacological ascorbate (high levels of vitamin C) as a simple, safe, and effective radiosensitizer for pancreatic cancer treatment, with immediate implications for clinical evaluation.

3327 Proteolysis of EphA2 Converts it from a Tumor Suppressor to an Oncoprotein

Naohiko Koshikawa, Daisuke Hoshino, Hiroaki Taniguchi, Tomoko Minegishi, Taiso Tomari, Sung-Ouk Nam, Mikiko Aoki, Takayuki Suet, Takashi Nakagawa, Shingo Miyamoto, Kazuki Nabeshima, Alissa M. Weaver, and Motoharu Seki

Précis: This important study sheds light on long-standing questions about the basis for the paradoxical actions of EphA2 in tumor progression.

3340 Naturally Occurring Mutations in the MPS1 Gene Predispose Cells to Kinase Inhibitor Drug Resistance


Précis: This study defines resistance mechanisms that may arise to a new class of cell-cycle checkpoint inhibitors being developed as cancer therapy—important during the early stages of drug development for several reasons—but it also reports an unexpected finding that many drug resistance mutations might be found in some normal and malignant cells even before drug treatment has started.

3355 Therapeutic Targeting of the Warburg Effect in Pancreatic Cancer Relies on an Absence of p53 Function

N.V. Rajeshkumar, Prasanta Dutta, Shinichi Yabuuchi, Roeland F. de Wilde, Gary V. Martinez, Anne Le, Jurre J. Kamphorst, Joshua D. Rabinowitz, Sanjay K. Jain, Manuel Hidalgo, Chi V. Dang, Robert J. Gillies, and Mark D. Guard

Précis: The p53 status of a tumor may be a major factor in determining an efficacious response to inhibitors of lactate dehydrogenase, as a strategy to target the Warburg effect in solid tumors.
A Polymer-Based Antibody–Vinca Drug Conjugate Platform: Characterization and Preclinical Efficacy

Alexander V. Yurkovetskiy, Mao Yin, Natalya Bodyak, Cheri A. Stevenson, Joshua D. Thomas, Charles E. Hammond, Lianliang Qin, Bangmin Zhu, Dmitry R. Gumerov, Elena Ter-Ovanesyan, Alex Uttard, and Timothy B. Lowinger

Précis: This study shows how efficacious antibody-drug conjugates can be prepared based on a novel, polymer-based conjugation approach that overcomes physicochemical limitations, enabling higher drug-antibody ratios and therefore uses for less potent drug payloads.

Depleting MET-Expressing Tumor Cells by ADCC Provides a Therapeutic Advantage over Inhibiting HGF/MET Signaling

Anna Hultberg, Virginia Morello, Leander Huyghe, Natalie De Jonge, Christophe Blanchetot, Valerie Hanssens, Gitte De Boeck, Karen Silence, Els Festjens, Raimond Heukers, Benjamin Roux, Fabienne Lamballe, Christophe Ginestier, Emmanuelle Charafe-Jauffret, Flavio Maina, Peter Broeckaert, Michael Saunders, Alain Thibault, Torsten Dreier, Hans de Haard, and Paolo Michieli

Précis: These findings offer evidence that killing MET-expressing cancer cells by ADCC is therapeutically more advantageous than simply inhibiting HGF/MET signaling, based on studies of a novel ADCC-enhanced anti-MET antibody entering clinical development.

Oncogenic G Protein GNAQ Induces Uveal Melanoma and Intravasation in Mice

Jenny Li-Ying Huang, Oscar Urtatiz, and Catherine D. Van Raamsdonk

Précis: This study reports the first transgenic mouse model of uveal melanoma, one of the most aggressive cancers, which will be useful for developing in vivo understanding of etiology and metastatic progression of this disease.

Diverse Targets of β-Catenin during the Epithelial–Mesenchymal Transition Define Cancer Stem Cells and Predict Disease Relapse

Yi-Wen Chang, Ying-Jhen Su, Michael Hsiao, Kuo-Chen Wei, Wei-Hsin Lin, Chi-Jung Liang, Shin-Cheh Chen, and Jia-Lin Lee

Précis: In discovering that Wnt signaling must accompany the epithelial-mesenchymal transition to generate cancer stem-like cells, this study defines a five-gene signature for these cells that may be a valuable prognostic marker in lung cancer patients.

PML-RARα-Regulated miR-181a/b Cluster Targets the Tumor Suppressor RASSF1A in Acute Promyelocytic Leukemia

Daniela Bräuer-Hartmann, Jens-Uwe Hartmann, Alexander Arthur Wurm, Dennis Gerloff, Christiane Katzerke, Maria Vittoria Verga Falzacappa, Pier Giuseppe Pellici, Carsten Müller-Tidow, Daniel G. Tenen, Dieter Niederwieser, and Gerhard Behre

Précis: These findings identify a pivotal microRNA cluster and tumor suppressor gene as determinants of the outgrowth versus effective therapeutic control of acute promyelocytic leukemias.
ABOUT THE COVER

Radiation-induced gastrointestinal toxicity is highly relevant to the treatment of pancreatic cancer with radiation. To determine if pharmacological ascorbate changes the response of the gastrointestinal tract following radiation in a clinically meaningful way, a crypt cell assay was performed. The addition of pharmacological ascorbate partially reversed the decreases in jejunal crypt regeneration in both the 10 Gy and 13 Gy groups of mice, suggesting that ascorbate may protect the gastrointestinal tract from the damaging effects of radiation. For details, see article by Du and colleagues on page 3314.