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MASTERS OF IMMUNOLOGY

- 219** The Shared and Contrasting Roles of IL2 and IL15 in the Life and Death of Normal and Neoplastic Lymphocytes: Implications for Cancer Therapy
CME Thomas A. Waldmann

CANCER IMMUNOLOGY MINIATURES

- 228** Peptide/MHC Tetramer-Based Sorting of CD8⁺ T Cells to a Leukemia Antigen Yields Clonotypes Drawn Nonspecifically from an Underlying Restricted Repertoire
 Sally A. Hunsucker, Colleen S. McGary, Benjamin G. Vincent, Atim A. Enyenihi, Jennifer P. Waugh, Karen P. McKinnon, Lisa M. Bixby, Patricia A. Ropp, James M. Coghill, William A. Wood, Don A. Gabriel, Stefanie Sarantopoulos, Thomas C. Shea, Jonathan S. Serody, Gheath Alatrash, Tania Rodriguez-Cruz, Gregory Lizée, Adam S. Buntzman, Jeffrey A. Frelinger, Gary L. Glish, and Paul M. Armistead
Synopsis: Hunsucker, McGary, Vincent, and colleagues report that low-frequency, antigen-specific T-cell responses may be specifically tested using tetramer-based, single-cell sorting and sequencing of the antigen-specific TCRβ clonotypes, and then mapping them onto a patient's TCRβ to quantify antigen-driven clonal expansion.

PRIORITY BRIEF

- 236** Induced PD-L1 Expression Mediates Acquired Resistance to Agonistic Anti-CD40 Treatment
AC Alfred Zippelius, Jens Schreiner, Petra Herzig, and Philipp Müller
Synopsis: Zippelius and colleagues report that anti-CD40 treatment induces T cell- and IFNγ-dependent PD-L1 expression on tumor-infiltrating monocytes and macrophages. Consequently, the combination of anti-CD40 therapy with PD-1/PD-L1 blockade elicits effective tumor rejection in mouse models of breast and colon cancer.

RESEARCH ARTICLES

- 245** CD25 Identifies a Subset of CD4⁺FoxP3⁻ TIL That Are Exhausted Yet Prognostically Favorable in Human Ovarian Cancer
 Ronald J. deLeeuw, David R. Kroeger, Sara E. Kost, Peh-Ping Chang, John R. Webb, and Brad H. Nelson
Synopsis: deLeeuw and colleagues analyzed tumor-infiltrating lymphocytes (TIL) in primary high-grade serous ovarian cancer and discovered a novel subset of CD4⁺ TIL that are strongly associated with patient survival and hence warrant consideration as effector cells for immunotherapy.

- 254** Inhibition of CD39 Enzymatic Function at the Surface of Tumor Cells Alleviates Their Immunosuppressive Activity
 Jeremy Bastid, Anne Regairaz, Nathalie Bonnefoy, Cécile Déjou, Jérôme Giustiniani, Caroline Laheurte, Stéphanie Cochaud, Emilie Laprevotte, Elisa Funck-Brentano, Patrice Hemon, Laurent Gros, Nicole Bec, Christian Larroque, Gilles Alberici, Armand Bensussan, and Jean-François Eliaou
Synopsis: Bastid and colleagues show that CD39 is highly expressed on tumor-infiltrating lymphocytes, tumor stroma, but also on tumor cells; treatment with CD39 inhibitors or blocking antibody alleviated the tumor-induced inhibition of T-cell proliferation and increased CTL- and NK cell-mediated cytotoxicity.

- 266** Retargeting T Cells to GD2 Pentasaccharide on Human Tumors Using Bispecific Humanized Antibody
 Hong Xu, Ming Cheng, Hongfen Guo, Yuedan Chen, Morgan Huse, and Nai-Kong V. Cheung
Synopsis: Xu and colleagues describe a novel, fully humanized, aglycosylated bispecific antibody targeting GD2 pentasaccharide with femtomolar cytotoxic EC₅₀ against cancer cell lines that activates T cells in situ, drives intravenous T cells and monocytes to infiltrate tumor stroma, and ablates neuroblastoma and melanoma xenografts.

- 278** Resiquimod as an Immunologic Adjuvant for NY-ESO-1 Protein Vaccination in Patients with High-Risk Melanoma
 Rachel Lubong Sabado, Anna Pavlick, Sacha Gnjatic, Crystal M. Cruz, Isabelita Vengco, Farah Hasan, Meredith Spadaccia, Farbod Darvishian, Luis Chiriboga, Rose Marie Holman, Juliet Escalon, Caroline Muren, Crystal Escano, Ethel Yepes, Dunbar Sharpe, John P. Vasilakos, Linda Rolnitzsky, Judith D. Goldberg, John Mandeli, Sylvia Adams, Achim Jungbluth, Linda Pan, Ralph Venhaus, Patrick A. Ott, and Nina Bhardwaj
Synopsis: Sabado, Pavlick, and colleagues show that NY-ESO-1 protein in Montanide with or without topical resiquimod is safe, well-tolerated, and induces antibody and CD4 T-cell responses in most patients, but the addition of topical resiquimod is not sufficient to induce consistent NY-ESO-1-specific CD8 T-cell responses.

Table of Contents

288 Impact of NRAS Mutations for Patients with Advanced Melanoma Treated with Immune Therapies

Douglas B. Johnson, Christine M. Lovly, Marisa Flavin, Katherine S. Panageas, Gregory D. Ayers, Zhiguo Zhao, Wade T. Iams, Marta Colgan, Sarah DeNoble, Charles R. Terry, Elizabeth G. Berry, A. John Iafrate, Ryan J. Sullivan, Richard D. Carvajal, and Jeffrey A. Sosman

Synopsis: Johnson, Lovly, and colleagues performed a retrospective analysis of clinical outcomes following immunotherapy on 229 patients with melanoma with or without NRAS mutations and report that NRAS mutations in advanced melanoma correlate with increased benefit from immune-based therapies compared with other genetic subtypes.

296 Requirement for Innate Immunity and CD90⁺ NK1.1⁻ Lymphocytes to Treat Established Melanoma with Chemo-Immunotherapy

Marina Moskalenko, Michael Pan, Yichun Fu, Ellen H. de Moll, Daigo Hashimoto, Arthur Mortha, Marylene Leboeuf, Padmini Jayaraman, Sebastian Bernardo, Andrew G. Sikora, Jedd Wolchok, Nina Bhardwaj, Miriam Merad, and Yvonne Saenger
Synopsis: Moskalenko, Pan, and colleagues show in a B16 melanoma model that tumor clearance from the combined regimen of cytotoxic doses of cyclophosphamide and an antibody targeting melanoma differentiation antigen tyrosine-related protein 1 requires Fcγ receptors and innate CD90⁺NK1.1⁻ lymphocytes, not classical NK cells.

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ABOUT THE COVER

The cytokines interleukin-2 (IL2) and IL15 have pivotal roles in the control of the life and death of lymphocytes. The IL2 and IL15 heterotrimeric receptors share the common γ chain (γ C) and the IL2/IL15R β chain. The high-affinity forms of IL2R and IL15R contain a third subunit that is cytokine specific, IL2R α or IL15R α . These cytokine/receptor systems have similar and contrasting roles. Both IL2 and IL15 stimulate T-cell proliferation, induce the generation of cytotoxic T lymphocytes, and facilitate the maintenance of natural killer (NK) cells. They have distinct roles in adaptive immune responses, which are maintained by a variety of mechanisms. IL2 is predominantly a secreted cytokine that binds to preformed high-affinity heterotrimeric receptors. IL15 is a membrane-associated molecule that signals at an immunological synapse between antigen-presenting cells and CD8 T cells or NK cells. IL15R α on the surface of activated monocytes or dendritic cells presents IL15 *in trans* to cells that express IL2/IL15R β and γ C, thereby allowing signaling through these complexes. The cover image illustrates the mode of interaction of cytokines IL2 and IL15 with their receptors. Through its role in maintaining the fitness of regulatory T cells and in activation-induced cell death (AICD), IL2 is involved in the elimination of self-reactive T cells and prevention of autoimmunity. IL15 inhibits AICD and is critical for the maintenance of long-lasting, high-avidity T-cell responses to invading pathogens, a function that it achieves by supporting the survival of CD8 memory T cells. IL2 has been approved by the FDA for the treatment of malignant renal cell cancer and metastatic melanoma. Clinical trials of IL15/IL15R are ongoing. For details, see the Masters of Immunology primer by Thomas A. Waldmann that begins on page 219 of this issue.



Table of Contents

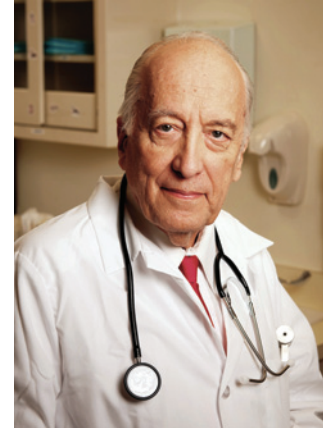
ABOUT THE MASTER

Thomas A. Waldmann, MD, is an NIH Distinguished Investigator and the chief of the Lymphoid Malignancies Branch of the National Cancer Institute (NCI) at the NIH. Dr. Waldmann is known for his seminal translational work on the IL2/IL2R system and the clinical application of IL2R-directed monoclonal antibody-mediated therapy for certain lymphoid malignancies and autoimmune diseases, including multiple sclerosis. He codiscovered IL15 and has translated this insight into the use of IL15 for treatment of metastatic malignancy.

Dr. Waldmann was born in New York, NY. He received his AB degree from the University of Chicago, his MD degree from Harvard Medical School, and served his residency in internal medicine at the Massachusetts General Hospital. Dr. Waldmann joined the NCI in 1956, where he became chief of the Metabolism Branch (now termed Lymphoid Malignancies Branch) in 1973. In studies with NIH colleagues at that time, Stanley Korsmeyer and Philip Leder, Dr. Waldmann introduced molecular genetic analysis of immunoglobulin and T-cell receptor gene rearrangements in the analysis of lymphoid neoplasms. His early research focus was on the critical immunologic role played by the IL2R on the growth, differentiation, and regulation of normal and neoplastic T cells. He defined two of the three IL2R elements including IL2R α and IL2R β using the first monoclonal antibody to a cytokine receptor termed anti-Tac (anti-CD25, daclizumab) that he developed. Dr. Waldmann demonstrated the effectiveness of daclizumab in the treatment of multiple sclerosis and in the reduction of renal transplant rejection episodes, an application for which this agent has been approved by the FDA. In a pivotal recent finding, Dr. Waldmann demonstrated that many patients with refractory and relapsed Hodgkin lymphoma could be effectively treated with daclizumab armed with the β -emitting radionuclide Yttrium-90.

Furthermore, Dr. Waldmann codiscovered IL15, a cytokine that inhibits activation-induced cell death, stimulates T-cell proliferation, promotes survival of CD8-memory T cells, and supports the development and maintenance of natural killer cells. IL15 binds to the β and γ chains that are common to both the IL15R and IL2R. Dr. Waldmann has recently completed a study of IL15 in the treatment of patients with metastatic malignancy. The shared and contrasting roles of IL2 and IL15 in the life and death of normal and neoplastic lymphocytes is the focus of Dr. Waldmann's Masters primer in this issue of *Cancer Immunology Research*.

Dr. Waldmann's scientific efforts have been recognized with numerous honors, including the Henry Stratton Medal, the Paul Ehrlich Medal, the Lila Gruber Prize, the Simon Shubitz Prize, the Ciba-Geigy Drew Award, the Abbott Prize in Immunology, the Milken Family Medical Foundation Distinguished Scientist Award, the Artois-Baillet Latour Health Prize, the Bristol-Myers Squibb Award, and the American Association of Immunologists-Dana Foundation Award in Human Immunology Research. As a tribute for his many seminal contributions to human immunology, including the landmark studies of catabolism of immunoglobulins and immunoglobulin gene rearrangement, the Foundation of Primary Immunodeficiency has established the annual Thomas Waldmann Award for Excellence in Human Immunology. Dr. Waldmann is an elected member of the U.S. National Academy of Sciences (NAS), the American Academy of Arts and Sciences, the Institute of Medicine of the U.S. NAS, the Association of American Physicians and American Society for Clinical Investigation, the UK Royal Society of Medical Sciences, and the Hungarian Academy of Sciences.



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3 (3)

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