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MICROENVIRONMENT AND IMMUNOLOGY

1642 Dissection of T-cell Antigen Specificity in Human Melanoma
Rikke Sick Andersen, Charlotte Albek Thrue, Niels Junker, Rikke Lyngaa, Marco Donia, Eva Ellebæk, Inge Marie Svane, Ton N. Schumacher, Per Thor Straten, and Sine Reker Hadrup
Oncolytic Virus and Anti-4-1BB Combination Therapy Elicits Strong Antitumor Immunity against Established Cancer

**Précis:** The preclinical proof-of-concept offered by this study suggests a strategy to improve the clinical efficacy of oncolytic viruses for cancer immunotherapy by combining them with an immune agonist antibody that may help overcome tumor-mediated immune suppression.

Preclinical Evaluation of TriMix and Antigen mRNA-Based Antitumor Therapy
Sandra Van Lint, Cleo Goyvaerts, Sarah Maenhout, Lode Goethals, Aurélie Disy, Daphné Benzeyn, Joeri Pen, Aude Bonehill, Carlo Heirman, Karine Breckpot, and Kris Thielemans

**Précis:** This study presents important progress in the rapid development of simpler kinds of dendritic cell vaccines, the first ever of which was approved for patient treatment in the United States last year.

Intracellular Tumor-Associated Antigens Represent Effective Targets for Passive Immunotherapy

**Précis:** Contrary to a widely held but incorrect belief in the field, intracellular tumor antigens can offer highly effective targets for monoclonal antibody-directed therapy, as shown by this preclinical study.

Reprogramming Tumor-Associated Dendritic Cells In Vivo Using miRNA Mimetics Triggers Protective Immunity against Ovarian Cancer

**Précis:** Findings suggest it may be feasible to modulate microRNA activities in leukocytes in the tumor microenvironment without need of viral vectors or difficult clinical implementations.

Vascular Normalization by Loss of Siah2 Results in Increased Chemotherapeutic Efficacy
Christina S.F. Wong, Jaclyn Sceney, Colin M. House, Heloise M. Halse, Mira C.P. Liu, Joshy George, Titaina C.U. Potdevin Hunnam, Belinda S. Parker, Zhak Haviv, Ze’ev Ronai, Carleen Cullinane, David D. Bowtell, and Andreas Möller

**Précis:** Findings offer preclinical proof-of-concept that targeting the Siah2 ubiquitin ligase that regulates the hypoxia response factor HIF-1α can relieve hypoxia, normalize tumor vasculature, and improve responses to chemotherapy.

Vanilloid Receptor-1 Regulates Neurogenic Inflammation in Colon and Protects Mice from Colon Cancer
Amaya G. Vinuesa, Rocío Sancho, Carmen García-Limones, Axel Behrens, Peter ten Dijke, Marco A. Calzado, and Eduardo Muñoz

**Précis:** This important study offers compelling genetic support for the intriguing concept that neuronally controlled processes of inflammation may underlie the root inflammatory microenvironment that drives the development and progression of colon cancer, with implications for targeting neuroinflammatory receptors that control these processes as a wholly novel strategy to prevent or treat this major disease.

Cancer Vaccination Drives Nanog-Dependent Evolution of Tumor Cells toward an Immune-Resistant and Stem-like Phenotype
Kyung Hee Noh, Young-Ho Lee, Ju-Hong Jeon, Tae Heung Kang, Chih-Ping Mao, T.-C. Wu, and Tae Woo Kim

**Précis:** An important stem cell transcription factor is found to drive development of tumoral immune resistance after therapeutic vaccinations, suggesting possible strategies to enhance cancer immunotherapy.

RORα Suppresses Breast Tumor Invasion by Inducing SEMA3F Expression
Gaofeng Xiong, Chi Wang, B. Mark Evers, Binhua P. Zhou, and Ren Xu

**Précis:** Findings point to an important role for the Th17 immune transcription factor RORα in preventing the establishment of an immune-suppressive tumor microenvironment in mammary tissue.
Tumor Cell–Derived Angiopoietin-like Protein ANGPTL2 Is a Critical Driver of Metastasis


Précis: Findings have implications for a broad-based antibody-mediated strategy to blunt metastasis in various human cancers where an angiogenesis-related factor is implicated in this process.

19p13.1 Is a Triple-Negative–Specific Breast Cancer Susceptibility Locus

Kristen N. Stevens, Zachary Frederickson, Celine M. Vachon, Xianshu Wang, Sara Margolin, Anniika Lindblom, Heli Sevanlima, Dario Greco, Kristiina Attilomaki, Carl Blomqvist, Jenny Chang-Claude, Alina Vriend, Dieter Flesch-Jans, Hans-Peter Sinn, Shan Wang-Gehrke, Stefan Nickels, Hilfrud Brauch, on behalf of the GENICA Network, Yor-Dschun Ko, Hans-Peter Fischer, Rita K. Schmutzler, Alfons Meindl, Claus R. Barthram, Sarah Schott, Christoph Engel, Andreas M. Metzler, and Christa Stegmaier

Précis: This important study has immediate clinical implications because it suggests ways that autophagy inhibitors such as chloroquine might be combined with antiangiogenic therapies to limit a mechanism of resistance and thereby extend efficacy.
Paclitaxel Enhances Therapeutic Apoptosis and Tumor Suppression Elicited by Combination of MEK (Selumetinib) and mTOR Kinase Inhibitors (AZD8055)


Precise: Findings offer a preclinical proof-of-concept for combining MAPK and mTOR kinase inhibitors in clinical trials to achieve robust tumor growth inhibition while limiting risks of chemoresistance.

Paclitaxel Enhances Therapeutic Efficacy of the F8-IL2 Immunocytokine to EDA-Fibronectin–Positive Metastatic Human Melanoma Xenografts

Michele Moschetta, Francesca Pretto, Alexander Berndt, Kerstin Galler, Petra Richter, Andrea Bassi, Paolo Oliva, Edoardo Micotti, Giovanni Valbusa, Kathrin Schwager, Manuela Kaspar, Eveline Trachsel, Hartwig Kosmehl, Maria Rosa Bani, Dario Neri, and Raffaella Giavazzi

Precise: Findings offer a preclinical proof-of-concept for an effective application of IL-2-based immunotherapy for melanomas that is targeted to fibronectin, an extracellular matrix protein expressed by many melanomas.

Retinoic Acid/Alpha-Interferon Combination Inhibits Growth and Promotes Apoptosis in Mantle Cell Lymphoma through Akt-Dependent Modulation of Critical Targets

Jessica Dal Col, Katy Mastorci, Damiana Antonia Faè, Elena Muraro, Debora Martorelli, Giorgio Inghirami, and Riccardo Dolcetti

Precise: A clinical drug combination explored for treatment of numerous types of cancer may be especially suited to treatment of a deadly type of non-Hodgkin lymphoma that remains particularly difficult to treat.

Rapamycin Resistance Is Linked to Defective Regulation of Skp2

Hana Totary-Jain, Despina Sanoudou, Cula N. Dautriche, Hillary Schneller, Lester Zambrana, and Andrew R. Marks

Precise: This study defines a candidate drug response marker for mTOR inhibitors, an important class of experimental therapeutics of growing interest for the generalized treatment of human cancer, with immediate implications for clinical evaluation in mTOR inhibitor trials.

Cancer Stem Cell Vaccination Confers Significant Antitumor Immunity

Ning Ning, Qin Pan, Fang Zheng, Seagal Teitz-Tennenbaum, Martin Egenti, Ji Yet, Mu Li, Christophe Ginestier, Max S. Wicha, Jeffrey S. Moyer, Mark E.P. Prince, Yingxin Xu, Xiao-Lian Zhang, Shiang Huang, Alfred E. Chang, and Qiao Li

Precise: Vaccines that use purified cancer stem cells are highly immunogenic and trigger antitumor immunity with greater potency than that triggered by vaccines composed of unselected tumor cells.
### miRNA Signatures Associate with Pathogenesis and Progression of Osteosarcoma

Kevin B. Jones, Zaidoun Salah, Sara Del Mare, Marco Galasso, Eugenio Gaudio, Gerard J. Nuovo, Francesca Lovat, Kimberly LeBlanc, Jeff Palatini, R. Lor Randall, Stefano Volinia, Gary S. Stein, Carlo M. Croce, Jane B. Lian, and Rami I. Aqeilan

**Précis:** Osteosarcoma is a leading cause of death in adolescents yet remains mainly devoid of development of sounder tools to improve prognosis or therapy.

### Pten Loss and RAS/MAPK Activation Cooperate to Promote EMT and Metastasis Initiated from Prostate Cancer Stem/Progenitor Cells

David J. Mulholland, Naoko Kobayashi, Marcus Ruscetti, Allen Zhi, Linh M. Tran, Jiaoti Huang, Martin Gleave, and Hong Wu

**Précis:** Development of a prostate cancer model that addresses the major metastatic burden accompanying late-stage human disease addresses a gap in the field that may permit the development of more effective targeted treatment strategies.

### Jab1/CSN5 Negatively Regulates p27 and Plays a Role in the Pathogenesis of Nasopharyngeal Carcinoma

Yunbao Pan, Qingshu Zhang, Ling Tian, Xin Wang, Xiaohang Fan, Huizhong Zhang, Francois X. Claret, and Huiling Yang

**Précis:** Definition of a cell-cycle regulatory role for a component of the signalosome, a protein turnover complex analogous to the proteosome but less understood, suggests new strategies to treat an aggressive cancer endemic in East Asia.

### Lactate-Induced IL-8 Pathway in Endothelial Cells—Letter

Céline Pinheiro, Adhemar Longatto-Filho, Rosete Nogueira, Fernando Schmitt, and Fátima Baltazar

### Lactate-Induced IL-8 Pathway in Endothelial Cells—Response

Frédérique Végran, Emmanuel Seront, Pierre Sonveaux, and Olivier Feron

### Correction: Significance of MAD2 Expression to Mitotic Checkpoint Control in Ovarian Cancer Cells

Tumor metastasis represents a major cause of cancer mortality. Despite intense effort, strategies designed to inhibit metastasis have been unsuccessful, in part due to lack of understanding of mechanisms underlying the process. In this study, a shortened period of disease-free survival was observed after surgery in lung cancer patients showing high angiopoietin-like protein 2 (ANGPTL2) expression in tumor cells within primary tumor sites. Furthermore, tumor cell–derived ANGPTL2 increased tumor cell motility and invasive capacity in an autocrine/paracrine manner, resulting in acquisition of metastatic tumor phenotypes. In tumor cell–implanted mouse models, tumor cell–derived ANGPTL2 accelerated metastasis and shortened survival periods; conversely, decreasing ANGPTL2 expression in tumor cells significantly attenuated metastasis and extended survival periods. This image represents CD44-stained human breast tumor cells expressing ANGPTL2 in lung metastasis in mice. For details, see the article by Endo and colleagues on page 1784 of this issue.