ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 520

CYTOKINES AND CHEMOKINES IN AUTOIMMUNE DISEASE

Edited by Pere Santamaria

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY
VOLUME 520

Cytokines and Chemokines in Autoimmune Disease

Pere Santamaria, M.D. Ph.D.
University of Calgary
Microbiology and Infectious Diseases
Associate Professor
Health Sciences Centre
Calgary, Alberta, Canada

LANDES BIOSCIENCE / EUREKAH.COM
GEORGETOWN, TEXAS
U.S.A

KLUWER ACADEMIC / PLENUM PUBLISHERS
NEW YORK, NEW YORK
U.S.A

Cytokines and Chemokines in Autoimmune Disease

Advances in Experimental Medicine and Biology Volume 520

Landes Bioscience / Eurekah.com
and
Kluwer Academic / Plenum Publishers

Kluwer Academic / Plenum Publishers, 233 Spring Street, New York, New York, U.S.A. 10013
http://www.wkap.nl/

Please address all inquiries to Landes Bioscience / Eurekah.com:
Landes Bioscience / Eurekah.com, 810 South Church Street, Georgetown, Texas, U.S.A. 78626
Phone: 512/ 863 7762; FAX: 512/ 863 0081; www.Eurekah.com; www.landesbioscience.com
Landes tracking number: 1-58706-088-4

Cytokines and Chemokines in Autoimmune Disease, edited by Pere Santamaria, Landes / Kluwer dual imprint/ Advances in Experimental Medicine and Biology Volume 520, ISBN 0-306-47693-2

Library of Congress Cataloging-in-Publication Data

CIP applied for but not received at time of publication.

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Recent Volumes in this Series

Volume 506
LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROME 3: BASIC SCIENCE AND CLINICAL RELEVANCE
Edited by David A. Sullivan, Michael E. Stern, Kazuo Tsubota, Darlene A. Dartt, Rose M. Sullivan, and B. Britt Bromberg

Volume 507
EICOSANOIDS AND OTHER BIOACTIVE LIPIDS IN CANCER, INFLAMMATION, AND RADIATION INJURY 5
Edited by Kenneth V. Honn, Lawrence J. Marnett, Santosh Nigam, and Charles Serhan

Volume 508
SENSORIMOTOR CONTROL OF MOVEMENT AND POSTURE
Edited by Simon C. Gandevia, Uwe Proske and Douglas G. Stuart

Volume 509
IRON CHELATION THERAPY
Edited by Chiam Hershko

Volume 510
OXYGEN TRANSPORT TO TISSUE XXIII: OXYGEN MEASUREMENTS IN THE 21ST CENTURY: BASIC TECHNIQUES AND CLINICAL RELEVANCE
Edited by David F. Wilson, John Biaglow and Anna Pastuszko

Volume 511
PEDIATRIC GENDER ASSIGNMENT: A CRITICAL REAPPRAISAL
Edited by Stephen A. Zderic, Douglas A. Canning, Michael C. Carr and Howard McC. Snyder III

Volume 512
LYMPHOCYTE ACTIVATION AND IMMUNE REGULATION IX: LYMPHOCYTE TRAFFIC AND HOMEOSTASIS
Edited by Sudhir Gupta, Eugene Butcher and William Paul

Volume 513
MOLECULAR AND CELLULAR BIOLOGY OF NEUROPROTECTION IN THE CNS
Edited by Christian Alzheimer

Volume 514
PHOTORECEPTORS AND CALCIUM
Edited by Wolfgang Baehr and Krzysztof Palczewski

Volume 515
NEUROPILIN: FROM NERVOUS SYSTEM TO VASCULAR AND TUMOR BIOLOGY
Edited by Dominique Bagnard

Volume 516
TRIPLE REPEAT DISORDERS OF THE NERVOUS SYSTEM
Edited by Lubov T. Timchenko

Volume 517
DOPAMINERGIC NEURON TRANSPLANTATION IN THE WEAVER MOUSE MODEL OF PARKINSON'S DISEASE
Edited by Lazaros C. Triarhou

Volume 518
ADVANCES IN MALE MEDIATED DEVELOPMENTAL TOXICITY
Edited by Bernard Robaire and Barbara F. Hales

Volume 519
POLYMER DRUGS IN THE CLINICAL STAGE
Edited by Maeda, et al.

Volume 520
CYTOKINES AND CHEMOKINES IN AUTOIMMUNE DISEASE
Edited by Pere Santamaria

Volume 521
IMMUNE MECHANISMS OF PAIN AND ANALGESIA
Edited by Halina Machelska and Christoph Stein

DEDICATION

To Joan and Josefa, my parents, for their boundless love and devotion, and to Chus, my wife, for her unwavering support.

EDITOR

Pere Santamaria, M.D., Ph.D.
University of Calgary
Microbiology and Infectious Diseases
Associate Professor
Health Sciences Centre
Calgary, Alberta, Canada
Chapter 1

CONTRIBUTORS

Guillermo A. Arreaza
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 9

Alicia Babcock
McGill University
Montreal Neurology Institute
Montreal, Quebec, Canada
Chapter 8

Mark J. Cameron
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 2, 9

Yiguang Chen
University of Pennsylvania
Philadelphia, Pennsylvania, U.S.A.
Chapter 4

Youhai Chen
University of Pennsylvania
Philadelphia, Pennsylvania, U.S.A.
Chapter 4

Mark M.W. Chong
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

Urs Christen
The Scripts Research Institute
Division of Virology
La Jolla, California, U.S.A.
Chapter 12

Helene Coppin
Laboratorie d'immunologie Cellulaire
INSERM CJF 97-11
Hospital Pitie-Salpetriere
Paris, France
Chapter 3

Rima Darwiche
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

Terry L. Delovitch
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 9

Sylvie Ferrari-Lacraz
Beth Israel Deaconess Medical Centre
Boston, Massachusetts, U.S.A.
Chapter 6

Frederick A. Houssiau
Rheumatology Unit, Christian de Duve
Institute of Cellular Pathology
Universite Catholique de Louvain
Bruxelles, Belgium
Chapter 14

S. Hussain
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 9

Windy Irawaty
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

Thomas W.H. Kay
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

David J. Kelvin
Laboratory of Molecular Immunology
and Inflammation
Robarts Institute
London, Ontario, Canada
Chapter 2

B.R. Lauwerys
Rheumatology Unit, Christian de Duve
Institute of Cellular Pathology
Universite Catholique de Louvain
Bruxelles, Belgium
Chapter 14

Roland S. Liblau
Laboratorie d'immunologie Cellulaire
INSERM CJF 97-11
Hospital Pitie-Salpetriere
Chapter 3

Erik Lubberts
Rheumatology Research Laboratory
Department of Rheumatology
University Hospital Nijmegen
Nijmegen, The Netherlands
Chapter 11

Wlodzmierz Maslinski
Beth Israel Deaconess Medical Centre
Boston, Massachusetts, U.S.A.
Chapter 6

C. Meagher
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 9

Dorothée Nashan
Ludwig Boltzmann Institute for Cell
Biology and Inmmunobiology
of the Skin
Department of Dermatology
University of Munster
Munster, Germany
Chapter 13

Deborah O'Neil
Department of Molecular Biology
Ghent University and Flanders
Interuniversity Institute
for Biotechnology
Gent, Belgium
Chapter 15

Trevor Owens
McGill University, Montreal Neurology
Institute
Montreal, Quebec, Canada
Chapter 8

Helen L. Pennington
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

Alex Rabinovitch
University of Alberta,
Department of Medicine
Edmonton, Alberta, Canada
Chapter 10

Marie-Paule Roth
Laboratorie d'immunologie Cellulaire
INSERM CJF 97-11
Hospital Pitie-Salpetriere
Paris, France
Chapter 3

Pere Santamaria
Department of Microbiology
and Infectious Diseases
Faculty of Medicine, University
of Calgary
Calgary, Alberta, Canada
Chapter 1

Thomas Schwarz
Ludwig Boltzmann Institute for Cell
Biology and Inmmunobiology
of the Skin, Department of
Dermatology
University of Munster
Munster, Germany
Chapter 13

S. Sharif
The Robarts Research Institute
and University of Western Ontario
Department of Microbiology
and Immunology, and Medicine
London, Ontario, Canada
Chapter 9

Maria A. Staykova
Neurosciences Research Unit, Canberra
Hospital
Woden, Australia
Chapter 7

Lothar Steidler
Department of Molecular Biology
Ghent University and Flanders
Interuniversity Institute
for Biotechnology
Gent, Belgium
Chapter 15

Terry B. Strom
Beth Israel Deaconess Medical Centre
Boston, Massachusetts, U.S.A.
Chapter 6

Helen E. Thomas
The Walter and Eliza Hall Institute
Burnet Clinical Research Unit
Parkville, Victoria, Australia
Chapter 5

Wim B. van den Berg.
Rheumatology Research Laboratory
Department of Rheumatology
University Hospital Nijmegen
Nijmegen, The Netherlands
Chapter 11

Matthias G. von Herrath
The Scripts Research Institute
Division of Virology
La Jolla, California, U.S.A.
Chapter 12

David O. Willenborg
Neurosciences Research Unit, Canberra
Hospital
Woden, Australia
Chapter 7

Xin X. Zheng
Beth Israel Deaconess Medical Centre
Boston, Massachusetts, U.S.A.
Chapter 6

PREFACE

The field of immunoregulation by cytokines and chemokines has witnessed a remarkable progress over the last decade. The number of cytokines, chemokines and cytokine/chemokine receptors has dramatically increased and their physiological functions explored to an extent that was unforeseable a few years ago. Technological advances in genomics and genetic engineering in rodents have provided a wealth of information on cytokines and chemokines that spills over into different fields of biology and pathology. This book is an attempt to capture current knowledge on the role of cytokines and chemokines in autoimmunity by focusing on some of the most prevalent organ-specific or systemic autoimmune disorders that affect humankind. The lessons taught by research in the disorders dealt with in this work are likely applicable to other, less prevalent (albeit arguably as equally important) autoimmune disorders. Diseases not touched upon here include, for example, mysasthenia gravis, autoimmune thyroid diseases, autoimmune disorders resulting from immune complex deposits and other, where cytokines and chemokines undoubtedly also play a role.

This book is divided into 3 parts and contains 15 chapters written by world-class experts in their respective fields. Part I has two chapters. Chapter 1 provides an overview on the role of different cytokines and chemokines in autoimmunity, as a summary of what is discussed in depth in other chapters of the book (for specific autoimmune disorder or groups of disorders). Chapter 2 is a detailed synopsis of the function, genomics and structure of the known cytokines, chemokines and respective receptors. Part II is divided into four chapters that deal with the "genetics and mechanisms of action" of cytokines and their receptors in the context of autoimmunity. Part III groups nine chapters exploring the role of different cytokines and chemokines in various autoimmune disorders, including discussions on the proven and potential use of cytokines, chemokines or inhibitory reagents (i.e. antibodies or soluble receptors) in the clinic. The reader will realize that, as key communicators in immunobiology, cytokines and chemokines are promising targets for the prevention and/or therapy of autoimmune disorders. It will also become obvious to the reader that despite the enormous progress made to date, our knowledge in this area remains limited. It is my hope that this book will appeal to basic immunologists interested in clinical implications of cytokine and chemokine biology, as well as to clinicians interested in gaining an in depth understanding of the role of cytokines and chemokines in the pathogenesis and/or treatment of the autoimmune disorders that affect their patients.

Lastly, I would like to take this opportunity to thank the authors of this book for contributing their valuable time and expertise in preparing the different chapters. I am grateful to each of them for writing outstanding, thorough reviews of their respective areas of expertise.

Pere Santamaria

CONTENTS

CHAPTER 1

Cytokines and Chemokines in Autoimmune Disease: An Overview

Pere Santamaria

Introduction

Autoimmune diseases result from complex interactions among different immune cell types, including both T and B lymphocytes and professional antigen-presenting cells, such as macrophages and dendritic cells. These cellular interactions result in auto-aggressive responses that target a number of different cell types in different tissues and organs in a relatively large number of autoimmune disorders. Although the etiology of most autoimmune diseases is unknown, recent years have witnesed important advances in our understanding of how the different immune cell types involved in autoimmunity communicate with one another, how they trigger autoimmune inflammation and how they cause tissue damage. As key elements of this communication network, cytokines and chemokines orchestrate the recruitment, survival, expansion, effector function and contraction of autoreactive lymphocytes in autoimmunity. The different Chapters of this book detail the role of different cytokines and chemokines in specific autoimmune disorders. In this Chapter, I highlight the contributions of individual cytokines and chemokines to multiple autoimmune diseases as discussed in detail throughout the book.[1-14] The reader is referred to specific Chapters for details.

Pro-Inflammatory Cytokines

Interleukin-1 (IL-1)

Interleukin1-α (IL-1α) and IL-1β , along with TNF-α are key inflammatory cytokines in rheumatoid arthritis (RA),[9] dermatomyositis and pemphigus.[14] In vitro data suggest that IL-1 is also an important effector cytokine in type 1 diabetes (T1D), through a number of direct (i.e., beta cell toxicity) and indirect means (i.e., by marking beta cells for Fas-dependent destruction by autoreactive cytotoxic T-lymphocytes).[7] IL-1 is also expressed in the central nervous system (CNS) of animals with experimental autoimmune encephalomyelitis (EAE) and IL-1R antagonsists have been shown to have a moderate therapeutic effect in EAE. IL-1 may contribute to disease severity, rather than to susceptibility in this animal model.[5]

Tumor Necrosis Factor-alpha (TNFα)

TNFα has direct cytotoxic effects on the intestinal mucosa in Crohn's disease and ulcerative colitis but also contributes to the systemic manifestations seen in these diseases. Anti-TNFα antibodies have shown a clear anti-inflammatory effect in patients with Crohn's disease, but the authors raise a note of caution about the long-term effects of TNFα blockade in

Cytokines and Chemokines in Autoimmune Disease, edited by Pere Santamaria.

vivo, particularly in children.[14] There is evidence that some animal models of systemic lupus erythematosus (SLE) produce reduced levels of TNFα . Although the pathogenic role of TNFα in SLE remains unclear, both Lawerys and Houssiau and Nashan and Schwarz point to the observation that RA patients treated with anti-TNFα mAb tend to develop anti-DNA antibodies, and that low TNFα producers have increased susceptibility to develop SLE.[12,13] TNFα appears to have a pathogenic role in the blister lesions of bullous phemphigoid.[12] TNFα plays a critical role in the pathogenesis of RA, and treatment with TNFα and IL-1 blockers offers the highest degree of protection in animal models.[9,11] Furthermore, there is evidence indicating that some TNFα gene variants are markers of RA severity.[2]

TNFα is also a key cytokine in the development of T1D, contributing to beta cell dysfunction and death, as well as orchestrating antigen-presentation and T-cell activation in situ. The effects of TNFα in vivo, however, are age-dependent and there is evidence that TNFα can also have anti-diabetogenic effects.[7,8] TNFα may be key to the breakdown of tolerance to self antigens in virus-induced diabetes. Interestingly, late expression of TNFα in this model could restore normal beta cell function, possibly by inducing T-cell apoptosis.[10] This dichotomy is a recurrent issue with other cytokines as well.

TNFα has been suggested to play a divergent role in the development of EAE and MS, by causing demyelination and fostering the chronicity of the disease (EAE) or by downregulating the disease process (MS).[5] Willenborg et al, however, point out the existence of diametrically opposed views on the effects of TNFα in EAE in the literature, ranging from pro-EAE to anti-EAE. Some studies have indicated that EAE can be inhibited by TNFα blockade, whereas studies in humans have suggested that it may increase the number of clinical exacerbations.[5]

TNF-Related Apoptosis-Inducing Ligand (TRAIL)

Chen and Chen discuss the role of TRAIL in autoimmune responses. TRAIL may contribute to suppression of autoimmune inflammation, such as autoimmune arthritis and thus may have therapeutic value in autoimmune diseases.[3]

RANK-Ligand (RANKL)

RANKL appears to play a critical role in the bone erosion process that occurs in RA and RANKL blockade in vivo may have therapeutic value.[9]

TALL-1/BAFF

Lauwerys and Houssiau discuss a role for this tumor necrosis factor family member in SLE. BAFF is a TNF-family member that induces B-cell proliferation by engaging BCMA or TACI receptors on B-cells. Autoantibody production and lupus-like syndromes have been noted in BAFF-transgenic mice, and the levels of TALL/BAFF-1 are elevated in animal models of SLE and human SLE patients.[13]

Interleukin-2 (IL-2)

IL-2- and IL-2R-deficient mice develop an autoimmune syndrome characterized by haemolytic anemia and ulcerative bowel disease. The contribution of IL-2 to autoimmune phenomena may be indirect, i.e., by virtue of the role it plays in T-cell homeostasis.[3]

Interferon-gamma (IFN-γ)

Peripheral blood mononuclear cells (PBMCs) from SLE patients tend to produce lower levels of IFN-γ than control PBMCs ex vivo. Furthermore, exogenous IFN-γ increases disease severity in some animal models of lupus, and IFN-γ or IFN-αR blockade have beneficial effects.[12,13] Extensive evidence indicates that IFN-γ contributes to the pathogenesis of T1D, but neither IFN-γ nor IFN-γ Rβ-deficient NOD mice are resistant to the disease.[7,8] IFN-γ, however, appears to play a critical role in virus-induced diabetes.[10] There is also some evidence suggesting that INF-γ may be necessary for the development of regulatory T-cells and, when administered systemically for example, inhibits insulitis development.[8] IFN-γ appears to play

a downregulating role in EAE (possibly by inducing the production of nitric oxide). On the other hand, IFN-γ blockade appears to alleviate recurrent-relapsing MS (RR-MS).[5]

Interferon-alpha (IFN-α)

IFN-α appears to have a pro-inflammatory effect when expressed as a transgene in beta cells, but is anti-diabetogenic when administered systemically.[7]

Interleukin-6 (IL-6)

IL-6 is elevated in ex vivo organ cultures of inflammed colonic mucosa from both ulcerative colitis and Crohn's disease affected patients, and likely contributes to disease pathogenesis by inhibiting T-cell apoptosis, thereby perpetuating inflammation. Its contribution to pathology is reflected on the observation that IL-6R blockade suppresses colitis in animal models of inflammatory bowel disease.[14] There is also consensus in the literature implicating IL-6 in the development of EAE and possibly MS, but it may have an insignificant effect in disease pathology.[5]

Several lines of experimentation in mice have suggested an important role for IL-6 in the development of islet inflammation, as well as an inhibitory effect on its progression to overt diabetes, perhaps by inducing regulatory Th2 cells.[7]

IL-6 may also play a role in the pathogenesis of SLE and systemic sclerosis (SSc). IL-6 is elevated in sera of SLE and SSc patients and in the cerebrospinal fluid and urine of patients with cerebral lupus and lupus nephritis, respectively. IL-6 may also have a pathogenic role in skin lesions of SLE patients, as discussed extensively by Nashan and Schwarz.[12] IL-6 blockade improves disease outcome in (NZB x NZW) F1 mice, and IL-6 administration exacerbates disease progression.[12] IL-6 may also have a pathogenic role in the blister lesions of bullous phemphigoid.[12]

Interleukin-12 (IL-12)

O'Neil and Steidler note that the small intestine of patients with Crohn's disease contains elevated numbers of IL-12-producing macrophages. These cells are rare in ulcerative colitis lesions and thus may be key to immunopathological differences between these two disorders. IL-12 may contribute to damage of the gut wall by inducing the activation of matrix metalloproteinases. Anti-IL-12 therapy has shown promising results in reversing inflammation in the TNBS-induced model of colitis.[14]

IL-12 is indispensable for the induction of EAE, as indicated by studies of IL-12-deficient mice as well as anti-IL-12 mAb-treated animals.[5]

In contrast, there is impaired production of IL-12 in human SLE and murine models of the disease. As discussed by Lauwerys and Houssiau, IL-12 regulates immunoglobulin and autoantibody production and impaired IL-12 secretion may contribute to the pathogenesis of SLE.[13]

IL-12, as a Th1-driving cytokine, appears to play a key role in the initial phases of RA. IL-12 blockade or IL-12 administration inhibit or accelerate the development of RA, respectively.[9] The role of IL-12 in diabetogenesis is less clear. On the one hand IL-12 administration accelerates diabetes development in NOD mice, and anti-IL-12 treatment is anti-diabetogenic if initiated early, i.e., before development of insulitis. On the other hand, IL-12-deficient NOD mice develop diabetes, implying that Il-12 is dispensable in diabetogenesis.[7,8]

Interleukin 15 (IL-15)

IL-15 is increased in ex vivo cultures of Crohn's biopsy samples, but is absent in ulcerative colitis tissue and may play a role in driving local Th1 responses in Crohn's disease.[14] This cytokine is elevated in the synovial fluid of RA patients and may perpetuate the survival of autoreactive T-cells and promote the secretion of arthritogenic cytokines such as TNFα and IL-17. Zheng et al extensively discuss the therapeutic value of IL-15 blockade strategies in autoimmunity, particularly in RA.[11]