SUPERANTIGENS

SUPERANTIGENS

Molecular Basis for Their Role in Human Diseases

Edited by
Malak Kotb
and John D. Fraser

ASM PRESS
Washington, D.C.

Cover illustration: A hypothesized functional complex of SEB, MHC-II, and TCR (see Chapter 6 and Color Plate 6) (courtesy of Vickery Arcus).

Address editorial correspondence to ASM Press, 1752 N St., N.W., Washington, DC 20036-2904, USA

Send orders to ASM Press, P.O. Box 605, Herndon, VA 20172, USA
Phone: 800-546-2416; 703-661-1593
Fax: 703-661-1501
E-mail: books@asmusa.org
Online : http://estore.asm.org

Library of Congress Cataloging-in-Publication Data

Superantigens: molecular basis for their role in human diseases / edited by Malak Kotb and John D. Fraser.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-55581-424-3 (hardcover : alk. paper)
ISBN-10: 1-55581-424-7 (hardcover : alk. paper)
1. Superantigens. I. Kotb, Malak. II. Fraser, John D. III. American Society for Microbiology.
[DNLM: 1. Superantigens—physiology. 2. Bacteria—immunology. 3. Virulence Factors. QW 573 S9594 2007]

QR186.6.S94S875 2007
616.07′92—dc22

2007013806

10 9 8 7 6 5 4 3 2 1

This book is dedicated to the memory of Edwin H. Beachey,
a great scientist, mentor, and friend

CONTENTS

CONTRIBUTORS

K. Ravi Acharya • Department of Biology and Biochemistry, University of Bath, Building 4 South, Room 0.29, Claverton Down, Bath BA2 7AY, United Kingdom

Gila Arad • Department of Molecular Virology, The Hebrew University-Hadassah Medical School, 91120 Jerusalem, Israel

Vickery L. Arcus • AgResearch Protein Engineering Laboratory, Department of Biological Sciences, University of Waikato, Private Bag 3105, Hamilton, New Zealand

Edward N. Baker • Centre for Molecular Biodiscovery, School of Biological Sciences, University of Auckland, Private Bag 92-019, Auckland, New Zealand

Matthew D. Baker • Department of Biology and Biochemistry, University of Bath, Building 4 South, Room 0.29, Claverton Down, Bath BA2 7AY, United Kingdom

Gregory A. Bohach • Department of Microbiology, Molecular Biology, and Biochemistry, University of Idaho, Moscow, ID 83846

Sang-Hyun Cho • Department of Dermatology, The Catholic University of Korea, Seoul, Korea 403-720

Barry C. Cole • Division of Rheumatology, University of Utah School of Medicine, Salt Lake City, UT 84132

Alexander Emmer • Neurology Hospital, Martin Luther University, D-06097 Halle-Wittenberg, Germany

John D. Fraser • School of Medical Sciences, University of Auckland, Private Bag 92019, 85 Park Rd., Grafton, Auckland, New Zealand

Kristina Gerlach • Neurology Hospital, Martin Luther University, D-06097 Halle-Wittenberg, Germany

Goutam Gupta • Los Alamos National Laboratory, Bioscience Division, Los Alamos, NM 87545

Dalia Hillman • Department of Molecular Virology, The Hebrew University-Hadassah Medical School, 91120 Jerusalem, Israel

Brigitte T. Huber • Department of Pathology, Tufts University School of Medicine, 150 Harrison Ave., Boston, MA 02111

Raymond Kaempfer • Department of Molecular Virology, The Hebrew University-Hadassah Medical School, 91120 Jerusalem, Israel

Malte E. Kornhuber • Neurology Hospital, Martin Luther University, D-06097 Halle-Wittenberg, Germany

Malak Kotb • University of Tennessee Health Science Center, 930 Madison, Suite 468, Memphis, TN 38163

Teresa Krakauer • Department of Immunology, Integrated Toxicology Division, United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21702-5011

Meghan Kunkel • Los Alamos National Laboratory, Bioscience Division, Los Alamos, NM 87545

Donald Y. M. Leung • Department of Pediatrics, National Jewish Medical and Research Center, Denver, CO 80206, and University of Colorado Health Sciences Center, Denver, CO 80262

Revital Levy • Department of Molecular Virology, The Hebrew University-Hadassah Medical School, 91120 Jerusalem, Israel

Donald E. Low • Department of Microbiology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario M5G 1X5, Canada

Eva Medina • Department of Microbial Pathogenesis and Vaccine Research, Infection Immunology Research Group, GBF-German Research Center for Biotechnology, Mascheroder Weg 1, D-38124 Braunschweig, Germany

Tohru Miyoshi-Akiyama • Department of Infectious Disease, International Medical Center of Japan, Tokyo 162-8655, Japan

Hong-Hua Mu • Division of Rheumatology, University of Utah School of Medicine, Salt Lake City, UT 84132

Iris Nasie • Department of Molecular Virology, The Hebrew University-Hadassah Medical School, 91120 Jerusalem, Israel

Anna Norrby-Teglund • Karolinska Institutet, Center for Infectious Medicine, Karolinska University Hospital, Huddinge, S-141 86 Stockholm, Sweden

Thomas Proft • School of Medical Sciences, University of Auckland, Private Bag 92019, 85 Park Rd., Grafton, Auckland, New Zealand

Patrick M. Schlievert • Department of Microbiology, University of Minnesota Medical School, 420 Delaware Street S.E., Minneapolis, MN 55455

M. S. Staege • Children's Cancer Research Center, Division of Pediatric Hematology and Oncology, Martin Luther University, D-06097 Halle-Wittenberg, Germany

Albert K. Tai • Department of Pathology, Tufts University School of Medicine, Boston, MA 02111

Andrej Tarkowski • Department of Rheumatology and Inflammation Research, Göteborg University, Guldhedsgatan 10, S-413 46 Göteborg, Sweden

Takehiko Uchiyama • Department of Microbiology and Immunology, Department of Infectious Diseases, Institute of Laboratory Animals, School of Medicine, Tokyo Women's Medical University, Tokyo 162-8666, Japan

Hidehiro Ueshiba • Institute of Laboratory Animals, Tokyo Women's Medical University, Tokyo 162-8666, Japan

Björn Walse • SARomics AB, Scheelevägen 22, SE-220 07 Lund, Sweden

PREFACE

Microbial superantigens are fascinating proteins that have structurally evolved to interact in a unique manner with host immune defense systems. These molecules are unusual in the sense that they can simultaneously activate cells involved in innate immunity as well as T cells, which normally mediate acquired immune responses. As a result of this unusual mode of interaction, superantigens have the capacity to stimulate large numbers of immune cells to release inflammatory mediators that, if uncontrolled, can inflict serious damage upon the host and may even cause death. Through our studies of the various superantigens, we have learned so much about immune system activation and regulation and about the various mechanisms by which different cells of the immune system interact and exchange biochemical signals that program their response and function.

Years prior to their designation as superantigens and the discovery of the mechanism by which they function, several laboratories had been studying these proteins and noticing the unconventional way by which they elicit immune activation. The massive proliferative response they elicit in resting leukocytes resembled that of polyclonal mitogens, yet the requirement for cells expressing HLA class II molecules to induce leukocyte activation resembled antigenic responses. Unlike conventional antigens, however, these molecules required no processing by antigen-presenting cells and their presentation to T cells was MHC unrestricted. These seemingly perplexing properties were resolved when it became evident that the superantigens interact in a unique manner with HLA class II as well as with specific elements within the variable region of the β chain of the αβ T cell receptor (TCR). Furthermore, it was found that superantigens use these receptors as a means to bring different types of cells closer, forcing them to interact and exchange activation signals that trigger biochemical cascades, resulting in the elaboration of potent inflammatory cytokine responses and massive T cell proliferation.

Shortly after their discovery, it was believed that all superantigens were alike, that they interact in the same way with immune cells, and that they cause similar diseases, namely toxic shock, serious skin infections, and food poisoning. A common remark was "if you've studied one superantigen, you've studied them all." We now know that nothing could have been further from the reality of these molecules. The fact that bacteria like *Streptococcus pyogenes* have over twelve different superantigens suggested that these microbial proteins are functionally nonredundant.

Thousands of articles have been published on superantigens, with a marked increase in the past two years, underscoring the fact that the field has been advancing considerably. This, we believe, is a result of the advent of sophisticated technologies and bioinformatics tools that unraveled new structure-function information and considerable differences in the way that distinct superantigens interact with HLA class II and/or TCR molecules. These new discoveries provided an impetus for more in-depth studies of molecular features underlying differences in the biological function of superantigens, their tissue specificity and capacity to cause or exacerbate different diseases.

Although several outstanding books on superantigens have been published, we wanted this book to highlight several new and exciting findings. We assembled an outstanding team of scientists with highly diverse expertise but a common interest in superantigen structure, function, and biology. These authors brilliantly captured some of the latest advances in the field, presenting information on newly discovered superantigens in bacteria and viruses, demonstrating how some superantigens interact with receptors other than, or in addition to, HLA class II and TCR molecules, and proposing novel mechanisms for the association of certain superantigens with various types of acute and chronic diseases, including autoimmune diseases. Exciting developments in therapeutic modalities for superantigen-mediated diseases are also highlighted in this book. This latter aspect has been given some priority in recent years, particularly since certain superantigens, in the aerosolized form, have potential for use as biological weapons and in bioterrorism.

More importantly, we wanted the readers of this book to develop a better appreciation for how newly discovered structural variations among superantigens affect the mode by which they interact with immune cells. We hope that the readers will have a better understanding of how these structure/function differences may explain why different superantigens contribute to the initiation and/or exacerbation of distinct diseases, why certain ones are effective in some tissues but not others, and how the host's genetic makeup can grossly alter the course of superantigen-mediated diseases. We also hope that the readers of this book will appreciate how this new information has informed the design and development of novel intervention strategies or suggested the use of existing modalities to ameliorate or modulate superantigen responses in severe acute infections or certain chronic illnesses.

On the flip side, however, the powerful immune-stimulating potential of certain superantigens may be exploited to modulate and direct the type of inflammatory responses in a way that increases the host's efficiency in overcoming certain chronic diseases and infections. These new insights may provide information on disease mechanism and thereby focus efforts to develop effective therapeutics and intervention measures for superantigen-mediated illnesses.

Malak Kotb
John D. Fraser

INDEX