AUTOIMMUNITY

Genetic, Immunologic, Virologic, and Clinical Aspects

Edited by

NORMAN TALAL, M.D.

AUTOIMMUNITY

Genetic, Immunologic, Virologic, and Clinical Aspects

Edited by

NORMAN TALAL, M.D.

Department of Medicine School of Medicine University of California, San Francisco and Clinical Immunology and Arthritis Section Veterans Administration Hospital. San Francisco, California





COPYRIGHT © 1977, BY ACADEMIC PRESS, INC. ALL RIGHTS RESERVED. NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC. 111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by ACADEMIC PRESS, INC. (LONDON) LTD. 24/28 Oval Road, London NW1

Library of Congress Cataloging in Publication Data

Main entry under title:

Autoimmunity: genetic, immunologic, virologic, and clinical aspects.

Includes bibliographies and index.

Autoimmune diseases. Talal, Norman. [DNLM:

Autoimmune diseases, WD 300 T137a] 616.9'78 77-74062 RC600.A85

ISBN 0-12-682350-2

List of Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

- A. C. ALLISON (91), Division of Cell Pathology, Clinical Research Centre, Medical Research Council, Harrow, Middlesex, England
- ARTHUR J. AMMANN (479), Department of Pediatric Immunology, University of California, San Francisco, California
- FRITZ H. BACH (1), Immunobiology Research Center and Departments of Medical Genetics and Surgery, The University of Wisconsin, Madison, Wisconsin
- J. F. BACH (207), Inserm U25, Hospital Necker, Paris, Cedex, France
- M. A. BACH (207), Inserm U25, Hospital Necker, Paris, Cedex, France
- L. D. BACON (63), Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan
- P. E. BIGAZZI (63), Department of Pathology, University of Connecticut School of Medicine, Farmington, Connecticut
- PAUL H. BLACK (385), Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts
- F. M. BURNET (513), Department of Microbiology, University of Melbourne, Parkville, Victoria, Australia
- C. CARNAUD (207), Inserm U25, Hospital Necker, Paris, Cedex, France
- P. R. CARNEGIE (597), Russell Grimwade School of Biochemistry, University of Melbourne, Parkville, Victoria, Australia
- IRUN R. COHEN (231), Department of Cell Biology, The Weizmann Institute of Science, Rehovot, Israel
- M. DARDENNE (207), Inserm U25, Hospital Necker, Paris, Cedex, France
- DEBORAH DONIACH (621), Departments of Immunology and Nuclear Medicine, The Middlesex Hospital Medical School, London, England
- P. ESQUIVEL* (63), Facultad de Medicina, Departamento de Medicina Experimental, Universidad Austral de Chile, Valdivia, Chile

^{*} Present address: Universidad Austral de Chile, Valdivia, Chile.

RICHARD K. GERSHON (171), Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

- DAVID GLASS (531), Department of Medicine, Robert B. Brigham Hospital, Harvard Medical School, Boston, Massachusetts
- ALAN O. HAAKENSTAD (277), Division of Rheumatology, Department of Medicine, University of Washington, Seattle, Washington
- MARTIN S. HIRSCH (385), Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts
- HEINZ KOHLER (267), La Rabida-University of Chicago Institute, and Departments of Pathology and Biochemistry, University of Chicago, Chicago, Illinois
- Y. M. KONG (63). Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan
- JAY A. LEVY (403), Department of Medicine and Cancer Research Institute, University of California, San Francisco, California
- I. R. MACKAY (597), Clinical Research Unit, The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Victoria, Australia
- MART MANNIK (277), Division of Rheumatology, Department of Medicine, University of Washington, Seattle, Washington
- NICHOLAS J. MARSHALL (621), Department of Nuclear Medicine, The Middlesex Hospital Medical School, London, England
- J. C. MONIER (207), Hopital Edouard Herriot, Lyon, Cedex, France
- PHILIP Y. PATERSON (643), Department of Microbiology-Immunology, The Medical and Dental Schools, Northwestern University, Chicago, Illinois
- MAX R. PROFFITT (385), Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts
- N. R. ROSE (63), Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan
- DONALD R. ROWLEY (267), La Rabida-University of Chicago Institute, Chicago, Illinois
- PETER H. SCHUR (531), Department of Medicine, Robert B. Brigham Hospital, Harvard Medical School, Boston, Massachusetts
- R. S. SUNDICK (63), Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan
- NORMAN TALAL (183), Department of Medicine, School of Medicine, University of California, San Francisco, and Clinical Immunology and Arthritis Section, Veterans Administration Hospital, San Francisco, California
- NOEL L. WARNER* (33), Genetics Unit, The Walter and Eliza Hall Institute of Medical Research, Melborne, Australia
- WILLIAM O. WEIGLE (141), Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California
- HARTMUT WERKERLE (231), Max-Planck-Institut für Immunbiologie, Freiburg, Germany
 - * Present address: Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico.

List of Contributors xv

HANS WIGZELL (693), Department of Immunology, Biomedical Center, Uppsala University, Uppsala, Sweden

- RALPH C. WILLIAMS, JR. (457), Department of Internal Medicine, Bernalillo County Medical Center, University of New Mexico School of Medicine, Albuquerque, New Mexico
- ROLF M. ZINKERNAGEL (363), Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California
- NATHAN J. ZVAIFLER (569), Division of Rheumatology, Department of Medicine, University of California, San Diego, La Jolla, California

Preface

The pathogenesis of autoimmunity appears to involve genetic, immunologic, and viral factors interacting through complicated mechanisms still poorly understood. Recent evidence suggests that self-recognition of histocompatibility antigens may be a normal event in immune surveillance which promotes simultaneous recognition of viral or other new cell surface antigens. The "network theory" of immune regulation through idiotype recognition represents another physiological expression of autoimmunity which may have potential for immune tolerance and immunotherapy. The rapidly expanding area of autoimmunity directed against receptors for hormones and neurotransmitters opens the possibility that many presumed nonimmunologic diseases may actually have an underlying immune basis. The relationship between autoimmunity and malignant lymphoproliferation leads into the broad area of neoplasia and the normal control of cellular growth and differentiation.

Autoimmunity, then, is an important immunobiologic clue into the physiology and regulation of the immune system. At the same time, autoimmunity is an aspect of clinical medicine that is relevant to many afflictions involving several different organ systems. The task of editing a volume on autoimmunity becomes a challenge potentially as broad as immunology and medicine.

In selecting the contributors to this book, I hoped to create a compendium of fact and opinion that might state the problems and point out future directions in a way described so beautifully by George Santayana:

Our knowledge is a torch of smokey pine which lights the path but one step ahead across a void of mystery and dread.

If successful, each chapter in this volume may serve as a torch illuminating a small area of the problem. Hopefully, the whole will be greater than

xviii Preface

, the sum of its parts and the biologic mystery of autoimmunity will be found on and between these pages.

I am deeply grateful to the busy scientists and clinicians who found time to prepare these chapters, to Maurice Landy who suggested that I undertake this responsibility, and to the staff of Academic Press whose help has been invaluable. To the reader, I apologize not for what is on these pages, but for the many areas not included.

Norman Talal, M.D.

Contents

List of Contributors

Preface

Part I GE	NETIC ASPECTS	
Chapter 1	The Major Histocompatibility Complex and Its Relationship to Autoimmune Disease	
	FRITZ H. BACH	
III. MHC Lo IV. Genetic C V. Techniqu VI. Modifica VII. In Vivo I	for MHC Genes Doci Control of CML Les for Detection of MHC LD Antigens tion of the SD Antigens Role of MHC Antigens Susceptibility Genes	4 8 9 15 16 19 22 22 29 30
Chapter 2	Genetic Aspects of Autoimmune Disease in Animals	
	NOEL L. WARNER	
III. Immune	tion Analysis of Autoimmunity in NZ Mouse Strains Responsiveness of NZ Mouse Strains Control in Other Autoimmune Diseases	33 35 49 56

xiii

xvii

vi	Contents
V. Conclusions References	59 59
Chapter 3 Genetic Regulation in Autoimmune Thyroiditis N. R. ROSE, L. D. BACON, R. S. SUNDICK, Y. M. KONG, P. ESQUIVEL, AND P. E. BIGAZZI	
 I. Human Thyroid Disease II. Experimentally Induced Thyroiditis III. Spontaneously Appearing Thyroiditis IV. Conclusions References 	63 66 75 84 85
Part II IMMUNOLOGIC ASPECTS	
Chapter 4 Autoimmune Diseases: Concepts of Pathogenesis and Control	
A. C. ALLISON	
I. Introduction II. The T Lymphocyte Bypass Concept III. The Concept of T Lymphocyte Suppression of Autoimmunity IV. Autoimmune Diseases Mediated by Autoantibodies V. Collaboration of Autoantibodies and Complement VI. Collaboration of Autoantibodies and Mononuclear Phagocytes VII. Pathogenesis of Disease by Autoantibodies Generating Immune Complexes VIII. Collaboration of Autoantibodies with Nonspecific Effector Cells (K Cells) IX. Autoimmune Disease Mediated by T Lymphocytes X. Collaboration of Autoantibodies and Cell-Mediated Immunity References	92 95 109 115 117 120 122 124 128 132
Chapter 5 Cellular Events in Experimental Autoimmune Thyroiditis, Allergic Encephalomyelitis, and Tolerance to Self	
WILLIAM O. WEIGLE	
I. Introduction H. Immunologic Tolerance HI. Autoimmunity IV. Summary	141 142 149 166

167

References

	for Autoimmunity	
	RICHARD K. GERSHON	
III. Potential IV. Potential Autoimm	n of T Cell Subclasses with Anti-Ly Sera Role of the Ly 123 Cell Causes of Breakdown in T Cell Regulation Which Could Lead to unity of Suppressor Activity to Histocompatibility Antigens	17 17: 17: 17: 17: 18:
Chapter 7	Autoimmunity and Lymphoid Malignancy: Manifestations of Immunoregulatory Disequilibrium	
	NORMAN TALAL	
Mice III. Monoclor IV. Other Exp V. Clinical E	unity and Lymphoid Malignancy in NZB and NZB/NZW F ₁ (B/W) and Immunoglobulins and Autoimmunity perimental Models of Autoimmunity and Malignant Lymphoproliferation experiences with the Association of Autoimmunity and Lymphoma all Considerations ons	18: 19: 19: 20: 20: 20: 20:
Chapter 8	Thymic Hormones and Autoimmunity	
	J. F. BACH, M. A. BACH, C. CARNAUD,/ M. DARDENNE, AND J. C. MONIER	
I. Thymus I II. Thymus I III. Swan Mic Reference	Aormones and the Control of Autoimmunity	200 213 223 223
Chapter 9	Autoimmunity, Self-Recognition, and Blocking Factors	
*	IRUN R. COHEN AND HARTMUT WEKERLE	
III. BlockingIV. FxamplesV. Do Block	etion of Lymphocytes That Recognize Self-Antigens Factors of Blocking Factors ing Factors Regulate Self-Tolerance? -Recognition Have a Normal Function in the Immune System?	231 232 238 241 252 255 261

Chapter 6 Suppressor T Cell Dysfunction as a Possible Cause

***	Contents
VIII	

		20-20-20-20-20-20-20-20-20-20-20-20-20-2
Chapter 10	Self-Recognition: The Basic Principle in the Immune System	
	HEINZ KOHLER AND DONALD A. ROWLEY	
III. The Effects IV. The Concep	nition in the Immune System of Autoimmune Responses: Control of the Expression of Receptors pt of the Interaction of Complementary Clones ntary Clonal Interaction during Evolution	267 268 270 271 272 274 274
Chapter 11	The Biology of Immune Complexes	
	ALAN O. HAAKENSTAD AND MART MANNII	K
III. Biologic Pr IV. Models of I Complexes V. Detection of	of Antigen Antibody Complexes roperties of Immune Complexes Immune Complex Diseases and the Fate of Circulating Immune of Immune Complexes of Human Immune Complex Diseases	278 278 286 313 337 348 350
Part III VI	RAL ASPECTS	
Chapter 12	H-2 Restriction of Cell-Mediated Virus-Specific Immunity and Immunopathology: Self-Recognition, Altered Self, and Autoaggression ROLF M. ZINKERNAGEL	
III. Murine Ly IV. H-2 Restri V. Is Virus-S Self Indep VI. Immune P	ts of T Cell-Mediated Immunity Imphocyte Choriomeningitis Virus Infections Iction of CMI to Virus Infection pecific Cytotoxicity Directed against "Altered Self" or against Virus and endently? Irotection and Immunopathology vidence for Cytotoxicity against "Normal" Self during Virus	363 366 367 373 d 374 376 379 381 381

Contents

Contents		
Chapter 13	Viruses, Autoimmunity, and Murine Lymphoma	
	MAX R. PROFFITT, MARTIN S. HIRSCH, AND PAUL H. BLACK	
I. Introduction	on	385
	diated Autoreactivity in a Model of Murine Lymphomagenesis	386
	vity of Thymocytes from MuLV-M Carrier Mice	387
	zation of Autoaggressive Thymocytes from MuLV-M Carrier Mice of Virus-Associated Autoreactivity	389 389
	of the Protective Effect Conferred on Syngeneic Target Cells by	367
Infection w	vith MuLV-M	390
	of Target Cell Killing by Autoaggressive MuLV-M Carrier	200
Thymocyte VIII. Discussion		390 393
References		398
Chapter 14	C-Type RNA Viruses and Autoimmune Disease	
	JAY A. LEVY	
I. Introduction	on	404
II. C-Type Vi		407
	ne Disease of New Zealand Black Mice	414
	ectious Anemia Virus stemic Lupus Erythematosus	423 429
	racteristics of C-Type Virus Infection Which May Be Involved in the	427
	sis of Autoimmunity	432
	ruses and Autoimmune Disease in Man	436
VIII. Discussion	ns and Summary	440
References		444 446
		110
Part IV CI	LINICAL ASPECTS	
Chapter 15	Infection and Autoimmunity	
	RALPH C. WILLIAMS, JR.	
I. Introduction	on	457
II. Rheumato		461
III. Antinuclea		471
	uscle Antibodies	472
	totoxic Antibody ous Autoantibodies Associated with Infections	473 474
References		475

	Contents

Chapter 16	Immunodeficiency Disorders and Autoimmunity	
	ARTHUR J. AMMANN	
I. Introductio	on of Antibody-Mediated Immunity Associated with Autoimmunity	479 481
III. Disorders of IV. Abnormality	of Cell-Mediated Immunity Associated with Autoimmunity by of Phagocytosis Associated with Autoimmunity: Chronic	498
V. Conclusion	tous Disease	503
References	5	506 508
Chapter 17	Autoimmunity and Aging	
•	F. M. BURNET	
L. Current Vie	ews of the Aging Process	513
	onitoring Function of the Immune System in Relation to Aging	515
	pecific Incidence of Autoimmune Disease	517
IV. Association	of Autoimmune Disease with Certain HLA Types	519
	pliferative Processes	522
VI. Amyloidosi		524
	toimmunity in Animal Models	525
VIII. Conclusion		527
References		528
Chapter 18	Autoimmunity and Systemic Lupus	
	Erythematosus	
	DAVID GLASS AND PETER H. SCHUR	
I. Introduction	ńn	532
Ik. SLE: Gene	tic Predisposition	532
	atus of SLE Patients	538
	esponse to Nuclear Substances	540
	immune Antibodies	548
VI. Drug-Induc		549
	Immune Complex-Mediated Disease	549
VIII. Discussion		556 559
IX. Summary References		560
Chapter 10	Rheumatoid Arthritis	
Chapter 19		
	NATHAN J. ZVAIFLER	
	atures of Rheumatoid Arthritis	569
II. Rheumatoi		571
	sis of Rheumatoid Joint Disease	573
References	llar Manifestations of Rheumatoid Arthritis	583 592
References		392

Contents	xi
----------	----

Chapter 20	Cell-Surface Receptors and Autoimmune Responses	
	I. R. MACKAY AND P. R. CARNEGIE	
IV. Diabetes M V. Other Endo VI. Multiple So	a Gravis and and Graves' Disease fellitus ocrinopathies clerosis te Receptors for Antigen	597 601 606 607 610 611 613 614
Chapter 2.1	Autoantibodies to the Thyrotropin (TSH) Receptors on Thyroid Epithelium and Other Tissues	
	DEBORAH DONIACH AND NICHOLAS J. MARSHALL	
I. Introduction II. Clinical Ba III. Pathogenes IV. Conclusion References	ackground sis of Thyrotoxicosis	621 622 624 637 638
Chapter 22	Autoimmune Neurological Disease: Experimental Animal Systems and Implications for Multiple Sclerosis	
	PHILIP Y. PATERSON	
Neuroimm III. Immunopa IV. EAE as an	Concepts of Neuroallergy and Autoimmune CNS Disease and autoiverological Mechanisms Implicated in MS atthogenesis of EAE Experimental Model System for MS arological Mechanisms in MS	644 645 654 673 678 684 691
Chapter 23	Positive Autoimmunity	18
	HANS WIGZELL	
I. Introduction II. "Anti-Self" Lymphocy	"Reactivity May Be a Normal Feature of All Immunocompetent T	693 694

xii	ži.			

-				
	on	10	-	4 4"
•	VII			

	111	Positive Consequences of Induced Autoimmunity: A Discussion as to Possible	
		Future Applications	697
	IV	Conversion of Tumor-Associated Proteins into Self-Immunogens	698
	\mathbf{V} .	Regulation of Endocrine Functions via Auto-Anti-Hormone Antibodies	700
	VI	Specific Autoimmunity against Antigen-Binding Receptors on Lymphocytes: A	
9		Way to Induce Specific Immunologic Tolerance in B as well as T Lymphocytes	701
	VII	Concluding Remarks	705
		References	706
	Index		709

æ

Part I

GENETIC ASPECTS