Advances in Experimental Medicine and Biology 1172

Tengchuan Jin
Qian Yin *Editors*

Structural Immunology

Springer

Advances in Experimental Medicine and Biology

Volume 1172

Advances in Experimental Medicine and Biology presents multidisciplinary and dynamic findings in the broad fields of experimental medicine and biology. The wide variety in topics it presents offers readers multiple perspectives on a variety of disciplines including neuroscience, microbiology, immunology, biochemistry, biomedical engineering and cancer research.

Advances in Experimental Medicine and Biology has been publishing exceptional works in the field for over 30 years and is indexed in Medline, Scopus, EMBASE, BIOSIS, Biological Abstracts, CSA, Biological Sciences and Living Resources (ASFA-1), and Biological Sciences. The series also provides scientists with up to date information on emerging topics and techniques. 2018 Impact Factor: 2.126.

More information about this series at http://www.springer.com/series/5584

Tengchuan Jin · Qian Yin
Editors

Structural Immunology

Springer

Editors
Tengchuan Jin
The First Affiliated Hospital of USTC,
Division of Life Sciences and Medicine
University of Science and Technology
of China
Hefei, Anhui, China

Qian Yin
Department of Biological Science
Florida State University
Tallahassee, FL, USA

ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-981-13-9366-2 ISBN 978-981-13-9367-9 (eBook)
https://doi.org/10.1007/978-981-13-9367-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword by Prof. Zhigang Tian

It is my honor to write a foreword for this book. I do believe this book is right on time for the readers in related fields.

Immunology is a discipline that studies the immune system, which is highly complex in terms of its molecular, cellular, and organ components, as well as biological functions. The most established roles of the immune system include both defense against infections and destruction of aberrant cells. However, uncontrolled immune responses could cause severe damage. Immunology as a discipline has thrived over the past half century. Indeed, from the characterization of T and B cells in 1960s and 1970s to the identification of checkpoint receptors, i.e., PD-1 and PD-L1 and pattern recognition receptors, i.e., TLRs in 1990s, our understanding of the immune system has reached unprecedented breadth and depth.

Nowadays are exciting times in Immunology, where significant advances have been made in many areas, including tumor immunology, immunotherapy, vaccine research, microbial and viral immunology, autoimmunity, immunometabolism, system biology, and neuroimmunology. Furthermore, the development of new technologies including genomics, proteomics, and CRISPR-mediated genome editing further enlarged the boundaries of immunology. Immunological researches used to focus on cellular events, while today it is common to explore immune responses at gene levels and molecular levels. The molecular details of protein modification, ligand–receptor interactions, and protein conformational changes during immune recognition and signaling are often studied by structural biology approaches.

Structural biology is an ancient discipline as well, which uses physical approaches in the study of biological molecules. Structural biology reveals the molecular and even atomic details of how macromolecules work. The cross of structural biology and immunology has been really fruitful in the past 50 years. Indeed, the structural studies of immune molecules have greatly contributed to the elucidation of the immune system at molecular level. Plenty of important structures have been reported, including the structure of full-length antibodies, the structure of HIV glycoprotein gp120 in complex with CD4 receptor, the dimeric structure of Toll-like receptors, the peptide loaded MHC complex structures, the complex

structures of cell surface receptors and ligands, MyDDosome and PIDDosome structures, and so on. These structures of important immune molecules have broadened our knowledge about ourselves. Many of these structures are discussed in more detail in this book. Data from structural studies not only validate the mechanism of immune molecules found at cellular and tissue level but also create novel insights for immunologists. The structural studies of important drug targets often lead to discovery of novel drugs.

In summary, structural immunology is highly interdisciplinary, and it has been evolved to be one integral part of immunology disciplines. I am sure structural immunologists will continue to make great contributions to the understanding of life.

Hefei, China
December 2018

Prof. Zhigang Tian

Preface

Immune system is one of the most important systems in living organisms. It is involved in normal physiological processes including development and growth, as well as pathological events such as cancer and in host defense. The field of structural biology concerns with macromolecular machineries and has made great contribution to the understanding of life, disease, and drug discovery. Although structural immunology as a scholarly discipline is a relatively new, structural immunologists all over the world have made unprecedented contributions to the field of immunology.

Different from classical immunology books, in which immune system is often viewed by coordination of different immune organs, or different cell types, in this book, we classify immune system by important molecular machines, by protein families and cellular localizations from the angle of structural biologists, just like after the discovery of microscope Robert Hooke, who viewed lives in the form of cells. We focus on molecular structures, interactions, structural changes, structural comparison, and signaling mechanism at molecular level.

The first five chapters cover cell surface receptors, since they mediate cell–cell communication and receive external stimuli in the immune system. The subsequent six chapters cover intracellular receptors and adaptors, which response to signals inside the cell. Lastly, some important components in the nucleus are also included, which convert external stimuli into transcriptional signals, and amply and execute immune responses.

This book is dedicated to students, scientists, and public who are keen to find out the molecular details of how our immune system functions.

Lastly, we would like to express our appreciation to chapter authors of this book. Without your hard work, this book cannot be fulfilled.

Hefei, China — Tengchuan Jin
Tallahassee, USA — Qian Yin
December 2018

Contents

1 **Structural Basis for Signaling Through Shared Common γ Chain Cytokines** 1
Huilin Yang, Rakeeb Kureshi and Jamie B. Spangler

2 **MHC Molecules, T cell Receptors, Natural Killer Cell Receptors, and Viral Immunoevasins—Key Elements of Adaptive and Innate Immunity** 21
Jiansheng Jiang, Kannan Natarajan and David H. Margulies

3 **Structures of Immune Checkpoints: An Overview on the CD28-B7 Family** 63
Weifeng Liu and Xingxing Zang

4 **Interleukin-10 Family Cytokines Immunobiology and Structure** 79
Huaxing Wei, Bofeng Li, Anyuan Sun and Feng Guo

5 **Structural Insights into the Interleukin-17 Family Cytokines and Their Receptors** 97
Shenping Liu

6 **Structural Biology of NOD-Like Receptors** 119
Xinru Yang, Guangzhong Lin, Zhifu Han and Jijie Chai

7 **AIM2 Inflammasome Assembly and Signaling** 143
Bing Wang, Yuan Tian and Qian Yin

8 **Structures of RIG-I-Like Receptors and Insights into Viral RNA Sensing** 157
Xiaojiao Fan and Tengchuan Jin

9 Structural Insight of Gasdermin Family Driving Pyroptotic Cell Death 189
Jianbin Ruan

10 NF-κB, IκB, and IKK: Integral Components of Immune System Signaling 207
Maria Carmen Mulero, Tom Huxford and Gourisankar Ghosh

Contributors

Jijie Chai School of Life Sciences, Innovation Center for Structural Biology, Tsinghua-Peking Joint Center for Life Sciences, Tsinghua University, Beijing, China;
Max-Planck Institute for Plant Breeding Research, Cologne, Germany;
Institute of Biochemistry, University of Cologne, Koeln, Germany

Xiaojiao Fan Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei, China

Gourisankar Ghosh Department of Chemistry & Biochemistry, University of California San Diego, La Jolla, CA, USA

Feng Guo The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, People's Republic of China

Zhifu Han School of Life Sciences, Innovation Center for Structural Biology, Tsinghua-Peking Joint Center for Life Sciences, Tsinghua University, Beijing, China

Tom Huxford Structural Biochemistry Laboratory, Department of Chemistry & Biochemistry, San Diego State University, San Diego, CA, USA

Jiansheng Jiang Molecular Biology Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Tengchuan Jin Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei, China

Rakeeb Kureshi Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA

Bofeng Li The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, People's Republic of China

Guangzhong Lin School of Life Sciences, Innovation Center for Structural Biology, Tsinghua-Peking Joint Center for Life Sciences, Tsinghua University, Beijing, China

Shenping Liu Discovery Sciences, Pfizer Inc., Groton, CT, USA

Weifeng Liu Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY, USA;
Pfizer Inc., South San Francisco, CA, USA

David H. Margulies Molecular Biology Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Maria Carmen Mulero Department of Chemistry & Biochemistry, University of California San Diego, La Jolla, CA, USA

Kannan Natarajan Molecular Biology Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Jianbin Ruan Department of Immunology, University of Connecticut Health Center, Farmington, CT, USA

Jamie B. Spangler Department of Chemical & Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA;
Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA

Anyuan Sun The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, People's Republic of China

Yuan Tian Department of Biological Science, Florida State University, Tallahassee, FL, USA

Bing Wang Department of Biological Science, Florida State University, Tallahassee, FL, USA

Huaxing Wei The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, People's Republic of China

Huilin Yang Department of Chemical & Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

Xinru Yang School of Life Sciences, Innovation Center for Structural Biology, Tsinghua-Peking Joint Center for Life Sciences, Tsinghua University, Beijing, China

Qian Yin Department of Biological Science, Florida State University, Tallahassee, FL, USA;
Institute of Molecular Biophysics, Florida State University, Tallahassee, FL, USA

Xingxing Zang Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, USA

Chapter 1
Structural Basis for Signaling Through Shared Common γ Chain Cytokines

Huilin Yang, Rakeeb Kureshi and Jamie B. Spangler

Abstract The common γ chain (γ_c) family of hematopoietic cytokines consists of six distinct four α-helix bundle soluble ligands that signal through receptors which include the shared γ_c subunit to coordinate a wide range of physiological processes, in particular, those related to innate and adaptive immune function. Since the first crystallographic structure of a γ_c family cytokine/receptor signaling complex (the active Interleukin-2 [IL-2] quaternary complex) was determined in 2005 [1], tremendous progress has been made in the structural characterization of this protein family, transforming our understanding of the molecular mechanisms underlying immune activity. Although many conserved features of γ_c family cytokine complex architecture have emerged, distinguishing details have been observed for individual cytokine complexes that rationalize their unique functional properties. Much work remains to be done in the molecular characterization of γ_c family signaling, particularly with regard to intracellular activation events, and looking forward, new technologies in structural biophysics will offer further insight into the biology of cytokine signaling to inform the design of targeted therapeutics for treatment of immune-linked diseases such as cancer, infection, and autoimmune disorders.

Keywords Cytokine · Common γ chain · Interleukin · Protein crystallography · Lymphocytes · Structural immunology

1.1 Introduction

Cytokines are secreted proteins that interact with surface-embedded receptors to regulate virtually all aspects of immune cell function, including differentiation, proliferation, migration, and survival, orchestrating both the innate and adaptive immune

H. Yang · J. B. Spangler
Department of Chemical & Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

R. Kureshi · J. B. Spangler (✉)
Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA
e-mail: jamie.spangler@jhu.edu

T. Jin and Q. Yin (eds.), *Structural Immunology*, Advances in Experimental Medicine and Biology 1172, https://doi.org/10.1007/978-981-13-9367-9_1

responses [2–4]. The canonical model for cytokine signaling involves initial engagement of receptor extracellular domains (ECDs) to activate signaling either by enforcing receptor oligomerization or by reorienting pre-existing receptor oligomers in the cell membrane [4–9]. Formation of the functional cytokine/receptor ECD complex results in phosphorylation of specific residues on receptor intracellular domains (ICDs) by constitutively associated proteins known as Janus kinases (JAKs). Phosphorylated ICD residues recruit and activate signal transducer and activator of transcription (STAT) proteins, which then translocate to the nucleus to initiate genetic programs that regulate immune cell fate [10–12]. Although JAK/STAT is the dominant pathway for cytokine signaling, some cytokines also activate the Akt and Erk pathways, as well as other signaling networks [13–16]. Cytokines and their respective receptors are broadly classified as type I (hematopoietic) or type II (interferon), and the type I cytokines are further grouped based on shared receptor subunits, namely the common β (β_c), common γ (γ_c), and gp130 cytokine families [2]. This chapter focuses on the structural mechanisms that define γ_c family cytokine activity.

The γ_c family of cytokines is comprised of six short-chain four α-helix bundle cytokines: interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 (Fig. 1.1). These cytokines signal through distinct receptor complexes, all of which include the γ_c chain, and are instrumental in the development, growth, and maintenance of multiple immune cell subsets [17, 18]. The γ_c chain is broadly expressed across all hematopoietic cell lineages; thus the activity of each family member is regulated by expression of its nonshared receptor chain(s). Due to their central role in orchestrating immune function, γ_c cytokines have become attractive therapeutic targets for the treatment of immune-linked diseases such as cancer, infectious diseases, and autoimmune disorders. IL-2 has been approved for over 20 years in cancer treatment, and IL-7 and IL-21 have also been incorporated into clinical trials [17, 19]. This chapter will focus on how each γ_c family member interacts with its cognate receptor chains to offer insight into activation mechanisms. Detailed biophysical insights into this important family of immune regulators will prove critical in designing effective therapeutic interventions.

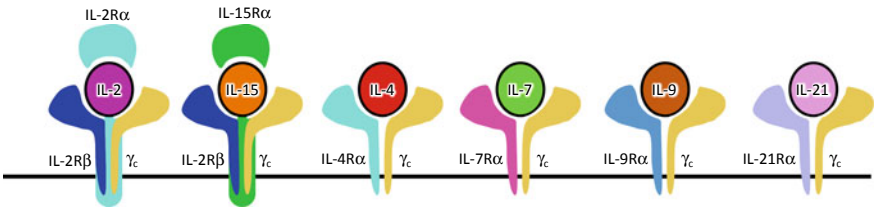

Fig. 1.1 Layout of cytokine/receptor complexes of the γ_c family. Schematics of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 cytokines with their respective receptor chains