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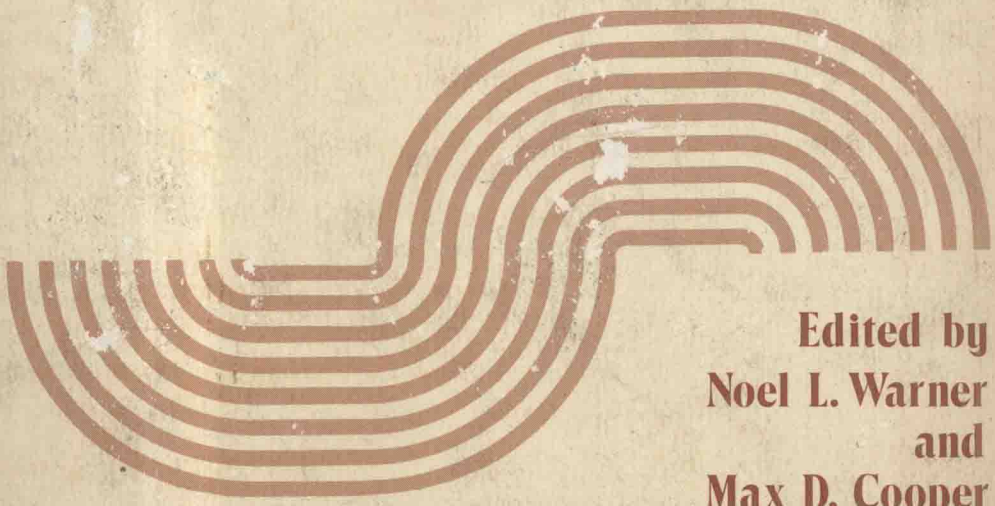
Volume 8



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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

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Graham F. Mitchell

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J. Stephen Haskill, Pekka Häyry, and Leslie A. Radov

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 *in vitro*	*I*	–	Rosenthal *et al.* (1975)
Mouse		*I*	–	R. H. Schwartz *et al.* (1976)
Mouse		*I*	–	Peck *et al.* (1977)
Man		*HLA-D*	–	Bergholtz and Thorsby (1977)
Mouse	Optimal cooperation between primed T and B lymphocytes for *in vivo* antibody responses	*I-A*	T_H (Ly-1)	Katz and Benacerraf (1975)
Mouse	Optimal induction of T_H cells by macrophage-associated antigen *in vitro*	*I-A*	T_H (Ly-1)	Erb and Feldmann (1975)
Mouse	T cells cytotoxic to:			
	(a) virus-infected target cells	*K* or *D*	T_C (Ly-2,3)	Doherty *et al.* (1976)
	(b) chemically modified target cells	*K* or *D*	T_C (Ly-2,3)	Shearer *et al.* (1975)
	(c) non-H2-alloantigen	*K* or *D*	T_C	Bevan (1975)
	(d) H-Y antigen	*K* or *D*	T_C	Gordon *et al.* (1975)
Man	T cells cytotoxic to H-Y antigen	*HLA-A*	T_C	Goulmy *et al.* (1977)
Mouse	Transfer of delayed-type hypersensitivity to:			
	(a) proteins and polypeptides	*I-A*	T_D (Ly-1)	Miller *et al.* (1975, 1977)
	(b) contact chemicals	*I*, *K*, or *D*	T_D (Ly-1 and Ly-2,3)	Miller *et al.* (1976)

[a]For 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, 1976*a*).

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