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# PROTEINS AND THE MOLECULAR BASIS OF CELL-MEDIATED IMMUNITY

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The mechanisms of cell-mediated immunity are extremely complex and involve several cell surface and soluble protein molecules. The identification of these proteins and an understanding of their functions have been augmented greatly by the combined use of in vitro functional assays and the tools of molecular biology. These methods have been especially valuable in identifying and characterizing the proteins involved in T-cell activation and antigen recognition. Several of these structures have been well characterized, and a model has evolved to describe their organization and interactions. Table 1 is a summary of the salient features of protein antigens with known important functions.

References:

MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS; Glycoprotein, T cells, Interleukin 2, Lymphocytes, (AW)  
Cell surface molecules that play a critical role in self-non-self discrimination are encoded for by the genes of the major histocompatibility complex (MHC) located on chromosome 6. There are three classes of MHC genes: classes I and II, which regulate cell-cell interactions in immune responses and class III, which encodes the C2, C4, and Bf complement components (reviewed in Reference 34).

Class I molecules, the original transplantation antigens, are composed of Mr 40,000-45,000 transmembrane glycoproteins noncovalently associated with the Mr 12,000  $\beta_2$ -macroglobulin protein. The molecules are expressed on virtually all nucleated cells and normally function as restriction elements for virus-specific cytotoxic T lymphocytes and the target antigens of alloreactive T cells. Cytotoxic T cells tend to recognize antigen in conjunction with the class I molecule. As described below, the recognition of the class I glycoprotein is apparently mediated through the T8 glycoprotein of cytotoxic T lymphocytes and the T-cell receptor complex. The class I protein is highly polymorphic and normally only interacts with T cells of the same allelic specificity [91]. Both the Mr 45,000 and  $\beta_2$ -macroglobulin polypeptides are structurally related to class II MHC and immunoglobulin proteins, and the genes for these proteins are included in the immunoglobulin supergene family (reviewed in References 29 and 75).

Class II antigens consist of two noncovalently associated polypeptides, an  $\alpha$  chain of Mr 30,000-35,000 and a  $\beta$  chain of Mr 27,000-30,000. These molecules serve as recognition elements for helper T cells, apparently interacting with the T4 glycoprotein in con-

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TABLE 1 Proteins Involved in Immune Response Mechanisms

Protein	MW (reduced)	Distribution	Protein function	Effect of monoclonal antibodies
MHC class I	~45,000	Most nucleated cells	Antigen-specific CTL recognition marker	Block allospecific CTL
MHC class II	~34,000 ~28,000	Antigen presenting cells (e.g. macrophages, dendritic cells), $\beta$ lymphocytes, activated T cells	Antigen-specific helper T-cell recognition marker	Inhibit helper T cell induction
T-cell antigen receptor	~40,000 ( $\alpha$ ) ~40,000 ( $\beta$ )	All mature T lymphocytes	T-cell antigen receptor	Stimulate T-cell proliferation and inhibit antigen-specific T-cell responses
T3	~25,000 ( $\alpha$ ) ~20,000 ( $\alpha$ ) ~20,000 ( $\beta$ )	All mature T lymphocytes	Functional association with T-cell antigen	Stimulate T-cell proliferation and inhibit antigen-specific T-cell responses
T4	~62,000	Thymocytes and peripheral T lymphocytes	Antigen-specific adherence between helper T cell and class II MHC	Inhibit T-cell association with cells expressing class II MHC proteins
T8	~34,000 ~46,000	Thymocytes and peripheral T lymphocytes	Antigen-specific adherence between CTL and class I MHC	Inhibit CTL effectors directed at class I MHC-gene products
Interleukin-2 receptor	~52,000	T cells (and B cells)	IL-2 receptor	Inhibit antigen and mitogen-stimulated T-cell proliferation
Interleukin-1	~15,000	Secreted by activated macrophages	Promote secretion of IL-2 and expression of IL-2 receptors	
Interleukin-2	~15,000	Secreted by activated T cells	T-cell growth factor	Inhibit T-cell proliferation
Lymphocyte function associated	175,000 ( $\alpha$ ) 95,000 ( $\beta$ )	T and B lymphocytes, thymocytes, or granulocytes	Leukocyte adhesion	Inhibit T-cell response to antigens

junction with the and for antibody antigens for T4-p numbers on anti found on B lymph cells. Class II mo line and are high DR homologous murine I-A antigen in vivo and in vitro interactions with

### GLYCOPROTEIN

#### T-Cell Receptor

The surface receptor of T-cell immunity. It is the site of response of T cells that act in the presence of accessory cells.

When responding to an antigen, an individual T cell and a determinant on the surface of the cell recognition of the sets of T-cell products, and T-cell products. However, II MHC antigen.

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The T-cell about 80,000 d each about 40,0 has revealed sub to several differences in the amino terminal region associated with a remarkably similar constant region [22,90]

Three classes identified:  $\alpha$ ,  $\beta$ , and glycopeptides;

junction with the T-cell receptor to induce helper function for cell-mediated immunity and for antibody production by B cells. Class II MHC antigens may also serve as target antigens for T4-positive cytotoxic T cells. The class II glycoproteins expressed in large numbers on antigen-presenting cells, such as macrophages and dendritic cells, are also found on B lymphocytes and activated T cells and may be induced in a number of other cells. Class II molecules also contain considerable sequence homology to immunoglobulins and are highly polymorphic, with several distinct families of antigens, including HLA-DR homologous to the murine I-E subregion molecules, and HLA-DS, homologous to murine I-A antigens. Monoclonal antibodies directed at class II glycoproteins have potent *in vivo* and *in vitro* effects, suppressing a variety of processes dependent upon T-lymphocyte interactions with other cell types (reviewed in Reference 32).

### GLYCOPROTEINS ON T CELLS

#### T-Cell Receptor

The surface receptor by which T cells recognize antigen plays a central role in cell-mediated immunity. Antigen recognition initiates a series of events that direct the immediate response of the T cell to this antigen, as well as the response of an array of other cells that act in the immune system, such as B cells, macrophages, and a variety of other accessory cells.

When responding to foreign antigens the individual T cells are specific both for the antigen recognized and the class I or class II products of the MHC complex [91]. Thus, individual T cells appear to recognize simultaneously an epitope of the foreign antigen and a determinant in the polymorphic domain of the MHC products expressed on the surface of the cell presenting the antigen. Major histocompatibility complex-restricted recognition of foreign antigens forms the basis for grouping T cells into two general subsets: (1) cytotoxic T cells that generally recognize antigen in association with class I MHC products, and (2) helper T cells that recognize antigen in association with class II MHC products. However, cytotoxic T cells of the helper phenotype with specificity for class II MHC antigens have been demonstrated [35,49].

Success in identifying the T-cell antigen receptor came with the production of monoclonal antibodies but not other T cells [1,20,30,47,61]. These monoclonal antibodies inhibit a number of functions dependent upon the antigen receptor: binding of T cells to antigen-producing cells, antigen-specific interleukin-2 (IL-2) release, cytotoxic effector function, and antigen-specific proliferation.

The T-cell protein immunoprecipitated by these antibodies is a glycoprotein of about 80,000 daltons (D) composed of sulfhydryl-associated  $\alpha$  subunit and  $\beta$  subunit, each about 40,000 D [2,20,48]. Examination of molecules from different T cell clones has revealed subunit heterogeneity. Each polypeptide contains constant regions common to several different T-cell clones and a variable domain, which are clone specific, situated in the amino terminal portion of the molecule. The molecules appear to be noncovalently associated with the T3 glycoprotein. The structures of the receptor molecules are remarkably similar to the immunoglobulin light chains. However, in addition to variable and constant regions there is an additional hydrophobic region anchored in the cell membrane [22,90].

Three classes of T-cell-specific complementary DNA (cDNA) clones have been identified:  $\alpha$ ,  $\beta$ , and  $\gamma$  [23,56,64,90]. The  $\alpha$  and  $\beta$  cDNA clones correspond to the  $\alpha$  and  $\beta$  glycopeptides; the protein product of the  $\gamma$  cDNA has not been identified. Sequences of



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the cloned cDNA revealed the presence of variable, constant, and joining regions remarkably similar in size and sequence to those encoding immunoglobulin proteins. In each case, the genomic DNA encoding these cDNA clones is rearranged in T lymphocytes.

It is not yet clear whether there is a molecular distinction between the T-cell receptors of the different classes of functional T cells. On the basis of the current data, there may be differences between the gene pools controlling the variable regions of these molecules, distinguishing the helper and cytotoxic T cells. Two variable region genes showed approximately 20% similarity between helper and cytotoxic cells. A comparable similarity is present between the constant region of the  $\beta$  subunit and that of the immunoglobulin light chain [20,28,48].

### T3

T3 is a cell surface protein complex present on all mature T lymphocytes and a fraction of thymocytes. The proteins appear to be closely associated with the T-cell receptor in a T3-T-cell receptor complex [59]. The T3 molecule consists of three polypeptide chains of Mr 25,000 (T3  $\gamma$ ), Mr 20,000 (T3  $\delta$ ), and Mr 20,000 (T3  $\epsilon$ ). The  $\gamma$  and  $\delta$  chains are glycoproteins, whereas the  $\epsilon$  chain has no detected oligosaccharides. The three polypeptides are structurally unrelated [85].

cDNA clones that encode the complete amino acid sequence of T3  $\delta$  have been isolated. The sequence of this gene corresponds to a 171-amino acid polypeptide with a signal peptide, a 79-amino acid extracellular domain, one transmembrane region, and a 44-amino acid intracellular domain. The predicted Mr of the T3  $\delta$  polypeptide is 16,719. The molecule is not homologous to the T-cell receptor or MHC-gene products (immunoglobulin supergene family) [85].

A distinctive feature of this molecule is the effect of anti-T3 monoclonal antibody at a low concentration ( $10^{-12}$  M) to induce proliferation of T cells. Antibodies against T3 also inhibit antigen-specific T-cell proliferation and allogenic cytotoxicity [9,58,86]. The insightful hypothesis from these findings was that anti-T3 antibodies react with the T-cell antigen-recognition structure [9]. This suggested association of T3 and the T-cell antigen receptor has been confirmed by a series of experiments involving antibody-induced modulation of T3 from the cell surface; it was found that the specific recognition of antigen by T cells and the effector functions of T4 and T8 cytotoxic clones were linked to cell surface expression of the T3 molecule [59]. A model for these interactions envisions close association of the T-cell antigen receptor molecule and T3 molecules (reviewed in Reference 48). The central role for the T3 glycoprotein in T-cell function and its presence in all mature human T cells has stimulated the trial usage of the OKT3 monoclonal antibody in the treatment of acute renal allograft rejection [10].

### T4 and T8

The T4 and T8 cell surface antigens define different T-cell subsets in relation to recognition of the MHC class I and class II glycoproteins. One subset of T cells [Lyt 2<sup>+</sup> in mice and T8<sup>+</sup> (Leu 2<sup>+</sup>) in human] is correlated with recognition of class I antigens and contains most cells capable of cytotoxic function. Another subset [L3T4 in mice and T4<sup>+</sup> (Leu 3<sup>+</sup>) in human], recognizes class II MHC antigens and contains the major fraction of helper activity. Murine T cells that respond to class I MHC antigens express high levels of Lyt-2 antigen, and anti-Lyt 2 antibodies block cytotoxic T-cell function [27,54,68,77]. In contrast, T cells that respond to class II antigens are generally Lyt 2<sup>-</sup> and are

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inhibited by anti-L3T4 antibodies but not be anti-Lyt 2 antibodies [78]. Similar findings were obtained with human cells [7,35,36,39,40,49,58]. Human T lymphocytes with cytotoxic or suppressor function (analogous to the murine Lyt 2 cells) are distinguished by the T8 cell surface glycoprotein, and T8-positive cells interact solely with targets expressing class I MHC molecules. Human T cells with helper/inducer functions specific to class II MHC carry the T4 antigen.

The specificities of the T4 and T8 proteins are substantiated by the effects of monoclonal antibodies inhibit allogenic cytotoxic activity [7,15,58]. Antibodies against the T4 antigens block T4<sup>+</sup> T-cell proliferation in vitro and production of IL-2 by T cells in the presence of antigen [15]. Moreover, administration of a monoclonal antibody against the T4 molecule of murine T cells prevented the development of experimental allergic encephalomyelitis and reversed the disease when given to paralyzed animals [87].

The T8 glycoprotein isolated by immunoprecipitation from peripheral blood and lymphocytes was identified by polyacrylamide gel electrophoresis, under reducing conditions, as a Mr 34,000 glycoprotein [69]. Under nonreducing conditions the molecule showed a complex multimeric structure with several components. In thymocytes, a Mr 46,000 polypeptide as well as a Mr 34,000 molecule was present. The Mr 34,000 and Mr 46,000 molecules appeared to differ in both protein and carbohydrate structure. The sequence of cDNA clones reveals that the molecule is a transmembrane glycoprotein with an N-terminal domain homologous to immunoglobulin variable region light chains [44]. Moreover, the gene for T8 is closely linked to the K light chain locus on human chromosome 2 [76].

The T4 molecule consists of a membrane glycoprotein of Mr 62,000 [80]. Genetic polymorphism of this molecule has been detected in the case of individuals with a normal population of inducer/helper T cells but a reduced number of antigenic epitopes reactive with anti-T4 monoclonal antibodies [31,65].

Considerable data suggest that these glycoproteins function as cell adhesion molecules to promote strong adherence between the T cells and target cells. Monoclonal antibodies that bind T4 or T8 appear to inhibit T cell function by diminishing this interaction of the T cell with its target. The ligands that bind to the T4 or T8 molecules have not been identified. Possibly, the specificity of T cell populations and different target cells results from an interaction of T8 or T4 with the class I or class II MHC molecules (reviewed in Reference 46) [7,39,83].

### Interleukin-2 Receptor

The immune response to a foreign antigen involves the amplification of those T lymphocytes with receptors for the antigen. Phenotypic changes in the induced cells include the expression of cell surface receptors for IL-2. Expression of IL-2 receptors is one of the early events after activation by antigen, occurring within the first 4-6 hr [11,55]. The IL-2 receptor is an intrinsic plasma membrane glycoprotein synthesized as a peptide backbone of approximately 33,000 D and then posttranslationally modified by the addition of both N-linked and O-linked oligosaccharides to form the mature molecule of about 50,000-55,000 D [41,50]. The molecule is also sulfated and phosphorylated [42]. Purification of the molecule from a T-cell lymphoma cell line and from activated T lymphocytes has been achieved [84]. The molecules differed slightly in apparent molecular weight but contained the same NH<sub>2</sub>-terminal protein sequence. A monoclonal antibody against the IL-2 receptor inhibited both IL-2 binding to cells and multiplication of

IL-2-dependent cell lines. The antibody also blocked antigen- and mitogen-induced T-cell proliferation, the generation of cytolytic T lymphocytes in allogeneic cell coculture, and T-cell-dependent activation of B-cell immunoglobulin production [13]. Purified IL-2 reversed the inhibitory effects of the antibody.

## SOLUBLE FACTORS

### Interleukin-1

A critical event in the initiation of the immune response is the activation of helper T cells by interleukin-1 (IL-1) produced by macrophages and monocytes (reviewed in Reference 14). These cells can be stimulated to produce IL-1 by a variety of agents, including microbes, microbial products, inflammatory agents, plant lectins, and antigens. The protein, initially called the lymphocyte activation factor [16], appears to function by acting on T cells to promote the secretion of optimum amounts of IL-2 and to induce the expression of IL-2 receptors on the T-cell surface [33]. Interleukin-1 also has been associated with a number of other activities: endogenous pyrogen [53], collagenase synthesis by fibroblasts [57] and rheumatoid synovial cells [51], release of acute phase reactants by the liver [73], and fibroblast proliferation [67].

Interleukin-1 has recently been purified as a Mr 15,000 molecule [66]. Concentrations of the purified material of  $10^{-10}$  M gave half-maximal stimulation in a thymocyte proliferation assay. A human IL-1 cDNA of 1580 bases that encodes a polypeptide of 269 amino acids, Mr 35,000, has been obtained from endotoxin-stimulated monocytes [5]. A similar cDNA has also been obtained from mouse cells [43]. The natural glycoprotein of about Mr 15,000, with high biologic activity, is the carboxy terminus of the Mr 35,000 precursor. The receptor for IL-1 has not been identified.

### Interleukin-2

Interleukin-2, originally called T-cell growth factor [52], is released into tissue culture media by human T cells when activated by antigens or mitogens. Media containing IL-2 has made it possible to clone and propagate T cells in vitro. The molecule purified from human T leukemia cells or peripheral mononuclear cells [74] is highly homologous to the polypeptide of Mr 14,800 predicted from the nucleotide sequence of cDNA clones [79]. The structure of the molecule has also been confirmed by peptide mapping and protein sequencing [60]. Purified IL-2 has been found to enhance thymocyte mitogenesis, stimulate the proliferation in vitro of antigen-specific helper or killer T-cell lines, augment the lytic activity of natural killer cells, and induce the development of plaque-forming B cells (reviewed in Reference 17). Antibodies to purified mouse IL-2 inhibit a variety of immune responses: antigen- and lectin-stimulated T-cell mitogenesis, cytotoxic lymphocyte generation in vitro, and T-cell helper function for antibody production in culture [13,18]. In addition, anti-IL-2 antibodies injected into mice reduce the in vivo development of alloreactive cytotoxic lymphocytes in response to allogeneic cells [18].

## OTHER IMPORTANT MOLECULES IN IMMUNE RESPONSES: LYMPHOCYTE FUNCTION-ASSOCIATED ANTIGEN

T cells respond to foreign antigens only when those antigens are presented on the surface of other cells that bear the appropriate MHC antigens [91]. In addition to the T-cell

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specific proteins already described, other cell membrane proteins are important in the generation of immune responses.

One of the best characterized of these other proteins is the lymphocyte function-associated antigen (LFA-1) [12,25,36,37,62,63,88]. This molecule is one of a family of leukocyte cell surface antigens that contain two noncovalently associated subunits: a common  $\beta$  subunit of Mr 95,000 and a cell-specific  $\alpha$  subunit. The LFA-1 molecule is expressed on T and B lymphocytes, thymocytes, macrophages, granulocytes, and subpopulation of bone marrow cells and contains an  $\alpha$  subunit of Mr 175,000. The macrophage-specific Mac-1 antigen contains an  $\alpha$  subunit of Mr 165,000 [24,38,70,71]. An  $\alpha$  subunit of Mr 150,000 of unknown function has also been identified on macrophages and monocytes [24,63]. The murine LFA-1 molecule is polymorphic and has been found to correspond to the Ly 15 cell membrane alloantigen [26].

A monoclonal antibody against murine Mac-1 cross-reacts with human monocytes [4] and has been shown to inhibit binding of C3bi-coated erythrocytes to murine and human macrophages [6, 70, 71]. These and similar results of [24, 89] indicate that the Mac-1 antigen is closely associated with or represents the type 3 complement receptor (CR<sub>3</sub>). Human Mac-1 antigen (HMac-1) appears to be identical in tissue distribution and structure to the OKM-1 and Mo 1 human monocyte antigens [8, 24, 81, 82].

Monoclonal antibodies against LFA-1 block a wide variety of T-cell functions, including the mixed lymphocyte reaction, response to mitogens, and lysis of target cells by cytotoxic T lymphocytes [12,19,24,25,88]. In general, the HLFA  $\alpha$ -specific antibody inhibits only T-cell-associated functions and the HMac-1  $\alpha$ -specific antibody inhibits only a monocyte/macrophage-associated function, but anti- $\beta$  antibodies inhibit all functions tested [24]. It is possible that the functional specificity of the HMac-1 and HLFA antigens is determined by the  $\alpha$  subunits whereas the primary functional molecule is the shared  $\beta$  subunit. Antibodies directed against the LFA molecules have also been reported to prolong allograft survival in a mouse model system [21].

There is strong evidence that the anti-HLFA antibodies inhibit T-cell functions by preventing the conjugation of T cells with other cells [35,45]. It thus appears that the HLFA and HMac-1 antigens may serve as leukocyte adhesion molecules. It is of interest that both adhesion of CTL to target cells (blocked by anti-LFA-1 antibodies) and adhesion through CR<sub>3</sub> (blocked by anti-Mac-1 antibodies) occur through a Mg<sup>2+</sup>-dependent step [63].

Recently, a clinical syndrome characterized by recurrent bacterial infections, delayed wound healing, and granulocytoses has been described (reviewed in Reference 3). This deficiency has been associated with a defect in the  $\beta$  subunit of the LFA-1 and Mac-1 molecules, corresponding to a deficiency in the adherence and other functions of granulocytes and mononuclear leukocytes [72].

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