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MASTERS OF IMMUNOLOGY

- 503 Pathogen-Sensing and Regulatory T Cells: Integrated Regulators of Immune Responses**



William E. Paul and Zvi Grossman

CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 510 VISTA Is a Novel Broad-Spectrum Negative Checkpoint Regulator for Cancer Immunotherapy**
J. Louise Lines, Lorenzo F. Sempere, Thomas Broughton, Li Wang, and Randolph Noelle

COMMENTARY

- 518 Can We Predict Mutant Neopeptides in Human Cancers for Patient-Specific Vaccine Therapy?**
Eric R. Lutz and Elizabeth M. Jaffee
See related article, p. 522

CANCER IMMUNOLOGY MINIATURES

- 522 HLA-Binding Properties of Tumor Neopeptides in Humans**
Edward F. Fritsch, Mohini Rajasagi, Patrick A. Ott, Vladimir Brusic, Nir Hacohen, and Catherine J. Wu
Synopsis: Tumor neoantigens are common T-cell targets in humans with regressing or sometimes long-term stable disease. Fritsch and colleagues analyzed their predicted HLA-binding properties, and herein show that they provide important guidance for neopeptide selection for personalized cancer vaccines.
See related commentary, p. 518

- 530 Tumor MHC Class I Expression Improves the Prognostic Value of T-cell Density in Resected Colorectal Liver Metastases**
Simon Turcotte, Steven C. Katz, Jinru Shia, William R. Jarnagin, T. Peter Kingham, Peter J. Allen, Yuman Fong, Michael I. D'Angelica, and Ronald P. DeMatteo
Synopsis: Using a tissue microarray of liver metastases from 158 patients with colorectal cancer, Turcotte and colleagues show that high MHC class I expression with dense intratumoral T-cell infiltration identifies patients with favorable outcomes independent of conventional prognostic factors.

RESEARCH ARTICLES

- 538 Immune-Escape Markers in Relation to Clinical Outcome of Advanced Melanoma Patients Following Immunotherapy**
Esther P.M. Tjin, Gabrielle Krebbers, Kimberley J. Meijlink, Willeke van de Kastelee, Efraim H. Rosenberg, Joyce Sanders, Petra M. Nederlof, Bart A. van de Wiel, John B.A.G. Haanen, Cornelis J.M. Melief, Florry A. Vyth-Dreese, and Rosalie M. Luiten
Synopsis: Tjin and colleagues analyzed a large panel of immune markers in patients with stage IV advanced melanoma prior to autologous tumor-cell vaccination and report that high density of intratumoral CD4⁺ and CD8⁺ T cells with elevated granzyme B expression is correlated with favorable clinical outcome.

- 547 Cancer-Testis Antigen 7 Expression and Immune Responses Following Allogeneic Stem Cell Transplantation for Multiple Myeloma**
Eleanor M. Tyler, Achim A. Jungbluth, Sacha Gnjatic, Richard J. O'Reilly, and Guenther Koehne
Synopsis: Tyler and colleagues show that cancer-testis antigen 7 (CT7) protein expression in the bone marrow and CT7-specific T-cell responses in blood are associated with the disease course of patients with multiple myeloma following allogeneic stem cell transplantation, supporting immunotherapeutic targeting of CT7 as a treatment for multiple myeloma.

- 559 The Dose-Dependent Tumor Targeting of Antibody-IFN γ Fusion Proteins Reveals an Unexpected Receptor-Trapping Mechanism In Vivo**
Teresa Hemmerle and Dario Neri
Synopsis: Hemmerle and Neri show in three syngeneic murine tumor models that immunocytokine F8-IFN γ targets tumoral fibronectin, recruits and activates leukocytes, and needs relatively high doses to localize on tumors, and that its antitumor activity is potentiated by combination with F8-IL4 without additional toxicities.



Table of Contents

568 **TLR7 Ligand Augments GM-CSF–Initiated Antitumor Immunity through Activation of Plasmacytoid Dendritic Cells**

Megumi Narusawa, Hiroyuki Inoue, Chika Sakamoto, Yumiko Matsumura, Atsushi Takahashi, Tomoko Inoue, Ayumi Watanabe, Shohei Miyamoto, Yoshie Miura, Yasuki Hijikata, Yoshihiro Tanaka, Makoto Inoue, Koichi Takayama, Toshihiko Okazaki, Mamoru Hasegawa, Yoichi Nakanishi, and Kenzaburo Tani

Synopsis: Narusawa and colleagues found that type 1 IFNs and plasmacytoid dendritic cells in the tumor-draining lymph nodes mediate GM-CSF–induced antitumor immunity in immunocompetent mice, and they report that the synthetic TLR7 ligand imiquimod could overcome tolerance and enhance autologous GM-CSF antitumor effects.

581 **Antitumor Effects of Cisplatin Combined with Tecemotide Immunotherapy in a Human *MUC1* Transgenic Lung Cancer Mouse Model**

Chiao-Jung Kao, Gregory T. Wurz, Arta M. Monjazeb, Daniel P. Vang, Timothy B. Cadman, Stephen M. Griffey, Michael Wolf, and Michael W. DeGregorio

Synopsis: Kao and colleagues report that concurrent cisplatin/tecemotide therapy induced additive reduction in lung tumor foci associated with a Th1 immune response. They further suggest that localized lung radiotherapy may enhance the CTL-driven antitumor activity of tecemotide.

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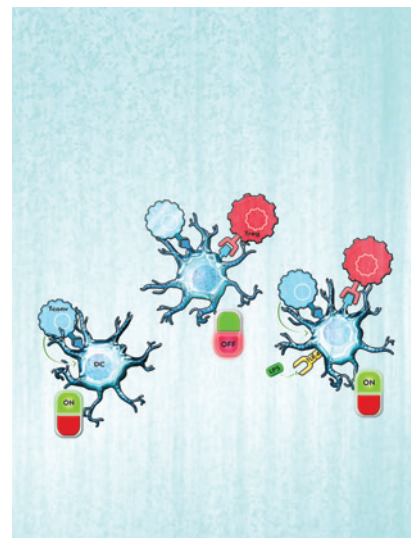
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Table of Contents

ABOUT THE COVER

Dendritic cells (DC; large cells with dendrites) are master regulators of immune responses: They are the principle antigen-presenting cells for adaptive immune responses, and they have receptors for sensing pathogens and danger signals for innate immune responses. The competency of a DC to activate a robust immune response, particularly against weak antigens such as tumor antigens, depends on the countervailing effects of pathogen-sensing and regulatory T cells (Treg; salmon color cells). In the absence of Tregs, a naïve, conventional CD4 T cell (Tconv; sky blue cells), interacting with a DC presenting an antigen in an MHC complex (blue spikes from DC) for which the TCR of the Tconv is specific and binds with high affinity, induces the reciprocal activation of the Tconv and DC and the subsequent immune responses. In the presence of Tregs that also recognize peptide/MHC complexes on the same DC, the DC is prevented from becoming activated, thus restraining T-cell activation. If the DC receives a signal through its pathogen-sensing receptors, shown here as endotoxin bacterial lipopolysaccharide (LPS; dark green) stimulating the pathogen-sensing Toll-like receptor 4 (TLR-4; yellow receptor), it will then become activated even in the presence of Tregs. The activated DC will then stimulate the specific conventional CD4 T cell to undergo its full range of responses. For details of the proposed model of pathogen-sensing and Tregs as integrated regulators of immune responses, see the Masters of Immunology primer by William E. Paul and Zvi Grossman on page 503 of this issue. [Cover image adapted from Paul et al. *Cold Spring Harb Symp Quant Biol* 2013 Oct 15. Epub ahead of print.]



ABOUT THE MASTER

William E. Paul, MD, is an NIH Distinguished Investigator, and chief of the National Institute of Allergy and Infectious Diseases (NIAID) Laboratory of Immunology. Dr. Paul is best known for his path-breaking work on cytokine biology, including the discovery of interleukin-4, and its role as the key regulator of allergic inflammatory diseases. He delineated the mechanisms of differentiation of naïve CD4 T cells into T-helper effector cells, a subject that remains one of the dominant themes of contemporary immunology.

Dr. Paul was born in Brooklyn, NY. He received his BA degree, *summa cum laude*, from Brooklyn College, and his MD, *cum laude*, from the State University of New York Downstate Medical Center. He served his internship and residency in medicine at the Boston Medical Center. He was a research fellow in the laboratory of Nobel laureate Dr. Baruj Benacerraf at the New York University School of Medicine. In 1968, Dr. Paul joined the NIAID, where he became chief of the Laboratory of Immunology in 1970. From 1994 to 1997, during his tenure as Assistant Surgeon General of the United States, he served as the director of the NIH Office of AIDS Research (OAR) and the associate NIH director for AIDS. As OAR director, Dr. Paul was responsible for, at that time, a new emphasis on HIV vaccine research and development and the creation of the Vaccine Research Center on the NIH campus.

Dr. Paul has been elected to the U.S. National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He has served as president of the American Association of Immunologists (AAI) and of the American Society of Clinical Investigation. Dr. Paul has received numerous honorary degrees, awards, and recognitions, including the 1980 Founder's Prize of the Texas Instruments Foundation, the 1988 Life Sciences Award from the Federation of American Societies for Experimental Biology, the Tovi Comet-Wallerstein Prize of Bar-Ilan University, Lifetime Achievement Awards from the AAI and the International Cytokine Society, the 2008 Max Delbruck Medal, and the 2009 Clemens von Pirquet Medal. He is a Raymond and Beverly Sackler Senior Professor by Special Appointment at Tel Aviv University and an Adjunct Professor of Pathology and Laboratory Medicine at the University of Pennsylvania Medical School. Dr. Paul is a prolific researcher and educator. He has authored more than 600 scientific articles and has edited two of the most influential immunology text and reference books. He served as founding editor-in-chief of the *Annual Review of Immunology* for its first 31 editions. He is the editor of the advanced textbook, *Fundamental Immunology*, now in its seventh edition. He has mentored many prominent immunologists, including the late Charles Janeway Jr, Ron Schwartz, Laurie Glimcher, Mark Davis, and Tony DeFranco.



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