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T-Cell Clones and T-Cell Receptors

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INTRODUCTION

The T-cell receptor for antigen (TCR) has finally been identified and characterized biochemically, and considerable information has been obtained about the organization of the genes that code for the TCR peptides. Why did this structure remain elusive for so long? It had been clear for many years that T lymphocytes play a central role in immune reactions, carrying out important effector and regulatory functions. On the basis of the immunological specificity of T-lymphocytes responses, it was clear that these cells have specific receptors which enable them to recognize particular antigens. It proved difficult, however, to identify these structures.

This problem was related in large part to the complexity of the requirements for T-cell activation. Antigen molecules appear not to react directly with responding T cells; rather, antigen must be processed into suitable fragments which are then presented by an appropriate accessory cell (234). Direct binding of antigen by T cells can be demonstrated only rarely (209). In addition, the antigen-presenting cell (APC) must express the appropriate cell surface glycoproteins encoded in the major histocompatibility complex (MHC) (257). For most helper T lymphocytes (HTLs), these are class II antigens of the MHC; for most cytolytic T lymphocytes (CTL), these are class I antigens of the MHC. The molecular basis for this MHC-restricted antigen recognition by T cells is not known. It is tempting to assume that it can be explained by the association of the nominal antigen with MHC molecules on the cell surface to produce a complex that is recognized by the T cell (202). Regardless of the mechanism, the phenomenon of MHC restriction is a key feature of T-cell responses. This restriction also indicates that T-cell activation involves more than a simple interaction of nominal antigen with the antigen receptor. It should also be noted that the restriction pattern for antigen recognition appears to be acquired during T-cell development in the thymus (58).

Two other factors have complicated the analysis of antigen recognition by T cells. First, T-cell responses are defined almost entirely in operational terms; an interaction between antigen and T lymphocytes can be recognized only by the effects that it produces. Usually, proliferation or secretion of lymphokines in response to a specific antigenic challenge or cytolysis of target cells bearing specific antigens is measured, although recently biochemial events have been used as earlier indicators of T-cell activation. Second, as noted above, more than one cell type is involved in T-cell responses. Often, bulk populations of cells from lymphoid tissues of immunized animals are studied; these cell preparations include macrophages and distinct T- and B-lymphocyte subsets as well as other cells. In such populations, cells present in very low numbers can produce responses that can be measured accurately. However, the essential biochemical processes associated with such responses cannot be analyzed accurately because the proportion of responding cells is small.

The same sort of unsatisfactory situation formerly existed with respect to antibodies. Until it was possible to characterize antibodies chemically as immunoglobulins, an antibody could be defined only in terms of its reactivity with a given antigen, and an antigen was defined in terms of its reactivity with an antiserum. The development of homogeneous sources of immunoglobulin and of immunoglobulin-producing cells made it possible to define first the chemical and later the genetic basis for immunoglobulin structure. Myeloma proteins and myeloma tumor cells and, later, hybridoma antibodies and antibody-producing hybridoma cells provided the materials that were necessary for deter-

mination of the structure of the immunoglobulin molecule and the organization of the genes encoding that structure.

The development of homogeneous sources of T cells enabled the rapid progress in characterizing the TCR. Much is now known about the structure of the receptor peptides and the organization of the genes that encode these peptides. The TCR has been the topic of a number of recent reviews (6, 45, 46, 75, 79, 93, 109, 144, 153, 182, 197). However, information about the structure of and the genetic basis for the TCR has not yet provided much insight into the cellular and molecular mechanisms involved in T-cell activation that is induced by specific antigen. It is clear that cell surface molecules other than the antigen receptor also are involved. Therefore, this review will consider both the specific receptor for antigen and some of the other cell surface molecules that participate in the process of T-cell activation. Both human and murine T lymphocytes will be considered, since a remarkable degree of structural homology exists for the T-cell surface molecules involved in antigen recognition in these two species.

CLONAL POPULATIONS OF T LYMPHOCYTES

To identify and characterize the TCR, it was necessary to obtain large numbers of homogeneous cells for biochemical and genetic studies. Several different approaches have been used to obtain such T cells in sufficient numbers. Many T-cell lymphomas can be cloned and grown readily in culture. However, an independent identification of the antigen receptor on lymphoma cells may prove to be difficult. Although T-cell lymphomas may occasionally retain inducible immunologic functions, such tumors apparently occur infrequently (65). Attempts to induce T lymphomas having a particular function sometimes have been successful (57, 59, 186). As noted below, despite these difficulties, a T-cell lymphoma was used in one of the earliest studies that demonstrated the presence of the TCR biochemically (5).

Construction of T-cell hybridomas, by using modifications of the fusion method that has been applied so successfully for obtaining antibody-producing B cell hybridomas, was a successful alternative approach for obtaining clonal populations of T cells. However, T-cell hybridomas are inherently susceptible to chromosome loss, and repetitive cloning at frequent intervals is necessary to maintain phenotypic and genetic homogeneity. The tumor cell partner may contribute to the observed functions in ways that may be difficult to recognize (35, 172, 250). In addition, identification of particular hybrid cells as the fusion product of two T cells may not always be direct. Some hybridomas formed by fusion of B and T tumor cell lines express the Thy-1 antigen of each parent cell (227).

A third source of large numbers of uniform functional T lymphocytes is cloned normal T cells. The discovery of interleukin 2 (IL-2) made this approach feasible (163). Although it may be possible to grow activated T cells in IL-2 alone, the number of cells capable of growing under these conditions appears to be low (74). Activated T cells cultured in IL-2 alone often grow well for about 2 months and then undergo a "crisis," with slowing of the growth rate. Cells then either die or suddenly begin to grow more quickly. The characteristics of uncloned lymphocytes that survive after passage in IL-2 for several months often suggest that they are clonally derived (74), but such cells also may be functionally unstable (168). Most, if not all, cells grown in IL-2 alone for extended periods have chromosomal abnormalities, probably reflecting the selective growth of variant cells (101).

Cloned T lymphocytes that retain normal phenotypic characteristics can be obtained by repetitive stimulation at about weekly intervals with the appropriate antigen in the presence of accessory cells and relatively small amounts of IL-2 (56, 66, 160, 185). For T cells reactive with conventional soluble antigens, irradiated syngeneic spleen cells usually are used as a source of accessory cells, but clonal populations of B lymphoma cells may be used (67). The accessory cells serve as antigen-presenting cells, but they may also carry out other functions as well. IL-1, secreted by or bound to accessory cells, appears to be required for the growth of at least some cloned murine T lymphocytes (110, 118). For alloreactive T lymphocytes, irradiated allogeneic murine spleen cells or transformed human peripheral blood B lymphocytes usually are used as a source of alloantigen; these cells meet other accessory cell requirements as well. Cloned T cells maintained in this manner usually are functionally stable and appear to be normal in phenotype and karyotype.

Maintenance of cloned cells with antigen and small amounts of IL-2 appears to provide a strong selective pressure for T cells that respond to specific antigenic stimulation. Exposure to antigen increases the expression of IL-2 receptors, thus favoring the growth of specifically reactive T cells (89). Passage at intervals of at least 7 days was empirically found to be optimal (66). This rather lengthy culture cycle seems to be required for HTLs because this type of cell becomes unresponsive to restimulation after antigenic stimulation (244), apparently as a result of exposure to IL-2 secreted in response to the initial antigenic stimulus (246).

Each of these methods for obtaining homogeneous populations of T lymphocytes has advantages and disadvantages. It is relatively easy to obtain large numbers of lymphoma or hybridoma cells. However, it is not possible to use such cells for studying the regulation of cell proliferation. Each source of cells has provided important information about the molecules that are involved in the recognition of antigen by T lymphocytes.

BIOCHEMISTRY OF THE T-LYMPHOCYTE ANTIGEN RECEPTOR

The first molecular candidate for the TCR was identified indirectly. A monoclonal antibody (MAb) reactive with a tumor-specific epitope on a murine T-cell lymphoma was found to precipitate a cell surface molecule that was composed of disulfide-linked 39- and 41-kilodalton (kDa) peptide subunits (5). Although this MAb did not react with normal splenic lymphocytes, a similar heterodimeric structure could be identified when lysates of surface-labeled splenic T cells and thymocytes but not B cells were examined by the technique of two-dimensional electrophoresis (5). In this procedure, cell extracts are separated first by electophoresis under nonreducing conditions. The gel containing the separated peptides is then treated with a reducing agent, and electrophoresis is carried out in the second dimension at right angles to the first. Disulfide-linked structures are located off-diagonal in such gels. A set of peptides from normal T lymphocytes which appeared in an off-diagonal location in two-dimensional gels were located in the same positions as the peptides precipitated by the tumor-specific MAb. The characteristics of this structure indicated that it was not one of the previously identified T-cell-specific molecules, and it seemed a likely candidate for the long-sought-after TCR. Subsequently, a xenoantiserum was obtained by immunizing rabbits with immune precipitates prepared from the T-cell lymphoma with the clonotypic MAb. Immunoprecipitates

prepared with this antiserum showed that molecules from different T-cell populations had homologous structure. Two-dimensional tryptic peptide maps indicated that both peptides had regions of constant and variable structure, which are properties expected for the TCR (151).

Because an antigen-specific function for this T-cell lymphoma-specific cell surface molecule could not be demonstrated, its identity as an antigen receptor remained uncertain. As noted above, an interaction between antigen and T lymphocytes is recognized only by the effects that it induces. An antibody which reacted with the TCR would be expected to block antigen-specific T-cell responses. However, the size of the T-cell repertoire, at least for CTLs, is rather large (208). This is true even when T-cell responses are limited to the differences associated with the substitution of a single amino acid in the α chain of the H-2K^b molecule (205). Given this extensive repertoire for antigen recognition, the prospect of developing antireceptor antibodies that would block T-cell activities became realistic only when functional T-cell clones were developed. Several groups of investigators attempted to develop "clonotypic" antibodies which reacted specifically with individual cloned T cells, on the reasonable assumption that the TCR would be the most likely structure to be distributed clonally. Several clonotypic antibodies were obtained, but the general experience has been that their frequency is very low. In 1982, Infante et al. described antisera that stimulated proliferation of the appropriate T cell clone but not other clones; however, the antisera also bound to irrelevant clones (97). Thus, these sera appeared to contain both antibodies reactive with the TCR as well as antibodies of other specificities.

The first reported monoclonal clonotypic antibody was found to bind specifically with, and to block the cytolytic activity of, the cloned CTL line used for immunization; it did not react with other cloned CTLs (120). Based on the amount of antibody bound, it was estimated that there were about 10^4 receptor molecules per cell (200). However, attempts to obtain immunoprecipitates with this antibody were unsuccessful. Additional monoclonal clonotypic antibodies soon were described (80, 110, 154, 156, 194, 221). It seems certain that these antibodies reacted with the TCR because they were clone specific, they blocked or stimulated antigen-specific responses of the appropriate T-cell clone, and they specifically precipitated from these T-cell clones similar but not identical structures that had both variable and constant peptide regions. It is somewhat surprising that immunization with cloned T cells has yielded mainly clonotypic antibodies, which presumably are reactive with the variable regions of the TCR (110). No antibodies reactive with the constant regions of the TCR have been identified as yet. Two MAbs reactive with an allotypic determinant of the TCR have been derived independently (78, 222); they seem to have the same specificity and react with about 20% of T cells from many common mouse strains, although the determinant appears to be absent in several strains. One of these MAbs has been shown to react with epitopes encoded by a limited subset of V_β genes (211).

Meuer et al. provided the first conclusive information about the biochemical structure of the functional TCR. They developed alloreactive human CTL clones and showed that such clones bearing the T4 surface structure reacted with class II MHC antigens, while clones bearing the T8 surface structure reacted with class I MHC antigens (160). They then derived clonotypic MAbs reactive with clones of each phenotype and demonstrated that these MAbs blocked antigen-specific cytolytic activity and antigen-induced proliferation of the appropriate clones (154, 156). However, these MAbs did not affect the proliferation induced by IL-2. About 30,000 sites were present per T cell (154), and peptides of 43 and 49 to 51 kDa were identified in immunoprecipitates prepared with these MAbs (154, 156). The observation that clonotypic MAbs linked to a solid support could induce proliferation and IL-2 secretion by the appropriate cloned T cell provided additional evidence that the cell surface structure identified by these MAbs was indeed the TCR (161). Similar structures also were found on human inducer T lymphocytes (155).

At about the same time, clonotypic antibodies reactive with the TCR of murine T-cell hybridomas were identified on the basis of inhibition of antigen-induced lymphokine secretion (80, 194). There were 15,000 to 25,000 receptor sites per cell, and two distinct peptides of 40,000 to 44,000 and 45,000 to 50,000 kDa were found in immunoprecipitates (106, 193). Although most of the clonotypic MAbs reacted only with the immunizing murine clone, one was found to react with a small proportion of cells enriched for T cells reacting with the same alloantigen (121). Also, Marrack et al. screened about 400 T-cell hybridomas for reactivity with one of their clonotypic MAbs and found one hybrid that reacted strongly (148). This cross-reactive hybridoma was shown to have a fine specificity pattern of antigen recognition identical to that of the original hybridoma, both in terms of nominal antigen and MHC restriction. In addition, the maps of tryptic digests prepared from receptor peptides of the two cloned hybridomas were identical, suggesting that these two independently derived hybridomas had identical TCRs (148). Recently, a third hybridoma sharing these properties has been identified (250). These findings would be expected if the TCR is clonally distributed.

The relatively small number of TCR molecules per cell made detailed biochemical studies difficult. It seemed clear from the studies described above that the TCR consisted of disulfide-linked peptides that differed somewhat in size. When subjected to two-dimensional isoelectric focusing and nonequilibrium pH gradient electrophoresis, clear differences were observed even with peptides that were similar in size in conventional reducing gels. When TCR peptides were isolated from murine and human T cells, one of the peptide subunits was found to be more acidic, with an isoelectric point (pI) of about 5; the other was more basic, with a pI of about 7 (5, 105, 106, 184); these peptides were designated α and β, respectively, initially on the basis of their pI. Additional information about the organization of the TCR was provided by peptide maps prepared with trypsin digests of the α and β chains (1, 3, 151). Both α and β chains were shown to contain variable and constant regions, but they apparently differed significantly in amino acid composition.

Although most of the information regarding the fine structure of the TCR peptides has been deduced from the nucleotide sequences of the complementary deoxyribonucleic acid (cDNA) clones that encode the peptides, a limited amount of information has been obtained by direct determination of the amino acid sequence. Tumor cell lines have been used to obtain sufficient material for partial sequencing. A weak but definite homology was found between amino acids 1 through 12 of the β chain from the human T-cell tumor REX and the first framework region of the human λ light chain. A portion of the α chain of this tumor showed about 40% homology with the third framework region of the V region of immunoglobulin heavy and light chains (55). The α chain of the TCR from the human T-cell tumor line HPB-ALL was found to have a blocked NH_2 terminus; however, this chain was found to be highly homologous to a

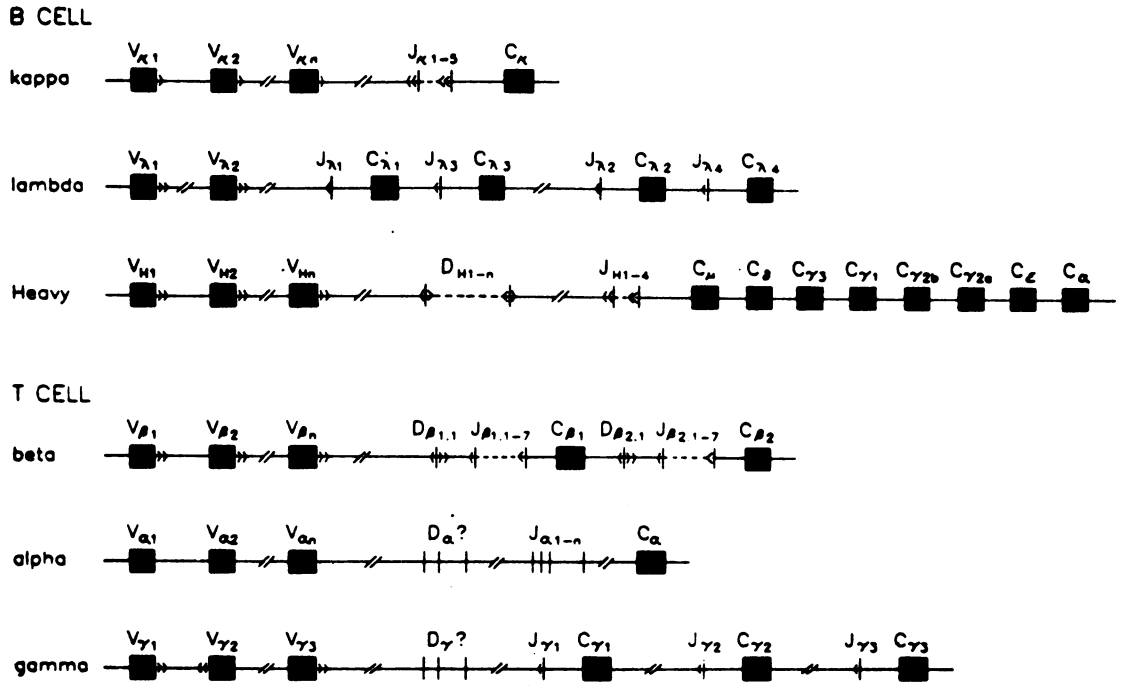

FIG. 1. Organization of immunoglobulin and T-cell receptor genes. The relative positions of variable (V), diversity (D), joining (J), and constant (C) segments for each gene are indicated. Nonconserved spacer sequences of 12 or 23 nucleotides (denoted > and >>, respectively) are shown. (Reprinted from Cell 40:225–229, 1985, with permission of Cell and L. Hood.)

putative murine α chain (103). The β chain from this tumor shares 50% homology with two other human T-cell tumors, REX and MOLT-3, suggesting that HPB-ALL has a homologous yet distinct V region segment (103).

ORGANIZATION OF THE GENES OF THE T-LYMPHOCYTE ANTIGEN RECEPTOR

The successful isolation of cDNA clones encoding the peptides of the TCR followed a strategy based on the following assumptions: genes for the TCR would be expressed in T cells but not B cells; the messenger ribonucleic acids (mRNAs) for these receptor proteins would be found on membrane-bound polysomes; the genes should be rearranged in T cells in a manner comparable to that of immunoglobulin genes; and they should have constant and variable regions (85). The first gene isolated by this approach encoded the β chain of the TCR. The next gene that was isolated was thought at first to encode the other chain of the TCR (192). However, the amino acid sequence of the predicted protein was not compatible with the sequence of the second TCR peptide chain expressed by human T-cell tumor lines (76, 103). Very soon, a third cDNA encoding a peptide consistent with the amino acid composition of the second TCR chain was obtained (33). The second gene that had been identified earlier then was designated γ; its structure and the fact that it rearranges in T cells indicates that it encodes an immunoglobulinlike receptor peptide, but antibodies reactive with this structure have not yet been developed. The structure of the cDNA indicates that it should be expressed at the cell surface. The organization of the genes for immunoglobulin heavy and light chains and the genes for TCR α, β, and γ chains is shown diagramatically in Fig. 1.

β Chain

The subtractive approach that was used to isolate the genes for the β chain involved the use of cDNA from an antigen-specific T-cell hybridoma. These cDNAs were hybridized with mRNA from B cells to remove shared sequences and yielded material that represented ca. 0.5% of the input cDNA. Ultimately, 10 distinct T-cell-specific cDNA clones were identified, one of which hybridized to a region of the genome that had undergone rearrangement in a T-cell lymphoma and several T-cell hybridomas (85). Variable, constant, and joining regions were discovered when the nucleotide sequence of this cDNA clone was compared with those of cross-reacting cloned cDNAs isolated from a thymocyte library. These regions were remarkably similar in size and sequence to comparable regions found in genes encoding immunoglobulin peptides (87). Almost simultaneously, a cDNA clone having very similar properties was obtained by the same general strategy and by using a human T-cell tumor line as starting material (253). Variable (V), joining (J), and constant (C) regions also were identified in the human gene. In addition, the relative positions of cysteine residues were found to be similar to those of murine and human immunoglobulin light chains, providing further evidence that this gene might encode a peptide of the TCR (253). The gene identified initially in these studies proved to encode the β chain of the TCR (2). Additional cDNA probes were developed and used to define the detailed organization of the genes for the β chain, and the general approach has been applied in the characterization of other TCR genes.

Several interesting observations have been made about the organization of the β-chain genes. First, there are two similar but quite distinct constant regions, designated $C_{\beta 1}$ and $C_{\beta 2}$ (34). The two C-region genes are 8 kilobases (kb) apart and are strikingly similar over their entire coding-region sequences. These genes are arranged in four exons and are interrupted by introns of nearly identical length that are located at exactly the same positions as those found in immunoglobulin genes (64, 146). The exons appear to encode an external domain, a small hingelike region, a trans-

membrane region, and a cytoplasmic tail. The amino acid composition of the two C regions is almost identical. There are only four substitutions out of 173 amino acids in the two C-region genes of the mouse (64); the two human C-region genes differ at only five positions (231). However, polymorphism of the human C_β genes has been reported; this is reflected by differences in the length of restriction fragments that segregate with parental haplotype (188).

Second, clusters of J-region genes are located 5′ of each C region. The $J_{\beta 1}$ cluster consists of seven closely spaced genes; six appear to be active genes and one is a pseudogene (34, 146). The $J_{\beta 2}$ cluster also consists of seven genes that are spaced somewhat further apart; again, one appears to be a pseudogene (64, 146). This arrangement of J gene segments in association with C-region gene segments resembles that found in the immunoglobulin λ light-chain gene, although in the immunoglobulin λ chain only a single J-region gene segment is associated with each λ C-region gene segment (93). Third, an additional eight-nucleotide sequence, encoding a single D region, is located 5′ to each J-region cluster (15, 107). A similar D-region gene segment also exists in the human (36).

The expressed V_β gene repertoire appears to be quite limited. V_β gene segments have been grouped into eight subfamilies, six with only one member, one with two members, and one with three members (15, 174). In one study, only 10 different V_β gene segments were found when the sequences of 15 variable genes of the mouse TCR were examined, leading to the conclusion that the total number of V_β gene segments may be 21 or fewer (15, 174). In another study, only 14 different V_β genes could be defined from a total of 25 cDNAs, and the maximal number of germ line V_β genes was estimated to be fewer than 30 (17). Thus, murine TCR V_β genes seem to be much less numerous than the 100 mouse immunoglobulin heavy-chain V genes (25) or the 90 to 320 kappa light-chain V genes (39).

Homology of the β chain with immunoglobulin heavy and light chains is evident in terms of both genetic organization and the structure of the coded peptides. The spacing between J and C elements is more like that of immunoglobulin light chains than immunoglobulin heavy chains, and the amino acid sequence of the C region is more homologous to the light chain (40%) than is the rest of the gene (25%) (64). The cysteine found in the hingelike region may form an interchain disulfide bond. Although there is homology with immunoglobulin in amino acid sequence of some of the domains, the putative transmembrane region does not resemble that of immunoglobulin even though it consists largely of hydrophobic amino acids (64).

As yet, there is no evident correlation between the use of any of the β-chain gene segments and particular T-cell characteristics including function, antigen specificity, and MHC restriction. The identical V_β gene segment expressed in a cloned HTL reactive with chicken erythrocytes (174) also was found in an alloreactive CTL (191); in the cloned CTL this gene segment was found as part of a productive V_β-$J_{\beta 1}$-$C_{\beta 1}$ rearrangement without an intervening D_β segment. A cloned HTL specific for hen egg lysozyme and restricted by the class II MHC molecule I-A^b expressed the same rearranged V_β segment as did a HTL hybridoma specific for cytochrome *c* and restricted by the I-E^k molecule (72). The β-chain gene was studies in 35 different murine T-cell lines having helper, cytotoxic, or suppressor function (86). The β chain gene of all HTL had undergone rearrangements (86). In some cases, the rearrangements were predictable on the basis of antigen specificity and MHC restriction. However, HTLs restricted by class II MHC antigens and CTLs restricted by class I MHC antigens could use the same TCR C_β gene (86). Similar conclusions were reached in studies with human T-cell clones (189). However, most suppressor T-lymphocyte hybridomas showed no β-chain gene rearrangements (20, 86) and appeared to have deleted this locus contributed by the normal T-lymphocyte fusion partner (86). The observation that no new gene rearrangements were found in these STL hybridomas using a genomic J region probe suggests that the failure to detect functional β chain genes was not the result of rearrangements involving a V-D-J switch to a new C region isotype (86). However, two murine suppressor T-cell lymphomas (164) and one human cloned suppressor T lymphocyte (189) were found to express a rearranged β gene. Some cloned murine natural killer (NK) cell lines and freshly isolated NK cells were found to rearrange and express TCR β-chain genes (251). Only $T11^+$,$T3^+$ human NK clones contained β-chain RNA transcripts and expressed disulfide-linked cell surface heterodimers; $T11^+$,$T3^-$ NK clones expressed only truncated β-chain transcripts (187). These observations are consistent with the hypothesis that a subpopulation of NK cells is related to T cells.

The conclusion that V_β gene usage is not restricted to any functionally or phenotypically defined T-cell subsets also was supported by studies that involved the use of both a MAb reactive with an epitope on the β subunit of the TCR from the human T-cell tumor REX and a cDNA clone encoding the REX V_β gene (1). The MAb, which reacts with an epitope expressed on ca. 2% of human T lymphocytes, was used in the selection of T-cell clones from peripheral blood lymphocytes. $T4^+$ or $T8^+$ clones with inducer, cytolytic, or suppressor function were obtained. Individual members of the REX V_β gene family were linked to different D_β- or J_β- and C_β-region segments in these cells, and no correlation was found between the use of any of these gene segments and any T-cell function or phenotype. In addition, these results suggest that, at least for the V_β segment, there are no restrictions on the mechanisms that generate combinatorial or junctional diversity (1).

It is not clear why two essentially identical C-region genes are necessary. It is of interest that an 8.8-kb segment of DNA containing $C_{\beta 1}$, $D_{\beta 2}$, and the $J_{\beta 2}$ cluster has been deleted in New Zealand White mice (111). Although the TCR of New Zealand White mice must be derived from a single set of β-chain gene segments, this mouse strain has functional T cells and is phenotypically normal. This strain, however, does contribute to the lupuslike autoimmune disease that develops in New Zealand Black × New Zealand White F_1 hybrid mice.

α Chain

The substractive technique that was successful in characterizing genes encoding the β chain of the TCR also was used to isolate genes encoding the α chain (33, 192). Although the experimental details differed somewhat, the approaches were similar in principle. Labeled cDNA synthesized from mRNA of a helper T-cell hybridoma (33) or a CTL clone (192) were used to identify T-cell-specific clones in a cDNA library. As would be expected for a TCR component, the genes encoding the cDNA clones showed distinct signs of rearrangement in different T cells. The nucleotide sequence of the cDNA indicated that the encoded peptide had regions corresponding to leader, variable, J, constant, transmembrane, and intracytoplasmic regions (33, 192). Also, four potential N-linked glycosylation sites were identified (33, 192). The mRNAs for the β chain and the putative α

chain were expressed at similar levels in T-cell hybridomas and in mitogen-stimulated spleen cells, providing further evidence that the newly identified cDNA encoded the α chain of the TCR (33). The human genes for the α chain of the TCR were found to have similar characteristics (252).

Analysis of cDNA clones from a number of T cells indicates that there are similarities but also significant differences in the organization of α- and β-chain genes. As is true for the β-chain genes, mouse and human α-chain genes have a similar organization (8, 81, 248, 254). The α chain has only a single C region (81, 248, 254). The C region of the α chain is shorter than that of the other TCR genes. The first exon encodes a C domain of only 87 amino acids; the second exon encodes a short, cysteine-containing region of similar size but not homologous in sequence to the hinge region of immunoglobulin; the third exon primarily encodes the putative transmembrane domain and the cytoplasmic tail; and the fourth exon encodes only the 3′ untranslated region (81, 254). A separate exon for the 3′ untranslated region is not found in immunoglobulin genes or β-chain genes (81, 254). At least two allelic forms of the human α chain have been defined on the basis of restriction fragment length polymorphism (94). The presence of additional nucleotides between rearranged V_α and J_α sequences suggests that there may be at least one D-region segment (81, 248, 254). However, there are alternative explanations for this observation: J_α segments are longer than those of immunoglobulin and the β chain, and the V_α segments may also differ in length; or N-region diversification with junctional addition of additional nucleotides may occur (248, 254).

The structure of 19 J_α gene segments has been analyzed, and 18 of these are distinct (8); therefore, it is likely that the total number of J_α segments is considerably larger. However, three of the J_α gene segments are closely linked and seem to be closely related to one another, suggesting the existence of subfamilies (248). The known J_α segments are spread over at least 60 kb of DNA and are significantly more polymorphic than the J_β gene segments (248). One consequence of the large cluster of J segments is the presence of an unusually long intron between V_α-(D_α)-J_α and C_α segments in at least some rearranged α genes; the nuclear transcript for the α gene must vary from 6 to >60 kb (81, 248). On the basis of the analysis of 21 α-chain cDNA sequences, there are at least 10 subfamilies of V_α gene segments, each containing 1 to 10 members (6, 16). Restriction fragment length polymorphism is observed among different mouse strains for V_α but not for V_β gene segments; this probably represents the duplication or deletion, or both, of V_α gene segments in the various inbred strains of mice (8).

γ Chain

The murine γ chain also was identified by a subtractive approach. T-cell-specific cDNA clones were divided into two classes: those which were encoded by genes that were rearranged in a cloned CTL line and those which were not (192). Two cDNA probes were identified in the latter category. On the basis of the nucleotide sequence, one appeared to represent the gene for the β chain of the TCR of this CTL (192). Although related, the other cDNA was clearly distinct. The encoded peptide had a similar degree of homology with immunoglobulin heavy and light chains as did the β chain and consisted of two immunoglobulinlike domains, a transmembrane region, and an intracytoplasmic portion; it was suggested that this peptide constituted the α chain of the TCR (192). However, this peptide lacked sites for N-glycosylation (192), a major problem, since both the α and β chains of the TCR have at least three N-linked oligosaccharide side chains (152). This gene was designated γ when the correct α-chain gene was identified (82).

Relatively limited information is available about the structure and organization of the murine γ-chain genes. There are three C regions, each containing three exons (82). The first exon encodes an immunoglobulinlike domain; the second encodes a short cysteine-containing hinge region; and the third appears to encode a transmembranous region and a short intracytoplasmic tail, as well as the 3′ untranslated sequence (82). Two C-region genes located about 16 kb apart have been identified in the human; however, an additional C region has not been excluded (134). At least one J segment is located 5′ to each C-region gene segment (82). D segments have not been identified. Three V segments have been identified; two are ca. 2.5 kb apart and are arranged head-to-head (82).

The function of the γ gene is unknown. Evidence for expression of the γ chain so far has been found only at the mRNA level. All cloned CTLs exhibited the same rearrangement of the γ-chain gene, although the rearrangement patterns obtained with the probe for the β chain gene were highly diverse (114). It is also of interest that the rearranged γ genes in different CTLs seems to have been assembled from the same germ line V and J gene segments (114). HTL lines and hybridomas expressed variable amounts of γ-chain mRNA, ranging from ca. 30% of the levels observed in cloned CTLs to undetectable levels (88). However, none of the four cDNA clones isolated from different HTL hybridomas could encode a complete γ chain (88). The observations that the γ gene is productively rearranged and expressed at the mRNA level in CTLs but is not necessarily expressed in class II MHC-restricted T cells have led to the suggestion that the γ chain is involved somehow in the recognition of class I MHC molecules (88). If the putative γ chain is expressed at the cell surface, it is likely that it is either only loosely associated with the other chains of the TCR or is part of a separate membrane structure (82). Multiple rearrangements of the human γ gene have been found in a variety of T cells as well as in different types of T-cell leukemia (134).

Expression of T-Cell Receptor Genes during Ontogeny

Several observations indicate that TCR expression first occurs during thymic ontogeny, although these studies are complicated by the imperfect understanding of pathways for T-cell development within the thymus. Murine thymocytes that do not express L3T4 or Lyt-2 but express low levels of Lyt-1 (designated dLy1 cells) are thought to be the precursors of functional T cells within both the fetal and the adult thymus (61). These cells are a minority population in the adult thymus, but constitute the majority of cells in the very early fetal thymus. In fetal thymocytes, γ-chain mRNA appears at about day 14 of fetal development, reaches maximal levels at day 15, and then declines rapidly (179, 213). In contrast, α-chain mRNA appears later and reaches maximal levels at day 19, while β-chain mRNA levels remain relatively constant after day 16 (21, 179, 213). In human thymocytes, β gene activation also appears to precede α gene activation (190), and the CD3 complex appears in parallel with the TCR molecule (3). D-J joining preceded other types of rearrangements of the β-chain genes in fetal murine thymocytes (21). To obtain large numbers of homogeneous thymic T-cell precursors, murine hybrid cells were constructed by using the BW5147 T-cell lymphoma cells and dLy1 cells (196). Among these hybridomas, which may

represent thymocytes arrested at early developmental stages, four had β genes in the germ line configuration and eight showed β gene rearrangements (196). These constructs should be useful for further characterizing the rearrangements of TCR genes and other changes that occur during T-cell development. In the adult murine thymus, dLyl cells expressed V-to-D-to-J and D-to-J rearrangements of the β chain, but no rearrangements of the α chain (196). Most adult murine thymocytes, including the small cortical cells, most of which die within the thymus, appear to express TCR (214).

Mechanisms for Diversification of the T-Cell Receptor

A similar recognition signal for gene rearrangement seems to be shared by immunoglobulin and the three rearranging genes of the TCR. The spacing of the signal sequences for DNA rearrangement in the TCR V region seems to follow the same 12/23 base pair (bp) rule established for the recombination of immunoglobulin gene segments, and the heptamer/nonamer sequences are also similar to those used by immunoglobulin genes (81, 107, 212, 248, 254). However, the D segment of the TCR β-chain gene is flanked on the 5′ side by a 12-bp spacer sequence and on the 3′ side by a 23-bp sequence; the 5′ flanking sequence of the J segment has 12 bp. Thus, direct V-J joining as well as V-D-D-J joining are possible in addition to the usual V-D-J joining (36, 107).

Diversification of the β chain seems to occur mainly through variable V_β-D_β-J_β joining. Different V_β, D_β, and J_β gene segments can be used to form a V_β gene. Each D_β gene segment seems capable of joining any downstream J_β segment, and any V_β segment may join any D_β-J_β combination (15, 174). Also, there is variability in the sites at which the V_β, D_β, and J_β segments may be joined (107, 212). In addition, random nucleotides may be added to either side of a D_β gene segment during its joining to V_β and J_β gene segments (107, 212). Similar mechanisms seem to operate in rearrangements of the V_α and V_γ genes, although, as noted above, D segments have not been identified with certainty in these genes. Three identical V_α sequences have been found to be associated with three distinct J_α segments (8). There appears to be little or no somatic mutation contributing to the diversity of the β chain of the TCR (15); although less information is available, this also appears to be true for the α chain (8). However, mutations can occur in TCR subunits; murine T-cell hybridomas, selected for a change in specificity for recognition of class II MHC molecules that serve as restriction elements, showed structural differences in both α and β chains of the TCR (10).

The V_β genes appear to have seven distinct variability peaks when analyzed by the Wu-Kabat variability plot (249). Three of these peaks correspond to immunoglobulin κ-light-chain hypervariable regions, two correspond to regions in V_H and V_κ that are more variable than framework regions but less variable than hypervariable regions, and two peaks do not have any precedent in immunoglobulin (174). These latter two regions lie external to the immunoglobulinlike putative antigen-binding site, and it has been suggested that these regions may participate in interactions of the outer surface of the TCR with polymorphic MHC determinants (174). Available information for the V_α region indicates that its secondary structure is similar to that of the V_β, V_H, and V_κ regions (8). Variability analysis shows that although V_α sequences are not as variable at any major peak as either V_H or V_β is, these peptides have similar patterns of organization (16). V_α and V_β segments share the region of variability in the N-terminal portion of the molecule that is not found in immunoglobulin, although the additional region of variability present between residues 67 and 86 in V_β is not found in V_α (16).

Chromosomal Location of Genes for the T-Cell Receptor

Two approaches have been used to identify the chromosomal location of the genes encoding the peptides that make up the TCR as well as several other peptides that are involved in T-cell activation by antigen. In the first, DNA isolated from a panel of interspecies somatic cell hybrids that retain a limited number of chromosomes from the species of interest is subjected to Southern blot analyses with cDNA clones coding for the peptide of interest. Assignment to a particular chromosome is made on the basis of concordance between the presence of particular chromosomes and hybridization with the cDNA probe. In the second, metaphase chromosome spreads are prepared, and the cDNA clone is hybridized with the chromosomal DNA in situ. The location of the gene to particular chromosome bands is then determined by autoradiography. Table 1 summarizes the information obtained by these approaches. The chromosomal locations of the genes encoding the peptides of the TCR have been confirmed by several groups of investigators, and there is general agreement in the assignment to specific regions.

The human α-chain gene is found on chromosome 14 (13, 38, 40, 54, 102) in the region 14q11-q12 (40). The V_α segment appears to be located proximal to the C_α segment within chromosome band 14q11.2 (54). The murine α-chain gene is found on chromosome 14, possibly in regions D1 or D2 (47, 113). The human β-chain gene is found on chromosome 7 (14, 27, 98, 128, 165), and both V_β and C_β gene segments are located on this chromosome (27). This gene was reported initially to be located on the short arm of chromosome 7 in region 7p13-21 (27). However, several other studies have located the β chain gene on the long arm of chromosome 7, assigning it to region 7q22-qter (37), 7q32 (165), or 7q35-q36 (98, 128). The region assigned initially (7q13-21) was found

TABLE 1. Chromosomal location of genes that may be involved in T-lymphocyte activation[a]

Gene		Chromosomal location in:	
		Human	Mouse
TCR			
α chain		14q11-q12	14
β chain		7q32-q36	6
γ chain		7p15	13
MHC		6	17
Other human cell surface molecules			
Human	Murine		
CD3δ	T3δ	11q23-11qter	9
CD4	L3T4	?	?
CD8	Lyt-2,3	2p13	6
CD2	?	?	?
CD1	?	?	?
Thy-1	Thy-1	11q23-q24	9
LFA-1	LFA-1	?	?
Immunoglobulin			
Heavy chain		14	12
κ light chain		2	6
λ light chain		22	16

[a] References regarding the chromosomal location of the various genes are included in the text. If the homologous molecule has not been identified or if the chromosomal location is not known, this is indicated by a question mark.

by other investigators to be a secondary hybridization site (98, 165). The murine β-chain gene is located on the proximal half of chromosome 6 (27, 133), probably in region B (27). Both human and murine β chain genes show very little polymorphism in the length of restriction fragments, suggesting that the organization of these genes is relatively conserved in both species (27). The human γ-chain gene appears to be located on chromosome 7; hybridization in situ indicates that it is located in region 7p15 (167). However, secondary sites of hybridization were found on chromosomes 1, 11, and 14 (167); the significance of these sites is not clear. As noted above, region 7p15 is the site of secondary hybridization observed with β-chain gene probes. The murine γ-chain gene is found on chromosome 13, probably in the proximal region A2 or A3 (113).

The particular chromosomal locations of the genes for the TCR have several interesting implications. Murine TCR genes have been linked to the MHC (112, 207). This linkage appears not to relate to the location of any of the genes for the TCR on the chromosome that bears the MHC complex, 17 for the mouse (240) and 6 for man (166). Serologic, genetic, and immunologic approaches have been used in the past to link the murine TCR genes to the immunoglobulin heavy-chain locus (100, 115, 178, 205). Again, this linkage appears not to relate to the location of genes for the TCR on the chromosomes that bear immunoglobulin heavy-chain genes. In fact, there seems to be no obligatory linkage between immunoglobulin and TCR genes. Although genes for the α chain of the human TCR and human immunoglobulin heavy chain (41) are on chromosome 14, none of the mouse TCR genes are found on chromosome 12, the location of the murine immunoglobulin heavy-chain gene (90). Also, although the murine β chain of the TCR is located on chromosome 6 along with the murine immunoglobulin κ gene (90), none of the human TCR genes are located on chromosome 2, which bears the human immunoglobulin κ gene or on chromosome 22 which bears the human immunoglobulin λ gene (150). Thus, B cells and T cells seem to use distinct genes to generate their antigen receptors.

It has been suggested that the localization of the immunoglobulin genes and the immunoglobulinlike TCR genes on different chromosomes is not fortuitous (113). The presence of two related but not yet extensively diverged gene families on the same chromosome would have presented opportunities for detrimental crossing-over events. In the single instance in mouse and man in which a gene for a TCR chain is located on the same chromosome as the gene for an immunoglobulin chain, it seems likely that the evolutionary precursors of these two gene families had become diversified before becoming located on the same chromosome.

Translocations and rearrangements affecting each of the chromosomal locations of genes for the TCR have been reported in disorders that affect T lymphocytes. The locus of the α chain was found to be split in T-cell leukemias (54); the C_α segment was translocated to chromosome 11 ($11p^+$), while the V_α segment remained on the involved chromosome 14 ($14q^-$). Rearrangements involving region q11-q13 of human chromosome 14 also have been observed in T-cell neoplasms (84, 233, 247, 255, 256). Abnormalities in chromosome 7 are found frequently in disorders affecting T cells. Rearrangements involving band 7q35-q36 have been described in T-cell lymphomas (63), and a gain of chromosome 7 has been reported in human T-cell lymphadenopathy virus (HTLV)-positive leukemia (232). Both clonal and nonclonal rearrangements affecting band 7q35 occur at a high frequency in circulating T cells in patients with the autosomal recessive immunodeficiency disorder ataxia telangiectasia (11, 98, 165). Deletion of one of the γ gene constant regions was reported in three cases of T-cell leukemia (167). Thus, abnormalities involving the chromosomal location of all three genes of the TCR have been found in T-cell disorders.

Transcriptional deregulation of the c-*myc* gene appears to occur in Burkitt lymphoma, a disorder involving a chromosomal translocation in which the activated c-*myc* is placed in close proximity to one of the three immunoglobulin loci (42, 43, 53). It is tempting to think that abnormal activation of oncogenes may also occur as a result of the chromosomal abnormalities in T-cell disorders. Indeed, the c-*erbB* gene is located in region p12-q22 of chromosome 7 (51) in reasonable proximity to the TCR β- and γ-chain genes. It has been proposed that a proto-oncogene, designated *tcl-1*, may become activated in translocations affecting chromosome 14 (40). Additional information regarding the importance of chromosome translocations and oncogene activation in T-cell malignancies should be forthcoming.

OTHER CELL SURFACE MOLECULES INVOLVED IN ANTIGEN RECOGNITION BY T LYMPHOCYTES

Multiple lymphocyte cell surface antigens have been defined by MAbs (129, 181). Several of these T-cell surface molecules also participate in antigen recognition by T lymphocytes. These structures were designated initially by the MAbs with which they reacted. However, MAbs derived by different investigators often were found to react with the same molecular complex, although not necessarily with the same epitope on that complex. This resulted in several different designations for the same cell surface structures. To avoid this problem, the recently proposed standard nomenclature (99) generally will be used to describe these molecules. However, a particular peptide will be identified by the MAb with which it reacts when this designation seems to be more appropriate. Properties of these cell surface structures are summarized in Table 2.

CD3 Molecular Complex

The CD3 molecular complex (defined by OKT3, anti-Leu-4, and UCHT1 MAbs) appears late in thymic ontogeny and is found on all human peripheral T lymphocytes (181). On human T cells, this molecular complex consists of at least three structurally distinct peptides: a 25- to 28-kDa γ chain and two 20-kDa chains, designated δ and ξ; the γ and δ chains are glycoproteins, while the ξ chain does not contain detectable oligosaccharides (22). MAbs specific for the δ and ξ chains have been developed; on the basis of reactivity with these MAbs, it appears that the δ but not the ξ chain is expressed on the T-cell surface (175). The human CD3 molecular complex may contain other peptides as well (22). The gene for the δ chain of the human CD3 complex has been cloned (236). The sequence of 171 amino acids deduced from this cDNA contained a signal peptide, a 79-amino-acid extracellular domain, a transmembrane region, and an intracellular domain 44 amino acids long. The CD3 δ chain shows no homology with TCR peptides, immunoglobulin, or MHC genes (236). The gene for the δ chain resides on human chromosome 11q23 (235).

The murine homolog of the human CD3 molecular complex has been characterized incompletely. Murine mRNA for the CD3 δ chain has been identified on the basis of cross-hybridization with the cDNA probe for the human δ chain, and the murine δ chain gene has been located on chromosome 9 (236), the location of the mouse Thy-1 gene (50). However, MAbs reactive with the murine homolog of

TABLE 2. T-cell surface molecules (in addition to the T-cell receptor) involved in T-cell activation

Molecules[a]	Characteristics:	Comments	Function
CD3 (T3/Leu-4) [?]	25- to 28-kDa γ chain 20-kDa δ chain 20-kDa ε chain ? others	Associated with TCR β chain	Signal transduction (?)[b]
CD4 (T4/Leu3) [L3T4]	55-kDa peptide	Immunoglobulin-homology	Class II MHC recognition (?)
CD8 (T8/Leu2) [Lyt-2]	34-kDa peptide (on peripheral T cells, homomultimers, in thymus, heteromultimer with T6, a 46-kDa peptide	Immunoglobulin-homology	Class I MHC recognition (?)
CD2 (t11, Leu-5, LFA-2) [?]	50-kDa peptide		Three epitopes $T11_1$-sheep erythrocyte binding $T11_2$-(?) $T11_3$-neo-epitope on activated cells (?)
LFA-1 [LFA-1]	177-kDa α chain, 95-kDa β chain		Associative recognition (?)
MAC-1 (mo-1, OKM-1) [Mac-1]	165-kDa α chain, 95-kDa β chain	Member, LFA-1 family	CR3
"Third member" [?]	150-kDa α chain, 95-kDa β chain	Member, LFA-1 family	CR4 (?)
T44 [?]	44-kDa disulfide-linked homodimer		(?)
IL-2 receptor [IL-2 receptor] (TAC)	ca. 55 kDa		Receptor for IL-2
Transferrin receptor [Transferrin receptor]	ca. 100 kDa	Found on many types of activated cells	Receptor for transferrin

[a] The names for the human structure as determined by MAbs are listed within parentheses where appropriate. The name within brackets designates the murine homolog when it is known.

[b] A question mark indicates that information is either unavailable or that the information is not known with certainty.

the human CD3 structure have not yet been identified unequivocally. Several groups have described MAbs which react with murine Thy-1 and which stimulate T-cell proliferation (73, 122, 139). These MAbs, however, do not block specific T-cell antigen recognition and do not coprecipitate the TCR (73). However, immunoprecipitates of cell surface peptides from a murine T lymphoma prepared with anti-TCR MAbs contained a 29- and a 24-kDa peptide in addition to the murine TCR α and β chains (4, 195a). These peptides probably are part of the murine CD3 complex. If Thy-1 is also part of this complex, it appears not to be one of these peptides, since peptide maps of these non-TCR structures differed from peptide maps of Thy-1 (4).

However, Thy-1 may be related in some way to the CD3 complex. The human Thy-1 gene has been cloned and was found to be similar in structure to the murine Thy-1 gene (204). As is true for those of the mouse (31) and rat (203), the coding sequence is divided into three exons (204). The first encodes part of the signal peptide, the second encodes the rest of the signal peptide and amino acids 1 through 105 of the mature protein, and the third encodes the remaining 37 amino acids, including a hydrophobic stretch of 20 amino acids (204). The human and rodent genes differ in the size of the introns; also, human Thy-1 has two sites of N-glycosylation, while rodent Thy-1 has three sites (204). Thy-1 seems to be excluded as one of the components of CD3 by the observation that human Thy-1 is not expressed in HPB-ALL cells, which do express CD3 (204). However, both human Thy-1 and the CD3 δ-chain genes are located in the same chromosome region, 11q23 in man (235, 238) and 9 in the mouse (50, 236).

The involvement of this molecule in antigen recognition was suggested first by the observation that MAbs reactive with CD3 block both the induction of CTLs as well as the lytic activity of CTLs; anti-CD3 MAbs also inhibit antigen-induced T-cell proliferation (155, 180). Anti-CD3 MAbs may be mitogenic for T cells (239). Modulation of the CD3 complex by MAbs also modulates the expression of the cell surface TCR (156), and immunoprecipitates obtained with anti-CD3 MAbs frequently include antigen-receptor peptides (23, 184). However, neither anti-CD3 nor anti-receptor MAbs inhibit the binding of the other MAbs to the surface of T cells (183). Further evidence for an association between TCR proteins and the CD3 molecular complex was provided by experiments in which cell surface proteins of T lymphocytes were cross-linked by using bifunctional reagents (24). Immunoprecipitates prepared with either anti-receptor or anti-CD3 MAbs contained both CD3 and TCR subunits. The predominant association appeared to be between the β chain of the TCR and the 28-kDa γ chain of the CD3 complex (24).

The TCR and the CD3 molecular complex are closely associated physically but are not covalently linked in the T-cell membrane. In addition, there appears to be obligatory requirement for the coexpression of these structures. This requirement was discovered through the selection of mutants of the T-cell tumor line Jurkat which lacked either CD3 (with MAb OKT3) or the TCR (with a clonotypic MAb). However, all mutants selected either for the loss of CD3 or the TCR failed to express both of these molecules on the cell surface (243). Three of the mutants that did not express a full-length β-chain mRNA also had diminished levels of α-chain mRNA and did not express surface CD3 (171).

However, transfection of one of these mutants with TCR β-chain cDNA induced the expression of normal levels of α-chain mRNA and led to the expression of a functional CD3-TCR complex on the cell surface (171). The basis for this linked regulation of expression of the TCR and the CD3 molecular complex is not clear, but these findings emphasize the importance of the CD3 structure in functional recognition of antigen by T lymphocytes.

Additional evidence for the involvement of CD3 in T-cell activation may be provided by the observation that 20- and 25-kDa proteins, precipitated along with α- and β-chain peptides by anti-receptor MAbs, are phosphorylated in response to activation of a murine T-cell hybridoma by antigen or concanavalin A (195, 195a). Although evidence that these peptides are part of the CD3 complex is indirect, the size and characteristics of these and other peptides found in the immunoprecipitation suggest strongly that this is the case (195a). The TCR peptides themselves are not phosphorylated during activation (195). The CD3 complex may play a major role in the transduction of the signal initiated by triggering of the TCR by antigen.

CD4 and CD8 T-Cell Surface Structures

Cell surface antigens expressed on mutually exclusive subsets of T lymphocytes were first identified in the mouse (29). With bulk cell populations, T cells with helper-inducer function were found to be Lyt-1$^+$, Lyt-2$^-$, Lyt-3$^-$ while cytolytic-suppressor T cells were Lyt-1$^-$, Lyt-2$^+$, Lyt-3$^+$ (29). When MAbs reactive with human T cells became available, it appeared that helper-inducer T cells expressed CD4 (defined by OKT4 and anti-Leu-3 MAbs) and cytolytic-suppressor T cells expressed CD8 (defined by OKT8, anti-Leu-2, and UCHT4 MAbs) (52, 129, 181). However, the validity of Lyt-1 as a phenotypic indicator of murine HTLs and the murine homolog of human CD4 was challenged by the later finding that most, if not all, murine T cells expressed Lyt-1 when more sensitive methods of analysis were used (130). This disturbing gap in the homology between mouse and man was filled by the discovery of MAbs that appear to react with the murine homolog L3T4 of the human CD4 (48, 176). As cloned T cells became available, cell surface antigen expression was found to correlate primarily with the class of MHC antigen recognized by the T cell and only incidentally and imperfectly with T-cell function. Most T lymphocytes that react with or are restricted by class I MHC antigens express CD8; most T lymphocytes that react with or are restricted by class II MHC antigens express CD4. This is true both with human (116, 160) and murine (49) lymphocytes. However, exceptions to these distinctions have been reported (12, 32, 60, 176, 218).

The genes encoding human T4 (143) and human T8 (108, 138, 224) have been cloned. The protein structures for these two molecules, deduced from cDNA, reveal that both molecules are integral membrane proteins which share significant amino acid and structural homologies with members of the immunoglobulin supergene family. Each consists of an N-terminal domain resembling a variable region, another extracellular domain, a transmembranous region homologous to that of class II MHC β chains, and an intracytoplasmic domain (108, 138, 143, 224). The T8 gene does not seem to be rearranged in cells that express the protein (224). A J-like region has been identified in the T4 molecule (143). The murine Lyt-2 gene also has been cloned and showed considerable (56%) homology with human T8 (169). There are both similarities and differences in the protein sequences deduced from T4 and T8 cDNAs, consistent with their postulated role as recognition molecules which react with different structures (143). The human T8 and the murine Lyt-2 loci are closely linked to the immunoglobulin κ light-chain locus, with both genes being located on chromosome 2 in man (26, 225) and chromosome 6 in the mouse (71). The chromosomal locations of genes encoding human T4 and murine L3T4 are not known.

T4 consists of a 55-kDa peptide that does not appear to form a covalently linked dimeric structure in association with itself or another molecule (143, 228). CD4 may exist as a single-chain structure, or T4 may associate with other cell surface molecules through noncovalent interactions. The structure of CD8 is more complicated. T8 exists in homodimers or homomultimers on peripheral T cells, but on thymocytes the T8 molecule also can form disulfide-linked heterodimeric complexes with T6 (CD1), a 46-kDa peptide (216, 217). During ontogeny, T6 appears on thymocytes after antigens T9 and T10; T6 is lost at the time that CD3-TCR become strongly expressed (181). Lyt-2 and Lyt-3 are present on thymocytes in a variety of multimeric forms (132, 241). Lyt-3 can be removed from CTL populations and clones by proteolytic digestion with little loss of cytolytic activity (132).

A role for these structures in antigen recognition by T cells was indicated by the effects of MAbs on T-cell functions. Antigen-specific cytolysis by CD8$^+$, CD4$^-$ cloned human T cells reactive with class I MHC antigens was inhibited by anti-CD8 MAbs (125, 159, 160); antigen-specific cytolysis by CD4$^+$, CD8$^-$ cloned human T cells reactive with class II MHC antigens was inhibited by anti-CD4 MAbs (160). Comparable results were observed with mouse T cells. Antigen-specific cytolysis by Lyt-2$^+$, 3T4$^-$ cloned murine T cells reactive with class I MHC antigens were inhibited by anti-Lyt-2 MAbs (131, 141, 142, 201); antigen-specific cytolysis by L3T4$^+$, Lyt-2$^-$ cloned murine T cells reactive with class II MHC antigens was inhibited by anti-L3T4 MAbs (49, 176). The appropriate MAb also blocked antigen-induced lymphokine release and proliferation by cloned T cells (48, 123, 147, 226, 245).

Among murine T cells, clonal heterogeneity was observed in the functional requirement for Lyt-2 (141, 142) and for L3T4 (147). In both situations there seems to be an inverse relationship between susceptibility to inhibition by MAbs and the apparent avidity of the T cells for antigen, measured indirectly. T cells that by other criteria appeared to have receptors of higher avidity were less readily inhibited by MAbs reactive with Lyt-2, for class I-reactive cells (141, 142), or by MAbs reactive with L3T4, for class II-restricted T cells (147). These observations led to the conclusion that these structures are "associative recognition" molecules, serving to increase the overall avidity of the reaction between T cells and APCs rather than being involved directly in the recognition of specific antigen (19, 140, 147, 183, 200).

The homology of T4 and T8 and their murine homolog L3T4 and Lyt-2 with immunoglobulin is consistent with a recognition function for these molecules. If so, their specificity might differ if they existed in homomultimeric or heteromultimeric forms. The structure of T6 (and Lyt-3) are not known, but T8 (and Lyt-2) complexed with such molecules probably would have a different binding specificity from that found with a homodimeric complex. Limited polymorphism of Lyt-2 and Lyt-3 has been observed in the mouse (28). A single polymorphism seems to exist for T4 in man (223). Multiple epitopes on the T8 molecule have been defined by MAbs (215). However, the extent of polymorphism observed in CD4 and CD8 molecular complexes

suggests that they do not contribute directly to the recognition of specific antigenic epitopes.

The target molecules on stimulating cells with which CD4 and CD8 interact are not known with certainty. Nonpolymorphic determinants on MHC molecules are reasonable candidates as target structures, class I molecules for $CD8^+$ and class II molecules for $CD4^+$ lymphocytes. Although direct evidence supporting this hypothesis is lacking, rather strong support is provided by several observations. Planar synthetic lipid membranes into which purified $I\text{-}A^d$ class II MHC molecules have been incorporated and to which peptide fragments have been added are sufficient for activation of antigen-specific T-cell hybridomas (242). The L3T4 structure on the responding T-cell hybridoma appears to be involved in antigen recognition in this situation, since activation of T-cell hybridomas by these synthetic planar membranes is blocked by anti-L3T4 MAbs (242). In this simple model system, class II MHC antigen seems to be the only possible target for the L3T4 molecule. The membrane-proximal domain of class II MHC antigens may contain the target sites for L3T4 binding. A subset of alloreactive CTLs can specifically lyse L-cell transfectants expressing an isolated polymorphic MHC class II $A_{\beta 1}$ domain, and this lysis is blocked by anti-L3T4 MAb (70).

LFA-1 Molecular Complex

The lymphocyte function-associated antigen-1 (LFA-1) is a widely expressed leukocyte antigen, being found on B and T lymphocytes, thymocytes, monocytes, granulocytes, and a portion of bone marrow cells (117). Inhibition of cytolytic activity by anti-LFA-1 MAbs provided the first evidence for involvement of this structure in antigen recognition by T cells; this was the basis for its designation as an LFA-1 (44, 177, 200). LFA-1 appears to participate in the adhesion step of CTL-mediated cytolysis (220). Anti-LFA-1 MAbs also inhibit antigen-induced lymphokine release (123). The human and murine LFA-1 structures each consist of two peptide chains, an α subunit of approximately 117 kDa, and a β subunit of 95 kDa; the subunit are not covalently linked (198, 200). A genetically determined polymorphism of the murine LFA-1 complex is detected by anti-Ly-15 MAbs, although it is not known whether this polymorphism reflects differences in the α or the β chain (92). A clonal heterogeneity in the functional requirement for LFA-1 has not been observed (140).

The LFA-1 molecular complex appears to be a member of a family of cell surface molecules involved in cell recognition events. The human cell surface structure, identified by several MAbs (Mol/MAC-1/OKM1), and the murine homolog (Mac-1) are found on granulocytes, monocytes, some bone marrow cells, and NK cells (219, 229). This stucture also consists of two peptide chains, an α subunit of approximately 165 kDa and a β subunit of 95 kDa that are not covalently linked (119, 199). This structure appears to be identical to the complement receptor type 3 (CR3) which is responsible for the adhesion of myeloid cells to C3bi-coated particles (18). The α subunits of LFA-1 and MAC-1 are distinct, as indicated by differences in isoelectric focusing and tryptic peptide mapping patterns; the β subunits apparently are identical (199). A third member of this polypeptide family sharing the β subunit has been identified; the α chain of this structure is a peptide of 150 kDa (126, 199). The function of this structure is not known, although indirect evidence suggests that it may be the CR4 which mediates C3d binding to neutrophils (124).

All three members of this leukocyte differentiation antigen family appear to mediate cell adhesion events. Patients genetically deficient in this family of polypeptides have recurrent bacterial infections and severe impairment in a number of granulocyte-mediated adhesion-dependent functions (7, 9). Available data suggest that LFA-1 on T cells serves as an accessory recognition molecule that is not linked to the TCR. On the basis of results obtained with MAbs reactive with the two subunits, it appears that the functions of this family of molecules may be determined by the α subunit, although both chains bear functionally important epitopes (91). The target molecule for LFA-1 interaction is not known. The inhibitory effects of anti-LFA-1 MAbs on T-cell responses have been observed when cells of hemopoietic origin were used as antigen-presenting cells. No inhibition by anti-LFA-1 MAbs was evident when L-cell fibroblast lines transfected with the appropriate class II MHC antigens were used as APCs, although anti-L3T4 did block responses with these APCs (69). Anti-LFA-1 also did not inhibit T-cell responses stimulated with polyvalent anti-receptor MAbs (69). Although many APCs of hemopoietic origin bear LFA-1, the B-cell lymphoma cell line A20.2J (which can present antigen) does not, and T-cell responses stimulated by A20.2J APCs are blocked by anti-LFA-1 MAbs (69). It is of interest that anti-LFA-1 as well as anti-L3T4 MAbs inhibited activation of a T-cell hybridoma by plana lipid membranes into which class II MHC antigens and an immunogenic peptide had been incorporated (242).

Thus, LFA-1 seems to be involved in interactions between T cells and APCs, but only when the APCs are of hemopoietic origin. However, MAbs reactive with LFA-1 do not inhibit the stimulation of T cells by APCs that are not of hemopoietic origin. Although this discrepancy cannot be explained at present, it seems to exclude a simple steric blocking mechanism for the inhibitory effect of anti-LFA-1 MAb.

CD2 T-Cell Surface Structure

The CD2 structure (defined by OKT11, anti-Leu-5, anti-LFA-2 MAbs) apparently consists of a 50-kDa peptide and is the human T-cell surface receptor for sheep erythrocytes (95). The naturally occurring ligand for CD2 is not known. It is the first marker specific for the T-cell lineage to appear in human ontogeny (104). Although found in other primates (83, 137), a comparable structure has not yet been identified in the mouse. Involvement of CD2 in T-cell function was first indicated by the observations that MAbs reactive with this structure inhibited the cytolytic activity of cloned T cells (117, 149, 173). Recent studies suggest that CD2 may also be involved in T-cell activation. Three epitopes on the peptide have been defined by MAbs (158). One ($T11_1$) is associated with the sheep erythrocyte-binding site, and another ($T11_3$) is expressed on activated but not resting lymphocytes or thymocytes (158). The $T11_3$ epitope appears within 24 h after activation with lectins and also is induced within 30 min by exposure to anti-$T11_2$ MAbs. Proliferation and lymphokine release by resting T cells and cloned human T cells is induced by exposure to anti-$T11_2$ and anti-$T11_3$ together but not by exposure to either alone; anti-$T11_1$ alone or in combination with anti-$T11_2$ or anti-$T11_3$ is not mitogenic (158). However, the CD3 structure (and presumably the TCR) is required for the activation of T cells by anti-T11 MAbs; cloned T cells in which expression of surface CD3 has been modulated by incubation with anti-T3 MAbs do not proliferate when exposed to anti-T11 MAbs (158).

Antibodies reactive with CD2 also have other biological effects. Expression of IL-2 receptors by thymocytes that

have not yet acquired the TCR-CD3 complex can be induced by MAbs reactive with T11 (3, 62). In contrast to the finding noted above that anti-T11 MAbs can inhibit antigen-specific cytolytic activity of human CTLs, anti-$T11_3$ in combination with either anti-$T11_1$ or anti-$T11_2$ caused cloned human CTLs to lyse inappropriate target cells (210). This combination of anti-T11 MAbs also induced lysis of NK-cell-resistant target cells by $CD2^+CD3^-$ cloned human NK cells which lacked a TCR; however, cloned human alloreactive noncytolytic inducer T cells were not triggered to kill (210).

The precise role of the CD2 molecule in T-cell function is not clear. However, it probably is a structure that can be involved in activation events as well as participating in associative recognition of antigen.

Other Cell Surface Molecules

Other cell surface molecules may be involved in T-cell activation. The functional importance of most of the structures discussed above for antigen recognition was shown by the inhibitory effects of MAbs reactive with them on T-cell activities. However, some, including TCR, CD3, and CD2, seem to be involved directly in T-cell activation, since MAbs reactive with the these structures also can activate T cells. The T-cell surface structure T44 may fit in the latter category. The MAb 9.3, which reacts with a T-cell-specific peptide of 44 kDa, can induce human peripheral blood mononuclear cells to release IL-2 and to proliferate (77, 162). There is disagreement about the effects of modulation of the CD3 complex on activation by anti-T44 MAbs; one group found that modulation of CD3 had no effect on activation (77), whereas another group reported that such modulation caused inhibition (162). The latter group found that modulation of T44 had no effect on activation induced by anti-CD3 or anti-CD2 MAbs and that neither the TCR, CD3, nor CD2 comodulated with T44 (162).

Proliferation of T cells is induced by IL-2 which reacts with specific receptor molecules on the T-cell surface (30). Indeed, it has been suggested that proliferation of many T cells involves an autocrine pathway (157). According to this model, triggering of the TCR-CD3 complex induces the expression of IL-2 receptors and secretion of IL-2. Cell proliferation then results from the interaction of the secreted IL-2 with cell surface receptors for IL-2. Certainly, antibodies reactive with IL-2 receptors inhibit T-cell proliferation induced by exogenous IL-2 (135, 145), but there may be an IL-2-independent pathway for T-cell proliferation as well (D. W. Lancki, R. L. Moldwin, W. L. Havran, K. C. Herold, and F. W. Fitch, Fed. Proc. **44**:5152a, 1985). The gene for the human IL-2 receptor is on the short arm of chromosome 10p14 (136).

The cell surface receptor for transferrin, also designated T9, is composed of a peptide of ca. 100 kDa, which is expressed as a disulfide-linked homodimer (68, 230). Transferrin receptors are not found on normal resting lymphocytes, but their expression is induced by mitogenic stimulation (127). This structure is selectively expressed on proliferating cells and appears to be important for replication of all cell types. MAb reacting with the transferrin receptor inhibits thymidine incorporation by stimulated T lymphocytes (170). The transferrin receptor gene is located on chromosome 3 (96, 237).

SUMMING UP

Both B and T lymphocytes react with specific antigens. Although they utilize homologous yet quite different cell surface structures to carry out this process, they differ considerably in the strategy they use for antigen recognition. Antigen can bind directly to B cells, leading to activation. T cells appear to react only with antigens that are present on cell surfaces; binding of antigen to T cells can be demonstrated only rarely. Antigen-stimulated B cells secrete antibody molecules which are structurally identical, except for the absence of the transmembrane portion and the cytoplasmic tail, with the B cell surface antigen receptor. Secretion of functional receptor molecules, analogous to antibodies, by T cells has not been observed. B-cell functions seem to be mediated primarily if not exclusively through secreted antibody molecules. In addition to direct cell-mediated effector functions such as cytolysis, T cells carry out many activities through secreted lymphokine molecules.

T cells use several cell surface structures for recognition of antigen. The TCR appears to be the only structure which can account for the specificity of T-cell reactions. It somehow interacts with antigen, but the specific MHC restriction element apparently is recognized as well. It is not known whether the TCR is involved directly in antigen-induced T-cell activation. The TCR is closely associated with, but not covalently linked to, the CD3 molecular complex which consists of at least three different peptides. There appears to be an obligatory requirement for the coexpression of TCR and CD3. Several lines of evidence suggest that CD3 participates in the transduction of the signal(s) initiated by the interaction of antigen with a TCR. It may be that the TCR serves only as a specific recognition structure which is linked functionally with the separate CD3 complex which, in turn, is responsible for conveying the signal to the inside of the T cell.

Other surface molecules also are involved in the interaction of the responding T cell with the APC. Several of these molecules appear to serve as associative recognition structures, contributing to the overall avidity of interaction between the responding T cell and the APC. Two of these, CD4 and CD8, are expressed on mutually exclusive T-cell subsets. Expression of these structures initially was thought to be related to T-cell function; CD4 is found on helper-inducer T cells, and CD8 is found on cytolytic-suppressor T cells. When clonal populations of T cells become available, it became clear that correlation was better with the class of MHC antigen serving as the T-cell restricting element than with T-cell function; CD4 generally is found on T cells restricted by class II MHC antigens, and CD8 generally is found on T cells restricted by class I MHC antigens. However, even this correlation is imperfect. It seems likely that nonpolymorphic determinants on MHC molecules are the target structures for CD4 and CD8, although this has not been demonstrated directly. If so, the basis for the imperfect correlation between expression of these molecules and the class of MHC molecules serving as restriction element is not easily explained.

The LFA-1 molecular complex, one member of a family of related surface recognition molecules, also seems to have an associative recognition function. The natural ligand for LFA-1 is not known. Clonal heterogeneity has not been observed among T cells in the extent to which anti-LFA-1 MAbs inhibit T-cell function. However, there is heterogeneity among APCs with respect to the effects of anti-LFA-1 on the ability to stimulate T cells.

In addition to these structures, which are involved in antigen recognition, other cell surface molecules influence T-cell proliferation. CD2 (which is the human T-cell receptor for sheep erythrocytes) and T44 (whose function is unknown) also may be involved in T-cell activation, perhaps

through interactions with the CD3 complex. The natural ligands for these structures are not known. Expression of IL-2 receptors is influenced both by antigen and by IL-2. Transferrin receptors are expressed by activated but not by resting T cells. These receptors and perhaps the associative recognition structures may serve to modulate the responses initiated by antigen.

The molecules of the T cell receptor and two of the associative recognition structures, CD4 and CD8, are members of the immunoglobulin supergene family which also includes class I and class II antigens of the MHC, β_2-microglobulin, and Thy-1 (93). Although antibodies and TCRs are quite similar in general structure, the extent of similarity, although significant, is less than might have been expected. For example, the β chain of the TCR, like the immunoglobulin λ chain, has J segments associated with each C region, but the β chain of the TCR also has a D segment which is found only in immunoglobulin heavy-chain genes. There is no obligatory genetic linkage between any of the immunoglobulin and TCR genes. Thus, while T cells and antibodies use similar genetic mechanisms for generating an extensive repertoire of antigen recognition, they do not seem to share specific genetic information to accomplish this. Any shared recognition of antigenic epitopes or shared idiotypes by T cells and antibodies apparently must occur by chance.

Three other features of T-cell biology deserve emphasis. First, T-cell responses are restricted by class I or class II antigens of the MHC, and for nominal antigens, self MHC molecules are required as the restriction elements. Second, the genetic specificity of this MHC restriction of T cells is determined by the thymic environment in which the T cell develops; in chimeric animals, the restriction pattern of both class I and class II MHC-restricted T cells is determined by the MHC of the recipient thymus rather than the MHC of the donor animal. Third, the TCR first appears during thymic ontogeny. Thus, there appears to be selection within the thymus for T cells which have acquired the ability to recognize self (as reflected by the thymic environment) together with nominal antigen. The mechanisms for this selection process have not been defined. Further characterization of the involvement of the antigen receptor and the other cell surface molecules in T-cell activities will provide additional insight into these important but incompletely characterized events that determine the T-cell repertoire.

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