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Functional Specificity of Thymus-Dependent Lymphocytes

A relationship between the specificity of T lymphocytes and their functions is proposed.

William E. Paul and Baruj Benacerraf

Two principal classes of lymphocytes, the thymus-independent (B) and the thymus-dependent (T) lymphocytes, participate with macrophages in the reactions and interactions that constitute the immune response. The specificity of the B lymphocytes is well understood, largely because these cells and their progeny secrete specific antibody molecules. The antigen-combining sites of antibodies are identical to the combining sites of the surface receptors of the B lymphocytes that were responsible for their secretion (*1*). Since the range of specific chemical configurations against which antibodies can be made is very large (*2*), the variation in B cell receptors must be equally extensive.

By contrast, information on the specificity of T lymphocyte receptors has been limited to the results of functional analyses (*3*). That is, T cell receptors have been studied by determining which substances would initiate a given response and which would not, because, until very recently, no antigen-specific T cell products were available. Even now, the analysis of specific T lymphocyte factors has just begun, and only very limited specificity data have yet been obtained.

Nevertheless, as a consequence of functional analysis of T lymphocyte receptors, we are now aware of the restricted range of specificity of these cells, particularly when compared with B cells. This restriction of the specificity of T lymphocytes must directly reflect the types of functions which these cells mediate: (i) the recognition of histocompatibility antigens (*4*), and (ii) the regulatory and surveillance functions of the immune response (*5*). In mediating these functions, the T cell takes part in precise types of interactions with other cells, and hence the T lymphocyte is required to recognize the surface markers of the cell with which it interacts.

In this article, we relate the specificity restrictions of T lymphocytes to these functional characteristics. We also attempt to draw some conclusions concerning the nature of the T lymphocyte receptors and the mechanism by which T cells exert their regulatory functions from our knowledge of (i) these specificity restrictions and of (ii) the genetic control of T lymphocyte functions.

Specificity of T Lymphocyte–Mediated Responses

Against thymus-dependent antigens. The concept of the restricted nature of the range of specific responses that T lymphocytes can mount was first developed as a result of studies of delayed hypersensitivity and contact reactivity (*6*). These T lymphocyte–dependent phenomena and their in vitro counterparts—namely, antigen-stimulated lymphocyte proliferation (*7*) and production of migration inhibition factor (MIF) (*8*)—develop principally in response to immunization with protein and polypeptide antigens. By contrast, immunization with polysaccharides (*9*) or with multivalent haptens (*9*) fails, in most instances, to initiate a state of delayed hypersensitivity, and cells from animals immunized with these materials do not express in vitro correlates of delayed hypersensitivity.

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Table 1. Assignment of immunological phenomena to regions of the major histocompatibility complex (MHC).

Functions of the MHC	H-2 regions
Antigens stimulating tissue rejection and specific cytolytic T cells	K and D > I
Cytolytic T cells specific for cell membrane antigens: virally coded, chemically modified, tumor-associated or minor histocompatibility	K and D
Mixed leukocyte reaction; graft versus host reactions	I > K and D
Specific immune responses to thymus-dependent antigens (*Ir* genes)	I (I-A, I-B, I-C)
Specific immune suppression by T cells. Immune suppression genes	I
Antigenic specificity on suppressor cells and suppressor factor	I-J
T and B cell cooperative interactions in secondary IgG responses	I-A
Antigen presentation to T cells by macrophages and specificity contribution in secondary responses and delayed hypersensitivity	I-A
Complement (C) components linked to the MHC in man, mice, and guinea pigs: serum levels of the components of complement C_4, C_2, and C_3; factor B	S and other loci outside the MHC

Conversely, B lymphocyte receptors and antibody molecules display no such restriction in their specificity.

In the last 10 years, T lymphocytes have been shown to exert a powerful regulatory effect on antibody responses (*10*). Cells expressing both positive regulatory effects (helper T lymphocytes) (*11*) and negative regulatory effects (suppressor T lymphocytes) (*12*) have been described. Analysis of the types of antigens capable of stimulating responses of helper cells and of the specificity of the responses of these cells revealed a degree of restriction similar to that observed in the study of delayed hypersensitivity and contact reactions (*13*).

An immediate corollary of the description of helper T lymphocytes and their function in regulating antibody responses was the recognition that antigens could be divided into two broad classes, depending on whether they could initiate responses in the presence or absence of helper cells (*14*). The antigens that either require or are very much helped by T lymphocytes to bring about a response are referred to as thymus-dependent antigens. The antigens that stimulate B cells without the cooperation of specific T cells are designated thymus-independent antigens. As we would expect, the thymus-dependent antigens proved to be molecules of precisely the same class as those capable of stimulating helper cells and as those capable of initiating delayed hypersensitivity or contact reactions (or both).

An important feature of immune responses to thymus-dependent antigens is that they are strictly controlled, in an antigen-specific manner, by the operation of a group of genes found in the major histocompatibility complex (MHC) of higher vertebrates (*15, 16*). The specific regulatory action of these immune response (*Ir*) genes has been demonstrated through the study of structurally simple antigens. It is increasingly apparent, however, that genes of this type regulate immune responses to all thymus-dependent antigens. Furthermore, the specific action of MHC-linked *Ir* genes on immune responses to thymus-dependent antigens is not limited to positive regulation. Genes mapping within the MHC also regulate specific suppressive responses (*17*).

Thus, immune responses to thymus-dependent antigens are regulated in both a positive and negative sense by the operation of regulatory T lymphocytes. These T lymphocytes, as well as T lymphocytes that mediate responses such as delayed hypersensitivity and contact reactivity, have a restricted range of functional specificity, involving proteins, polypeptides, and, as described later, a series of MHC-encoded cellular antigens. Finally, such positive and negative thymus-dependent responses are controlled, in a specific manner, by a series of MHC-linked immune response genes.

Against MHC gene products. The MHC-linked *Ir* gene control of immune responses to individual thymus-dependent antigens takes on additional significance when it is considered that a major function of T lymphocytes is to recognize and react with MHC gene products of the same and other species (*4*).

The MHC is a complex of genes, first recognized as controlling the acceptance or prompt rejection of tissue or organ allografts (*18*). This complex, found in all mammalian species thus far studied, is now known to control a large number of immunologically important functions (*19*). In the mouse, the complex has been divided into five principal regions (K, I, S, G, and D) (Table 1). The K and D regions, which appear to have arisen by gene duplication, contain genes which code for membrane glycoproteins, the H-2K and H-2D antigens, which are expressed on most cells of the body, are important in graft rejection, and appear to be the principal targets for alloreactive cytotoxic T lymphocytes. The S region regulates the level of complement components (*20*); and the marker gene for this region, the *Ss* gene, has been shown to be the structural gene for the fourth component of complement (*21*). The I region, which has now been divided into several subregions (I-A, I-B, I-J, I-E, and I-C), contains (i) the specific immune response genes, (ii) genes which regulate mixed lymphocyte reactivity, and (iii) genes which code for a class of membrane glycoproteins, called the Ia antigens, with principal representation on lymphocytes and macrophages (*19*).

There are several very important characteristics of the reactivity of T lymphocytes with MHC gene products. First, a substantial fraction (from 3 to 6 percent) of all T lymphocytes appears to be specifically reactive to the membrane antigens encoded by any individual allogeneic MHC haplotype (*22*). Second, T lymphocytes are now recognized to be a heterogeneous cell population in terms of their functions and the surface antigens they express. Interestingly, T lymphocytes of different functional classes (*23*), although sharing a restricted range of specificity and high reactivity with alloantigens, nonetheless differ from each other in the particular class of MHC-encoded antigens which they recognize; thus, one population of T lymphocytes contains cells that can lyse allogeneic (*23*), xenogeneic (*24*), or modified syngeneic target cells (*25*). These cytotoxic T lymphocytes (killer T cells) principally recognize antigenic determinants coded for in the K and D regions of the mouse H-2 complex (*26*) and in corresponding genetic regions of other mammalian species (*27*). The antigens encoded in these regions are expressed on virtually all cells. The other principal T cell population reactive with the MHC antigens recognizes Ia antigens (*28*), which are the set of antigens coded for in the I region of the MHC, the region in which the *Ir* genes are mapped. The responses mediated by this population of cells are the mixed lymphocyte reaction and the graft-versus-host reaction. In addition, these cells play a regulatory role in amplifying the immune response that leads to the appearance of killer T cells (*29*).

Thus, in contrast to B lymphocytes, T lymphocytes are highly specialized in their capacity to recognize or to be activated by MHC gene products (or both). Furthermore, their capacity to respond to conventional protein antigens is regulated by a set of genes (the *Ir* genes) that are encoded in the MHC.

Cell populations specific for thymus-dependent antigens and for the MHC gene products. The findings that T lymphocytes recognize the thymus-dependent antigens, the H-2K and H-2D antigens (and their congeners in other species), and products of the I region of the MHC raise the issue of whether the capacity to recognize thymus-dependent antigens and MHC gene products is characteristic of a single T cell population or of independent T cell populations. As we mentioned earlier, cytotoxic T lymphocytes and T lymphocytes reactive in mixed lymphocyte responses belong to distinct T cell classes, which may be distinguished from each other by the expression on their membranes of distinctive differentiation antigens, termed Ly antigens (*23–25*). Moreover, as we have also noted, the relative number of T lymphocytes involved in one or the other form of reactivity with MHC gene products is substantial. Approximately 5 percent of T lymphocytes are reactive to the MHC gene products of a single allogeneic haplotype (*22*).

If all the types of T cell specificities are clonally distributed, the question arises as to how can we accommodate the T lymphocytes from nonimmunized donors which are reactive with (i) all alloantigens controlled by the relevant MHC region; (ii) MHC-controlled xenoantigens; (iii) modified autologous antigens, such as those that appear to be formed in virus-infected cells or in tumor cells and for which specific syngeneic killer T cells have been identified; and (iv) all the numerous conventional thymus-dependent antigens.

Simply on the argument of available numbers of T lymphocytes, the possibility must be considered, as proposed by Simonsen (*30*) and by Heber-Katz and Wilson (*31*), that the same clones of T cells that are reactive with MHC gene products may also be reactive with thymus-dependent antigens. Furthermore, within the framework of a single concept of T lymphocyte activation we must attempt to reconcile the existence of two apparently disparate types of restriction in the recognition by T cells of the MHC antigens and of the thymus-dependent antigens. Recent findings that responsiveness of specific T lymphocytes to conventional (that is, non-MHC) antigens depends on the capacity of these cells to recognize an MHC gene product may provide the basis for a unifying hypothesis, as will be discussed in the following section.

Participation of MHC gene products in stimulation of T lymphocytes by thymus-dependent antigens. A dramatic demonstration that MHC gene products do participate in the specificity of T lymphocyte responses which appear to be principally directed at non-MHC antigens has been provided by studies of Zinkernagel and Doherty (*32*) and of Shearer *et al.* (*33*). These investigators examined the specificity of T lymphocyte–determined lysis of syngeneic target cells that were either infected by virus or chemically modified. It was shown that killer T lymphocytes, derived by conventional priming procedures and nominally specific for virus-induced or chemically modified cell membrane antigens could express their killer activity most effectively only when the target cells (which also carried the viral or chemical antigen) were of the same H-2D or H-2K type as the killer cells. Two alternative explanations of this MHC restriction in T lymphocyte–mediated killing were then considered. (i) The requirement for similarity at H-2D or H-2K could reflect a requirement that the killer and target cells have the same MHC antigens, perhaps as a self-recognition mechanism required for the cellular interaction process that leads to T lymphocyte–mediated lysis. (ii) The sensitizing cell (that is, the virus-infected or chemically modified cell which stimulates the primary in vivo or in vitro response) and the target cell had to share similar MHC antigens. The MHC restriction might then signify that the same "determinants" (that is, MHC gene products and thymus-dependent antigen) must be used for both primary (sensitizing) and secondary (killer) responses.

To choose between these alternatives, lymphocytes were obtained from radiation chimeras prepared by reconstituting lethally irradiated F_1 mice with bone marrow derived from one parental strain. As a result of development in the F_1 environment, these parental lymphocytes become unresponsive to the histocompatability antigens of the other parent. These cells can be immunized in vitro by chemically or virally modified cells bearing the tolerated allogeneic H-2 haplotype. The cytotoxic or killer T lymphocytes generated in this way preferentially lyse modified allogeneic cells rather than similarly modified syngeneic target cells (*34*). These experiments indicate that the MHC restriction reflects a need for similarity between the sensitizing cell and target cell rather than a requirement for similarity between killer and target cells.

The concept that MHC gene products play a critical role in sensitization and elicitation of T lymphocyte responses to conventional antigens is supported by studies of (i) activation of T lymphocytes by macrophages that had been briefly exposed to antigen and then washed (antigen-exposed macrophages) and of (ii) the collaboration of T and B lymphocytes. In vitro (and presumably in vivo) activation of most T lymphocyte responses to thymus-dependent antigens, with the possible exception of suppressor functions, appears to require antigen presentation by macrophages (*35*). It was initially demonstrated that the activation of proliferation by primed T lymphocytes from guinea pigs required that the T cells and the antigen-presenting macrophages have the same I region determinants. This requirement has been confirmed for activation of proliferative responses by murine T cells (*36*), for in vitro priming of helper T cells (*37*), and for induction of secondary antibody responses in vitro to a random linear amino acid copolymer of glutamic acid, alanine, and tyrosine (GAT) (*38*). Furthermore, the transfer of delayed hypersensitivity from donor to recipient, where primed T cells are derived from the donor and macrophages are probably largely recipient in origin, depends on MHC similarity between donor and recipient (*39*). In each of these cases, the MHC region involved is the I region rather than either the H-2D or K regions.

Essentially comparable results have been obtained in the study of collaboration between primed T and B lymphocytes in the elicitation of secondary antibody responses (*40*). Such responses are most efficiently achieved if donors of the B and T lymphocytes are similar in the I-A subregion of the MHC.

The experiments with macrophages and T lymphocytes and those with T lymphocytes and B lymphocytes were initially interpreted as suggesting the need, if responses are to be elicited, for similarity between the interacting cells in a membrane determinant controlled by a gene within the I region (*41, 42*). However, several lines of evidence now suggest that, for both systems, the restriction in collaboration arises from the requirement that the macrophage or B cell which participates in the primary response must be similar in its I region to the macrophage or B cell which participates in the secondary response. In favor of this second possibility are the following findings from studies of interactions of macrophages and T lymphocytes.

1) In F_1 hybrid guinea pigs, the population of antigen-reactive T lymphocytes that may be activated by antigen associated with macrophages of one parent is independent of the population that can be activated by the same antigen associated with the macrophages of the other

parent (*43, 44*). Since available evidence gives no support for allelic exclusion of I region genes, this result is most easily explained by postulating that each population was primed by presentation of antigen in association with I region antigens of one or the other parental type, displayed on F_1 macrophages; thereafter, such cells can only be activated by restimulation with antigen-exposed macrophages bearing I region determinants of the same type as those involved in the initial activation of that population of T cells. Indeed, direct support for this concept has recently been provided by studies indicating that T lymphocytes derived from inbred guinea pigs of one strain can be primed in vitro by allogeneic trinitrophenyl (TNP)-conjugated macrophages if T lymphocytes reactive to alloantigens are depleted. Thereafter, these primed cells can be stimulated to proliferate by TNP-conjugated allogeneic macrophages of the type used for priming but not by TNP-conjugated syngeneic macrophages (*44*).

2) It was previously shown that primed T cells from F_1 mice can successfully transfer delayed hypersensitivity to recipients of either parental type as well as to syngeneic F_1 animals (*39*). The question was then asked whether F_1 T cells sensitized in one of the parental strains can transfer delayed hypersensitivity to both parental strains or only to that strain in which they were originally sensitized. Use was made of congenitally athymic (*nu/nu*) mice bearing one of the parental H-2 haplotypes as the recipient of the F_1 thymocytes. Thus, (BALB/c × CBA)F_1 T cells were sensitized to a thymus-dependent antigen in a *nu/nu* BALB/c parental environment and then transferred to unsensitized BALB/c or CBA mice to test their ability to transfer delayed hypersensitivity (*45*). The F_1 T cells sensitized in *nu/nu* BALB/c recipient mice could transfer delayed hypersensitivity to BALB/c and not to CBA mice; and, reciprocally, F_1 T cells sensitized in *nu/nu* CBA mice transferred delayed hypersensitivity to CBA but not to BALB/c mice. These results indicate that sensitization of an F_1 mouse for delayed hypersensitivity normally results in the activation of two subsets of F_1 T cells which differ with respect to their ability to recognize the same antigen presented or macrophages in association with I-A gene products contributed by one of the other parental strain.

3) A system has also been developed in which it is possible to prime mice with the linear random polymer GAT associated with macrophages (*38*). Spleen cells from these primed mice can be tested in vitro for secondary antibody responses to GAT by challenging with macrophages exposed to GAT. If initially primed with syngeneic macrophages exposed to GAT, secondary responses can be elicited by GAT-exposed syngeneic but not by GAT-exposed allogeneic macrophages. In contrast, initial priming with GAT-exposed allogeneic macrophages prepares mice for a secondary response when stimulated by GAT on allogeneic macrophages of the type used in priming, but not by GAT on either syngeneic or on allogeneic macrophages of a type different from that used for initial priming. Such restrictions do not obtain, however, in the primary responses which can be elicited equally well by GAT-exposed syngeneic or allogeneic macrophages.

As was mentioned earlier, studies on collaboration of primed T cells with B cells led to a similar conclusion, namely, that the interacting cells must be obtained from donors which are similar in the I-A subregion of the MHC. This was originally demonstrated for the secondary response to conjugates of hapten with protein (*40*). However, the collaborative potential of unprimed T and B lymphocytes does not appear to be restricted by the MHC provided that care is taken to avoid allogeneic effects. If alloreactive cells are removed, collaboration between allogeneic T and B lymphocytes in primary response is reported to be possible (*46*). Similarly, if F_1 radiation chimeras are produced by the injection of parental bone marrow cells and the reconstituted animals are primed with sheep red blood cells (SRBC), T cells of one parental genotype will collaborate with B lymphocytes from the alternative parent in developing antibody to SRBC (*47*). However, in confirmation of the earlier findings of Katz and Benacerraf (*40*), if T cell populations from which specific alloreactive cells have been removed are primed in a syngeneic environment, they are required to interact with B cells bearing the same H-2 haplotype for secondary responses to occur (*48*).

Each of these experiments suggests that the MHC restrictions in T cell and B cell cooperation, as in the case of macrophage–T cell interactions, arise as a result of the priming process; and that T lymphocytes specific for thymus-dependent antigen and, in addition, specific for gene products of a given I region (or H-2D or K region) are selected during primary responses.

Thus, responsiveness to the well-recognized thymus-dependent antigens depends in turn on the recognition of the antigen in the context of an appropriate MHC gene product. This responsiveness relates two of the principal types of antigens for which T cells appear to be specific. These observations also provide a framework for the understanding of the mechanism of action of specific immune response gene products. The function of these gene products and their mapping within the I region of the MHC may now be considered with respect to their regulation of these cellular interactions. Indeed, one principal function of *Ir* genes may be to specify or regulate molecular associations of antigen and MHC gene products on the macrophage or B cell (or both) to produce an immunogenic product. A second function may be expressed in T lymphocytes as part of the recognition system through which either thymus-dependent antigen or MHC gene product is recognized on the cell surface.

Finally, these interactions between thymus-dependent antigens and MHC gene products may also clarify some of the diverse functional properties of T lymphocytes. They may provide us with insight as to how the capacity to recognize thymus-dependent antigens arose, in an evolutionary sense, in a class of cells whose principal functions were the regulation of cellular interactions and the discrimination of distinctions between self and nonself.

Regulatory Function of T Lymphocytes

It is increasingly clear that T lymphocytes exert critical regulatory controls on the immune response of B lymphocytes and of other T lymphocytes. It is now recognized that separate classes of T cells mediate the positive (helper) (*49*) and negative (suppressor) functions (*49, 50*). Furthermore, the regulatory action exerted by T cells must be considerably more complex than a simple negative or positive control of antibody responses in general. This regulation appears to involve the selective action of T lymphocytes, in conjunction with antigen, upon clones of responding cells with distinctive functional phenotypes.

We now describe some of the phenomena that reflect this fine regulatory activity of T lymphocytes on B lymphocyte differentiation and function.

1) The stimulation of antibody responses of immunoglobulin G (IgG) as compared to immunoglobulin M (IgM) (*51*).

2) The selection of precursors of cells that secrete a given class, or subclass of immunoglobulin (Ig) and even a given allotypic variant of that subclass (*52*).

3) The increase in the affinity of antibody that occurs in the course of immune responses (*53*).

4) The selective activation of a clonally restricted hapten-specific antibody that depends on the thymus-dependent carrier molecule to which the hapten is conjugated (*54*).

5) The expression of common idiotypes on antibody molecules specific for distinct antigenic determinants presented on the same carrier molecule (*55*).

6) The selection of precursors of antibody-forming cells which produce hapten-specific antibody of a net charge opposite to that of the carrier molecule used to form the hapten-carrier conjugate (*56*).

The salient features of some of these findings will be described in order to provide illustrations of the specificity of the regulatory functions exerted by T lymphocytes. Let us first consider the role of T lymphocytes in the determination of the relative amounts of IgM and IgG antibody which are produced in a given response. For thymus-dependent antigens, such as simple proteins, the participation of T lymphocytes is required for the production of both IgM and IgG antibody. However, distinctions in the interactions that result in the secretion of these two immunoglobulin classes can be made. For example, lysis of a population of B lymphocytes bearing Ia antigens with antiserum to Ia and complement largely eliminates in vitro thymus-dependent primary responses of the IgG class but has been reported to have little or no effect on antibody responses of the IgM class to the same antigen (*51*). This difference indicates that precursor of cells that secrete antibody of the IgG class express Ia antigens on their surface. Furthermore, the addition of specific antiserum to Ia (anti-Ia serum) without complement at culture initiation blocks in vitro thymus-dependent IgG but not IgM responses (*57*), suggesting that the precursor cell not only bears Ia molecules on its membranes but that Ia molecules may be important sites for activation of IgG responses by the action of T lymphocytes and antigen. This concept is further strengthened by the fact that allogeneic effects mediated by the interaction of alloantigen-specific T lymphocytes with Ia molecules on B lymphocytes stimulates the synthesis of IgG antibodies in situations in which only IgM antibody would have been produced had there been no allogeneic effect (*58*). These experiments indicate that the population of B cells responsive to T cell help can be subdivided into IgM precursors and IgG precursors on the basis of the expression of Ia antigens and that the Ia site may be important in receiving the T lymphocyte "signal." This, in turn, suggests that the collaborative mechanism which T lymphocytes use for the Ia-bearing IgG precursor and for the IgM precursor, which presumably has little or no Ia, must be quite different.

A second example of T lymphocyte regulation of B lymphocyte differentiation and function comes from studies suggesting that helper T lymphocytes are uniquely specific in their interaction with precursors of antibody-forming cells that bear a given class or subclass of Ig and even a given allotypic variant of an IgG class. This has been demonstrated in the allotype suppression system of Herzenberg *et al.* (*52*) and in studies of the distinctive requirements of the activation of precursors of cells that secrete IgG and those that secrete IgE (*59*).

Finally, it has been recognized for some time that helper T lymphocytes are required for the events involved in the progressive selection of clones of cells secreting high-affinity antibody (*53*). For example, the affinity of the hapten-specific antibody is determined by the nature of the thymus-dependent carrier molecule used in immunization, as one would anticipate for a T lymphocyte–regulated function. Conversely, hapten-specific antibodies which are of limited heterogeneity (oligoclonal) are seen particularly when carriers of restricted immunogenicity for T lymphocytes are used (*54*). Good examples of these are antigens that stimulate reponses which are controlled by single *Ir* genes.

Table 2. Negative selection with the use of bromodeoxyuridine and light of (strain 2 × strain 13)F_1 T lymphocytes responsive to antigens presented on parental macrophages. T lymphocytes were obtained from (strain 2 × strain 13)F_1 guinea pigs that had been immunized to ovalbumin (OVA) emulsified in complete Freund's adjuvant. The cells were initially incubated with strain 2 macrophages exposed to OVA or strain 13 macrophages exposed to OVA. At 48 hours, bromodeoxyuridine ($3 \times 10^{-6}M$) was added, and the cells were exposed to light 24 hours later. The cells were then washed and recultured with strain 2 or strain 13 macrophages exposed to nothing, OVA, or PPD. ^{3}H-Labeled thymidine was added after 2 days, and incorporation of isotope was measured 1 day later. Results represent the number of counts per minute incorporated as a result of stimulation with macrophages that had been exposed to antigen minus the number of counts per minute incorporated as a result of stimulation with macrophages not exposed to antigen. Underlined values indicate instances of specific negative selection. [Data adapted from (*41*)]

OVA-exposed parental macrophages*	Subsequent responses to antigen-exposed macrophages (10^3 count/min)			
	Strain 2 exposed to		Strain 13 exposed to	
	OVA	PPD	OVA	PPD
Strain 2	<u>0.9</u>	85.8	19.5	51.0
Strain 13	75.9	68.5	<u>1.9</u>	65.3

*Used in initial culture.

Significance of the Specificity of T Lymphocytes for Regulatory Function

Thus far, we have considered three aspects of T lymphocyte specificity: the capacity of T lymphocytes to be stimulated by thymus-dependent antigens, their responsiveness to products of the major histocompatibility complex, and their highly specific regulatory functions. Moreover, the recognition and response of T lymphocytes to thymus-dependent antigens depends upon the recognition of MHC gene products. Indeed, negative selection studies provide strong evidence that individual T lymphocytes recognize both MHC gene products and thymus-dependent antigens (*43, 44*). In these studies, illustrated in Table 2, T lymphocytes from (strain 2 × strain 13)F_1 guinea pigs immune to ovalbumin and to purified protein derivative of tuberculin (PPD) were stimulated in vitro with ovalbumin-exposed macrophages from strain 2 parental guinea pigs. After 48 hours, bromodeoxyuridine was added to the culture, and 24 hours later the cultures were exposed to light. Bromodeoxyuridine is a thymidine analog and is incorporated into DNA as it is synthesized. On exposure to light, bromodeoxyuridine becomes activated and causes cross-linkage of chromatin strands preventing cellular proliferation. Consequently, when these cultures were restimulated with ovalbumin-exposed strain 2 macrophages, they failed to respond with the characteristic increased DNA synthesis observed in control cultures; however, they responded normally when challenged with either strain 2 macrophages exposed to PPD or with strain 13 macrophages exposed to ovalbumin. Several lines of evidence demonstrate that the critical gene products by which antigen-exposed strain 2 and strain 13 macrophages are distinguished by F_1 T lymphocytes are the Ia antigens. This result indicates, therefore, that one population of F_1 T lymphocytes recognizes both ovalbumin and strain 2 Ia antigens, and an independent population recognizes ovalbumin and strain 13 Ia antigen on macrophages. Selective respon-

siveness to strain 2 macrophages exposed to ovalbumin and to strain 13 macrophages exposed to ovalbumin could not be dependent on the concerted action of one population of T cells recognizing Ia antigens and a second population recognizing ovalbumin, because in the latter case the treatment with bromodeoxyuridine and light would have had to eliminate at least one of these populations in order to ablate the response to strain 2 macrophages exposed to ovalbumin. If the ovalbumin-responsive population had been eliminated, then the response to strain 13 macrophages exposed to ovalbumin should have also been abolished; on the other hand, elimination of the population of F_1 T cells which recognized strain 2 Ia antigens should have ablated responses to strain 2 macrophages exposed to PPD. The fact that both strain 13 macrophages exposed to PPD and strain 2 macrophages exposed to PPD stimulated responses indicates that one cell population recognizes both MHC gene product and thymus-dependent antigen.

Formal experiments of this type have not yet been performed on specific T lymphocytes which mediate regulatory functions, but the evidence that helper activity displays restrictions determined by the I region suggests that individual helper T lymphocytes also must express this dual recognition function. Since certain aspects of the regulatory function mediated by these cells are highly specialized in that the helper activity may be limited to B lymphocytes capable of synthesizing antibody of a given class, allotype, or idiotype, it is quite probable that T lymphocytes must display a third type of specificity—namely, the ability to recognize distinct membrane markers on B lymphocytes capable of subsequently secreting immunoglobulin of a given class, allotype, or idiotype. The membrane markers that such helper T lymphocytes recognize might be of two general types. Such markers might be the immunoglobulins themselves, expressed on the cell membrane. That is, the T lymphocytes, or a soluble product of the T lymphocytes, might be specific for the constant portion of the immunoglobulin molecule (in the case of class or allotype selection) or for idiotypic determinants of the variable regions of immunoglobulin. Alternatively, B cells capable of secreting antibody of a distinct class, allotype, idiotype, or charge may bear individual acceptor molecules, nonimmunoglobulin in nature, capable of interacting with the T cell or its product. The second of the two possibilities seems less likely, as it requires that B cells of a given potential express both a specific immunoglobulin and a distinct membrane marker characteristic for the immunoglobulin type expressed. In either case, however, the specificity of the regulatory activity suggests that an individual helper T lymphocyte would express three different kinds of specificity: the capacity to recognize thymus-dependent antigens, MHC gene products, and membrane markers reflecting the immunoglobulin potential of the B cell. It might be argued, and it has been suggested (*42*), that, in fact, MHC gene products, such as Ia antigens, on the B cell act as acceptors for T cell regulatory action, thus limiting the number of types of recognition to two. This would require that B cells capable of secreting distinct types of immunoglobulin molecules would bear distinctive I region gene products. No evidence for this has yet been provided, nor does any critical data exclude it.

Since it appears that interactions between macrophages and T lymphocytes and interactions between T lymphocytes and B lymphocytes involve recognition by T lymphocytes of thymus-dependent antigen and Ia determinants, it is instructive to consider the possible relation between these two situations. A population of T lymphocytes, selectively stimulated because it could interact with the antigen and with Ia molecules expressed on macrophages, would appear to be uniquely equipped to interact with B lymphocytes that had bound antigen because of their specific antigen-binding receptors and that bore the same Ia molecules as the macrophages used for priming. This idea emphasizes that the macrophage and the B lymphocyte may play a symmetrical role in initiation and expression of T lymphocyte functions; that is, the presentation to T lymphocytes of both specific thymus-dependent antigens and Ia molecules.

In this regard, it is of interest that, when Ia antigens were first described, it was anticipated that they would be principally expressed on T lymphocytes because the genes specifying Ia antigens were either closely linked or identical to the H-linked *Ir* genes, and the function of these genes was then believed to be expressed mainly within T lymphocytes (*15*). However, it was soon recognized that Ia antigens, although found on some classes of T lymphocytes and their products, were principally expressed on B lymphocytes and on certain classes of macrophages (*60*). This was perplexing until evidence was brought forth that the recognition of I region antigens expressed on macrophages was critical for the triggering of T cells. This line of study, together with cell-mixing experiments, now suggest that *Ir* gene products, as well as Ia antigens, may express their functions in both macrophages and B lymphocytes (*61*).

The T Lymphocyte Receptor

Let us now consider the molecular mechanisms involved in T lymphocyte recognition of antigen and in the multiple specificities which these cells express. The T lymphocytes are endowed with a high degree of discrimination with respect to their capacity to recognize specific moieties of the three general types described. The discrimination among individual thymus-dependent antigens is very precise, including a capacity to distinguish dinitrophenyl derivatives of protein from trinitrophenyl and mononitrophenyl derivatives (*62*). Similarly, mutant MHC gene products can be very well distinguished from the wild type by specific T cells, even when minimal serologic differences are found (*63*). Finally, the regulatory function of T lymphocytes distinguishes different allotypic forms of immunoglobulin molecules of the same class (*52*). Neither the chemical nature of the receptors nor the issue whether the T lymphocyte uses independent receptors specific for each of its recognition functions or a complex unit capable of recognizing both Ia molecules and conventional thymus-dependent antigens has yet been resolved. It is now generally accepted that T lymphocytes do not bear endogenously synthesized immunoglobulin of any of the classes known to be expressed on B lymphocytes, nor do they bear identifiable κ or λ light chains of the immunoglobulin molecule. Yet, recent evidence indicates that T lymphocytes bear idiotypic determinants similar to those expressed on the heavy chain of some antibodies directed to the same antigen (*64*). This has led to the view that variable regions of the immunoglobulin heavy chain are part of the T lymphocyte receptor, or of one of the receptors, if multiple distinct recognition structures are involved. At the same time, factors with antigen specificity have been obtained from primed T lymphocytes (*65, 66*). These factors are able to mediate some of the specific regulatory activities that T lymphocytes exert on the immune response. These antigen-specific suppressor or helper factors, being products of specific cells, are also good candidates for involvement in the recognition sys-

tem of T lymphocytes. Consequently, a careful examination of their characteristics promises to provide information on the mechanism by which T lymphocytes recognize antigens. The results from several laboratories (*65, 66*) where these factors have been studied agree that the T cell factors (i) are obtained from T lymphocytes; (ii) are specific for the antigen used to prime the cells from which the factors are obtained; (iii) do not bear antigenic determinants of the immunoglobulin heavy or light chain constant region; (iv) bear antigenic determinants coded for in the I region of the MHC; and (v) have an estimated molecular size in the range of 40,000 to 60,000 daltons.

In addition, the suppressor factor specific for the random linear polymer GAT demonstrates the same range of avidity for antigen as do antibodies produced in the same mouse strain (*66*), and can be purified by absorption to, and elution from, immunoadsorbents bearing the antigen for which the factor is specific. The activity of material eluted from such an antigen column is removed by immunoadsorbents bearing antibodies specific for Ia antigens. This indicates that the same molecular complex has antigen-binding activity and bears Ia determinants (*66*).

The molecular basis of the specificity that is expressed by Ia-bearing factors has not been determined. In particular, whether these molecules bear idiotypic determinants similar to those expressed on the variable regions of heavy chains derived from antibodies of the same specificity is not known.

The issue now to be resolved is the relation of the Ia-bearing antigen-recognition molecule to the molecule bearing heavy chain idiotype. Furthermore, whether the molecules involved in the recognition of MHC gene products and the regulatory recognition are the same or different from those involved in the recognition of thymus-dependent antigen must be determined. The recent rate of progress in the identification of soluble T cell factors promises that the resolution of these issues can be accomplished in the near future.

Conclusion

The understanding of T and B lymphocyte specificity involves the consideration of the different requirements for distinct specific defense mechanisms. The B lymphocyte system is characterized by an enormous variety of immunoglobulins with virtually all conceivable antigenic specificities capable of being recognized by at least a few B lymphocyte clones. This is a system that is well designed to deal with unpredictable and unforseen microbial and toxic agents.

By contrast, the T lymphocyte system appears to have arisen in order to recognize antigens *on cell surfaces* and thus to monitor self from nonself on *live* cells. We propose that such a system could derive its maximal efficiency from concentrating upon the recognition of a single, highly represented class of cell membrane molecules. The histocompatibility antigens of the MHC constitutes a class of cell membrane molecules of this type. By concentrating on the recognition of MHC molecules, a large number of T lymphocytes of broadly similar specificity can be brought to bear. Perhaps more important is that small changes in an individual MHC molecule could be easily detected and lead to an effective response. As was noted previously, mutant H-2K and H-2D molecules are detected by the T cell system far better than by serological techniques (*67*).

In parallel, because of the precision with which MHC gene products and their variants could be recognized, it would seem reasonable that MHC molecules should have evolved to be capable of interacting with viral or chemical agents so that interaction products are produced that allow cells with such unwanted variations to be recognized and eliminated by the T lymphocyte system.

Such a T lymphocyte recognition mechanism based on detection of MHC gene products and variants of them could have evolved from an already existing mechanism for the control of differentiation during embryogenesis. Such control must rely on cell to cell interactions and the recognition of key membrane components. One such system, the control of morphogenesis by T region genes of the mouse (*68*), is an especially attractive candidate for this progenitor role, as others have already proposed (*69*). This is particularly so since the T region genes are encoded on the same chromosome of the mouse as the MHC, and structural similarities between T region gene products and products of the MHC appear to exist (*70*).

Finally, a system of this sort having been principally evolved to recognize cell surface changes by focusing large numbers of T lymphocyte clones on certain selected cell membrane molecules lends itself admirably to regulating the selective antigen-stimulated differentiation of the immune system. To accomplish this purpose, these regulatory T cells interact with immunocompetent cells as they themselves react to antigens. Thus, the Ia antigens could function as targets for the physiologic regulation of the immune system as well as mechanisms for discrimination between self and nonself.

Summary

Thymus-dependent lymphocytes display a restricted range of specificity when compared to thymus-independent (B) lymphocytes. They react particularly to thymus-dependent protein and cell surface antigens and to products of genes encoded in the MHC. In addition, T lymphocytes have important functions in regulating the immune response and in discriminating of self from nonself. Recent work indicates that individual T lymphocytes possess receptors that interact with both thymus-dependent antigens and MHC gene products, either independently or as associated structures. We attempt to relate this complex specificity pattern to the regulatory and surveillance functions of T lymphocytes.

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Compulsory Sterilization: The Change in India's Population Policy

Kaval Gulhati

Twenty-five years ago India was the first country to undertake a national family planning program. In the past year it has become the first in which compulsory sterilization has been officially advocated—a dubious distinction, no doubt, but one which may well be a portent of population policies in other developing countries.

Many professionals in the family planning establishment, dismayed at this new direction in India's population policy, argue (i) that India has never provided voluntary birth control services effectively on a mass scale, as—say—Korea and Taiwan have done, and (ii) that compulsory measures will be counterproductive by increasing the resistance to family planning of any kind.

It would be fair to say, however, that the new turn in India's policy has caused relief as well. The dismay stemmed from the shift to compulsion without improvement of the voluntary effort. The relief springs from the reversal of an earlier policy announced in 1974. At the World Population Conference held in Bucharest in August of that year, India's Minister for Health and Family Planning, Karan Singh, made an official statement which was heavily in favor of depending upon economic development to provide the incentive for fertility control. He said, "It will be difficult for many countries to accept family limitation as a goal in itself unless it is clearly linked to a more equitable distribution of world resources" and "Population policy . . . cannot be effective unless certain concomitant economic policies and social programs succeed in changing the basic determinants of high fertility. It has truly been said that the best contraceptive is development" (*1*).

This was an unsettling statement from a leader whose country was expected to provide the greatest support at Bucharest for the advocates of antinatalist policies and programs, and help in drafting a strong world plan. The document which finally emerged from the conference as the "World Plan of Action" (*2*) was disappointing to those committed to vigorous furtherance of fertility reduction. It gave great emphasis to sovereign rights and human rights, to the international economic order, and to the reduction of mortality. It recommended integration of family planning with health programs, but was unfavorable to employing disincentives to reproduction. While giving explicit quantitative goals for mortality reduction, it suggested merely that countries might "consider" quantitative goals for lowering fertility.

The new change in India's policy is, in effect, an admission that the population factor is paramount in the development effort and that the voluntary family planning program has failed to meet its objec-

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