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Cancer Immunology Research

Illuminating the Interplay of Cancer and the Immune System

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Roni Nowarski, Nicola Gagliani, Samuel Huber, and Richard A. Flavell

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Concurrent Radiotherapy and Ipilimumab Immunotherapy for Patients with Melanoma

Christopher A. Barker, Michael A. Postow, Shaheer A. Khan, Kathryn Beal, Preeti K. Parhar, Yoshiya Yamada, Nancy Y. Lee, and Jedd D. Wolchok

Synopsis: Findings from preclinical studies and case studies of patients indicate potential synergy between radiation therapy and ipilimumab immunotherapy. Barker and colleagues performed a retrospective study on the outcome of melanoma patients treated with this therapeutic combination and found no significant increase in adverse events or compromise in efficacy, suggesting that prospective evaluation of this regimen is warranted.

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Transnuclear TRP1-Specific CD8 T Cells with High or Low Affinity TCRs Show Equivalent Antitumor Activity

Stephanie K. Dougan, Michael Dougan, Jun Kim, Jacob A. Turner, Souichi Ogata, Hyun-Il Cho, Rudolf Jaenisch, Esteban Celis, and Hidde L. Ploegh

Synopsis: Using somatic cell nuclear transfer, which generates mice bearing T cells with the rearranged TCR genes expressed from endogenous loci under physiologic control, Dougan and colleagues have generated mouse models to investigate the role of TCR affinity in the immune response to melanoma.

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Immune Heterogeneity of Glioblastoma Subtypes: Extrapolation from the Cancer Genome Atlas

Tiffany Doucette, Ganesh Rao, Arvind Rao, Li Shen, Kenneth Aldape, Jun Wei, Kristine Dziurzynski, Mark Gilbert, and Amy B. Heimberger

Synopsis: Doucette and colleagues analyzed The Cancer Genome Atlas glioblastoma database and found differential expression of distinct glioma antigens and immunosuppressive and effector genes among the glioblastoma subtypes, which may influence responses to immune therapeutic strategies in patients.

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Antigen-Specific Bacterial Vaccine Combined with Anti-PD-L1 Rescues Dysfunctional Endogenous T Cells to Reject Long-Established Cancer

David C. Binder, Boris Engels, Ainhua Arina, Ping Yu, James M. Schlauch, Yang-Xin Fu, Theodore Karrison, Byron Burnette, Christian Idel, Ming Zhao, Robert M. Hoffman, David H. Munn, Donald A. Rowley, and Hans Schreiber

Synopsis: Mobilizing the latent pool of tumor-specific T cells in patients is a goal for immunotherapy. Using *Salmonella typhimurium* to deliver tumor-specific antigens into the tumor, Binder and colleagues found that when combined with α PD-L1 blocking antibodies, this regimen rescued endogenous dysfunctional tumor-specific CD8 T cells and eradicated the established tumors.

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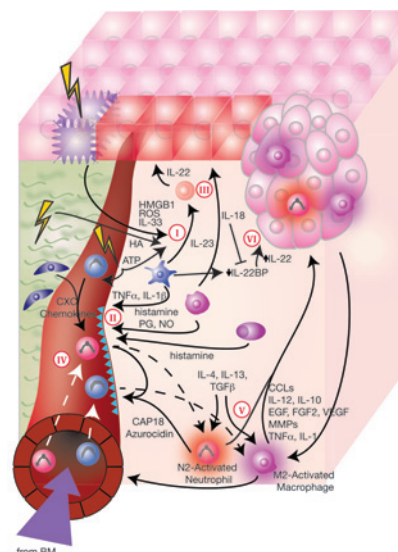
Radretumab Radioimmunotherapy in Patients with Brain Metastasis: A ^{124}I -L19SIP Dosimetric PET Study

Gian Luca Poli, Claudia Bianchi, Giorgio Virotta, Anna Bettini, Renzo Moretti, Eveline Trachsel, Giuliano Elia, Leonardo Giovannoni, Dario Neri, and Andrea Bruno

Synopsis: Poli and colleagues used immuno-PET imaging after dosimetric administration of ^{124}I -L19SIP to predict the doses to be delivered by subsequent radretumab (^{131}I -L19SIP) radioimmunotherapy in patients with brain metastases from solid tumors. They describe the method they developed for accurate determination of the expected ^{131}I -L19SIP radioimmunotherapy doses to the bone red marrow, lesions, and healthy organs and identify an unexpected variability of antibody uptake in different lesions within the same patient.

ABOUT THE COVER

Innate immune response to tissue damage: (I) DAMPs released from necrotic cells and damaged tissues activate PRRs in resident, patrolling, and recruited innate immune cells, leading to the secretion of inflammatory mediators and vasodilators. (II) Activation of endothelial cells and production of CXC chemokines by innate and stromal cells recruit neutrophils. (III) Regulated activation of inflammasomes promotes regeneration of the epithelium. (IV) Migration of recruited neutrophils and inflammatory monocytes to the affected tissue. (V) Type 2 polarization and production of protumorigenic mediators. (VI) Persistent and unregulated inflammasome signaling promotes tumorigenesis. For details, see the “Masters of Immunology” article by Nowarski and colleagues on page 77 of this issue.



ABOUT THE MASTER

Richard A. Flavell is Sterling Professor of Immunobiology at Yale School of Medicine, New Haven, Connecticut, and an Investigator of the Howard Hughes Medical Institute, Home Institution. He received his B.Sc. (Honors) and Ph.D. in biochemistry from the University of Hull, England, and performed postdoctoral work with Piet Borst in Amsterdam and Charles Weissmann in Zurich. Before joining Yale, Flavell was Assistant Professor at the University of Amsterdam; Head of the Laboratory of Gene Structure and Expression at the National Institute for Medical Research, Mill Hill, London; and President and Chief Scientific Officer of Biogen Research Corporation, Cambridge, Massachusetts. Dr. Flavell is a fellow of the British Royal Society and a member of both the US National Academy of Sciences and the Institute of Medicine.

Richard Flavell is co-discoverer of introns in cellular genes; he showed DNA methylation correlates inversely with, and prevents, gene expression. He was the first to develop reverse genetics, with Weissmann, and pioneered the approach *in vivo* to study function. The Flavell laboratory uses mouse genetics to study activation in immunity and autoimmunity, apoptosis, and T-cell tolerance. Flavell was instrumental in discovering the molecular basis of T-cell differentiation from precursor cells into differentiated subsets, which led to the discovery of GATA3 as a critical regulator of the Th2 response and the first example of such a molecule in Th cell differentiation. He demonstrated the first case of regulation of gene expression in trans, via “chromosome kissing.” The Flavell laboratory has elucidated the role of TGF- β in the regulation of immune response, which has relevance both to the control of autoimmune diseases and to the evasion of immune response by tumors.

The Flavell laboratory has discovered the role of several Toll-like receptors and intracellular Nod-like receptor families in innate immune response, which led to the elucidation of function of Nod2 in inflammatory bowel diseases (IBD) and Nlrp proteins in the production of IL-1. Most recently, he has established a connection between inflammasomes, microbial homeostasis, and chronic diseases. He showed that inflammasome dysfunction causes dysbiosis of the microbiota, which, in conjunction with a susceptible diet, leads to IBD and various metabolic syndromes.



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