CANCER IMMUNOLOGY AT THE CROSSROADS: TUMOR MICROENVIRONMENT

83 The Complex Role of Neutrophils in Tumor Angiogenesis and Metastasis
Wei Liang and Napoleone Ferrara

CANCER IMMUNOLOGY MINIATURES

92 The Trojan Horse Tale Revisited: An Eye on Metastatic Spread of Carcinoma Cells
Rafael S. Grajewski, Jacobus J. Bosch, Heiko Bruns, Claus Cursiefen, and Ludwig M. Heindl
Macrophages expressing tumor markers were detected in the blood and eye of a patient with parotid gland carcinoma. These "Trojan horses" may transport tumor cells to distant organs, where carcinomas could grow and establish metastases in new environments.

95 Vaccines Combined with Immune Checkpoint Antibodies Promote Cytotoxic T-cell Activity and Tumor Eradication
Omar A. Ali, Sarah A. Lewin, Glenn Dranoff, and David J. Mooney
Despite dramatic clinical successes for cancer vaccines and immune checkpoint blockade, disease usually progresses. In a mouse model that combined vaccines with checkpoint blockade, significant CTL activation, tumor eradication, and long-term survival was achieved.

PRIORITY BRIEF

Vaccines Combined with Immune Checkpoint Antibodies Promote Cytotoxic T-cell Activity and Tumor Eradication
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Despite dramatic clinical successes for cancer vaccines and immune checkpoint blockade, disease usually progresses. In a mouse model that combined vaccines with checkpoint blockade, significant CTL activation, tumor eradication, and long-term survival was achieved.

RESEARCH ARTICLES

101 MIF Is Necessary for Late-Stage Melanoma Patient MDSC Immune Suppression and Differentiation
Kaviha Yaddanapudi, Beatriz E. Rendon, Gwyneth Lamont, Eun Jung Kim, Numan Al Rayyan, Jamaal Richie, Sabrin Albeituni, Sabine Waigel, Ashley Wise, and Robert A. Mitchell
Macrophage migration inhibitory factor (MIF) is produced by monocytes in cancer-bearing mice and humans. MIF was found to be critical for suppressive monocytic cells in melanoma patients, and when inhibited, the monocytic cells acquire antitumor phenotypes.

113 Retuning of Mouse NK Cells after Interference with MHC Class I Sensing Adjusts Self-Tolerance but Preserves Anticancer Response
Arnika Kathleen Wagner, Stina Linnea Wickström, Rossana Tallerico, Sadia Salam, Tadepalli Lalakhmikanth, Hanna Brauner, Petter Höglund, Ennio Carbone, Maria Helena Johansson, and Klås Kärre
NK cell-based immunotherapy may be hampered by adaptation to reduced inhibitory input from MHC molecules on surrounding cells. However, while such readjustment of responsiveness leads to tolerance to healthy cells, reactivity to cancer cells remains.

124 Glioblastoma Eradication Following Immune Checkpoint Blockade in an Orthotopic, Immunocompetent Model
Glioblastoma has been especially challenging to treat. In a systematic analysis of combinations of checkpoint therapies in a murine model, some single and dual immunotherapies increased intratumoral effectors, reduced suppressors, and eliminated the tumors.

136 Hypomethylation of the Treg-Specific Demethylated Region in FOXP3 Is a Hallmark of the Regulatory T-cell Subtype in Adult T-cell Leukemia
Yayoi Shimazu, Yutaka Shimazu, Masahide Hamaguchi, Yuya Nagai, Noriko Sugino, Sumie Fujii, Masahiro Kawahara, Norimitsu Kadokaki, Hiroyoshi Nishikawa, Shimon Sakaguchi, and Akifumi Takaori-Kondo
A subtype of adult T-cell leukemia cells can be distinguished based on the hypomethylated state of their FOXP3 gene. These cells have Treg properties, and the patients have a poor prognosis.

146 Intratumoral Delivery of TriMix mRNA Results in T-cell Activation by Cross-Presenting Dendritic Cells
Sandra Van Lint, Dries Remans, Katrijn Broos, Lode Goethals, Sarah Maenhout, Daphné Benteyn, Cleo Coyvaerts, Stephanie Du Four, Kevin Van der Jeugt, Lukasz Bialkowski, Véronique Flamand, Carlo Heirman, Kris Thielemans, and Karine Breckpot
Intratumoral injection of CTL-stimulatory agents could provide another avenue for immunotherapy. TriMix mRNA, comprising three DC-oriented stimulatory mRNAs, was examined in mouse models and provides a rationale for clinical testing in solid and accessible tumors.
Identification of Anti-CA125 Antibody Responses in Ovarian Cancer Patients by a Novel Deep Sequence–Coupled Biopanning Platform
Kathryn M. Frietze, Richard B.S. Roden, Ji-Hyun Lee, Yang Shi, David S. Peabody, and Bryce Chackerian
Ovarian cancer would benefit from the identification of early biomarkers of prognostic value. Deep sequence–coupled biopanning identified autoantibody responses to a CA125 epitope in a subset of ovarian cancer patients that correlated with extended survival.

Survivin Autoantibodies Are Not Elevated in Lung Cancer When Assayed Controlling for Specificity and Smoking Status
Ingrid Broedman, Martijn M. VanDuijn, Christoph Stingl, Lennard J.M. Dekker, Anastasios E. Germenis, Harry J. de Koning, Rob J. van Klaveren, Joachim G. Aerts, Jan Lindemans, and Theo M. Luider
Reports of autoantibodies to survivin in lung cancer sera lead to suggestions of roles as biomarkers. The authors tested patient serum with two approaches, controlling for specificity and using controls stratified for smoking habits. No autoreactivity was found.

Correction
Correction: Human Leukocyte Antigen (HLA) A*1101-Restricted Epstein-Barr Virus–Specific T-cell Receptor Gene Transfer to Target Nasopharyngeal Carcinoma

ABOUT THE COVER
Tumors create havoc by making their own rules. How cancer cells may travel and seed a new site, such as the immune-privileged eye, is not always clear. A case of "Trojan horse" travel is described by Grajewski and colleagues starting on p. 92 in this issue of Cancer Immunology Research. A covert parotid carcinoma may have traveled to the aqueous humor of the eye by fusing with migratory phagocytic cells to create monocyte–macrophage Trojan horses. The eye's trabecular network trapped these cells (the yellow section, lower left, of the iris), and they proliferated, causing a rare type of carcinoma in the aqueous humor. Artwork is by Lewis Long.