Current Topics in Microbiology and Immunology

Volume 319

Tim Manser
Editor

Specialization and Complementation of Humoral Immune Responses to Infection

Springer

Tim Manser, PhD
Department of Microbiology and Immunology
Jefferson Medical College
Philadelphia, PA
USA
e-mail: manser@mail.jci.tju.edu

Background Legend: Relapsing fever Borrelia spirochetes were fixed in methanol and exposed to a fluorescent labeled a single chain Fv derived from a complement-independent bactericidal antibody to observe binding via fluorescence microscopy. This image is at 100X magnification.

Inset Legend: A negative-stained transmission electron micrograph image of a live relapsing fever Borrelia that was exposed to a single chain Fv derived from a complement-independent bactericidal IgM is shown. Membrane blebbing can be observed as well as a disruption of the normal spiral morphology of the spirochete. Exposure of periplasmic flagella is very apparent in the image and signifies that the outer membrane of the spirochete has been disrupted. The magnification of the image is 23000X.

Both images are courtesy of Tim LaRocca and Jorge Benach (see this volume)

ISBN 978-3-540-73899-2 e-ISBN 978-3-540-73900-5

Current Topics in Microbiology and Immunology ISSN 007-0217x

Library of Congress Catalog Number: 72-152360

Cover Design: WMXDesign GmbH, Heidelberg, Germany

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

springer.com

Preface

The importance of specific antibodies for the clearance of and long-term resistance to many infectious pathogens has long been appreciated. Moreover, the role in these processes of the different antibody heavy chain isotypes, each tailored to induce diverse effector pathways such as those mediated by complement and Fc receptors and to promote antibody localization in distinct regions of the body, is well established. Insights into the molecular mechanism of isotype class switching showed that during an immune response B cells could change the heavy chain of the antibody they produced, without influencing the structure and specificity of the antigen-binding variable regions of this antibody (Honjo 1983). More recently, the germinal center pathway of B cell development was elucidated, in which antibody variable regions undergo extensive structural alteration via hypermutation followed by stringent phenotypic selection (Berek 1992; Kelsoe 1995). Emerging from this pathway are memory B cells and long-lived antibody-forming cells that express antigen receptors and secrete antibodies, respectively, with increased affinity and specificity for the foreign antigen.

Taken together, these findings led to a view of the acquisition of antibody-mediated resistance to infectious pathogens in mammals that involved extensive somatic maturation of antibody heavy and variable region structure and function during the immune response. This was in keeping with the concept that the B cell compartment comprises a major arm of the adaptive immune system. Such a view was reinforced by molecular analyses of antiviral antibody responses (Zinkernagel 1996). However, other past studies of antibody responses, in particular those using multivalent polysaccharide-based antigens, indicated that this notion of immunity might not apply to all pathogens. These latter examinations revealed that, unlike the antibody responses to most viruses or model protein antigens, the response to antigens derived from or thought to mimic bacterial capsule, cell wall, and outer membrane components did not require that B cells receive costimulatory signals from T cells (Mond et al. 1995). Further analysis of antibody responses to these T cell-independent (TI) antigens suggested that many did not display the same maturational characteristics as those to antigens for which efficient responses necessitated the participation of T cells (T cell-dependent, TD, antigens). In addition, investigators using hapten-protein and purified protein TD model antigens, such as myself, harbored the secret that such antigens had to be mixed with inflammation-inducing adjuvants to elicit strong antibody responses.

Superimposed on these analyses of TD and TI antibody responses were studies of the role of components of the evolutionarily hard-wired or innate immune system in conferring resistance to infectious pathogens, and of the ontogeny and function of various primary B cell subsets distinguished by cell surface phenotype and microenvironmental locale (Herzenberg and Herzenberg 1989). In the last 5 years, data from of all of these areas of research have coalesced, resulting in the emergence of a new and more complete understanding of how antibody-mediated resistance to pathogens is elaborated. The recent explosion of knowledge of Toll-like receptor (TLR) specificity and function (Takeda et al. 2003) has further embellished this understanding. It is now clear that there is not only extensive overlap and cross-complementarity in the action of innate and adaptive systems, but also specialization of function of the various B cell subsets and the types of antibodies they produce. This synergistic interaction of multiple components of these systems is perhaps best exemplified in antibody responses to bacteria. In extending invitations to potential contributors to this volume, I attempted to gather manuscripts that would highlight this new perspective on antibody responses to infection, as well as to convey its practical implications, such as for contemporary vaccine design.

The first contribution by Hinton, Jegerlehner, and Bachmann illustrates how the distinction between the function of TI and TD B cell responses in mediating resistance to viral infection has been blurred. These authors argue that patterns unique to antigens displayed on the surface of viruses and other pathogens lead to efficient TI B cell stimulation. Combined with an appreciation of the contribution of TLR recognition of viral components and the ability of TLR signaling to qualitatively and quantitatively influence the outcome of the antibody response, these findings have important implications for the design of viral vaccines and other antibody-mediated therapeutic strategies. Mond and Kokai-Kun extend this theme in their discussion of the nature of immune responses to TI antigens and the application of this knowledge to the development of vaccines for encapsulated bacteria. The idea here is that most pure TI antigens make poor pediatric vaccines—only by conjugating them to TD antigens, allowing induction of adaptive components of the immune system, is partial efficacy obtained. These authors also provide a summary of the current state of the art of vaccines for several common human bacterial pathogens, which aptly points out the inherent difficulties in translating basic discoveries in this field to practical application. Baumgarth and colleagues then discuss the role of various B cell subsets in the immune responses to viruses and bacteria, with an emphasis on B1 B cells. Their studies and those of others indicate that B1 and marginal zone B cells operate at the interface of innate and adaptive immunity. These subpopulations also cooperatively interact in the immune response to bacteria, and help in priming the more adaptive follicular B cell compartment for germinal center reactions to bacterial protein antigens and viruses.

Chapters in the second half of the volume focus on application of the concepts introduced in the first half to an understanding of how antibody responses are elicited and mediate resistance to two bacterial pathogens with very different lifestyles: the Borrelia spirochetes, causative agents of Lyme disease and relapsing

fever in humans, and Streptococcus mutans, the species centrally implicated in dental caries. LaRocca and Benach provide a comprehensive depiction of the humoral factors responsible for resistance to various Borrelia subspecies, as well as associated pathologies, and also discuss immune evasion strategies of these bacteria. They also describe an intriguing class of anti-Borrelia antibodies that are bactericidal in the absence of complement. Alugupalli discusses the recently discovered ability of the B1b B cell subset to confer long-lasting, IgM-mediated resistance to Borrelia hermsii, the blood-colonizing bacterium that is a causative agent of relapsing fever in rodents. The data he has obtained indicate that B1b cells may establish a T cell-independent, TLR-dependent state of immunity to B. hermsii and other bacteria that bears many of the hallmarks of follicular B cell memory. Finally, Smith and Mattos-Graner describe the role of antibodies, the IgA isotype in particular, in controlling colonization of the tooth surface by S. mutans-containing biofilms. Their contribution nicely illustrates the often extensive and dynamic interaction of host and pathogen, and how subtle changes in the host's response to infection can lead to resistance or disease.

Philadelphia Tim Manser
May 2007

References

Berek C (1992) The development of B cells and the B-cell repertoire in the microenvironment of the germinal center. Immunol Rev 126:5–19
Herzenberg LA, Herzenberg LA (1989) Toward a layered immune system. Cell 59:953–954
Honjo T (1983) Immunoglobulin genes. Annu Rev Immunol 1:499–528
Kelsoe G (1995) In situ studies of the germinal center reaction. Adv Immunol 60:267–288
Mond JJ, Vos Q, Lees A, Snapper CM (1995) T cell independent antigens. Curr Opin Immunol 7:349–354
Takeda K, Kaisho T, Akira S (2003) Toll-like receptors. Annu Rev Immunol 21:335–376
Zinkernagel RM (1996) Immunology taught by viruses. Science 271:173–178

Contents

Pattern Recognition by B Cells: The Role of Antigen Repetitiveness Versus Toll-Like Receptors **1**
H. J. Hinton, A. Jegerlehner, and M. F. Bachmann

The Multifunctional Role of Antibodies in the Protective Response to Bacterial T Cell-Independent Antigens **17**
J. J. Mond and J. F. Kokai-Kun

B Cell Lineage Contributions to Antiviral Host Responses **41**
N. Baumgarth, Y. S. Choi, K. Rothaeusler, Y. Yang, and L. A. Herzenberg

The Important and Diverse Roles of Antibodies in the Host Response to *Borrelia* Infections **63**
T. J. LaRocca and J. L. Benach

A Distinct Role for B1b Lymphocytes in T Cell-Independent Immunity **105**
K. R. Alugupalli

Secretory Immunity Following Mutans Streptococcal Infection or Immunization **131**
D. J. Smith and R. O. Mattos-Graner

Index **157**

Contributors

K. R. Alugupalli
Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, 233 South 10th Street, BLSB 726, Philadelphia, PA 19107, USA, kishore.alugupalli@mail.jci.tju.edu

M. F. Bachmann
Cytos Biotechnology AG, Wagistrasse 25, 8952 Zürich-Schlieren, Switzerland, martin.bachmann@cytos.com

N. Baumgarth
Center for Comparative Medicine, University of California, Davis, County Rd 98 & Hutchison Drive, Davis, CA 95616, USA, nbaumgarth@ucdavis.edu

J. L. Benach
Center for Infectious Diseases, 5120 Centers for Molecular Medicine, Stony Brook, NY 11794-5120, USA, jbenach@notes.cc.sunysb.edu

Y. S. Choi
Center for Comparative Medicine, University of California, Davis, County Rd 98 & Hutchison Drive, Davis, CA 95616, USA

L. A. Herzenberg
Department of Genetics, Stanford Medical School, Beckmann Center, Pasteur Drive, Stanford, CA 94205, USA

H. J. Hinton
Cytos Biotechnology AG, Wagistrasse 25, 8952 Zürich-Schlieren, Switzerland

A. Jegerlehner
Cytos Biotechnology AG, Wagistrasse 25, 8952 Zürich-Schlieren, Switzerland

J. F. Kokai-Kun
Biosynexus Incorporated, 9298 Gaither Rd, Gaithersburg, MD 20877, USA, johnkun@biosynexus.com

T. J. LaRocca
Center for Infectious Diseases, 5120 Centers for Molecular Medicine, Stony Brook, NY 11794-5120, USA

R. O. Mattos-Graner
Department of Oral Diagnosis, Piracicaba Dental School, State University of Campinas, Piracicaba, SP, Brazil

J. J. Mond
Biosynexus Incorporated, 9298 Gaither Rd, Gaithersburg, MD 20877, USA

K. Rothaeusler
Center for Comparative Medicine, University of California, Davis, County Rd 98 & Hutchison Drive, Davis, CA 95616, USA

D. J. Smith
Department of Immunology, The Forsyth Institute, 140 The Fenway, Boston, MA 02115, USA, dsmith@forsyth.org

Y. Yang
Department of Genetics, Stanford Medical School, Beckmann Center, Pasteur Drive, Stanford, CA 94205, USA