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MASTERS OF IMMUNOLOGY

CANCER IMMUNOLOGY MINIATURES

PRIORITY BRIEF

RESEARCH ARTICLES

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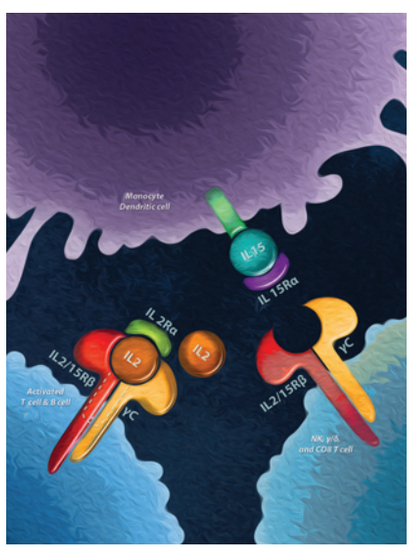
ABOUT THE COVER



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 (γc) and the IL2/IL15R β chain. The high-affinity forms of IL2R and IL15R contain a third subunit that is cytokine specific, IL2Rα or IL15Rα. 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. IL15Rα on the surface of activated monocytes or dendritic cells presents IL15 *in trans* to cells that express IL2/IL15Rβ and γc, 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.

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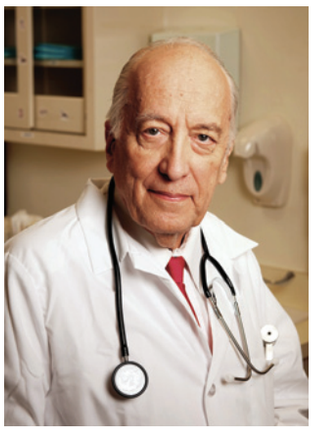
ABOUT THE MASTER



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 IL2Rα and IL2Rβ 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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