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Selection of Amino Acid Sequences in the Beta Chain of the T Cell Antigen Receptor

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The induction of an immune response in mammals is initiated by specifically reactive T lymphocytes. The specificity of the reaction is mediated by a complex receptor, part of which is highly variable in sequence and analogous to immunoglobulin heavy- and light-chain variable domains. The functional specificity of the T cell antigen receptor is, however, markedly different from immunoglobulins in that it mediates cell-cell interactions via the simultaneous recognition of foreign antigens and major histocompatibility complex–encoded molecules expressed on the surface of various lymphoid and nonlymphoid cells. The relation between the structure of the receptor and its functional specificity was investigated by analyzing the primary sequences of the receptors expressed by a series of T lymphocyte clones specific for a model antigen, pigeon cytochrome c. Within this set of T lymphocyte clones there was a striking selection for amino acid sequences in the receptor β-chain in the region analogous to the third complementarity-determining region of immunoglobulins. Thus, despite the functional differences between T cell antigen receptors and immunoglobulin molecules, analogous regions appear to be important in determining ligand specificity.

ANTIGEN RECOGNITION BY T LYMphocytes is mediated by a membrane-bound receptor complex, the T cell receptor (TCR), comprising at least eight polypeptide chains. Two of the chains, termed α and β, manifest a diversity characteristic of immunoglobulin (Ig) molecules (*1, 2*), and these two chains transmit the T cell specificity for antigen and major histocompatibility complex (MHC) molecules (*3*). The α-chain gene contains six exons, the second resulting from the somatic rearrangement of a variable gene segment encoding approximately 95 amino acids (V-region), and a joining gene segment encoding between 18 and 21 amino acids (J-region) (*4, 5*). The β-chain is also encoded by six exons, the second resulting from the somatic rearrangement of a variable gene segment encoding about 98 amino acids, a diversity gene segment encoding from 0 to 4 amino acids (D-region), and a joining gene segment encoding about 16 amino acids (*6, 7*). Additional amino acid residues, encoded by N-regions, are often present between each of the rearranging gene segments and originate from a template-independent addition of nucleotides (*8*).

Primary sequence analyses of Ig V-regions have shown three regions of sequence hypervariability resulting from evolutionary divergence and antigen-selected somatic hypermutation (*9, 10*). Crystallographic studies have shown that these hypervariability regions can roughly define the complementarity-determining regions (CDRs) that constitute the antigen contact residues (*11*). Several distinct characteristics of the TCR make similar studies problematic. A comparison of TCR sequences has not clearly revealed hypervariable regions (*5, 7*), and this is due, in part, to a lack of somatic mutations found in TCR genes (*12, 13*). In addition, T cells are always specific for MHC molecules, in contrast to the diverse specificity of Ig molecules, and neither the TCR nor its MHC ligand can be readily isolated in quantities necessary for x-ray crystallographic studies.

In this report we present an extensive sequence comparison of α- and β-chains expressed by T cells specific for pigeon cytochrome c. The absence of somatic mutations implies that it is difficult to determine by primary sequence analyses which of the amino acids in the α- and β-chains are important in determining specificity. However, if the TCR is analogous to Ig, then the highly variable V-(D)-J-region junction is predicted to encode the third CDR, and within a set of clones with a similar receptor specificity there may be a distinct selection of particular amino acids in forming a combining site. We show that for three different clonal phenotypes defined by antigen-MHC specificity, the V-D-J-region junction of the β-chain is selected for distinct amino acid sequences, whereas for the α-chain no such sequence selection is observed.

Information concerning the clones to be examined in this report is tabulated in Table 1. The T cell clones are arranged into three groups based on specificity for cytochrome c in association with either B10.A (MHC allele recognized is E^k), B10.A(5R) (E^b), or B10.S(9R) (E^s) antigen-presenting cells (APCs), and all but clone V1.9.2 respond to the carboxyl-terminal fragment of pigeon cytochrome c (amino acids 81 to 104).

The α- and β-chain sequences from nine clones that express the $V_\beta 3$ gene segment were analyzed together, and Fig. 1a shows the α-chain V-, J-region junction sequences of eight of the clones (*14*). The junctions of six of the eight clones are similar, with few N-region nucleotide additions, and this reflects the average α-chain junctional diversity (*15*). Among those expressing $V_\alpha 11$, one of the clones, C.F6, has a proline substituted for the more common alanine or threonine amino acids, and this substitution would be expected to alter the conformation of the CDR loop. Furthermore, quite a different junctional sequence was found in the α-chain of 2B4, including two additional ami-

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no acids, and yet there is no known difference in specificity between 2B4, C.F6, and the other clones. This pattern of sequences appears to reflect little selection for specific amino acids in the third CDR of the α-chain. Clone AP11.2 expresses a different V-region, $V_\alpha 4.3$ (see below).

Figure 1b shows the β-chain sequences of all nine cytochrome c–specific clones expressing $V_\beta 3$. In contrast to the lack of junctional selection in the α-chains, in the β-chains there is a striking selection for the V-D-J-region junction encoding the putative third CDR. All of the clones have the same number of amino acids spanning the region, and seven of eight clones have an asparagine at position 100. Comparison of the germline V-region and D-region sequences shows that the codon AAC is produced by the N-region addition of an adenylate nucleotide in all eight sequences. The addition of any other nucleotide would change the codon specificity. In clone AN14.4, the codon AAC appears to be entirely N-region encoded. One clone, AN6.2, lacks the asparagine and instead has a serine. The antigen specificity of this clone is unusual in that it responds to the pigeon-like peptide, Sp, at lower concentrations than the moth-like peptide, DASp (Table 1), and is even more sensitive to the synthetic peptide DAK (amino acid sequence KKANELIAYLKKATK) to which most clones respond poorly (*16*). The MHC specificity is also unusual in that there is a small but significant response to the peptides in association with E^s APCs in addition to $E^{k,b}$ APCs. Clone AP11.2 responds to antigen in association with E^s instead of $E^{k,b}$, and expresses an entire $V_\beta 3$-$J_\beta 1.2$ identical to that of C.F6. Since AP11.2 expresses $V_\alpha 4.3$, a comparison of the α- and β-chain sequences expressed by C.F6 and AP11.2 shows that a change in the α-chain changes the MHC specificity in cytochrome c–specific T cells.

For comparison, previously published β-chain sequences from two clones with specificity for antigens other than cytochrome c are presented. The T cell clone specific for lysozyme and A^k, 3H.25, expresses $V_\beta 3$ rearranged to $J_\beta 1.2$, and yet there is no adenylate addition or asparagine-100 present (*17*). This indicates that the selection for this sequence in TCR β-chains is not the result of a structural requirement at the RNA or protein levels. Also included is the β-chain sequence of a cytotoxic T cell clone also expressing $V_\beta 3$ and specific for trinitrophenylated H-2^k APCs. From hybridization studies it was deduced that the β-chains from similar clones also express $V_\beta 3$ and have a selected asparagine at position 102 (*18*). A selected amino acid has also been shown in the β-chain of two insulin-specific clones in which there is a conserved N-region–encoded aspartic acid (*19*).

Figure 2 shows the α- and β-chain sequences from nine T cell clones expressing either $V_\beta 1$ or $V_\beta 16$. All but one of these clones are specific for cytochrome c in association with either $E^{k,s}$ or E^s only (see below). The $V_\alpha 10$ gene segments (*20*) are expressed by a majority of the pigeon cytochrome c–specific clones from B10.S(9R) mice (*21*). $V_\alpha 10$ and $V_\alpha 11$ gene segments are not members of the same family, and yet there is a high amino acid sequence homology (51% maximum homology). $V_\alpha F4$ is not homologous to either $V_\alpha 11.1$ (23%) or $V_\alpha 10$ (25%). The sequences encoded by the V-J–region junction are shown (Fig. 2a), and as with the α-chains compared in Fig. 1, there are no apparent sequence selections.

In T cells specific for cytochrome c in association with E^k and E^s (B10, 4.C3, 1B6, D6, and F4), two different β-chain V-regions are rearranged to two different J-regions: $V_\beta 16$ is rearranged to $J_\beta 2.1$ and $V_\beta 1$ is rearranged to $J_\beta 1.2$ (Fig. 2b). $V_\beta 1$ and $V_\beta 16$ are relatively homologous (57%), especially in the second CDR, with the result that only $V_\beta 10$ shows an equivalent CDR-2 homology (*7*). In the β-chain V-D-J-region (Fig. 2b), there is a conserved amino acid, again at position 100. The codon for aspartic acid–100 is formed from the same dinucleotide found in the $D_\beta 1$ or the $D_\beta 2$ region, and the nucleotide at the third position in the codon originates from either N-region nucleotides or $D_\beta 1$ sequences. No other positions appear to be selected to nearly the same extent, although the two clones that have an identical phenotype, 1B6 and D6 (Table 1), also have identical β-chain nucleotide sequences. The α-chain sequence from 1B6 has not yet been determined although it has the same $V_\alpha 10$ rearrangement as D6 does. The three T cell clones specific for cytochrome c in association with E^s have either aspartic acid or glutamic acid at position 100. The aspartic acid codons in clones 3E11 and AP15.2 are formed in a manner similar to the $E^{k,s}$-reactive clones, whereas the conservative glutamic acid substitution in 1F8 is formed by a different portion of the $D_\beta 1$ probably rearranged to $D_\beta 2$. In contrast to position 100, the surrounding positions show a wide diversity. The exception to the aspartic acid–100 selection is from clone V1.9.2, which expresses $V_\alpha 11.1$-$J_\alpha 28$ and $V_\beta 1$-$J_\beta 1.1$. Although this clone came from mice immu-

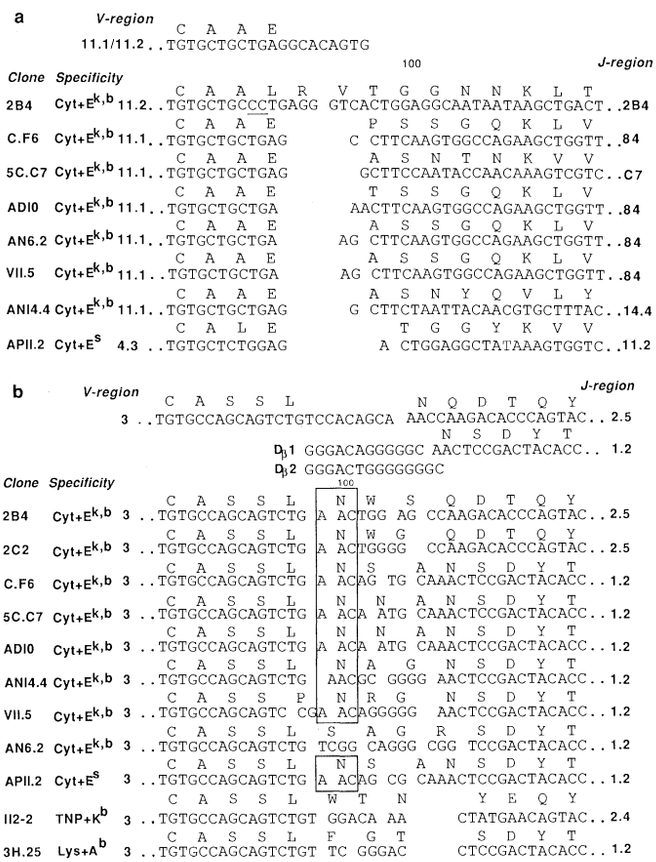

Fig. 1. The nucleotide sequences are presented, and the one-letter code designating the translated amino acid is shown above the second nucleotide in each codon: (**a**) α-chain sequences; (**b**) β-chain sequences. The breaks in the nucleotide sequence indicate the borders between V-, D-, J-, and N-regions when present. The numbering system for the α-chains was derived by numbering the longest α-chain we have sequenced ($V_\alpha F4$) (Fig. 2), and inserting gaps to retain the highest homologies. The 3′ germline sequences of $V_\alpha 11.1$ and 11.2 were generously communicated by R. Wallich and M. Davis (Stanford University), and the underlined cytidylate dinucleotide in the 2B4 sequence is an apparent somatic insertion first noted by these investigators. The numbering system for the β V-regions was derived by numbering the longest V_β sequence known which is $V_\beta 15$ (*7*). The germline β-chain V-region sequence of 2B4 has previously been reported (*12*). The selected residues at position 100 are noted by a rectangle. The D-region sequences are from Kavaler *et al.* and Siu *et al.* (*29*). The references for the sequences if different from this report are listed in Table 1.

nized with DASp (Table 1), it responds only to acetimidylated peptides in association with $E^{k,b}$ (*16*). V1.9.2 also has a different α-chain from other clones expressing $V_\beta 1$, although it expresses $V_\alpha 11.1$, which is similar to the α-chains expressed by clones B10 and 4.C3. Three examples of rearranged $V_\beta 1$ and $V_\beta 16$ genes from T cells not specific for cytochrome c have been reported, and they do not have an aspartic acid at position 100 (*1, 7*).

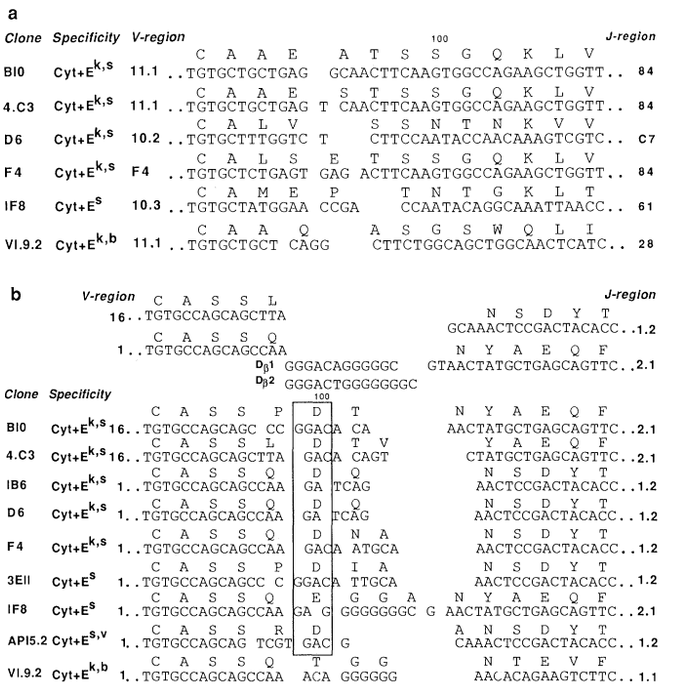

Fig. 2. See the legend to Fig. 1: (**a**) α-chain sequences; (**b**) β-chain sequences. The 3′ germline sequences of $V_\beta 1$ and $V_\beta 16$ have not yet been determined and thus the V-N-D-region border is somewhat arbitrary, but consistent with known complementary DNA (cDNA) sequences (*7*). The β-chain 1F8 sequence appears to be $V_\beta 1$-$D_\beta 1$-$D_\beta 2$-$J_\beta 2.1$, although $D_\beta 1$ would contribute only the GA dinucleotide. All sequences were from cDNA clones with the exception of 1B6 and 3.E11, and these were determined from rearranged genomic clones.

In a number of antibody responses analyzed, there are selected amino acids in the Ig light chains or heavy chains and often these amino acids are positioned at the V-(D)-J junctions (*22*). In the case of antibodies to *p*-azobenzenearsonate, Sharon *et al.* (*23*) showed by site-directed mutagenesis that one such selected amino acid is critical for antigen binding. Combined with the x-ray crystallographic information mapping the antibody combining site to include the CDR3 (*11*), these data have underscored the importance of the V-(D)-J-region in the specificity of antibodies. The data presented here show that the amino acid at position 100 in the β-chain of the TCR is selected in cytochrome c–specific T cells. In T cells expressing $V_\beta 3$ there is an asparagine, whereas in clones expressing $V_\beta 16$ or $V_\beta 1$ there is an aspartic acid. An interpretation of these data is that this amino acid position is critically important to the specificity manifest in the TCR of cytochrome c–specific T cells, and this in turn implies that the V-D-J-region junction of the β-chain can form part of the combining site of the TCR in a manner analogous to that in Ig chains. This interpretation supports the graphical and computational analyses of the TCR, which have predicted a structure consistent with those of immunoglobulin Fab fragments or light chain dimers (*24*).

In two of the sequences presented here and previously reported by Winoto *et al.* (*25*), there is no asparagine or aspartic acid at position 100, and perhaps it is no coincidence that both V1.9.2 and AN6.2 have an unusual specificity. The analysis of a third clone, AP11.2, showed an unexpected correlation between specificity and TCR gene expression. This clone has precisely the same β-chain sequence as C.F6, including the selected asparagine-100, and yet has a specificity for cytochrome c in association with E^s instead of the typical specificity of clones expressing this β-chain, which is $E^{k,b}$; the difference in MHC specificity must result from the expression of an alternate α-chain. However, comparing the α- and β-chain sequences expressed by C.F6 and B10 shows that a change in the β-chain also changes the MHC specificity in cytochrome c–specific T cells (*13*). These results indicate that either the α- or the β-chain can affect MHC specificity and show that there is no dichotomy of α- and β-chain function for MHC specificity even within a narrowly defined set of antigen-specific T cell clones.

One hypothesis for this sequence selection is that the amino acid at position 100 is a contact residue for either MHC or cyto-

Table 1. T cell clones that were analyzed for α- and β-chain receptor sequences. The designation of each of the clones is followed by the strain of origin: A, B10.A; 9R, B10.S(9R); 5R, B10.A(5R); $F_1 \rightarrow A$, $[B10.A \times B10.S(9R)]F_1 \rightarrow B10.A$ bone marrow–reconstituted radiation chimera. In each case mice were immunized with the designated immunogen (Imm.): P.cyt., native pigeon cytochrome c; Sp, pigeon-like peptide (KKANELIAYLKQATAK); DASp, moth-like peptide (KKANELIAYLKQATK). The specificity of each of the clones is indicated by the response to M, moth cytochrome c fragment 88–103 (ANERADLIAYLKQATK), or P, pigeon cytochrome c fragment 88–104 (KAERADLIAYLKQATAK). Clone V1.9.2 responds to acetimidylated (am) peptides. The allo designation indicates that the clone responds to the APCs indicated in the absence of added antigen. The MHC specificity in association with cytochrome peptides maps to the I-E–encoded molecule in all cases (*27, 28*). The sequence of the synthetic peptides is given in the one-letter code: A, alanine; C, cysteine; D, aspartic acid; E, glutamine; F, phenylalanine; G, glycine, H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine, V, valine; W, tryptophan; and Y, tyrosine.

T cell clone	Strain	Imm.	Response to APCs from			V_α	V_β	Reference
			B10.A (E^k)	B10.S(9R) (E^s)	B10.A(5R) (E^b)			
2B4	A	P.cyt	P^+M^+	P^-M^-	P^-M^+	11.2	3	*12, 27*(A-1)
2C2	A	P.cyt	P^+M^+	P^-M^-	P^-M^+	11	3	*
C.F6	A	P.cyt	P^+M^+	P^-M^-	P^-M^+	11.1	3	*13*
AD10	$F_1 \rightarrow A$	P.cyt	P^+M^+	P^-M^-	P^-M^+	11.1	3	*
5C.C7	A	P.cyt	P^+M^+	P^-M^-allo-A^s	P^-M^+	11.1	3	*13*
AN14.4	A	Sp	P^+M^+	P^-M^-	P^-M^+	11.1	3	*25*
V11.5	5R	DASp	P^+M^+	P^-M^-	P^-M^+	11.1	3	*25*
AN6.2	A	Sp	P^+M^+	P^-M^-	P^-M^+	11.1	3	*25*
V1.9.2	5R	DASp	P^+M^+(am)	P^-M^-	P^-M^+(am)	11.1	1	*25*
B10	A	P.cyt	P^+M^+	P^+M^-	P^-M^-	11.1	16	*13*
4.C3	A	P.cyt	P^+M^+	P^+M^+	P^-M^-	11.1	16	*13*
1B6	9R	P.cyt	P^+M^+allo-E^k	P^+M^+	P^-M^-	10.2	1	*27*(9R-2)
D6	9R	P.cyt	P^+M^+allo-E^k	P^+M^+	P^-M^-	10.2	1	*
F4	$F_1 \rightarrow 9R$	P.cyt	P^+M^+	P^+M^+	P^-M^-	F4	1	*
3.E11	9R	P.cyt	P^-M^-	P^+M^-	P^-M^-	?	1	*27*(9R-1)
1.F8	9R	P.cyt	P^-M^-	P^+M^+	P^-M^-	10.3	1	*
AP15.2	9R	DASp		P^+		?	1	*25*
AP11.2	9R	DASp		P^+		4.3	3	*25*

*This report.

chrome c peptide determinants. It seems less likely that it is selected for the overall conformation of the CDR-3 loop because the surrounding amino acids are quite variable. The most obvious common characteristic of these clones is the specificity for a peptide fragment of cytochrome c. If the amino acid at position 100 is contacting a part of the antigen peptide then in a simplistic way it is difficult to understand how one set of clones would select for an asparagine, whereas the other would select for an aspartic acid at the same position. Recent experiments indicate that the two types of clones recognize different epitopes on the same cytochrome c fragment (*26*), and this specificity is thus consistent with the selection for two different amino acids in the peptide-combining site of this set of TCR.

Perhaps, unlike antibody responses, the selection for sequences in the TCR could occur during one of two different phases of cell growth and differentiation: thymic selection for MHC recognition in the absence of foreign antigen, or immune induction via recognition of antigen bound to MHC molecules. Since there is no way to examine the selection for particular V-, J-region combinations, nor junctional sequences on a gross level, there are currently no data to determine the origin of these sequence selections. Further experiments would determine whether $V_\beta 3$ gene segments expressed as rearranged genes in certain unimmunized strains of mice show a selection for the asparagine-100 residue, or whether the selection is restricted to cytochrome c–specific T cells.

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