

# Perspectives

## Human T Lymphocyte Subsets Functional Heterogeneity and Surface Recognition Structures

Paul L. Romain and Stuart F. Schlossman

*Division of Tumor Immunology, Dana-Farber Cancer Institute,  
and Department of Medicine, Harvard Medical School,  
Boston, Massachusetts 02115*

### Introduction

T lymphocytes play a central role in the immune response by virtue of their ability to recognize antigens with a high degree of specificity, to act as effector cells, and to regulate the nature and intensity of the immune response. Advancements in our understanding of the T lymphocyte in the last decade have been facilitated to a large degree by a number of advances in diverse areas of basic research and technology (1-3). Over the last 5 yr, such studies have provided a large amount of information regarding T cell differentiation and the functional programs of the major subpopulations of T lymphocytes as defined by unique cell surface glycoproteins (4-6) (Table I) (referred to as surface antigens since they are identified by polyclonal antisera and monoclonal antibodies). More recently, new insights have been gained regarding functional and phenotypic heterogeneity within the two major T cell subsets and the functional roles of the T cell surface structures themselves, including the T cell receptor for antigen (7, 8). In this review, we will try to provide an overview of the developments of the last several years and will focus on some of these newer findings.

*Differentiation of T lymphocytes.* The thymic micro-environment is necessary for early T cell differentiation. Most of the migration of lymphocyte progenitors to the thymus takes place during embryonic and early postnatal life (9-12). These cells are processed, become functionally competent, and are then exported into the peripheral lymphoid compartments, although only a fraction of the cells which enter the thymus are eventually detectable in the peripheral lymphoid tissues and circulation. In addition, the thymic epithelium may have

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Address reprint requests to Dr. Romain in the Division of Tumor Immunology.

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an important, but as yet poorly understood role in thymocyte differentiation, by virtue of its capacity to produce various soluble factors and through certain cell-cell interactions.

The stages of T cell ontogeny correspond to profound changes in cell surface antigens (4, 13, 14). The earliest lymphoid cells within the thymus (~10% of thymic lymphocytes) lack most mature T cell antigens, with the exception of the E-rosette receptor (T11), but bear antigens shared by bone marrow cells of several lineages (T9 and T10) (stage I). With maturation, thymocytes lose T9 (the transferrin receptor), retain T10 (also detected on plasma cells), and acquire a thymocyte-distinct (in the T lineage) antigen defined by anti-T6. (T6 is  $\beta_2$ -M associated and homologous to murine TL. Anti-T6 also reacts with a determinant on the epidermal Langerhans cell.) Concurrently, these cells express the antigens defined by anti-T4 and anti-T8 (this antigen was initially identified by heteroantisera as TH<sub>2</sub> and by the anti-T5 monoclonal antibody) (stage II). Approximately 70% of the total thymic population coexpress T4, T8, T6, and T10. As thymocytes mature further they lose the T6 antigen, acquire and fully express the pan-T antigens, T1, T3, and T12, and segregate into the reciprocal T4+ and T8+ subsets (stage III). At this stage, immunocompetence is acquired in association with the appearance of the T3-associated antigen "Ti", but is not fully developed until the thymic lymphocytes are exported (15, 16). Once outside the thymus, the resting T4+ and T8+ subsets lose T10 and increase their expression of the T1, T3, and T12 antigens. These cells represent the circulating inducer (helper) and suppressor populations, respectively (5). The T4 antigen is expressed on ~55-70% of peripheral T cells, while the T8 antigen is expressed on ~25-40% of circulating T cells. In addition, the sheep erythrocyte receptor, identified by anti-T11 antibody, is expressed on all thymocytes as well as peripheral blood T cells. The 50,000-mol wt T11 antigen is the first known T lineage specific marker to appear in human ontogeny (17) and may play an important but as yet poorly understood role in lymphocyte differentiation, in view of its involvement in an antigen-independent alternate pathway of T cell activation (18). Analysis of surface antigen expression has shown that T cell malignancies exhibit phenotypic expression that corresponds to distinct stages of theoretically "frozen"

Table 1. Major Human T Lymphocyte Surface Antigens

Surface antigen*	Approximate molecular weight of molecules		T cell population defined	Comments
	Nonreduced	Reduced		
T3	20,000‡ 25,000‡	20,000‡ 25,000‡	Mature T cells and medullary thymocytes express T1, T3, Ti, and T12 (these can be expressed in low density on some cortical thymocytes). Each anti-Ti is unique for an individual T cell clone, and highly similar disulfide-linked heterodimers are expressed on all peripheral T lymphocytes and T3+ thymocytes.	Anti-T3 inhibits antigen-specific T cell responses and the activation of CTL, enhances IL-2 responsiveness, induces the loss of T3 (and Ti) from the cell surface (modulation), and triggers clonal activation when surface linked.
Ti	90,000	49–51,000 +41–43,000		Ti is the T cell receptor for antigen. Both the $\alpha$ - and $\beta$ -chains contain constant and variable regions with distant homology to Ig. Each anti-Ti has the same effect as anti-T3, but only on the individual clone with which it reacts. Anti-Ti antibodies induce the comodulation of Ti and T3 from the cell surface.
T1	67,000	67,000		T1 is homologous to murine Lyt1 and rapidly modulates with antibody binding.
T12		120,000		Unlike anti-T3, anti-T12 does not inhibit or mimic antigen-specific T cell responses.
T11	50,000	50,000	All thymocytes and T cells (greatest density on thymocytes and activated T cells).	T11 is the receptor for sheep erythrocytes and is a surface component of the alternative (antigen-independent) pathway of T cell activation.
T4	62,000	62,000	Majority of thymocytes and 55–70% of peripheral T cells are T4+.	T4+ peripheral T cells contain all inducer functions and class II MHC-specific CTL. Anti-T4 inhibits activation of the functional program and clonal expansion of T4+ cells. § The murine homologue is L3T4 and murine T4.
T8	76,000	33,000 +31,000	Majority of thymocytes and 25–40% of peripheral T cells are T8+.	T8+ peripheral T cells contain all suppressor effector function and class I MHC-specific CTL. Anti-T8 inhibits activation of the functional program and clonal expansion of T8+ cells. § The murine homologue is Lyt2,3.

\* Antibodies with these designations are available through Coulter Immunology, Hialeah, FL. Monoclonal antibodies with Leu and OK designations are available through Becton-Dickinson, Mountain View, CA, and Ortho Systems, Inc., Raritan, NJ, respectively. ‡ Major 20,000-mol wt protein recognized by anti-T3 is noncovalently associated with a 25,000-mol wt protein. § Inhibition with anti-T4 or anti-T8 may not be demonstrable for selected clones if the antigenic stimulus has very strong affinity for the T3-Ti antigen receptor complex.

T cell differentiation (19). Similarly, several immunodeficiency disorders can be characterized as abnormalities in T cell differentiation or as being related to imbalances in immunoregulatory T lymphocyte subpopulations (20).

*Functions of mature T lymphocyte subsets.* Recent studies have helped define functionally unique subsets of human T lymphocytes which exhibit a variety of regulatory and effector functions (5, 7, 21). The major division is between the reciprocal subpopulations that bear the 62,000- and 76,000-mol wt T4 and T8 antigens, respectively. With regard to their regulatory

roles, T4+ cells function to provide inducer/helper activities for T-T, T-B, and T-macrophage interactions, while T8+ cells function principally to suppress, or directly downregulate immune responses.

Only the T4+ population proliferates directly in response to soluble antigen or to autologous non-T cells, and provides the appropriate signals necessary to help B cell proliferation and differentiation into immunoglobulin-secreting cells (2, 22–25). In contrast, both T4+ and T8+ cells show a strong response to alloantigenic determinants (major histocompatibility

complex [MHC]<sup>1</sup> antigens derived from genetically different individuals). After allogeneic activation of unseparated T cells in mixed lymphocyte culture, the T8<sup>+</sup> subset contains the majority of cytotoxic T lymphocyte (CTL)<sup>1</sup> effectors (26). T4 cell cytotoxic function is enhanced, though, if their sensitization to the stimulator cells occurs in the absence of T8<sup>+</sup> cells. The optimal development of cytotoxicity by T8<sup>+</sup> cells, however, requires interactions with T4 cells or their soluble products (2). Antigen-triggered T4<sup>+</sup> cells, but not T8<sup>+</sup> cells, produce a number of nonspecific helper factors, although depending on the triggering stimulus, either T4<sup>+</sup> or T8<sup>+</sup> cells may secrete interleukin-2 or gamma-interferon (7, 27). T4 cells also produce factors important in hematopoietic differentiation, secrete osteoclast activating factor, and elaborate other soluble factors that can induce fibroblast proliferation and collagen synthesis, which may be important in the pathophysiology of a number of inflammatory and autoimmune disorders.

By contrast, the T8<sup>+</sup> subset contains mature populations of cells with cytotoxic and suppressor function, but without demonstrable inducer function (26, 22). Suppression of both mitogen-induced and antigen-specific antibody production has been convincingly shown to be a function of T8<sup>+</sup> cells, though just as with the generation of T8<sup>+</sup> CTL, a T4<sup>+</sup> cell is required for induction of T8<sup>+</sup> suppressor effectors (28).

It has become increasingly clear that considerable phenotypic, as well as corresponding functional heterogeneity exists within the two major T cell subsets. Such heterogeneity has become most evident through studies which have demonstrated requirements for collaboration between phenotypically distinct populations within these subsets for the activation of effector cells or the full expression of a particular regulatory activity. Such distinctions have been based, for example, on the expression of Ia antigens on activated cells and on the radiosensitivity of subpopulations of T4 or T8 cells (28–30). A subset of normal T4 cells reactive with sera from selected patients with juvenile chronic arthritides (T4+JRA+) as well as T4+Ia+ cells and a radiosensitive T4 subset have been reported to function as suppressor inducer cells (28, 30–32). The anti-TQ1 monoclonal antibody identifies a subset of T4 cells which contains the majority of T4+JRA+ cells (24), whereas the T4+TQ1– subset provides the majority of help for *in vitro* immunoglobulin production. Further evidence for distinct helper inducer (T4+JRA–) and suppressor inducer (T4+JRA+) subsets has also been described at the clonal level (33). In addition, the TQ1+ and JRA+ T4 cells (containing the inducers of suppression) proliferate much more strongly than the optimally antigen responsive TQ1– or JRA– T4 cells in the autologous mixed lymphocyte reaction (24, 25), which further supports the distinction between autoreactivity and antigen reactivity. Other monoclonal antibodies, including Leu

1. *Abbreviations used in this paper:* CTL, cytotoxic T lymphocyte; IL-2, interleukin-2; MHC, major histocompatibility complex; SLE, systemic lupus erythematosus.

8 (34, 35), have been described which may distinguish similar cell populations, and it is likely that newer antibodies which even more clearly define these subpopulations will be available shortly. An investigation of a series of patients with systemic lupus erythematosus (SLE) reported in this journal recently demonstrates the clinical relevance of such distinctions within the T4 population (36). There are numerous reports of suppressor cell dysfunction in association with the autoantibody production seen in SLE, and many patients with lupus have been shown to have anti-T cell antibodies. In this particular study, by carefully analyzing the effects of sera from patients with SLE on normal lymphocytes, such autoimmune sera were shown to contain complement-fixing IgM anti-T cell antibodies with specificity for T8<sup>+</sup> suppressor effector cells, the T4+JRA+ suppressor inducer subset, or for both. Patients whose sera contained anti-T8 antibodies (recognizing the suppressor effector subset) had abnormally high T4/T8 ratios, as previously reported for patients with systemically active SLE (36, 37), while those whose sera contained anti-T4 antibodies (directed against the suppressor inducer subset of T4<sup>+</sup> cells) or exhibited both patterns of reactivity had abnormally low T4/T8 ratios, as have been reported in SLE patients with severe renal disease and/or thrombocytopenia without other systemic manifestations (36, 38, 39). Thus, a functional defect in suppressor activity in SLE may be associated with either a high or low T4/T8 ratio, depending on the subset of T cells with which the autoantibodies react. Taken together with the prior *in vitro* studies, these data demonstrate the importance of recognizing the complexity of the T cell circuit, and in particular, the presence within the T4 population of distinct subsets responsible for providing help for antibody production and for inducing T8<sup>+</sup> suppressor effector cells. Moreover, the existence of T4+ suppressor inducers which may collaborate with small numbers of T8 suppressor effector cells (40), and the potential for activated T cells to mediate nonspecific suppression *in vitro* through absorption of nutrients or other required growth factors (41), require one to exercise caution in interpretation of *in vitro* assays of suppressor function.

Heterogeneity clearly exists within the T8<sup>+</sup> population as well, which includes pre-cytotoxic, cytotoxic, pre-suppressor, and both specific and nonspecific suppressor effector T cells. These subsets can be readily distinguished by functional assays, and attempts are being made to define each of the cellular components of the circuit by phenotypic determinants. For example, activated T8+Ia– cells are cytotoxic in standard cell-mediated lympholysis assays, while activated T8+Ia+ cells appear to be suppressive (22, 26, 42, 43). Furthermore, within the T8<sup>+</sup> population, both TQ1+ and TQ1– cells, as well as Leu 8 reactive and nonreactive cells, can be shown to collaborate in the generation of antigen-specific suppressor cells (34, 44), and it appears that activated Ia+T8+ cells collaborate with fresh T8+ cells to most effectively produce suppression (43). In addition, newer monoclonal antibodies have been reported which may discriminate between the cytotoxic and suppressor

subsets within the T8+ population (45, 46). Reports of activated T8+ cells, which may play an amplifying or "contrasuppressive" role (47-49), may be partially explained by the potent ability of Ia+ T cells to stimulate autologous or allogeneic T cell proliferation, which could potentially result in the generation of soluble helper factors (50, 51).

Although these data suggest a confusing network of interacting regulatory T cells, highly similar findings have also been made in murine systems, and it is likely that further work will soon allow a clearer dissection of the suppressor cascade, as well as a more precise phenotypic distinction between the functional subpopulations which exist within the T4 and T8 subsets. Further critically important distinctions between T4 and T8 cells can also be made with regard to the specific stimuli that are required for their respective activation, as described below.

*T lymphocyte activation and the T cell receptor for antigen.*

It has long been known that T cells recognize antigen in the context of membrane-bound products of the MHC with exquisite specificity (52, 53). The identification of the T cell structure analogous to surface Ig, the antigen binding receptor on B cells, has therefore been a matter of intensive investigation, but also of great controversy. Recent discoveries have shed important light on the T cell structures which are involved in antigen recognition, the cell-cell interactions necessary for T cell activation, and the nature of and mechanism by which soluble factors secreted by T cells regulate the clonal expansion of specifically activated T and B lymphocytes. This work has included extensive biochemical characterization of the various defined T cell surface molecules (reviewed in references 7 and 8).

A series of studies, employing both cloned and noncloned T cells with a wide variety of specificities and with either regulatory or cytotoxic effector functions have all demonstrated that the T4 and T8 subsets recognize products of different gene regions of the MHC (54-62). For example, allosensitized T4+ T cells are preferentially directed at class II (Ia) MHC antigens (HLA-Dr, SB, or DC), while T8+ T cells are directed at class I MHC antigens (HLA-A, B, or C) on the target cells (62). Similarly, autoreactive T4+ T cells recognize self-class II determinants, while T8+ cells, in addition to requiring help from stimulated T4 cells, must interact with self-class I determinants in order to proliferate during the autologous mixed lymphocyte reaction (61). Furthermore, since antibodies directed at the T4 or T8 glycoproteins selectively inhibit cytolytic effector function of the respective cell subpopulations, it is thought that these subset-restricted structures might themselves be required to facilitate recognition of and/or binding to different target antigens.

Numerous other studies have indicated that the T3-Ti structure is important in antigen-specific T cell responsiveness (63-67), though the T3 molecule itself is nonpolymorphic. Antibodies against T3 can be strongly mitogenic, and the binding of antibody to T3 blocks antigen-specific T cell

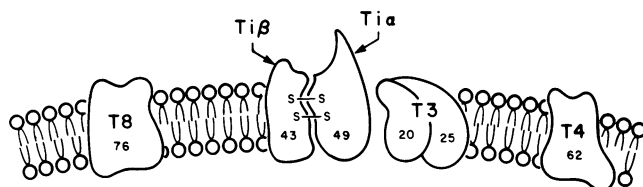
proliferative responses and cytotoxic effector functions and leads to loss of the T3 molecule from the cell membrane. Resynthesis of the T3 antigen is associated with recovery of T cell function. The T3-associated structure termed Ti, which was demonstrated using clone-specific monoclonal antibodies, is highly polymorphic (68-71). Anti-Ti monoclonal antibodies demonstrate the same stimulatory and inhibitory effects as anti-T3, but only for the clones with which they each specifically react (62, 68-70), and binding of either anti-T3 or anti-Ti modulates both structures from the cell membrane (68). Antigen-specific clones blocked by anti-T3 or anti-Ti interestingly exhibit an enhanced response to interleukin-2 (IL-2) (68) that is not observed with inhibition of T cell responses by anti-T4 or anti-T8. Ti is a 90,000-mol wt disulfide-linked heterodimer which consists of a 49-51,000-mol wt alpha and a 43,000-mol wt beta subunit (16, 71), and is noncovalently associated in the T cell membrane with T3. Approximately 30-40,000 molecules of Ti and T3 coexist on the surface of human T lymphocytes, and studies of thymocytes and T cell tumors have further confirmed that T3 and Ti appear at precisely the same time in T cell ontogeny. Ti molecules from different T cell clones, even when derived from the same individual, have differing isoelectric points and distinct peptide maps after partial proteolytic cleavage (71). Furthermore, the  $\alpha$  and  $\beta$  chains of the Ti complex appear to bear no precursor-product relationship to one another, but share common peptides with  $\alpha$  and  $\beta$  chains from other Ti molecules isolated from genetically unrelated individuals (16, 72).

Taken together with recently performed research in mice (73-75), this evidence suggests that the Ti molecule contains the variable regions of the T cell receptor for antigen, and that the structure consists of variable and constant regions analogous to immunoglobulin light and heavy chains. In addition, it appears that T4 and T8 are likely to act as restricting elements for a variety of cellular functions, including allospecific CTL generation, through their respective interactions with class II and class I MHC antigens on both allogeneic and autologous cells (Figure 1). Thus, inducer T cells recognize antigen presented by macrophages in the context of Ia (class II MHC encoded) molecules on the surface of the cells, and the MHC restrictions noted for cytotoxic T4 and T8 cells probably reflect the association of viral and other antigens with either class II or class I MHC gene products, respectively. Although the T4 and T8 molecules clearly appear to play a role in antigen recognition, perhaps by acting as stabilizing elements to facilitate cell-cell contact, the T3-Ti antigen receptor complex is the structure critical to antigen-specific T cell activation. It would be likely, therefore, that at the clonal level, effector cells with high affinity T3-Ti receptors for specific antigen exist that would be less dependent on T4 or T8 to interact with stimulator or target cells. Not surprisingly, such clones have been described, even occasionally in apparent contradiction to the usual T4/class II and T8/class I association (57, 60, 76).

Further important data regarding the Ti structure came

SUBUNITS OF THE HUMAN  
T CELL RECEPTOR

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*Figure 1.* Antigen recognition structures on human T lymphocytes. As schematically represented, each T lymphocyte possesses two types of recognition structures. The T8 and T4 glycoproteins, found on reciprocal T cell subsets, appear to facilitate interactions with nonpolymorphic regions of class I and class II MHC gene products, respectively. The T cell receptor, i.e., the T3-Ti complex, recognizes specific antigen in the context of a polymorphic MHC gene product. The approximate molecular weights are noted for each structure, e.g., 76 = 76,000 mol wt.

from detailed studies of the Ti molecule on a T3+ thymus-derived tumor line, REX, which could be grown in a large enough quantity to provide sufficient material for extensive study (77). Because of its extensive variability on previous peptide map analyses of a variety of clones (72), the  $\beta$  subunit primary structure was initially studied. Unambiguous N-terminal amino acid analysis of the purified Ti  $\beta$ -chain from the REX line was obtained, and a computer search for homologies between this N-terminal sequence and other proteins demonstrated significant homologies with the human and mouse light chain framework IV regions. Residues 2–11 demonstrated homologies with the first framework region of lambda light chains, while kappa homologies were seen when the search was extended to include residues 2–20.

Complementary studies by other groups directed towards identifying T cell antigen receptor molecules have utilized the subtractive hybridization technique, by which they have respectively described the isolation of human and mouse cDNA clones which were T cell specific, and in the case of the murine clones, that identified genes that could be shown to be rearranged in these T cells but not in other cell types (78–80). The human T cell DNA clone encodes a predicted 35,000-mol wt polypeptide with strong homology to human Ig lambda light chain in both N- and C-terminal regions, and particularly in the area of the cysteine residues (78). Recent studies of the Ti  $\alpha$ -chain confirm earlier demonstrations that this chain had constant and variable regions and bore homology to the immunoglobulin molecule. Importantly, comparison of the Ti  $\beta$  N-terminal sequence obtained from analysis of the REX Ti molecule (residues 2–20) with that of the predicted gene product from the human cDNA clone demonstrated identity at all residues that could be analyzed (77), thus providing the critical link between the 90,000-mol wt Ti heterodimer receptor

molecule and the genome. It is likely that the differences in molecular weight between the two (35,000 vs. 43,000 mol wt) are due to glycosylation, because the known human Ti  $\beta$  subunit is a glycoprotein, and at least two potential glycosylation sites for complex oligosaccharides have been identified on the human cDNA predicted gene product. The murine sequence and the human sequence appear to bear ~80% homology in the carboxy-terminal halves of the molecules, and the murine peptide also appears to have similarities to not only kappa and lambda light chains, but also with human IgM and IgA heavy chains and the  $\alpha$ -chain of a human class II MHC molecule (DC1). These data suggest that this clone represents the murine equivalent of the human Ti  $\beta$ -chain (79, 80).

It is likely that just as with immunoglobulin, T cell receptor diversity is generated by different gene rearrangements. This evidence, thus far most detailed for the  $\beta$ -chain of Ti, also suggests that the Ti structure and immunoglobulin and MHC proteins are not only functionally related, but structurally appear to be derived from a related family of molecules.

*Consequences of antigen-specific T cell activation.* Antigen-specific T cell activation leads to a number of interrelated cellular events including changes in the expression of surface structures and the secretion of lymphokines (Table II). IL-2 is a soluble factor which is critical for the clonal expansion of activated T cells (81). It is a 15,000-mol wt sialoglycoprotein which, once T cells are activated by antigen or mitogen, mediates their proliferation by binding to a highly specific receptor on the T cell surface (82–84). The extent of clonal expansion, and therefore the rate and magnitude of the T cell immune response, are directly dependent on IL-2 receptor levels and the available concentration of IL-2, which may be produced endogenously (“autocrine” regulation) or by a different T cell (“endocrine” regulation) (67, 82). The expression of the IL-2 receptor is markedly increased by mitogen or antigen binding to the cell or by the binding of anti-T3 or anti-Ti antibodies to the T3-Ti complex, thus explaining the mechanism by which these antibodies caused enhanced responses to IL-2 by IL-2 dependent antigen-specific T cell clones (67). Although IL-2 receptor expression can also be induced by anti-T3 or anti-Ti monoclonal antibodies in soluble form, endogenous production and secretion of IL-2 does not occur unless cells are triggered by either antigen presented in the context of MHC products or anti-T3 or anti-Ti antibody on either a cell surface or bound to Sepharose (67). Because the T3-Ti antigen receptor complex modulates from the cell surface in concert with antigen binding, the reciprocal appearance of T3-Ti and IL-2 receptors presumably leaves the cell in a state of responsiveness to either the hormone or antigen ligand. Thus, the transient expression of the IL-2 receptors serves to prevent uncontrolled cell growth by cells not specifically stimulated by antigen. In addition, activated T cells, such as IL-2 dependent antigen-specific T cell clones, express three- to fourfold greater numbers of either T4 or T8 surface molecules than resting T lymphocytes (69). Such enhanced expression of

Table II. Consequences of Antigen-specific T Cell Activation

Modulation of the T3-Ti antigen receptor complex from the cell surface.
Activation*
Induction of IL-2 receptor expression.
Increased expression of associative recognition structures (T4 or T8).
Expression of other activation structures.
Production and release of endogenous IL-2 and other lymphokines.
Clonal expansion‡

\* The precise timing of these events is not yet well defined. Once appropriately activated, the cell begins to express its functional program.

‡ In the absence of further antigenic stimulation, reexpression of T3-Ti and a return to the resting state occurs.

associative recognition elements could be important in facilitating cell-cell interactions. Although other soluble factors including interleukin 1 and gamma interferon have important immunoregulatory functions, a discussion of these mediators is beyond the scope of this review.

**Conclusions.** The new insights into T cell heterogeneity and immunoregulation, and into the structural and molecular basis of T cell recognition and activation, have greatly enhanced our understanding of the pathophysiology of many disorders of the human immune response, including immunodeficiencies, autoimmune syndromes, and lymphoproliferative and infectious diseases. It is anticipated that antibodies directed against the various critically important cell surface glycoproteins on T lymphocytes will not only serve as important probes to study the biology of the immune response and the pathophysiology of disease, but will become increasingly useful either alone or in combination with pharmacologic or toxic agents in the treatment of a variety of human diseases.

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