EDITORIAL

703 Cancer Immunology Research: A Two-Year Anniversary

MASTERS OF IMMUNOLOGY

704 Fc-Receptor Interactions Regulate Both Cytotoxic and Immunomodulatory Therapeutic Antibody Effector Functions

David J. DiLillo and Jeffrey V. Ravetch

CANCER IMMUNOLOGY AT THE CROSSROADS: FUNCTIONAL PROTEOMICS

714 Charting Immune Signaling Proteomes En Route to New Therapeutic Strategies

Eric B. Haura, Amer A. Beg, Uwe Rix, and Scott Antonia

PRIORITY BRIEF

721 CARD9 Promotes Sex-Biased Colon Tumors in the APCmin Mouse Model

Vonny I. Leo, Sze Huey Tan, Hanna Bergmann, Peh Yeann Cheah, Min Hoe Chew, Kiat Hon Lim, Jurgen Ruland, and Patrick T. Reilly

Synopsis: Leo and colleagues compared CARD9-competent and CARD9-deficient APCmin mice and show that CARD9 reduces viability in male mice and promotes tumorigenesis specifically in the large intestine, with a correlative disruption of plasma cytokine expression and immune infiltration of the tumors.

RESEARCH ARTICLES

727 SOCS3 Deficiency in Myeloid Cells Promotes Tumor Development: Involvement of STAT3 Activation and Myeloid-Derived Suppressor Cells

Hao Yu, Yudong Liu, Braden C. McFarland, Jessy S. Deshane, Douglas R. Hurst, Selvarangan Ponnazhagan, Etty N. Benveniste, and Hongwei Qin

Synopsis: Yu and colleagues show that the loss of SOCS3, a negative regulator of STAT3, in myeloid cells, leads to the development of MDSC and immunosuppressive activity within the tumor microenvironment via a G-CSF/STAT3 axis, and suggest targeting of SOCS3 in myeloid cells to regulate antitumor immunity.

741 Assessing the Effects of Concurrent versus Sequential Cisplatin/Radiotherapy on Immune Status in Lung Tumor–Bearing C57BL/6 Mice

Chiao-Jung Kao, Gregory T. Wurz, Yi-Chen Lin, Daniel P. Vang, Stephen M. Grifley, Michael Wolf, and Michael W. DeGregorio

Synopsis: Kao and colleagues performed a comprehensive analysis in a lung cancer mouse model and show that sequential chemoradiotherapy had an equivalent amount of antitumor activity compared with concurrent therapy, but the two regimens elicited differences in immune response biomarkers, including Tregs, microRNA-29c, CD28, and serum IFNγ.

751 PolySia-Specific Retargeting of Oncolytic Viruses Triggers Tumor-Specific Immune Responses and Facilitates Therapy of Disseminated Lung Cancer


Synopsis: Kloos and colleagues show that polysialic acid–specific retargeting of systemically administered oncolytic viruses leads to effective tumor infection, CD8 T-cell responses for mutated tumor neoepitope Gsta2-Y9H, and improved survival in an immunocompetent mouse model of disseminated lung cancer.

764 Committing Cytomegalovirus-Specific CD8 T Cells to Eliminate Tumor Cells by Bifunctional Major Histocompatibility Class I Antibody Fusion Molecules

Martina Schmittnaegel, Victor Levitsky, Elke Hoffmann, Guy Georges, Olaf Mundigl, Christian Klein, and Hendrik Knuettgen

Synopsis: Schmittnaegel and colleagues describe the generation of a novel tumor-peptide-MHCα–antibody fusion protein that redirects a highly functional subset of CMV-specific T cells to eliminate tumor cells by engaging a naturally occurring T-cell population in humans that controls cytomegalovirus infection.

777 Induction of HER2 Immunity in Outbred Domestic Cats by DNA Electrovaccination

Heather M. Gibson, Jesse J. Veenstra, Richard Jones, Ullka Vaishampayan, Michele Sauerbrey, Gerald Bepler, Lawrence Lum, Joyce Reyes, Amy Weise, and Wei-Zen Wei

Synopsis: Gibson and colleagues show that outbred domestic cats develop mammary tumors similar to those in humans. Electrovaccination of heterologous or point-mutated feline HER2 DNA overcomes T-cell immune tolerance in 40% of healthy cats and induces antibodies with distinct specificity.
ABOUT THE COVER

The cover image is an artistic rendition of the mechanism of antitumor vaccinal effect mediated by cytotoxic antibodies. Antitumor antibodies opsonize tumor cells and target them for killing by macrophages via FcγR-mediated antibody-dependent cellular cytotoxicity or phagocytosis (ADCC or ADCP), a process that generates antibody:tumor-associated antigen (TAA) immune complexes (IC). ICs engage activating FcγRs expressed by dendritic cells (DC), stimulating DC maturation and presentation of TAAs to T cells, thereby leading to the generation of antitumor effector T cells and long-term memory T cells. For details, see the Masters of Immunology article by DiLillo and Ravetch that begins on page 704 of this issue.

ABOUT THE MASTER

Jeffrey V. Ravetch, MD, PhD, is the Theresa and Eugene M. Lang Professor at The Rockefeller University and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology. Dr. Ravetch and his laboratory have made major discoveries contributing to our understanding of the biology of the Fc receptors (FcR) and their critical roles in inflammation and in shaping the immune response. Even though the existence of the FcRs was suggested decades earlier, the structures and functions of these receptors were not defined until Dr. Ravetch and his colleagues cloned and characterized two murine FcRs for the immunoglobulin G (IgG) isotype (FcγR) in 1986. In that seminal article they described the near homologous extracellular domains of these FcRs with distinct cytoplasmic tails, including the discovery of the immune-tyrosine inhibitory motif, thus providing the molecular basis for the functional heterogeneity of FcRs. Based on the cellular distribution and preferential expression patterns, they hypothesized that FcRs bind the same ligands but transmit different signals. Since then, using elegant biochemistry and mouse strains they generated with various components of the FcRs genetically modified, the Ravetch laboratory has defined mechanisms by which antibodies mediate their diverse biologic activities in vivo, establishing the preeminence of FcR pathways in host defense, inflammation, and tolerance. They have identified and described novel inhibitory signaling pathways to account for the paradoxical roles of antibodies as promoting and suppressing inflammation. The focus of the Ravetch laboratory is to continue to define the function and regulation of the IgG Fc domain and the diverse FcRs to which they bind. He has extended his studies into clinical applications for the treatment of neoplastic, inflammatory, and infectious diseases through collaborations with industry partners.

Dr. Ravetch has received numerous awards, including the Burroughs-Wellcome Scholar Award in molecular parasitology, the Pew Scholar Award, the Lee C. Howley Sr. Prize, the AAI-Huang Foundation Meritorious Career Award, the William B. Coley Award for distinguished research in basic and tumor immunology, the Sanofi-Institut Pasteur Award, the Canada Gairdner International Prize, and the Wolf Prize in Medicine. (Continued on the following page.)
ABOUT THE MASTER

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He received an honorary doctorate from Freidrich-Alexander University, Nuremberg/Erlangen. Dr. Ravetch was elected as a member of the U.S. National Academy of Sciences and the Institute of Medicine, as a Fellow of the American Academy of Arts and Sciences, and of the American Association for the Advancement of Science. He serves as a consultant or a member on the scientific advisory boards of numerous organizations, including charitable foundations that support scientific research and training, such as the Cancer Research Institute, the Irvington Institute for Medical Research, and the Damon Runyon Foundation, and various biotechnology and pharmaceutical companies. He has published more than 200 research articles, book chapters, and reviews and serves on the editorial boards of leading peer-reviewed journals.

Dr. Ravetch is a native of New York City. He received his BS degree, cum laude, in molecular biophysics and biochemistry from Yale University, where he worked with Donald M. Crothers on the thermodynamic and kinetic properties of synthetic oligoribonucleotides. He earned his PhD in genetics from The Rockefeller University under the tutelage of Norton Zinder and Peter Model, investigating the genetics of viral replication and gene expression for the single-stranded DNA bacteriophage f1, and his MD from Cornell University Medical School. Dr. Ravetch pursued postdoctoral training with Philip Leder at the NIH, identifying and characterizing the genes encoding human antibodies and the DNA elements involved in switch recombination. He was a member of the faculty of Memorial Sloan Kettering Cancer Center and Cornell Medical College before joining The Rockefeller University. Dr. Ravetch is an avid fan of poetry, dating back to his undergraduate days at Yale, where he earned a BA in English literature simultaneously with his BS degree. He is a passionate collector of 20th century American poetry, focusing on the works of Wallace Stevens, Robert Penn Warren, and Mark Strand. He served on the board of the American Academy of Poets and is currently a board member of the National Poetry Series. When not in the lab or on the road, Dr. Ravetch can be found at the opera or tending to his gardens in the Hudson Valley.