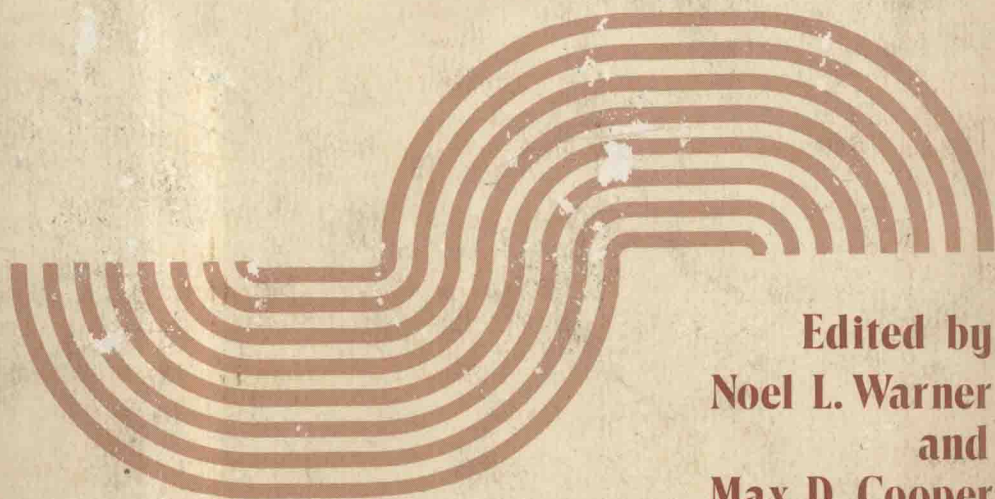


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Contemporary Topics in Immunobiology Volume 8



Edited by
Noel L. Warner
and
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CONTEMPORARY TOPICS IN IMMUNOBIOLOGY

VOLUME 8

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PLENUM PRESS • NEW YORK AND LONDON

The Library of Congress cataloged the first volume of this title as follows:

Contemporary topics in immunobiology. v. 1—

1972—

New York, Plenum Press.

v. illus. 24 cm. annual.

1. Immunology—Periodicals.

QR180.C632

574.2'9'05

79-179761

ISSN 0093-4054

Library of Congress Catalog Card Number 68-26769

ISBN 0-306-37808-6

© 1978 Plenum Press, New York

A Division of Plenum Publishing Corporation

227 West 17th Street, New York, N.Y. 10011

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Printed in the United States of America

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Preface

In this current volume of *Contemporary Topics in Immunobiology* we have chosen to continue with the multiple-theme approach that was developed in Volumes 1, 3, and 5 of this series. Immunobiology still shows little sign of decreasing its active growth rate, but rather is continuing to broaden its range of interests and applications, particularly as new techniques and methods are adapted from other fields of medical research.

This present volume reflects both several of the more classical areas of immunology now addressed in the light of contemporary immunology, and several newer directions that have been taken in other fields.

The general subject of T-cell heterogeneity and functions of T-cell subpopulations is addressed in Chapters 1 and 2. The potential role of genes of the major histocompatibility complex in controlling the immune functions of T lymphocytes still remains a major unresolved issue in immunogenetics, and the current status of this problem is excellently reviewed by J. F. A. P. Miller. The further elucidation of functional subpopulations of human T lymphocytes has been particularly hampered by the lack of available markers for characterizing and isolating such subpopulations. A major step in this direction has been made by L. Moretta, M. Ferrarini, and M. D. Cooper, who review their experience with Fc-receptor-bearing human T-lymphocyte populations.

Although the predominant interest in lymphocyte subpopulations has centered on the T-cell series, the subject of B-cell heterogeneity has become a considerably escalating field of research in immunobiology, in part through studies of the role or roles of membrane immunoglobulins as antigen receptors for immunity or tolerance. Progress in this field has also been considerably aided by the discoveries of murine IgD and allotypes of murine IgM and IgD, and these aspects are extensively covered by J. W. Goding in Chapter 7 and J. F. Kearney and E. R. Abney in Chapter 8.

Of considerable current interest in many areas of the world is the potential benefit to be gained from a better understanding of the role of the immune response in protection against parasitic infections. This field desperately requires

the application of “newer” immunobiological approaches and one facet of this, namely, studies with athymic nude mice, is well reviewed in Chapter 3 by G. F. Mitchell.

The remaining three chapters of this volume are devoted to the field of tumor immunology and reflect the still considerable uncertainty of the relative roles played by various cell types in immune responses to different tumor antigens. In addition to the anti-tumor response of T cells, B cells, and macrophages, a new cell type—termed the natural killer cell—has recently been recognized as another potential cell type that may be capable of lysing many tumor cell lines. In Chapter 6, R. Kiessling and O. Haller comprehensively review the evidence that these natural killer cells may play a major role in immunological surveillance. On a broader level, J. S. Haskill, P. Hayry, and L. A. Radov have considered the potential role of various cell types in allogeneic and anti-tumor immunity, but have particularly concentrated in Chapter 5 on a major aspect that is frequently overlooked and ill defined, namely the *in situ* tumor response, as contrasted with systemic immunity. The analysis of mechanisms of T-cell-mediated immunity to tumors is relatively difficult to assess in *in vivo* studies; as in many other systems, considerable efforts have been made to develop primary immune responses *in vitro*, and the experience in this field of R. C. Burton, S. E. Chism, and N. L. Warner is reviewed in Chapter 4, with particular emphasis on the potential to further analyze the nature of tumor antigens as recognized by T lymphocytes.

Thus, in this volume, we feel that the multiauthor multitheme approach may provide a cross-sectional view of the range of topics in contemporary immunobiology 1977–78, and we gratefully acknowledge the cooperation of all authors in the preparation of this volume.

Noel L. Warner
Max D. Cooper

Contents

Chapter 1

**Influence of Genes of the Major Histocompatibility Complex
on the Reactivity of Thymus-Derived Lymphocytes**

J. F. A. P. Miller

I. Introduction	1
II. Constraints Imposed on T-Cell Activities by Genes of the Major Histocompatibility Complex	2
III. Implications of MHC-Imposed Restrictions for Antigen Perception by T Lymphocytes	4
IV. MHC-Linked <i>Ir</i> Gene Control of Immune Responsiveness .	6
V. Relationship between MHC-Imposed Constraints and MHC-Linked <i>Ir</i> Gene Control of Immune Responsiveness .	8
VI. Concluding Remarks	11
VII. References	13

Chapter 2

**Characterization of Human T-Cell Subpopulations as Defined
by Specific Receptors for Immunoglobulins**

Lorenzo Moretta, Manlio Ferrarini, and Max D. Cooper

I. Introduction	19
II. Basic Features of Distinct T-Cell Subpopulations and Their Receptors for Immunoglobulins	21
A. Preparation of Purified Human T Cells	21
B. Rosette Techniques for Detection of Receptors for IgM and IgG	22
C. Specificity of T-Cell Receptors for IgM and IgG	23
D. Receptors for IgM and IgG Discriminate between Distinct Subpopulations of T Cells	25
E. Turnover of Receptors for IgM and IgG on T Cells ...	25

F.	Tissue Distribution of T _M and T _G Cells	27
G.	Morphology of T _M and T _G Cells	28
III.	Functional Analysis of T _M and T _G Cells	29
A.	Response to Mitogens and Allogeneic Cells	29
B.	Response to Pokeweed Mitogen as an <i>in Vitro</i> Model for Human T- and B-Cell Interactions	31
C.	Identification of T _M Cells as "Helper" Cells	33
D.	Suppressor Capacity of T _G Cells	33
E.	Mode of Suppression by T _G Cells	35
IV.	T _M and T _G Cells in Immunodeficiency Diseases and Malignancies	37
A.	Immunodeficiencies	37
B.	Leukemias	39
V.	Concluding Remarks and Speculations	39
VI.	References	45

Chapter 3

Metazoan and Protozoan Parasitic Infections in Nude Mice

Graham F. Mitchell

I.	Introduction	55
II.	Nematodes	57
A.	<i>Nippostrongylus brasiliensis</i>	58
B.	<i>Ascaris suum</i>	58
C.	Other Nematodes	59
III.	Cestodes	59
A.	<i>Hymenolepis</i> Species	59
B.	<i>Taenia taeniaeformis</i>	60
C.	<i>Mesocostoides corti</i>	60
IV.	Trematodes	61
A.	<i>Schistosoma mansoni</i> and <i>Fasciola hepatica</i>	61
V.	Protozoa	61
A.	<i>Giardia muris</i> and <i>Hexamita muris</i>	61
B.	<i>Plasmodium</i> and <i>Babesia</i> Species	62
C.	Other Protozoa	63
VI.	Concluding Remarks	63
VII.	References	64

Chapter 4

In Vitro* Induction and Expression of T-Cell Immunity to Tumor-Associated AntigensRobert C. Burton, Stanley E. Chism, and Noel L. Warner*

I. Introduction	69
II. Methodology	73
A. <i>In Vitro</i> Induction of Tumor-Specific Immunity	73
B. <i>In Vitro</i> Assay of Tumor-Specific Immunity: ⁵¹ Cr Release	74
C. Important Parameters of Induction and Assay	75
D. Cellular Competitive Inhibition <i>in Vitro</i> Assay	79
III. Induction of CL in "Unstimulated" Cultures	82
IV. Role of the MHC at the Inductive Phase of T-Cell Immunity <i>in Vitro</i> to TAA	87
V. Role of the MHC at the Effector Phase of T _C Immunity <i>in Vitro</i> to TAA	90
VI. Comments and Conclusions	95
VII. References	98

Chapter 5

Systemic and Local Immunity in Allograft and Cancer Rejection*J. Stephen Haskill, Pekka Häyry, and Leslie A. Radov*

I. Introduction	107
II. Histology of Allograft Rejection and Host Response against Solid Tumors	108
A. Histology of Allograft Rejection	108
B. Changes in the Central Lymphatic System during Allograft Rejection	111
C. Histology and Prognostic Significance of Host Response to Cancer	113
D. Histological Studies of <i>in Situ</i> Mechanisms of Antitumor Defense	115
E. Changes in the Central Lymphatic System during Tumor Growth	117
III. Effector Mechanisms in the Central Lymphatic System	119
A. Cytotoxic T Lymphocytes and Allograft Rejection	119
B. Functions of the Cytotoxic T Lymphocytes	121
C. Central Effector Mechanisms in Antitumor Responses	122

IV.	Isolation of Infiltrating Cells and Antibodies from Allografts and Tumors	126
V.	Identification of Infiltrating Cells in Allografts and Tumors	128
A.	Composition of Cellular Infiltrates in Allografts	128
B.	Receptor Specificity of Allograft-Infiltrating Cells	130
C.	Immunological Analysis of Tumor-Infiltrating Cells from Histological Sections of Solid Tumors	131
VI.	Effector Mechanisms Inside Allografts and Tumors	133
A.	Functional Analysis of Allograft-Infiltrating Cells	133
B.	Role of Antibody in Allograft Destruction	137
C.	Functional Analysis of Effector Cell Populations in Tumor Infiltrates	139
D.	Role of Antibody in Solid Tumors	145
VII.	Correlations between Local and Systemic Immunity	147
A.	In Antiallograft Responses	147
B.	In Antitumor Responses	148
VIII.	Concluding Remarks	153
IX.	References	155

Chapter 6

Natural Killer Cells in the Mouse: An Alternative Immune Surveillance Mechanism?

Rolf Kiessling and Otto Haller

I.	Introduction	171
II.	General Characteristics of the NK System	173
III.	Specificity of Mouse NK Cytolytic Activity	174
IV.	Effector Cell Analysis	176
A.	NK Cells Lack Characteristics of Mature T Cells	177
B.	NK Cells Lack Characteristics of B Cells and of Monocyte-Macrophages	177
C.	Relationship between NK Activity and ADCC	178
D.	NK Cells Possess HP Receptors	179
E.	Non-T-Cell Nature of Genetically Controlled Tumor Resistance	180
VI.	Influence of Genetic and Nongenetic Factors on NK Activity	183
A.	Age Influence on <i>in Vitro</i> NK Activity	183
B.	Age Influence on <i>in Vivo</i> Tumor Resistance	184
C.	Effect of Tumor Induction and of Immunization with Tumor Cells on NK Activity	184

D.	Induction of NK Cell Activity by Bacterial Adjuvants .	186
E.	Genetic Analysis of NK Activity	187
F.	Genetic Analysis of Resistance to YAC Cells in Semisynthetic Mice	189
VI.	Relationship between NK Activity and Resistance to Hemopoietic Grafts	192
VII.	Generation of NK Cells <i>in Vivo</i>	195
A.	Dependence on Intact Bone Marrow Function	195
B.	NK Function Is Preprogrammed at the Precursor Cell Level	196
C.	Role of the Thymus	196
D.	Role of the Spleen	197
VIII.	Concluding Remarks	198
IX.	References	199

Chapter 7

Allotypes of IgM and IgD Receptors in the Mouse:

A Probe for Lymphocyte Differentiation

James W. Goding

I.	Lymphocyte Surface Immunoglobulin	203
A.	Use of Antiimmunoglobulin Sera to Study Lymphocyte Receptors	203
B.	What Classes of Immunoglobulin Are Present on the Surface of Lymphocytes?	204
II.	Preparation of Antisera to Murine IgD	206
A.	Antigen Purification by Affinity Chromatography	206
B.	Antibodies to IgD in Murine Alloantisera	207
III.	Allotypes of Murine IgM	212
A.	Antibodies to IgM in "Conventional" Antiallotype Sera	212
B.	Antibodies to IgM in Antilymphocyte Alloantisera	213
C.	Specificity Analysis by Radioimmunoassay	215
IV.	Immunofluorescence Studies of Surface IgM and IgD	222
A.	General Method for the Study of Lymphocyte Surface Alloantigens by Indirect Immunofluorescence	222
B.	Organ Distribution of Surface IgM and IgD	223
C.	Ontogeny of IgM and IgD Receptors	225
D.	Surface Immunoglobulin on Antibody-Containing Cells	227
E.	Capping of Surface IgM and IgD	228
F.	Allelic Exclusion and Haplotype Exclusion	228

V.	Implications for Organization of Immunoglobulin Heavy-Chain Genes	229
A.	The Heavy-Chain Linkage Group	229
B.	Shared V Regions, Class Switches, Haplotype Exclusion, and Clonal Restriction	231
VI.	Functional Role of B-Cell Receptors	233
A.	Immature Cells	233
B.	Mature Cells	235
VII.	Summary	237
VIII.	References	237

Chapter 8

Immunoglobulin Isotype Expression

John F. Kearney and Erika R. Abney

I.	Introduction	245
II.	Ontogeny of Immunoglobulin Isotypes	247
III.	<i>In Vitro</i> Activation of Mouse B Cells	250
IV.	Conclusions	258
V.	References	262
Index		267

Chapter 1

Influence of Genes of the Major Histocompatibility Complex on the Reactivity of Thymus-Derived Lymphocytes

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I. INTRODUCTION

In the mouse the MHC (major histocompatibility complex, or *H-2*) is situated on chromosome 17 about 15 centimorgans from the centromere (Klein, 1975, 1976). It spans a distance of about 0.5 centimorgan and may be divided into five regions: *K*, *I*, *S*, *G*, and *D*. The *K* and *D* gene products were the first to be recognized since they control acceptance or prompt rejection of allografts. They can readily be detected by antisera produced by immunizing members of one inbred strain with histoincompatible cells from another inbred strain. The antigens detected by such antisera are found on all tissues after birth. By using different antisera many alleles were discovered at each locus. The *G* region determines alloantigens present on erythrocytes. The *S* region regulates the level of some complement components and codes for C4. The *I* region determines products of major importance for the genetic control of specific immune responses (*Ir*, or immune responsiveness, genes) (Benacerraf, 1973). It is divided into several subregions, *I-A*, *I-B*, *I-J*, *I-E*, and *I-C*, and these determine membrane glycoproteins known as *I*-associated (*Ia*) antigens. Products of the *I-A*, *I-C*, and *I-E* subregions are expressed on B lymphocytes, macrophages, epidermal cells, and spermatozoa (Shreffler and David, 1975), and products of the *I-J* subregion control determinants present on a subpopulation of T lymphocytes with suppressive functions (Murphy *et al.*, 1976). In addition, the *I* region codes for cell interaction molecules (Katz and Benacerraf, 1975) and components involved in stimulating mixed lymphocyte reactions (Shreffler and David, 1975).

The human genetic complex corresponding to the mouse MHC is known as HLA and is situated on chromosome 6. Among its products are alloantigens determined by the regions *HLA-A*, *HLA-B* (analogous to *K* and *D* in mice), and *HLA-C* and serologically detectable on all nucleated cells after birth. The *HLA-D*-region determinants have been defined by cell culture techniques and are mainly responsible for stimulation in mixed lymphocyte cultures. They also code for alloantigens expressed mainly on B lymphocytes, macrophages, epidermal cells, spermatozoa, and endothelial cells (Kissmeyer-Nielson, 1975).

The MHC exerts a profound influence on many aspects of T-cell (thymus-derived cell) functions. At least four effects deserve special mention:

1. The frequency of T cells reactive to cell surface alloantigens coded by the MHC is 100 to 1000 times that of T cells reactive to other antigens (Simonsen, 1967; Wilson *et al.*, 1977).
2. The control of the extent of a T-cell response to a variety of antigens is exerted by genes which have been localized to the *I* region of the MHC (Benacerraf, 1973).
3. The MHC imposes restrictions on the activities of sensitized T cells (see Section II).
4. Soluble factors, which bear MHC-coded determinants, influence the activation of a variety of T-cell subsets (Tada, 1978; Feldmann *et al.*, 1977; Munro and Taussig, 1975).

The aim of this chapter is to review briefly some of the recent work performed in mice which allows the formulation of a hypothesis that may be used to explain tentatively the relationships among MHC gene products, T-lymphocyte activation, and immune reactivity.

II. CONSTRAINTS IMPOSED ON T-CELL ACTIVITIES BY GENES OF THE MAJOR HISTOCOMPATIBILITY COMPLEX

Activation of some T lymphocytes requires antigen presentation by other cells, e.g., macrophages (Feldmann *et al.*, 1977). This has been well documented for helper T cells (T_H) involved in cooperating with B cells (bone-marrow-derived cells) to enable optimal production of IgG antibody (Basten *et al.*, 1975) and for T cells (T_D) involved in delayed-type hypersensitivity (DTH) (Oppenheim and Seeger, 1976). Some T cells, e.g., cytotoxic T lymphocytes (T_C), may be activated optimally when antigen is presented in association with "accessory" cells (Julius and Herzenberg, 1973). In the last few years it has become very clear that MHC gene products play a critical role in the sensitization of many of these T-lymphocyte subsets (Table I).

Table I. MHC-Imposed Constraints on the Reactivity of T Lymphocytes

Species	Experimental system	MHC region	T-cell subset and phenotype ^a	Reference
Guinea pig	Specific antigen-induced proliferation of sensitized lymphocytes <i>in vitro</i>	<i>I</i>	—	Rosenthal <i>et al.</i> (1975)
Mouse		<i>I</i>	—	R. H. Schwartz <i>et al.</i> (1976)
Mouse		<i>I</i>	—	Peck <i>et al.</i> (1977)
Man		<i>HLA-D</i>	—	Bergholtz and Thorsby (1977)
Mouse	Optimal cooperation between primed T and B lymphocytes for <i>in vivo</i> antibody responses	<i>I-A</i>	T _H (Ly-1)	Katz and Benacerraf (1975)
Mouse	Optimal induction of T _H cells by macrophage-associated antigen <i>in vitro</i>	<i>I-A</i>	T _H (Ly-1)	Erb and Feldmann (1975)
Mouse	T cells cytotoxic to: (a) virus-infected target cells	<i>K</i> or <i>D</i>	T _C (Ly-2,3)	Doherty <i>et al.</i> (1976)
	(b) chemically modified target cells	<i>K</i> or <i>D</i>	T _C (Ly-2,3)	Shearer <i>et al.</i> (1975)
	(c) non-H2-alloantigen	<i>K</i> or <i>D</i>	T _C	Bevan (1975)
	(d) H-Y antigen	<i>K</i> or <i>D</i>	T _C	Gordon <i>et al.</i> (1975)
Man	T cells cytotoxic to H-Y antigen	<i>HLA-A</i>	T _C	Goulmy <i>et al.</i> (1977)
Mouse	Transfer of delayed-type hypersensitivity to: (a) proteins and polypeptides	<i>I-A</i>	T _D (Ly-1)	Miller <i>et al.</i> (1975, 1977)
	(b) contact chemicals	<i>I, K, or D</i>	T _D (Ly-1 and Ly-2,3)	Miller <i>et al.</i> (1976)

^aFor the phenotypes, see Vadas *et al.* (1976) and Feldmann *et al.* (1977).

It was initially demonstrated that the activation of proliferation of sensitized guinea pig T lymphocytes required that the antigen-presenting macrophages had the same *I*-region determinants as the T cell (Rosenthal *et al.*, 1975). This was subsequently shown to apply to mouse (R. H. Schwartz *et al.*, 1976) and to human lymphocytes (Bergholtz and Thorsby, 1977). For example, the activation of T-lymphocyte proliferation in man in response to purified protein

derivative of tuberculin was strongest when macrophages in the culture had the same *HLA-D* determinants as those of the donor of the sensitized T lymphocytes. Essentially comparable findings have been obtained in studies of collaboration between primed T_H and B lymphocytes *in vivo* (Katz and Benacerraf, 1975) and in the induction of T_H cells for *in vitro* antibody responses (Erb and Feldmann, 1975).

Cytotoxic T lymphocytes derived by conventional immunization procedures and specific for virus-specified antigens (Doherty *et al.*, 1976) or chemically modified membrane antigens (Shearer *et al.*, 1975) expressed their cytotoxic potential effectively only when antigenic target cells and killer cells were of the same *H-2K* or *H-2D* type. The same restriction applied to T cells cytotoxic for cells bearing minor histocompatibility antigens (Bevan, 1975; Gordon *et al.*, 1975). Conversely, cells lacking *H-2K* or *H-2D* molecules on their surface (e.g., the teratocarcinoma line, F9) are apparently not recognized by cytotoxic T lymphocytes (Forman and Vitetta, 1975; Goldstein *et al.*, 1976; Doherty *et al.*, 1977).

MHC-imposed constraints have also been reported in the transfer of DTH in mice, the region involved being *I-A* for protein and polypeptide antigens (Miller *et al.*, 1975, 1977) and *I, K*, or *D* for contact chemicals, such as dinitrofluorobenzene (Miller *et al.*, 1976) and for some virus-infected cells (Zinkernagel, 1976a).

As has recently been realized, the MHC-imposed constraints on T-cell functions can, in some cases, arise as a result of sensitization (see Section III). Thus there need be no constraints on the activities of unprimed T cells, with the possible exception of the activation of T cells to antigens the response to which is under strict MHC-linked *Ir* gene control (see Section V). The restrictions imposed by the MHC on the functioning of sensitized T cells have clear implications for the means by which T cells are activated and recognize antigen.

III. IMPLICATIONS OF MHC-IMPOSED RESTRICTIONS FOR ANTIGEN PERCEPTION BY T LYMPHOCYTES

The transfer of DTH to protein antigens in mice was shown to be possible only in *I-A*-compatible recipients (Miller *et al.*, 1975; Vadas *et al.*, 1977). Various experiments made it unlikely that the inability to transfer DTH in MHC-incompatible recipients could be attributed to rejection of the injected cells, their total recruitment into areas such as the spleen, or their engagement in a mixed lymphocyte reaction (Vadas *et al.*, 1977). For example, DTH was successfully transferred from sensitized F_1 hybrid mice to naive mice of the parental strain which are competent to reject the F_1 cells (Table II). The possibility that suppressive influences were generated in an allogeneic environment found no