Multichain Immune Recognition Receptor Signaling
From Spatiotemporal Organization to Human Disease
Recent Volumes in this Series

Volume 632
CURRENT TOPICS IN COMPLEMENT II
Edited by John. D. Lambris

Volume 633
CROSSROADS BETWEEN INNATE AND ADAPTIVE IMMUNITY II
Edited by Stephen P. Schoenberger, Peter D. Katsikis, and Bali Pulendran

Volume 634
HOT TOPICS IN INFECTION AND IMMUNITY IN CHILDREN V
Edited by Adam Finn, Nigel Curtis, and Andrew J. Pollard

Volume 635
GI MICROBIOTA AND REGULATION OF THE IMMUNE SYSTEM
Edited by Gary B. Huffnagle and Mairi Noverr

Volume 636
MOLECULAR MECHANISMS IN SPERMATOGENESIS
Edited by C. Yan Cheng

Volume 637
MOLECULAR MECHANISMS IN XERODERMA PIGMENTOSUM
Edited by Shamin Ahmad and Fumio Hanaoka

Volume 638
SOMITOGENESIS
Edited by Miguel Maroto and Neil Whittock

Volume 639
BREAST FEEDING: EARLY INFLUENCES ON LATER HEALTH
Edited by Gail Goldberg

Volume 640
MULTICHAIN IMMUNE RECOGNITION RECEPTOR SIGNALING
Edited by Alexander B. Sigalov
Multichain Immune Recognition Receptor Signaling
From Spatiotemporal Organization to Human Disease

Edited by
Alexander B. Sigalov, PhD
Department of Pathology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Springer Science+Business Media, LLC
Landes Bioscience
DEDICATION

This book is dedicated in loving memory to my parents, Galina Ya. Sigalova and Boris L. Sigalov, who are the source of all great things in my life. Without their love, wisdom, understanding, faith, support, and guidance, I would not be the person I am today.
FOREWORD

Immunological recognition is a central feature of the adaptive immunity of vertebrates. With the exception of agnathans, which developed an entirely distinct set of immunologically-specific molecules, all vertebrates use a recognition system based on what Achsah Keegan and I suggested in 1992 be termed multichain immune recognition receptors (MIRRs). MIRRs consist of ligand-binding molecules that are immunoglobulin supergene family members associated with signal transducers and enhancers in such a way as both insure precise ligand recognition, discrimination and amplification of the signal.

Two of the prototypic sets of MIRRs, the T-cell and B-cell receptors, are among the most remarkable recognition molecules known. These are extraordinarily diverse molecules in which the range of ligands that can be potentially recognized probably exceeds the actual numbers of lymphocytes in the body. The discovery of the genetic basis of assembling these receptors and understanding how they bind to their cognate antigens are among the most stunning of scientific achievements. Yet these immensely specific binding chains (the heavy/light chain pair for immunoglobulin and the α/β chain pair for most T cells), when expressed as membrane molecules, have no obvious mechanism of signaling. For example, the μH chain cytosolic domain consists of three amino acids (lysine-valine-lysine) and the L chain is not even embedded in the membrane. Furthermore, there is no known direct mechanism to propagate information from the binding domain of the B-cell or T-cell receptors to the membrane-proximal domains of the same chains.

The solution is based on the assemblage of the multichain receptor complex, in which pairing of key chains can occur in the membrane, often based on the presence of oppositely charged residues at critical locations in the transmembrane portion of partner chains. The signaling process then depends on aggregation and/or structural rearrangement induced by binding of multivalent ligands and on the properties of the partner signaling chains, such as Igα and Igβ for the B cell receptor; the CD3 γ, δ and ε and the ζ chains for the T-cell receptor and FceRI β and γ for the high affinity IgE receptor. These partners contain one or more immunoreceptor tyrosine-based activation motifs (ITAMs). The phosphorylation of tyrosines within the ITAM
motif (YxxL/Ix6-8YxxL/I) is a key early event in signal transduction as a result of engagement and aggregation of the ligand-binding domain.

The multichain system links extraordinarily powerful ligand recognition mechanisms with highly effective signaling pathways capable of both immense amplification and precise discrimination between stimulatory ligands (agonists), inhibitory ligands (antagonists) and even partial agonists.

In *Multichain Immune Recognition Receptor Signaling: From Spatiotemporal Organization to Human Disease*, Alexander Sigalov and his colleagues present a comprehensive examination of the full range of MIRRs, of how they propagate signals, how they discriminate between classes of ligands, and the roles they play in physiologic responses and in various diseases. An outstanding set of scientist scholars have provided their expertise in dealing with virtually every aspect of this fascinating set of receptors and in thus providing a comprehensive treatment of this important and exciting area. The nature of this remarkable set of receptors, how they mediate their functions and the potential for abnormal function due to defects in signal transduction, amplification and discrimination, places this family of molecules at the center of the immune response. Dr. Sigalov is to be congratulated for undertaking this important task. Readers interested in this subject will benefit enormously from this important volume.

William Paul, PhD

*Laboratory of Immunology, National Institute of Allergy and Infectious Diseases*

*National Institutes of Health, Bethesda, Maryland, USA*
Multichain immune recognition receptors (MIRRs) represent a family of surface receptors expressed on different cells of the hematopoietic system and function to transduce signals leading to a variety of biologic responses. These receptors share common structural features including extracellular ligand-binding domains and intracellular signaling domains intriguingly carried on separate subunits. Another important feature that links members of the MIRR family is the presence of one or more copies of a cytoplasmic structural module termed the immunoreceptor tyrosine-based activation motif (ITAM). ITAMs consist of conserved sequences of amino acids that contain two appropriately spaced tyrosines (YxxL/Ix6-8YxxL/I, where x denotes non-conserved residues). Following receptor engagement, phosphorylation of ITAM tyrosine residues represents one of the earliest events in the signaling cascade. Although the MIRR-mediated ligand recognition and the MIRR-triggered downstream signaling cascades are believed to be among the best studied in biology in recent years, at present the spatial organization of the MIRRs, its reorganization in response to ligand binding as well as the molecular mechanisms underlying the initiation of MIRR signaling remain to be elucidated.

MIRR-mediated signal transduction plays an important role in both health and disease, making these receptors attractive targets for rational intervention in a variety of immune disorders. Thus, future therapeutic strategies depend on our detailed understanding of the molecular mechanisms underlying MIRR triggering and subsequent transmembrane signal transduction. In addition, knowing these mechanisms would provide a new handle in dissecting the basic structural and functional aspects of the immune response.

The central idea of this book is to show that the structural similarity of the MIRRs determines the general principles underlying MIRR-mediated transmembrane signaling mechanisms and also provides the basis for existing and future therapeutic strategies targeting MIRRs. The reviews assembled in this book detail the progress in defining and controlling the spatiotemporal organization of key events in immune cell activation. An improved understanding of MIRR-mediated signaling has numerous potential practical applications, from the rational design of drugs and vaccines to the engineering of cells for biotechnological purposes. Section I reviews
the spatial organization and physiological function of MIRR family members such as T-cell receptor, B-cell receptor, Fc receptors, natural killer cell receptors and the platelet collagen receptor glycoprotein VI. Section II focuses on current models of MIRR triggering and highlights modern technologies available to visualize cell-cell interaction contacts such as immunological synapse and also to measure protein-protein interactions in space in real time. Potential therapeutic strategies targeting MIRR-mediated signaling are briefly reviewed in Section III.

This book summarizes current knowledge in this field and illustrates how control of MIRR-triggered signaling could become a potential target for medical intervention, thus bridging basic and clinical immunology. Describing the molecular basis of MIRR-mediated transmembrane signaling, this volume addresses a broad audience ranging from biochemists and molecular and structural biologists to basic and clinical immunologists and pharmacologists.

Alexander B. Sigalov, PhD
ABOUT THE EDITOR...

ALEXANDER SIGALOV, PhD, is a Research Assistant Professor in the Department of Pathology at the University of Massachusetts Medical School in Worcester, Massachusetts, USA. His main research interests include protein intrinsic disorder and oligomericity in the context of transmembrane signal transduction, the molecular mechanisms underlying immune receptor-mediated signaling and ways to control these processes and thus to modulate the immune response, as well as the development and applications of novel targets and strategies for innovative immune therapy. He discovered and investigated a very unusual and unique biophysical phenomenon, the homooligomerization of intrinsically disordered proteins, thus providing the first evidence for the existence of specific interactions between unfolded protein molecules. In the field of immunology, he unraveled a long-standing mystery of transmembrane signaling and immune cell activation triggered by multichain immune recognition receptors. Later, he developed a novel concept of platelet inhibition and invented a novel class of platelet inhibitors. In the field of immune therapy, he proposed new therapeutic strategies for a variety of malignancies and immune disorders, including immunodeficiencies, inflammatory and autoimmune diseases, allergy and HIV. He is a member of the American Association for the Advancement of Science and the Biophysical Society USA. Alexander Sigalov received his academic degrees (MSc in Chemistry and a PhD in Organic Chemistry) from Moscow State University, Russia.
PARTICIPANTS

Balbino Alarcón
Centro de Biologia Molecular
Severo Ochoa
CSIC-Universidad Autónoma
de Madrid
Cantoblanco, Madrid
Spain

Marina Ali
Department of Rheumatology
Westmead Hospital
Westmead, New South Wales
Australia

Michael Amon
Department of Rheumatology
Westmead Hospital
Westmead, New South Wales
Australia

Vasso Apostolopoulos
Burnet Institute at Austin
Heidelberg
Australia

Raquel Bello
Centro de Investigaciones Biológicas
CSIC
Madrid
Spain

Veronika Bender
Department of Rheumatology
Westmead Hospital
Westmead, New South Wales
Australia

Roberto Biassoni
Molecular Medicine
Istituto Giannina Gaslini
Genova
Italy

Randall J. Brezski
Department of Pathology
and Laboratory Medicine
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania
USA

Daniel Coombs
Department of Mathematics
University of British Columbia
Vancouver, British Columbia
Canada
Elaine P. Dopfer
Department of Molecular Immunology
Max Planck-Institute for Immunobiology
University of Freiburg
Freiburg
Germany

Michael L. Dustin
Program in Molecular Pathogenesis
Skirball Institute of Biomolecular Medicine
and
Department of Pathology
New York University School of Medicine
New York, New York
USA

William S. Hlavacek
Center for Nonlinear Studies
and Theoretical Biology
and Biophysics Group
Los Alamos National Laboratory
Los Alamos, New Mexico
USA

P. Mark Hogarth
The MacFarlane Burnet Institute for Medical Research and Public Health
Austin Health
Heidelberg
and
Department of Pathology
The University of Melbourne
Parkville
Australia

James R. Faeder
Theoretical Biology and Biophysics Group
Theoretical Division
Los Alamos National Laboratory
Los Alamos, New Mexico
USA

Stephanie M. Jung
Department of Protein Biochemistry
Institute of Life Science
Kurume University
Kurume, Fukuoka
Japan

Tamas Fülöp
Research Center on Aging and Immunology Program
University of Sherbrooke
Sherbrooke, Quebec
Canada

Darja Kanduc
Department of Biochemistry and Molecular Biology
University of Bari
Bari
Italy

Byron Goldstein
Theoretical Biology and Biophysics Group
Theoretical Division
Los Alamos National Laboratory
Los Alamos, New Mexico
USA

Walter M. Kim
Department of Pathology
University of Massachusetts Medical School
Worcester, Massachusetts
USA
Participants

Tomohiro Kubo
Department of Experimental Immunology
Institute of Development, Aging and Cancer
Tohoku University
Sendai
Japan

Anis Larbi
Center for Medical Research (ZMF)
Tübingen Aging and Tumour Immunology Group
Section for Transplantation Immunology and Immunohematology
University of Tübingen
Tübingen
Germany

Eliada Lazoura
Burnet Institute at Austin
Heidelberg
Australia

Nicholas Manolios
Department of Rheumatology
Westmead Hospital
Westmead, New South Wales
Australia

Stephen D. Miller
Department of Microbiology-Immunology
Northwestern University Feinberg School of Medicine
Chicago, Illinois
USA

Susana Minguet
Department of Molecular Immunology
Max Planck-Institute for Immunobiology
University of Freiburg
Freiburg
Germany

Eszter Molnar
Department of Molecular Immunology
Max Planck-Institute for Immunobiology
University of Freiburg
Freiburg
Germany

John G. Monroe
Department of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania
USA

Masaaki Moroi
Department of Protein Biochemistry
Institute of Life Science
Kurume University
Kurume, Fukuoka
Japan

Akira Nakamura
Department of Experimental Immunology
and
CREST Program of Japan Science and Technology Agency
Institute of Development, Aging and Cancer
Tohoku University
Sendai
Japan

Angel R. Ortiz
Centro de Biología Molecular Severo Ochoa
CSIC-Universidad Autónoma de Madrid
Cantoblanco, Madrid
Spain
Participants

William Paul
Laboratory of Immunology
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland
USA

Graham Pawelec
Center for Medical Research (ZMF)
Tübingen Aging and Tumor
Immunology Group
Section for Transplantation Immunology
and Immunohematology
University of Tübingen
Tübingen
Germany

Joseph R. Podojil
Department of Microbiology-
Immunology
Northwestern University Feinberg
School of Medicine
Chicago, Illinois
USA

Pilar Portoles
Centro Nacional de Microbiología
Instituto de Salud Carlos III
Majadahonda, Madrid
Spain

Maree S. Powell
The MacFarlane Burnet Institute for
Medical Research and Public Health
Austin Health
Heidelberg
and
Department of Pathology
The University of Melbourne
Parkville
Australia

Jacob Rachmilewitz
Goldyne Savad Institute of Gene
Therapy
Hadassah University Hospital
Jerusalem
Israel

Michael Reth
Department of Molecular Immunology
Max Planck-Institute
for Immunobiology
University of Freiburg
Freiburg
Germany

Ruth M. Risueño
Centro de Biología Molecular
Severo Ochoa
CSIC-Universidad Autónoma
de Madrid
Cantoblanco, Madrid
Spain

Jose M. Rojo
Centro de Investigaciones Biológicas
CSIC
Madrid
Spain

Wolfgang W. A. Schamel
Department of Molecular Immunology
Max Planck-Institute
for Immunobiology
University of Freiburg
Freiburg
Germany

Gabrielle M. Siegers
Department of Molecular Immunology
Max Planck-Institute
for Immunobiology
University of Freiburg
Freiburg
Germany