Internal Medicine Grand Rounds

T LYMPHOCYTES IN HEALTH AND DISEASE

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1. INTRODUCTION

T lymphocytes play an important role in most aspects of the immune response. T lymphocytes are known to be the controlling element in cell-mediated immunity, the form of immune response characterized by effector functions of cells rather than serum antibodies. Additionally, antibody production to most antigens is T cell-dependent. Which means that B cells make very little or no antibody in the absence of helper T cells. T cell products appear to control the switch from IgM to IgG and probably also to other Ig isotypes such as IgA or IgE.

The magnitude of most immune responses is delicately balanced largely through interactions of positive (helper) and negative (suppressor) forces within the T cell compartment.

Moreover, T cell products exert effects over many other cells. T cell products modify the activities of cells of the monocyte/macrophage series. One T cell product that has recently been intensely investigated, gamma interferon, modulates the expression of surface antigens on most cells of the body.

While it has been known for many years that the reactions of T cells to antigen are highly specific, until recently the molecular basis of the antigen specificity of T cells was not known. It had been observed that the determinants recognized by T cells on a given antigen were often different from the epitopes reacting with serum antibodies. More importantly, it became clear that T cells virtually never recognized foreign antigen alone, but rather were triggered to action by their recognition of foreign antigen together with an antigen of the major histocompatibility complex expressed on accessory cells.

Because it was known that B cells were stimulated when soluble antigen combined with specific antibody molecules on their surface, it was speculated that similarly, T cells might be triggered by a surface immunoglobulin molecule. Efforts to demonstrate the presence of immunoglobulin structures on T cells were largely unsuccessful, however. Furthermore, more recent studies have clearly shown that immunoglobulin genes are not rearranged or activated in most T cells.

With the discovery of methods for the production and maintenance of T cells in continuous culture and the development of T cell clones, it became possible, within the last two years, to produce antibodies that recognized and permitted isolation and study of the antigen-specific T cell receptors. The year 1984 will be remembered in the history of immunology for the discovery of the T cell receptor and it's characterization as a surface glycoprotein, as well as the identification of the corresponding genes for T cell receptor alpha, beta and gamma polypeptide chains.

These and other developments have led to a remarkable

acceleration in the rate at which we have gained knowledge about T cells and their functional molecules. This rapid progress has been made possible through the development of methodology for T cell cloning, the ever wider use of monoclonal antibodies which have facilitated the molecular characterization of T cell products, and the widespread use of recombinant DNA technology which has led to description and structural analysis of the genes and study of their activation and transcription. It has also, in many instances, led to the availability of highly pure products for functional studies **in vitro** and **in vivo**.

Inevitably, this explosion of new knowledge will have an impact on a variety of medical problems. Already, rearrangements of the T cell receptor genes detected by Southern blotting are used for identification of T cell neoplasms. The same techniques are being used to investigate the early stages of development of T cells in the thymus and the origins of self-non-self discrimination. The implications of these studies for understanding the origins of autoimmune reactions are obvious. A new syndrome of immune deficiency characterized by the absence of a functional surface molecule (LFA-1, or CDw18), has been described. Recently discovered polymorphisms of the T cell receptor genes, detected by restriction enzyme digestion of genomic DNA, are being utilized to investigate the inheritance of T cell receptor alpha and beta haplotypes and their possible relationships with susceptibility for diseases such as diabetes mellitus Type I and rheumatoid arthritis. New studies of T cells and their functional molecules are also expected to shed light on our understanding of the rejection of organ allografts and the production of tissue injury in a variety of autoimmune diseases in which T cell immunity appears to play a predominant role.

2. HELPER, SUPPRESSOR AND CYTOTOXIC T LYMPHOCYTES.

It has been customary to classify T lymphocytes broadly into three functional groups: helper, suppressor and cytotoxic. **Helper** lymphocytes are programmed to amplify the functions of other cells such as B lymphocytes, other T lymphocytes or macrophages. In order to perform their helper functions they must first be stimulated.

Activation of **helper** T cells (Table 1) may occur when they encounter a specific foreign antigen in association with autologous class II MHC molecules. Stimulation also results from the admixture with cells that possess foreign class II MHC antigens, as in the mixed lymphocyte culture reaction. In addition, activation of helper T cells may be accomplished by a variety of substances such as lectins (PHA, concanavalin A), and antibodies that attach to and perturb, or crosslink, certain lymphocyte surface molecules. The specific T cell receptor for foreign antigen and self MHC determinants will be discussed in the following section. Other surface molecules that modulate the activation of T cells will be the topic of section number 5, of this review.

TABLE 1

ACTIVATION PATHWAYS FOR T LYMPHOCYTES

Stimulating Agent	Target Surface Molecules	T Cells Activated
Foreign antigen + self-MHC	Antigen-Specific T cell receptor	CD8+ cells, class I MHC CD4+ cells, class II MHC
Allogeneic MHC	T cell receptor	same as above
Self-MHC alone	Probably same	Fewer cells
Antibodies against Ti-CD3 complex	Ti or CD3	Most T cells
Antibodies against CD2	CD2 (sheep RBC receptor)	Most T cells
Other antibodies	9.3 CD5	CD4+, & cytotoxic CD8+ Augment proliferation of most T cells
Lectins	CD2, CD3	Most T cells with PHA

Cytotoxic T lymphocytes also called killer cells or effector cells, are able to destroy certain target cells such as other lymphocytes, macrophages, fibroblasts, neoplastic cells, etc. In order to develop into mature killer cells the percursor T cells must first be activated by a specific foreign antigen in association (most frequently) with an MHC class I molecule, and more rarely, with class II MHC molecules. They can also be stimulated by cells having allogeneic MHC antigens. The importance of allogeneic killing in the destruction of allografts and in the development of tissue lesions in autoimmune diseases will be discussed in subsequent sections. Cytotoxic T cells can also be activated by treatment with certain lectins or by the binding of antibodies to certain surface molecules. For example, attachment of monoclonal antibody to the CD3 molecules has been observed to trigger broadly reactive nonspecific killer activity.

Suppressor T lymphocytes are cells that can be shown to down-regulate the activities of other cells. Thus suppressor cells may act on certain effector cells such as B lymphocytes and inhibit Ig production or they may act on helper T cells and by suppressing their activity obtain an overall reduction of the immune response. The precursors of suppressor T cells are also activated by specific antigen in association with class II MHC antigens. Or they may be triggered by lectins such as Con A.

Even when the initial induction of suppressor cells is antigen specific the final effector cells often have been found to be non-specific.

Engleman and coworkers have studied the development of human suppressor cells in alloreactive and soluble-antigen-specific systems. In their typical experiments CD4+ T cells are activated by antigen (Figure 1) and act on fresh autologous CD8+ cells to induce specific suppressor T cells which subsequently inhibit

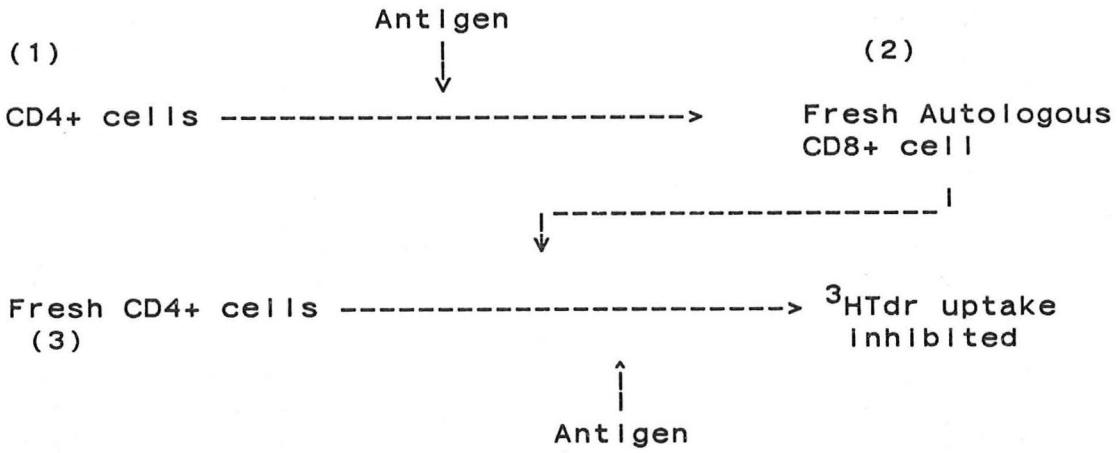

Figure 1. Generation of Human Suppressor Cells in vitro. Modified from Daniel, Mohagheghpour and Engleman. J. Immunol **132**:644, 1984.

the proliferation of fresh CD4+ cells to the antigen. In this case the suppressor cells generated were found to be antigen specific.

At this point, it is necessary to address the relationship between the above functional classification of T lymphocytes and certain cell surface markers detectable with monoclonal antibodies. The background to this was the discovery of the Lyt lymphocyte markers in mice by Boyse and coworkers and their application to the classification of T cells by Cantor and Boyse, about 10 years ago.

In man, it was generally accepted that cells reacting with OKT4 (Leu 3) were helper T cells and OKT8+ (Leu 2+) lymphocytes were suppressor/cytotoxic. In 1982, Ted Ball who was working in my laboratory as a fellow, was examining the phenotypic markers of human cytotoxic T cells that killed monocytes or B lymphocytes on which they recognized specific class II MHC antigens. He came across the astonishing finding that these killer cells were not eliminated, as expected, by treatment with OKT8 monoclonal

antibody and complement. Instead, the majority of these class II-specific killers were T4+ cells. Almost at the same time, Susan Swain working with mouse killer cells was making similar observations. Subsequently other investigators have tested clones of human cytotoxic T cells specific for class II MHC antigens and found them to have the T4 phenotype. The hypothesis has been put forth that the CD4/CD8 markers are associated with the type of MHC antigen recognized by the T cells (class I or class II) rather than with their functional classification. As will be seen later, this view is strengthened by other observations about the functional role of the CD4 and CD8 molecules.

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T cell lines and clones.

One of the technical advances that has given impetus to T cell research was the discovery that normal T cell populations can be propagated in culture for long periods of time by simply restimulating them periodically with antigen and by providing adequate amounts of the T cell growth-promoting factor, interleukin-2 (IL-2).

For cloning, in our laboratory such replicating T cells are diluted and cultured with irradiated filler cells in such a way that colonies develop which are derived from a single cell which was placed in a small well. Other workers develop colonies in semi-solid agar and pick them out mechanically. The principle is the same: a single cell gives rise to millions of cells which can be tested in functional assays such as proliferation or target cell killing.

T cell clones were found to be antigen specific. For example they proliferated in response to mumps virus antigen and not to keyhole hemocyanin or they recognized specifically the synthetic polypeptide GAT and not (T,G)-A--L. In addition, human T cell clones were dependent on the presence of accessory cells which processed and presented the foreign antigens, secreted soluble factors and provided also, on their surface, the class II MHC antigens needed to trigger the T cell response.

An interesting feature of these experiments was that monoclonal antibodies could be used to discriminate between the different class II MHC molecules. Using the technique of monoclonal antibody inhibition, it was observed that T cells specific for mumps virus were most often inhibited when the accessory cells were treated with monoclonal antibodies against HLA-DR. In contrast, T cells that recognized the polypeptide antigens GAT or (T,G)-A--L were more often inhibited by anti-DQ.

The interaction of antigen with immunologically competent cells may, under certain circumstances lead to a state of antigen-specific unresponsiveness which is usually called immunological tolerance. This is thought to be a major mechanism of discrimination between self and non-self. Lamb and coworkers have developed a model to study the changes that take place in T cell clones during tolerance induction **in vitro**. The antigen used was a synthetic peptide that corresponds to a small segment of the hemagglutinin of influenza virus. Exposure of CD4+ T cell clones to high concentration of the peptide reduced subsequent proliferation in response to the antigen by more than 90%. Tolerance induction was antigen-specific, long-lasting (at least one week), did not require suppressor cells and was inhibited by antibodies against HLA-DQ. Thus tolerance induction appears to be MHC restricted.

Interestingly, tolerized cloned T cells lost the property of binding to antigen-pulsed monolayer cells suggesting a functional loss or inactivation of the specific antigen receptor.

TABLE 2.

CHANGES IN T CELL SURFACE MOLECULES DURING

IN VITRO TOLERANCE INDUCTION WITH INFLUENZA HA PEPTIDE[1]

Molecule	Change Observed
CD3	Marked decrease
CD4	No change
TI	Marked decrease
HLA-DR	No change
CD2[2]	Increased
CD25[3]	Marked increase

[1] Modified from Feldmann, Zanders, Lamb, 1985.
[2] CD2 = SRBC rosette receptor
[3] CD25 = Tac or IL-2 receptor

T cell clones have recently been used to investigate various animal models of autoimmune diseases. The same technology is just beginning to be applied to the study of human patients. In one report, T cell lines were isolated from a patient with Chages' disease. The cell line was found to be specific for Trypanosoma Cruzi and was of the CD4+ phenotype. It proliferated in the presence of autologous but not of HLA-DR unrelated accessory cells.

Other investigators have recently reported developing T cell lines from patients with myasthemia gravis. As will be further discussed in Section 11, they found them to proliferate in response to a preparation of acetyl choline receptor antigens when presented by HLA-DR-compatible antigen-presenting cells.

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3. T CELL PRODUCTS: LYMPHOKINES.

T cells make a variety of products that work on other cells and act as mediators of a spectrum of T cell effects. These substances are quite diverse and their actions include stimulation of proliferation, enhancement of cellular differentiation, attraction and retention of cells at sites of inflammation, or growth inhibition and killing (Table 3).

The study of these factors has for a long time been considered one of the most difficult areas in immunology. Lymphokines were usually found in crude supernatants containing mixtures of many substances. They were produced in small amounts and methods for assay consisted of cumbersome observations of biologic effects.

However, this area also is yielding to technological advances. The genes are being cloned and sequenced. The structure of the hormones or factors are being elucidated. Pure materials are being produced by recombinant DNA technology.

A partial list of T cell factors to be considered is shown in Table 3. Among these, are several whose genes have been cloned: lymphotoxin, interleukin-2, interleukin-3, interferon-gamma. Two macrophage-derived factors have also recently been cloned. They are interleukin-1 and tumor necrosis factor.

TABLE 3

SOME SOLUBLE FACTORS PRODUCED BY T CELLS

Effect on Other Cells	Name of Factor	Target Cells
Proliferation	Interleukin-2	T lymphocytes
	Interleukin-3	Macrophages, mast cells, T cells
	BCGF	B lymphocytes
	GM-CSF	Granulocyte/monocyte precursors
Differentiation	Interferon	All cells
	BCDF	B lymphocytes
	Osteoclast activating factor	Osteoclasts
Collection	Chemotactic factors	Macrophages, leukocytes, T cells
	MIF	Macrophages
	LIF	Leukocytes
Inhibition/ cytotoxicity	Lymphotoxin	Many cells
	Growth inhibitory factors	Various types

Interleukin-2 (IL-2), also called T cell growth factor acts mainly on other T cells and induces them to proliferate. IL-2 also appears to be the main signal for the expression of IL-2 receptors. Thus IL-2 promotes growth of T cells by binding to specific membrane receptors the appearance of which is enhanced by the presence of IL-2. Resting T cells express few or no IL-2 receptors. When T cells are triggered by antigen, expression of IL-2 receptors is induced and simultaneously IL-2 is produced and secreted and bound to the receptors. Thus, the induction of the appearance of IL-2 receptors and the production and synthesis of IL-2 constitute a mechanism by which T cells accomplish their own replication and growth.

Factors affecting B cell growth and differentiation, produced by T cells, are required for antibody production. Three steps have been identified in the B cell activation process. In the first, resting B cells are acted upon by antigen or other substances that can crosslink the membrane-bound Ig receptor. Thus activated B lymphocytes become responsive to the action of T cell factors.

B cell growth factor (BCGF) was found to be distinct from IL-2. It acts on B cells triggered by antigen or anti-Ig, LPS or Staph aureus strain Cowan I, but not on resting B cells. The factor binds to such activated B cells but not to resting B cells or to T cells. Under the influence of BCGF B cells proliferate but do not mature into Ig-secreting cells.

Separate factors that induce B cells to differentiate and to secrete Ig but do not stimulate proliferation of B cells have been described by several investigators. The molecules that induce B cell differentiation were found to be distinct from several other lymphokines including IL-1, IL-2, G/M-CSF, IFN, IL-3 and BCGF.

T cell-derived B cell differentiation factors are also involved in the regulation of isotype expression. Ishizaka and coworkers found that they could differentiate between T helper populations that had preferential effects on either the IgG or the IgE antibody response. Other investigators observed T cell-derived factors that preferentially provided help to B cells secreting IgA antibodies.

Vitteta and coworkers have described separate factors that stimulate the production of IgM (BCDFμ) or IgG (BCDFγ). The latter factor, which appeared to bind on a non-Ig receptor on B cells, preferentially stimulated the production of IgG1 antibodies.

It appears that T cell factors that regulate isotype expression can be of two kinds: a. factors that bind to Ig of a certain type and are involved in the selective expansion or differentiation of committed B cells; b. factors that do not bind to Ig which might be responsible for isotype switch induction. In addition IL-2 and IFN-γ also appear to stimulate proliferation and differentiation of B cells.

Recent experiments by Milanese and coworkers have shown that BCGF is produced by both T4 and T8 subpopulations of human T lymphocytes. B cell differentiation activity was largely but not exclusively restricted to the CD4+ population. Triggering of T cells through either Ti-T3, or the CD2 pathway led to both BCGF and BCDF production.

The human genomic DNA sequence of the IFN-γ gene is located on the long arm of chromosome 12. It contains three introns and a repetitive DNA element. The molecule is composed of 146 amino acids, with a molecular weight of 17000 daltons. The 20 and 25,000 molecular weight products are produced by glycosylation.

Interferon exerts its action by binding to a membrane receptor. Except for its role in growth inhibition, where it appears to act in combination with lymphotoxin, most of the functions of IFN- appear to be stimulatory.

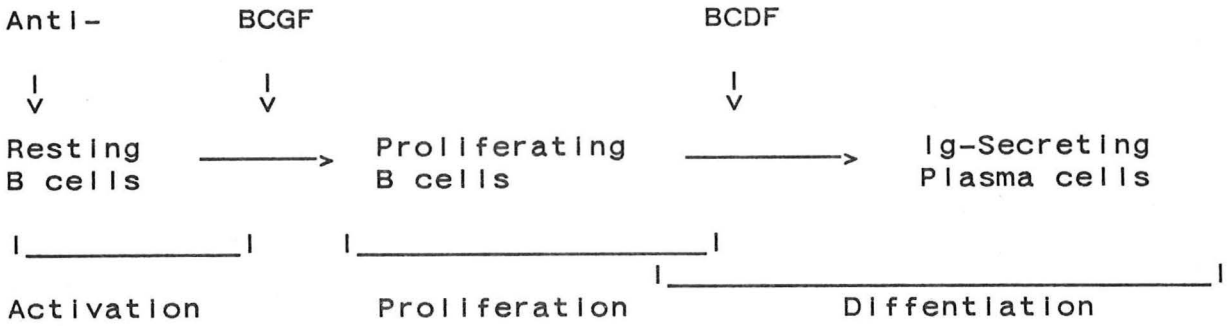

Figure 2. Activation and differentiation of B lymphocytes (Modified from Kishimoto, 1985).

Among the most striking effects is the induction of surface expression of the antigens of the major histocompatibility complex.

Other effects observed are the induction of high-affinity Fc receptors for IgG on neutrophils and monocytes, induction of differentation and activation of myelo-monocytic cells and enhancement of B cell differentiation.

Lymphotoxin has also been cloned recently. The protein consists of 181 amino acids. Pure material was biologically active but was enhanced by the simultaneous presence of IFN-γ.

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4. THE T CELL RECEPTOR.

Monoclonal antibodies have been produced against the antigen receptors of cloned T cells. These antibodies reacted with a 90KD disulfide-linked heterodimer glycoprotein, anchored in the T cell membrane. In rapid succession reports have appeared describing the cloning and sequence analysis of the genes encoding the alpha and beta chains that comprise the antigen receptor. In addition, a third T cell receptor gene called gamma has recently been described. Its product is presently unknown.

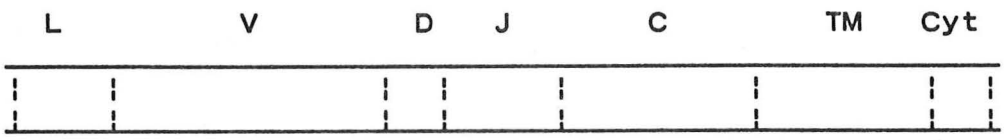

Figure 3. Schematic representation of the structure of the beta chain of the T cell receptor.

Genes for the beta chains were initially characterized most extensively. Analysis of the T cell receptor beta-chain gene complex showed striking similarities to the immunoglobulin genes in sequence and in organization into clusters containing variable (V), diversity (D), joining (J) and constant (C) region gene segments. In man the gene for the beta chain of the T cell receptor is located on chromosome number 7. The gene corresponding to the alpha chain is on chromosome 14. Both of these genes for T cell receptor chains are structurally similar to the genes encoding immunoglobulins and can be shown to undergo rearrangements in functional T cell clones and T cell neoplasms.

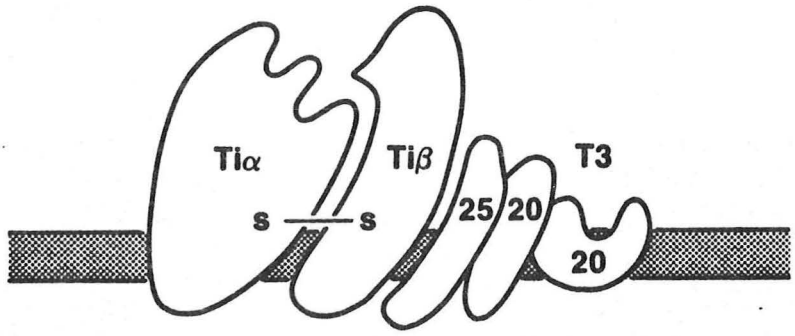

Figure 4. The T cell receptor-T3 complex. TI alpha and TI beta subunits are held together by S-S bonds and are associated with the 25 kilodalton chain of the T3 molecule. The alpha and beta subunits are anchored in the cell membrane with their transmembrane segments. The T3 complex consists of two additional subunits with molecular weights of 20 kilodaltons each.

The receptor for antigen on T cell clones of either cytolytic or helper type is associated with the T3 (CD3) trimolecular complex, as will be described below, the clonotypic structures can be

modulated by anti-CD3 antibodies.

Both the alpha and beta chain T cell receptor genes have recently been found to be polymorphic. Robinson and Kindt reported restriction enzyme fragment polymorphisms in the constant region of the gene for the beta chain. Hoover and coworkers found a polymorhism associated with the alpha chain genes. These markers were found to segregate in members of informative families, as expected, independently of the HLA genes. The possibility that inheritance of such genetic markers of the T cell receptor haplotypes may be linked to the V region alleles that determine the repertoire of T cell responses can now be investigated. The

role of T cell receptor polymorphic sites in predisposition to autoimmunity and especially, as additional genetic risk factors in diseases known to be associated with class II HLA antigens is now being studied.

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5. OTHER SURFACE MOLECULES THAT AFFECT T CELL FUNCTION.

The earliest step in T cell activation is the engagement of the T cell receptor by foreign antigen presented on the surface of an antigen-presenting cell in conjunction with the appropriate major histocompatibility complex molecules. Subsequent signal transduction may require the participation of additional T cell membrane products. In man, these include the CD3 complex, which associates noncovalently with the T cell receptor, and CD2 (T11), the sheep erythrocyte receptor. Another group of T cell surface molecules that play a role in the activation process are CD8 (T8, Leu 2) and CD4 (T4, Leu 3). The latter molecules define non-overlapping subsets of T cells in normal peripheral blood.

However, recently unusual T cells, positive for both CD4 and CD8 have been observed.

TABLE 4.

CLUSTERS OF DIFFERENTIATION (CD) SURFACE MOLECULES.

Workshop Designation	Other Designation	Molecular Weight ($X\ 10^{-3}$)	Cell Types Found
CD1	T6, Leu 7	45,12	Cortical thymocytes
CD2	T11, LFA-2 E-rosette receptor	50	All T cells forming E rosettes
CD3	T3, Leu 4	19-29	Mature T cells
CD4	T4, Leu 3	55	Helper/inducer T cells
CD5	T1, Leu 1	67	Pan T, Some B cells
CD6	T12	120	Mature T, Some B cells
CD7	3A1	41	Pan T
CD8	T8, Leu 2	32-33	Cytotoxic/suppressor T cells
CDw18	LFA-1	180,94	Leukocytes
CD25	Tac, IL-2 receptor	55	Activated T cells

The capacity of antibodies against CD4 to block class II-restricted antigen-specific proliferation and the ability of anti-CD8 to inhibit the effector phase of class I-restricted cytotoxic T lymphocytes have suggested that these membrane molecules are involved in attachment to nonpolymorphic epitopes of class II or class I molecules respectively.

In addition, a number of other lymphocyte function-associated (LFA) molecules have been described. LFA-1 is a broadly distributed leukocyte antigen involved in CTL and NK cell mediated lysis. LFA-2 is identical to CD2 or T11, the sheep erythrocyte receptor. It is found only on T cells and not on B cells. Monoclonal antibodies against CD2 inhibit sheep erythrocyte rosette formation and vary in their effects on T cell function. Antibodies against certain CD2 epitopes are inhibitory

of CTL and of mitogen-induced proliferative responses. Other monoclonal anti-CD2 antibodies have been found to induce T cell activation, expression of IL-2 receptors and T cell proliferation.

TABLE 5.

OTHER SURFACE MOLECULES OF LEUKOCYTES OF INTEREST IN T CELL STUDIES.

Designation	Molecular Weight	Cell Types Found	Effect of Antibodies
LFA-3	60-70	Leukocytes	Inhibition CTL, T_h proliferation
9.3	44	CD4+, CTL-CD8+	Enhance T proliferation
Leu 15		Suppressor-CD8+	
60.3	95-150	Leukocytes	Inhibition CTL, NK, T_h proliferation
GH5,3AC5	220	CD4+,CD8+, B,NK	Enhance T proliferation
T305	140	Activated T, monocytes	Not known

LFA-3 is a broadly distributed leukocyte antigen including T and B lymphocytes, monocytes and granulocytes. Anti-LFA-3 monoclonal antibody inhibited cytolysis by CD4+ or CD8+ T cells but not by NK cells. It also inhibited PHA and MLR proliferative responses. Anti-LFA-1 and LFA-2 antibodies block cytolysis by binding to the effector cells. LFA-3 monoclonal antibody, in contrast, blocked cytolysis by binding to the target cells.

All the different surface molecules were being defined with locally produced monoclonal antibodies and were being given a variety of names. Therefore, it became necessary to develop a standard nomenclature. In August 1983, after the First International Workshop on Human Leukocyte Differentiation Antigens a new nomenclature was developed by a IUIS-WHO

Nomenclature Subcommittee. The antigens were grouped into clusters of differentiation (CD) and given numerical designations. Thus T3 became CD3, T4 was called CD4 and T8 was given the name CD8. A letter, designating the typical cell of a particular CD or the cell type in which the molecular weight was determined, as well as the type of molecule (gp = glycoprotein, gl = glycolipid, cho = carbohydrate and u = unknown) and the molecular weight, are given in brackets. As in the HLA nomenclature, a "w" is used to indicate a CD designation is considered provisional.

A number of surface molecules that have been given official names are shown in Table 4. Some other surface molecules of interest in T cell studies are given in Table 5.

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6. THE IMMUNOGLOBULIN SUPERFAMILY

Since the discovery that beta-2-microglobulin has considerable amino acid sequence homology to immunoglobulin domains many other molecules have been added to the immunoglobulin superfamily. They include the class I and class II major histocompatibility complex antigens and the T cell receptor. These are the most

important family members since they are clearly involved in recognition by the T cell immune system. Other class I MHC antigens such as Qa and TL are expressed in lymphyoid cells and

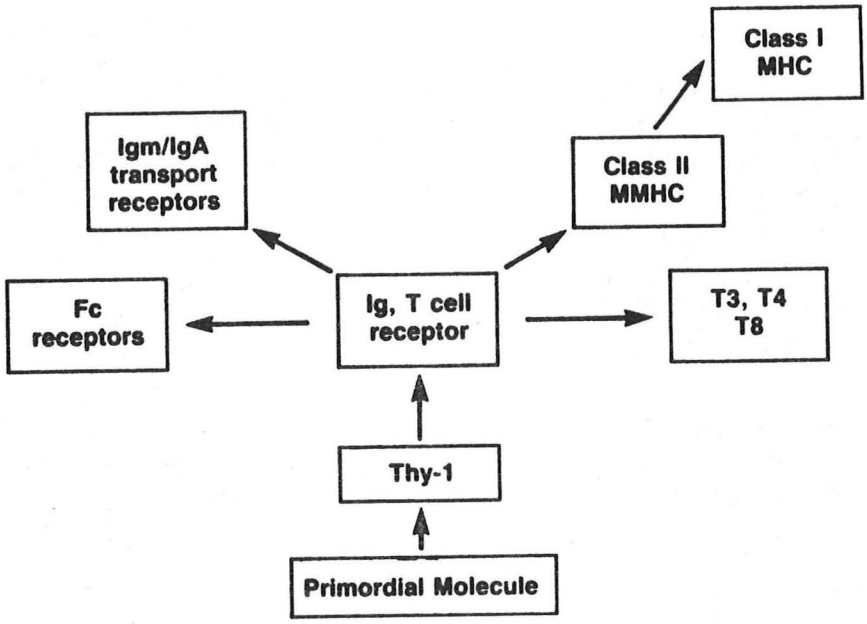

Figure 5. Evolution of the immunoglobulin superfamily (modified from Matsunaga, 1985).

liver and their function is unknown. The Thy-1 antigen is expressed predominantly in neuronal cells and thymocytes and in small amounts in other cells such as fibroblasts, epidermal cells, mammary glands and skeletal muscle. Thy-1 also is related structurally to the immunoglobulin superfamily but its function is unknown. This molecule is found on peripheral blood T cells in mice but not in man. It was recently reported that in mice antibodies against Thy-1 were able to stimulate CTL clones and spleen T cells. The genes for mouse Thy-1 have recently been cloned and sequenced by Silver and coworkers.

Also, receptor proteins for transport of IgM and IgA show a remarkable resemblance to Igs. Finally, the CD4 and CD8 molecules have also been suggested to be members of this superfamily.

7. T CELL ONTOGENY

We have known for some time that the thymus is essential for the development of normal T cell immunity. In its absence, as in the

DiGeorge syndrome in man, or in the nude congenitally athymic mouse, cell mediated immunity is deficient.

Stem cells orginating in the bone marrow migrate into the epithelial thymus and after a period of time emerge as mature T lymphocytes. During their residence in the gland, several things happen. The T cells acquire specific receptors for recognition of antigen. They learn to recognize foreign antigens only in conjunction with self MHC, on the surface of antigen presenting cells. In addition, they learn to discriminate between self and non-self. That is, self tolerance develops. These are obviously extremely important events which many investigators are now striving to explain.

At this time, the molecular basis by which self tolerance and MHC restriction are imprinted in the thymus are not yet understood. The thymus must eliminate autoreactive cells and at the same time expand clones of T cells capable of recognizing foreign antigen in association with self-MHC molecules.

Experiments with irradiated mice grafted with fetal thymus tissue and given bone marrow cells suggest that both the epithelial cells of the thymus and bone marrow-derived macrophages or dendritic are important. These are complex experiments and the results are still rather preliminary. They suggest that thymic epithelial cells are most critical for the imprinting of MHC restriction. While bone marrow-derived macrophages/dendritic cells appeared to be the major cells needed for the imposition of self tolerance.

Kappler and coworkers have investigated the maturation of T cells in the thymus by studying the expression of T cell receptors. They developed hybrid cell lines from mouse thymocytes during fetal development and examined their DNA for rearrangements of the T-beta genes. None were observed until day 14, with all the pattern having the normal genomic DNA structure. On days 15, 16 and 17 however, progressively more of the cells studied showed typical clonal rearrangements similar to those of mature T cells.

In other experiments the same workers made use of an antibody that recognizes an allelic determinant of the beta chain of the T cell receptor. In organ cultures of fetal thymus they found that around day 17 the receptor became detectable on the thymic lymphocytes. Initially, in the cortex, the staining was concentrated to the perinuclear area. All of the receptor protein was in the cytoplasm and none yet on the surface on the cells. In the medullary areas, cells were found that had receptor molecules on the surface. After examining many such cells, one was found on which the receptor protein was all aggregated or capped in close apposition to a thymic epithelial cell. The significance of this interaction is not known yet, but it suggests that thymocytes develop surface receptor protein and make an initial contact with epithelial cells in the thymus.

The following sequence of events has been suggested:

a. stem cells committed to a T cell phenotype migrate to the thymus from the bone marrow;

b. as these cells they randomly rearrange their alpha and beta chain genes generating a repertoire of receptors;

c. cells with anti-self receptor are selected;

d. specificity in some cells changes from anti-self to anti-antigen/self MHC;

e. T cells with strong anti-self reactivity are eliminated.

Early thymocytes that do not yet have T1-T3 structures do however, express CD2. It was therefore suggested by Reinherz that these cells may utilize the CD2 (T11) pathway for activation and proliferation.

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8. T CELL MALAGNANCIES

The diagnosis of human lymphocyte malignancies has been greatly facilitated by the introduction of monoclonal antibodies which recognize cell surface antigens. Labelling of surface markers in lymphoid tissue sections is being used for the immunological classification of malignant lymphomas as well as to distinguish between benign disorders and malignant conditions. However, in many cases it may be impossible to decide on the basis of surface staining. Recently it was shown that gene mapping with DNA probes for the immunoglobulin heavy and light chains provided another way of demonstrating the monoclonal origin of a B cell leukemia or lymphoma. The procedure involves demonstrating that the genes have undergone rearrangement in a clonal fashion. It is now possible to utilize a similar approach with cDNA probes for the beta chain of the T cell receptor.

With the availability of techniques for demonstrating rearranged genes of the beta chain of the T cell receptor, it is now possible to document the clonality of a given T cell population. The distinction between an inflammatory infiltrate of T cells and a monoclonal malignant process may be very difficult on the basis of morphologic features.

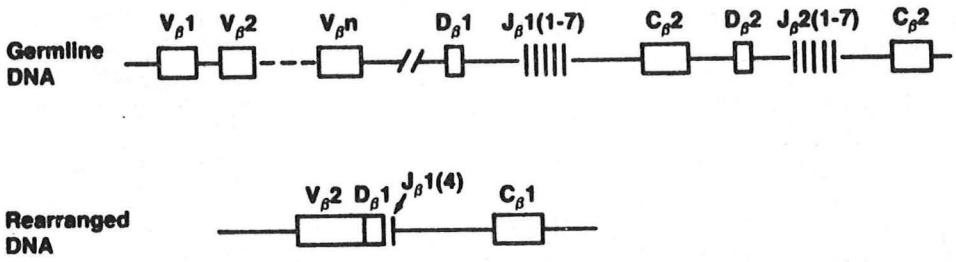

Figure 6. Assembly of the T cell receptor beta-chain gene from separately encoded variable (V β), diversity (Dβ), joining (J β) and constant (C β) segments.

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9. T CELLS IN ALLOGRAFT REJECTION

Allograft rejection mobilizes a broad spectrum of immune responses with either cellular or humoral mechanisms having the predominant role in different circumstances. While serum antibodies are well known to cause hyperacute graft failure and probably also play a predominant role in some forms of chronic rejection of vascularized grafts, the main effector mechanisms for graft rejection are known to be cellular. This was established years ago by adoptive immunity experiments and is attested in the tissue histology of grafts which are usually prominently infiltrated by mononuclear cells.

The identity of the T cells responsible for the rejection of grafts however, has been the subject of much controversy. Early investigators drew a parallel between tissue destruction during **in vivo** rejection of grafts and the killing of cells evident in experiments of cell mediated cytotoxicity **in vitro**. It was assumed that cell mediated lysis was a model of the graft rejection phenomenon. The same cells capable of killing target cells in the test tube were presumed to be responsible for destruction of grafts.

Then came the surface markers that identified T cell subsets and it became possible to put this hypothesis to the test. The surprising and totally unexpected finding from these experiments was that cells of the Lyt-2 (equivalent of CD8) phenotype could be removed from populations of cells used to transfer adoptive rejection and allograft destruction proceeded unmodified. From these results it was, perhaps too hastily, concluded that cytotoxic T cells were not required for rejection of allografts. The cells responsible were thought to be the effector cells of delayed-type hypersensitivity, known to be contained in the L3T4 (equivalent of CD4) subset.

In the meantime other workers showed that if cytotoxic T cells were injected directly into grafts marked destruction occurred at the site of inoculation. Such results suggested that cytotoxic T cells were capable of causing injury to tissue or organ allografts.

Moreover, as recently pointed out by Steinmuller, the cell transfer experiments did not take into account two important facts and should therefore be interpreted with caution. The first fact, is that the elimination of the Lyt-2-positive cells

from the population of cells given to transfer graft rejection was probably not complete. If sufficient numbers of contaminating cytotoxic cells remained the conclusions may not be valid.

The second fact, is that if the cyototoxic T cells were recognizing class II MHC antigens in the graft, they most probably were not of the Lyt-2 phenotype. It is now well known, as discussed above, that class II-specific killers are usually of the CD4+ type.

A number of investigators are now reporting experiments in which T cells obtained from rejection grafts are being cultured and cloned. Such clones can subsequently be characterized in regard to surface phenotype, functional activities and specificity of their receptors. Preliminary data suggest that some of these clones are cytotoxic and that they recognize HLA antigens present in the donor of the graft. Other clones have been isolated that react with antigens of the donor that are different from the major HLA specificities. Still other T cells are found that react against totally unreiated antigens.

More knowledge about the type of T cells involved and the antigens they recognize will undoubtedly be useful in the evaluation and treatment of graft rejection in the future.

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10. DEFECTIVE T CELL IMMUNITY

No attempt will be made here to review the large topic T cell deficiencies. Instead, three subjects in which there are recent developments of considerable interest will be briefly discussed.

The nature of the immunologic deficiency in AIDS has been the object of intensive study. The disease is characterized by a profound immunodeficiency with appearance of opportunistic infections and unusual malignancies. **In vitro** the immunodeficiency is reflected in diminution of mitogen responses, of proliferative responses to soluble antigens and to allogeneic lymphocytes. Interleukin-2 production, NK activity and pokeweed mitogen-induced B cell secretion of antibody are all impaired.

The major subset of T lymphocytes, defined phenotypically as CD4+ and functionally as the helper/inducer subset, is preferentially depleted. The initial diminution of CD4+ cells in the face of normal CD8+ cells results in the characteristic inversion of the CD4/CD8 ratio.

It has recently been found that HTLV-III/LAV selectively infects CD4+ cells, resulting in modulation of the CD4 antigen, virus production, cytopathic changes and cell death. CD4 protein itself, or something very close to it must be the receptor for attachment of the virus. Viral infection was blocked by antibodies against the CD4 antigen. In view of the functional importance of CD4+ cells this unique tropism can explain virtually all of the immunologic abnormalities of AIDS.

Another immune deficiency syndrome which has recently been characterized is the "bare lymphocyte" syndrome. It is so called because of absence of HLA class I and in some cases also class II antigens on blood mononuclear cells. Because of the importance of the MHC in the recognition of foreign antigens by T cells it has been speculated that the immunologic abnormalities might relate to the defect in MHC antigen expression. Studies with DNA probes have shown that HLA genes are present in genomic DNA but no mRNA is found. The absence of expression is thought to depend on a defective regulatory mechanism. It has been shown that HLA genotyping is possible using DNA probes.

In kindreds with this disease it is often desirable to determine as early as possible whether a newborn sib is also affected. It was reported recently that this can be accomplished by immunohistochemical staining of the placenta. In fact normal placentas demonstrated class I and class II HLA antigens in endothelial cells and cells of the mesenchymal stroma of the villi. In the placenta of a child born with the "bare

lymphocyte" syndrome, HLA antigens were not detected.

The third immunodeficiency syndrome to be discussed is a novel disorder characterized by recurent bacterial infections for which a molecular basis has recently been found.

The LFA-1 molecule was first defined in the mouse by monoclonal antibodies that inhibited T lymphocyte-mediated killing. Human LFA-1 was found to have the same functional properties. Anti-LFA-1 monoclonal antibodies inhibit the first step in T cell killing, the adherence of the killer to the target cell. NK and ADCC killing are also inhibited. These and other results suggest that LFA-1 is a cell adhesion molecule.

TABLE 6.

THE LFA-1, MAC-1 FAMILY

Mouse Human	LFA-1 LFA-1	Mac-1 Mac-1(OKM1,Mo1)	— P150,95
Subunits	$\alpha L;\beta$	$\alpha M;\beta$	$\alpha X;\beta$
MW($X10^{-3}$)	180; 95	170; 95	150; 95
Function	adhesion	complement receptor type 3	?
Cell Distribution	lymphocytes, granulocytes, monocytes	macrophages, monocytes, granulocytes	monocytes, granulocytes

(Modified from Springer, 1985).

Two other molecules are known to have identical beta subunits as LFA-1 with different alpha subunits. They are Ma-1 (OKM1, Mo1) and p150,95 (Table 6).

It appears that the primary deficiency in patient's cells is of the beta subunit. Normal alpha subunits are made but in the absence of the beta chain it is apparently not processed or transported to the cell surface.

Arnaout and coworkers studied 10 patients with this disease. They suffered from recurrent pyogenic infections starting in the first few weeks of life. They had recurrent skin infections,

sinusitis, recurent otitis media, gingivitis, tracheobronchitis, pneumonia, etc.

In some families the findings were consistent with an autosomal recessive mode of inheritance of the disorder. But this was not true in other families.

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11. T CELLS IN AUTOIMMUNITY

It has recently been recognized that T cells may be involved in the pathogenesis of at least some cases of aplastic anemia. *In vitro* studies suggested, already several years ago, that T cells from some patients with aplastic anemia could suppress the growth of erythroid and granulocyte colonies.

Recently Zoumbos and coworkers studied 12 patients with aplastic anemia and observed increased numbers of CD8+ cells in 10. These cells appeared to be activated because they expressed HLA-DR antigens on their surface. The same cells also were found to have IL-2 receptors (CD25, Tac) and when separated in a cell sorter only CD25+ cells produced interferon and inhibited the growth of hematopoietic precursor cells *in vitro*. Interferon has been implicated previously as a mediator of hematopoietic growth suppression.

A subset of patients with aplastic anemia appears to improve after treatment with anti-lymphocyte globulin. Presently there is no way of identifying which patients will repond to this therapy and which will not. If the lymphocyte abnormalities described above correlate with susceptibility to immunosuppressive treatment, it would aid in selecting patients for alternative methods of therapy such as bone marrow transplantation.

The pathogenesis of autoimmunity in diseases involving endocrine glands such as the thyroid is not well understood. One hypothesis that has become quite popular recently is that the endocrine parenchymal cells normally do not express class II MHC antigens but that these antigens may appear on their surface in the course of inflammatory reactions. Such aberrant class II MHC antigens would then present other tissue-specific antigens to T cells and initiate an autoimmune reaction. In support of this view, Davies recently cultured human thyroid cells with autologous T cells and observed appearance of class II molecules on the surface of the thyroid cells. It is now well established that class II antigens appear on many kinds of cells (including endothelial cells, fibroblasts, etc.) when they are exposed to gamma interferon. It has also been observed that keratinocytes become transiently Ia-positive in the course of inflammatory reactions in the skin. It seems unlikely that expression of Ia antigens alone would be sufficient to initiate autoimmunity. It appears to happen only in certain circumstances and in genetically predisposed individuals. It appears more likely that T cells have an active role in the initiation of autoimmune disease. Therefore, many investigators have studied the phenotype of T cells in tissues involved in autoimmune reactions. Activated T cells have been observed in the blood in the early stages of type I diabetes, in multiple sclerosis and in experimental models of these diseases, particularly experimental allergic encephalomyelitis. At the same time certain T cell subsets characterized by phenotypic markers of resting T lymphocytes were found to be decreased in such patients.

Bottazzo and coworkers described immunohistologic studies of the pancreas of a patient who died in ketoacidotic coma within 24 hours of the diagnosis of Type I diabetes mellitus. The majority of the infiltrating lymphocytes were of the CD8+ (cytotoxic/suppressor) phenotype. Some of the T cells were activated as evidenced by expression of DR antigens and IL-2 receptors. Affected islet cells showed increased expression of class I MHC antigens and were HLA-DR positive. The capillary endothelium around and inside islets was strongly HLA-DR positive.

Clones of T cells have been developed from patients. For example Hohlfeld and coworkers developed T cell lines specific for acetyl choline receptor from three patients with myasthenia gravis. However these studies were performed with antigens from the electric organs of Torpedo Californica and the responses, though HLA restricted, were clearly not limited to the DR3 haplotypes that are associated with risk for developing this disease.

T cell clones have also been produced from a variety of experimental animals with autoimmune diseases. T cell lines have been injected into normal recipient animals of the same inbred strain and have reproduced disease. For example, T cell clones against myelin basic protein were reported to have produced encephalomyelitis and T cells from animals with adjuvant-induced arthritis have been reported to have produced arthritis.

Perhaps one of the most interesting recent findings in the area of autoimmunity is the observation of a large deletion in the T-cell receptor beta-chain gene complex in New Zealand White mice. Mice of this strain together with New Zealand Black produce F1 hybrids with a severe form of murine systemic lupus erythematosus. The allele of the beta chain T cell receptor in these mice is lacking an 8.8 kilobase segment of DNA containing the $C_{\beta 1}$, $D_{\beta 2}$, and the $J_{\beta 2}$ clusters. The role, if any, of this deletion in the contribution of this strain to the autoimmune disease of the hybrid mice is presently not known. However, other strains of mice that are also prone to develop lupus have apparently normal T cell receptor genes.

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12. CONCLUSION

The study of T lymphocytes has for a long time been considered to be an obscure and difficult area of immunology. The last two or three years have witnessed a remarkable acceleration of activity and progress in this field. In this review I have attempted to touch on some of the highlights of this awakening which promises to revolutionize both basic immunology and many areas directly related to medical problems. The basis for the renewal was established with the development of methods of cloning T cells. The activity merged with the application of monoclonal antibodies and molecular approaches to the purification, elucidation of structure, gene cloning, and sequencing of T cell products and surface molecules. Some of the most exciting areas of present activity are the probing of T cell ontogeny, the study of functionally important surface molecules and the genetic analysis of the T cell receptor. Rearrangements of the T cell receptor are utilized as markers of clonality in T cell neoplasms. A new

immunodeficiency disease caused by the absence of a surface molecule, LFA-1, has been described. Efforts are continuing in the search for explanations and solutions to the puzzles of autoimmune diseases. The genes for the T cell receptor may provide new markers of inherited susceptibility for diseases such as diabetes mellitus type I or rheumatoid arthritis. Since T cells are known to be the major contributors to the pathogenesis of these conditions, improved understanding of T cell immunity should also lead us toward a better understanding of how and why autoimmune diseases develop and ultimately provide guidance for therapeutic interventions.