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A hypothetical model of the foreign antigen binding site of Class II histocompatibility molecules

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Class II and class I histocompatibility molecules allow T cells to recognize 'processed' polypeptide antigens[1–5]. The two polypeptide chains of class II molecules, α and β, are each composed of two domains (for review see ref. 6); the N-terminal domains of each, α_1 and β_1, are highly polymorphic[6–10] and appear responsible for binding peptides at what appears to be a single site[11–13] and for being recognized by MHC-restricted antigen-specific T cells[14,15]. Recently, the three-dimensional structure of the foreign antigen binding site of a class I histocompatibility antigen has been described[16,17]. Because a crystal structure of a class II molecule is not available, we have sought evidence in class II molecules for the structural features observed in the class I binding site by comparing the patterns of conserved and polymorphic residues of twenty-six class I and fifty-four class II amino acid sequences. The hypothetical class II foreign-antigen binding site we present is consistent with mutation experiments[18–28] and provides a structural framework for proposing peptide binding models to help understand recent peptide binding data[11,29–33].

An overall similarity in structures of class I and class II molecules is suggested by a similarity in domain and genomic organization[6], by high similarity in the C-terminal domain sequences[34], and by the observation that some T cells specific for either class of molecule use the same receptor[35,36]. Furthermore, the close association of N-terminal residues of the α_1 and β_1 domains in the class II intermolecular dimer, deduced from hemi-exon shuffling experiments[37,38], is consistent with the close association of N-terminal residues of the class I α_1 and α_2 domains in the 'intramolecular' dimer observed in the crystal structure[16]. By imagining an attachment of the class I α_1 domain to β_2-microglobulin, a four domain model of class II molecules can be produced from the class I structure[16]. Like the class I structure (Fig. 2*a*), such a class II molecule would have a cleft between the C-terminal α-helices of its polymorphic α_1 and β_1 domains with the bottom of the cleft formed by the N-terminal β-strands of each domain[17].

Pairwise sequence comparisons of class II α_1 domains with the polymorphic domains of class I (α_1 and α_2) revealed no significant sequence similarity, whereas comparisons of class II β_1 domains revealed weakly significant similarity with both the α_1 and α_2 domains of class I[39–41]. The choice to align class II α_1 to class I α_1 and class II β_1 to class I α_2 is suggested by the glycosylation site (Asn, X, Ser/Thr) at residue 86 (class II residues in the text have been renumbered to class I HLA-A2 numbering to facilitate comparisons to the class I three-dimensional structure, see legend to Fig. 1), which is completely conserved in all class I and class II α_1 sequences, and by the disulphide-linked cysteines (101 and 164) found in all class I α_2 and class II β_1 sequences[6] (Fig. 1). This choice has been supported both by similarities in the respective genomic structures[42] and by similarities in the alteration of T-cell recognition by a pattern of mutation at 152, 155, and 156 in both class I α_2

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Table 1 The effects of class II single amino acid mutations on monoclonal antibody binding and T-cell activation

Residue numbering HLA-A2		Ia	Substitution	Monoclonal antibody	T cells allo	T cells ag	Reference	Location on hypothetical class II structure
79	I-A^k_α	75	E→K	+(4/5)	−(0/2)	+(2/17)	18, 19	H2, solvent-accessible, pointing up
95	I-A^b_β	9	Y→H	−(0/12)	+(2/7)	−(0/3)	20	S1', pointing up into helix
95	I-A^k_β	9	H→V	−(0/8)	ND	ND	21	S1', pointing up into helix
98	I-A^k_β	12	Q→K	−(0/8)	ND	ND	21	S1', pointing down
99	I-A^b_β	13	G→P	−(0/12)	+(1/7)	+(1/3)	20	S1', pointing up in crevice
99	I-A^k_β	13	P→G	−(0/8)	ND	ND	21	S1', pointing up into site
100	I-A^k_β	14	F→E	−(0/8)	ND	ND	21	S1', pointing down
103	I-A^k_β	17	F→Y	−(0/8)	ND	ND	21	S1'–S2'
114	I-E^k_β	29	V→E	ND	ND	+(5/7)	22	S2', pointing up into site
114	I-A^k_β	28	I→T	−(0/8)	ND	ND	21	S2', pointing up into site
126	I-A^k_β	40	F→Y	−(0/8)	ND	ND	21	S3', pointing up into helix (see caption)
134	I-E^k_β	49	R→H	+(4/16)	−(0/2)	−(0/17)	23, 24	S4', solvent-accessible, pointing down towards the region of the lower domains
134	I-A^k_β	48	R→C	+(2/7)	−(0/2)	−(0/15)	*	S4', solvent-accessible, pointing down
145	I-A^k_β	59	E→D	+(3/10)	ND	ND	25	H1', solvent-accessible, pointing up
149	I-A^k_β	63	K→S	+(1/8)	ND	ND	21	H1'–H2', kink between helices
150	I-A^k_β	64	Q→P	+(7/10)	−(0/1)	+(7/15)	25, 26	H1'–H2', kink between helices
150	I-A^k_β	64	Q→R	+(1/10)	−(0/1)	+(2/15)	25, 26	H1'–H2', kink between helices
154	I-A^k_β	67	E→K	+(1/3)	ND	+(1/2)	27	H2', solvent-accessible, pointing up
152	I-A^b_β	67	I→F	−(0/6)	ND	+(5/6)	28	H2', into site
155	I-A^k_β	68	R→Q	+(4/10)	+(1/1)	+(11/15)	25, 26	H2', up and into top part of the site
155	I-A^b_β	70	R→Q	+(4/6)	ND	+(6/6)	28	H2', up and into the top part of the site
156	I-A^b_β	71	T→K	−(NC)	ND	+(5/5)	28	H2', into site
160	I-A^k_β	73	L→V	−(0/7)	ND	ND	21	H2', down towards strand
163	I-A^k_β	76	V→A	−(0/8)	ND	ND	21	H3', into site
170	I-A^k_β	83	K→G	−(0/8)	ND	ND	21	H3', up (?)
171	I-A^k_β	84	T→P	−(0/8)	ND	ND	21	H3', into site (?)
174	I-A^k_β	87	P→S	−(0/8)	ND	ND	21	H3', (?)

(*xyy*) Indicates a loss of reactivity with *x* parent Ia monoclonal antibodies, or *x* allospecific, or foreign antigen-restricted (ag) T cells out of a total of *y* antibodies/T-cell clones examined, as a result of the single substitution indicated. +, ($x > 0$) indicates that the residue is involved in monoclonal antibody or T-cell recognition. −, indicates that the residue may not be involved in monoclonal antibody or T-cell recognition. The mutation at 126, which does not cause loss of binding by any parent I-A^k_β-reactive antibodies, does cause a gain in binding by ('non-parent') I-A^d_β-reactive antibodies[21]. ND, no data; NC, not clear; *, Glimcher *et al.*, personal communication. The location of the altered side chains in the hypothetical class II model are consistent with these effects (see text).

(bm1 mutant) sequences[43] and class II β_1 (bm12 mutant) sequences[28,44].

Evidence for the presence of homologous α-helices in class I and class II structures is found in the pattern of conserved amino acids. In the α-helical regions of all class I sequences these occur every third or fourth residue[45] (conserved α_1 residues 68, 72, 75, 78, 84, conserved α_2 residues 148, 153, 154, 157, 158, 161, 164, 165, 168; solid columns in Fig. 1). These residues form one face of the α-helices in class I α_1 and α_2 domains[17] (Fig. 2*a*) and their positions are also conserved in class II α_1 and β_1 sequences (Fig. 1). Interspersed between the conserved residues on the α-helices of the class I structure are many of the most polymorphic residues[17]. Again, a similar pattern of polymorphic residues is also found in class II sequences [α_1: 74, 79, 80, 81; β_1: 152, 155, 156, 159, 163 (class I numbering, see Fig. 1)]. Structural similarity in the helical regions is further supported by the observation of a completely conserved i, i+4 helix-stabilizing salt bridge (Arg157-Acid161, see Fig. 2*b*) and the conserved Trp147 in the class I α_2 and class II β_1 domains, and the completely conserved Leu78 in class I and class II α_1 domains (Fig. 1).

In the β-strand region (N-terminal half of the sequences in Fig. 1), the distribution of polymorphic residues in class II sequences often match those in class I sequences. In Fig. 1, the most polymorphic positions in each strand in the class I α_1 domain are aligned to the polymorphic residues in the corresponding regions of class II sequences (9 in S1, 24 in S2, 32 in S3, 45 in S4; cross-hatched columns Fig. 1, see legend for a fuller explanation of alignment, particularly in S1). A similar alignment of polymorphic residues in class I α_2 and class II β_1 (95, 97, 99 in S1; 114, 116 in S2; Fig. 1) is provided by matching the conserved cysteine 101. These polymorphic residues form the 'bottom' of the cleft in the class I structure (Fig. 2*a*). The striking 'every other one' periodicity (95, 97, 99, and 114, 116) of the polymorphic residues is that expected for β-strand residues where every other side chain faces to one side of a sheet (see legend, Fig. 1).

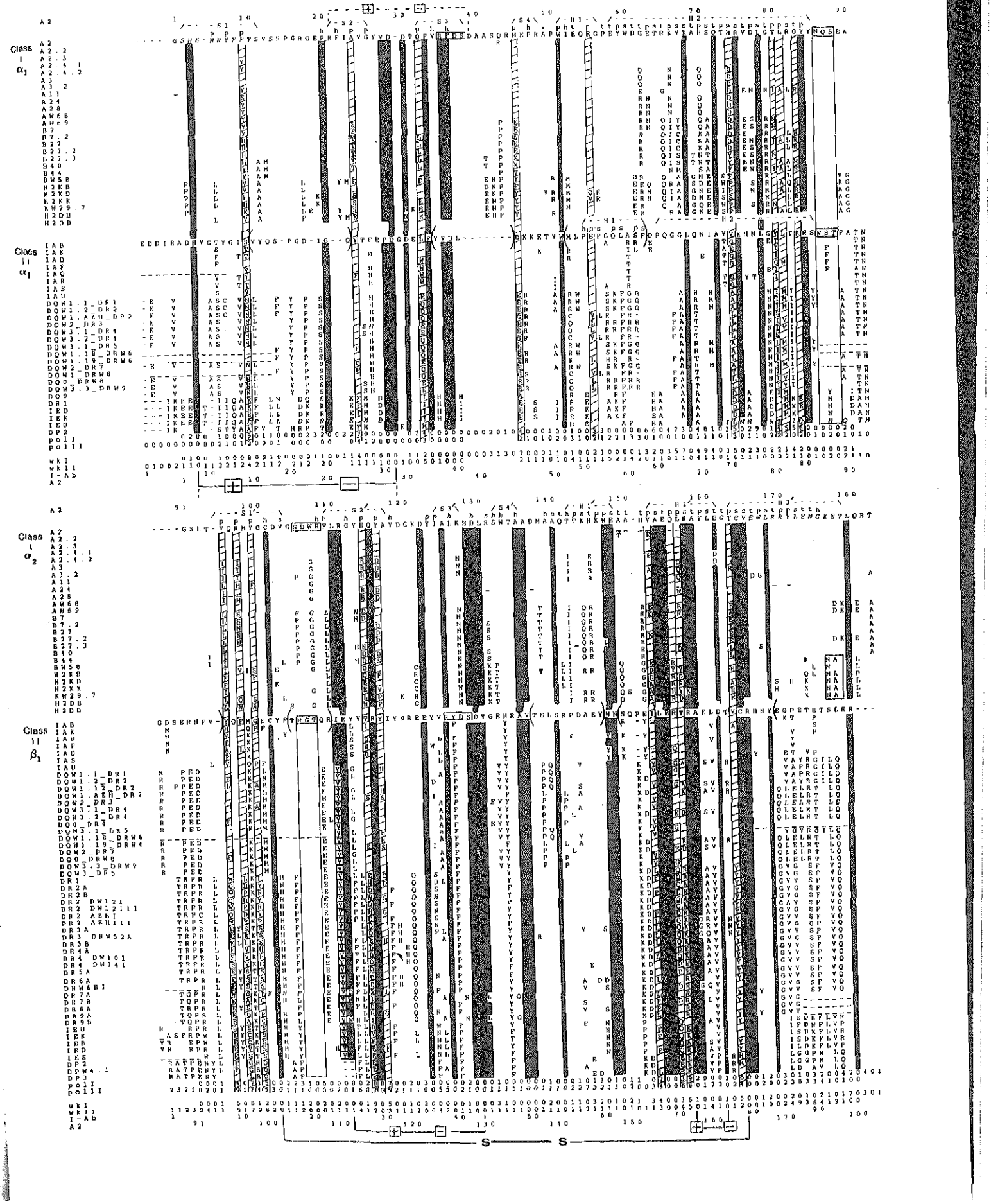
Structural homology in the β-strand region is further supported by the observation that the residues making up the two salt-bridges His3-Asp29 and Arg111-Asp129, which bridge across the open end of the two beta-strand 'hairpins' formed by S1 and S2 and by S2′ and S3′ (Fig. 2*b*), are conserved in all class I and class II sequences (Fig. 1*b*), and are the same distance from the first polymorphic residues of their β-strands in both class I and class II [in S1, I-A and DQ are aligned to other class II and class I sequences by introducing a β-bulge[46] at Val4 (Gly bulges out) which results in I-A polymorphic position 5 (residue 10 in I-A numbering), as well as the aligned polymorphic position 9 pointing up into the proposed site]. Interestingly, the pseudo-two-fold symmetric locations His93-Asp119 and Arg21-Asp39 (dotted lines in Fig. 2*b*) are conserved salt links in all class I sequences, but not class II sequences.

The regions between the aligned secondary structure elements are consistent with loop structures. Class I and class II share common amino acid residues in these regions (Fig. 2*b*). Insertions and deletions in Class II sequences relative to class I sequences occur in or at the boundary of these loops (Fig. 1). In class II, a glycosylation site at the loop containing residues 105-108 and a seven residue deletion of the loop at residues 35-38 (underneath a suggested shift in the bend of the α_1 α-helix described in the legend to Fig. 3) eliminate the sequences SDWR and RFDS, respectively, previously noted as potential CD8 interaction sites in class I[47] (see Fig. 2*b*).

The alignment presented in Fig. 1 allows us to propose a hypothetical structure for the foreign antigen recognition site of class II molecules based (Fig. 3*a*) on structural homology with the class I site[17]. The distribution of polymorphic residues (crosshatched, Fig. 3*a*) in the site is consistent with the conclusions that some of the polymorphic residues (for example, those on the bottom of the site) probably control interaction with antigen[22,48] whereas others control allele-related recognition by T cells[22,48]. It is also consistent with studies of natural[28] and site-directed mutants[18-27] of class II molecules (Table 1). Residues which are monoclonal antibody epitopes (79, 134, 145, 149, 150, 154, 155, Fig. 3*a*) protrude into solvent and residues implicated in antigen-restricted T-cell recognition face into the site (95, 99, 114, 152) or upwards (presumably toward the T cell) (79, 150, 154, 155, 156, Fig. 3*a*). Aspartic acid at position 143 in DQ (57 in DQ β numbering), which provides almost complete resistance to insulin-dependent diabetes (IDDM)[49,50], is predicted to form a salt bridge with Arg84 at one end of the site.

The hypothetical model provides a framework for generating testable models for peptide binding. There is currently no consensus as to the conformation that peptides adopt when bound[31-33], or even whether or not different peptides adopt similar backbone conformations upon binding. The size, shape, and residue composition of the site in HLA-A2 indicate that it

Fig. 1 (Opposite) Alignment of class II α_1 and β_1 domains to class I α_1 and α_2 domains. Because of lack of statistically significant pairwise homology between class II α_1 and class I α_1[39], this alignment is based on the matching of positions polymorphic in both class I and class II (hatched) and of positions conserved in both classes (solid). (Also included are positions 30, 75, 111, and 147, which are conserved in at least 90% of the sequences, and position 110, which is either Leu, Ile or Val in all sequences.) This analysis agrees with a previous pairwise alignment of DR2 β_1 and HLA-B7 α_2[41]. The sequence alignments include one letter code (deviations from A2 or I-A^b sequences), blanks (identity to HLA-A2 or I-A^b), dashes (deletions), or underscores (undetermined residues). Sequence numbers both of HLA-A2 (top) and of I-A^b (bottom) are shown. The approximate secondary structural boundaries observed in HLA-A2 (ref. 16) are indicated by S1 (first β-strand of α_1), S2 (second β-strand), H1 (first helix), S1′ (first β-strand of α_2), etcetera. Regions towards which HLA-A2 amino acid side chains point are described by p (processed antigen binding site), h (helical region), s (strand region), t ('T cell')[17]. Charge pair (+ −), and disulphide (S-S) interactions observed in HLA-A2 and conserved in the class I and the aligned class II sequences (see also Fig. 2) are shown as solid connections. Dashed connections indicate conservation of the charge pair through a third (but not a fourth) domain (see text). The alignments within the parentheses are not constrained by the structural evidence presented. WkI and wkII are normalized polymorphism values[55] of each position in the twenty-six class I and the fifty-four class II sequences, respectively. PolI and polII are normalized modified polymorphism values defined as: $\ln [\Pi_i\{VAR_i * SDHYD_i + VAR_i\}]$ where i is an isotype, VAR(i) is a position's variability index[55], within the isotype, and $SDHYD_i$, which de-emphasizes chance hydrophobic diversity[56], is the standard deviation of the hydrophobicity of the position's residues[57] within the isotype. The multiplication of the individual isotypes' modified polymorphism values results in the position's overall class polymorphism value (pol) to be zero only if the position is conserved within each isotype, whereas pol = 9 only if the position is polymorphic in each of the isotypes. Polymorphism in class I is highly correlated to proximity of the side chain to the processed antigen binding site[17]; 14 out of the 20 most polymorphic (wk) class I residues face into the site. This correlation using modified polymorphism values (pol) is even slightly higher, 16/20 and justifies the use of this measure to aid in the alignment of site residues. Those positions with modified polymorphism values (pol) among an individual domain's top 20 are considered polymorphic in this report. Structural considerations were used in the alignment of S1 to resolve the ambiguity of predictions based on polymorphism values alone. [In S1, position 5 has the same pol II value as position 9. The wk-II value (averaged over all isotypes) is greater for 9 than 5 but position 5 is more polymorphic than 9 if the I-A isotype is considered alone. However, the three side chains of S1 (positions 5, 7, 9) form the bottom of the cleft in the class I structure and only the alignment shown places both polymorphic residues (5, 9) in the site (Fig. 3*a*). This choice simultaneously preserves the distance between the residues and a conserved structural feature provided by His3 (see text and Fig. 2*b*).] In class I, the four isotypes used in the polymorphism calculations are HLA-A[58], HLA-B[58], H2K[59], H2D[59]. In class II, the five isotypes used are DR(1, 2a, 2b, 3a, 3b, 4a, 5a, 6a, 7a, 7b, 8a, 9a, 9b, others[49]), I-E[61], I-A (α_1[62], $_{sb}\beta_1$[63]), DQ ($w3$-dr5[64], 9[65], all others[49]) and DP[66]. An enlarged copy of this figure can be obtained from the authors or by Xerographic enlargement.


Class I α1
Class II α1
Class I α2
Class II β1
S S

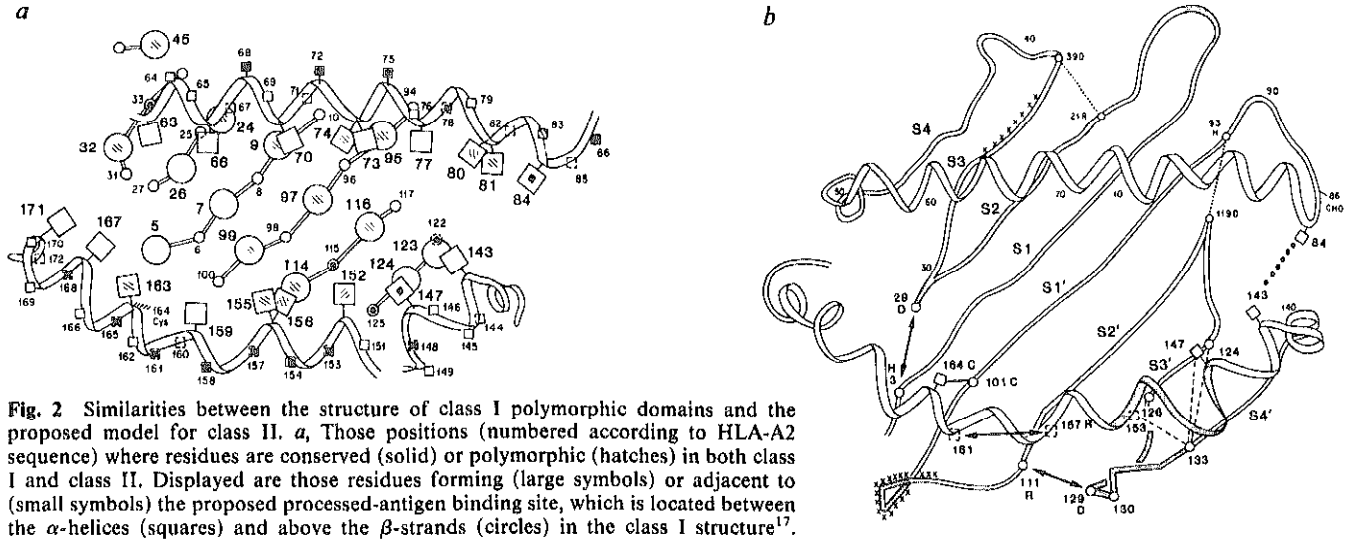


Fig. 2 Similarities between the structure of class I polymorphic domains and the proposed model for class II. *a*, Those positions (numbered according to HLA-A2 sequence) where residues are conserved (solid) or polymorphic (hatches) in both class I and class II. Displayed are those residues forming (large symbols) or adjacent to (small symbols) the proposed processed-antigen binding site, which is located between the α-helices (squares) and above the β-strands (circles) in the class I structure[17]. Positions of residues conserved in both MHC classes generally face away from the site, while those polymorphic in both classes face into the site. In both class I and class II molecules, different isotypes have different distributions of polymorphic residues[67]. Nevertheless, the sequence similarity among isotypes[6,7,58,59] argues that the structural features of the site are essentially the same in different isotypes and validates the construction of a single overall class II model. H1 is not shown here. The break at the kink between helices at 149 indicates a site of insertions and deletions. *b*, Intramolecular interactions observed in the HLA-A2 structure[16] and conserved in all class I and class II sequences (Fig. 1). Three salt bridges (solid lines bounded by arrows), whose residues are conserved in all class I and class II sequences (111 is Arg in all but three sequences, 157 is Glu or Asp), along with alignments of other conserved residues and of polymorphic residues (see Fig. 2*a* and text), argue that class I and class II have homologous β-strands and α-helices. Evidence for the similar positioning of the β-strands relative to the α-helices includes the disulphide bridges (101 to 164) and the hydrophobic cluster (dashed lines 124, 133, 147, 153) conserved in all class I and class II sequences. Bold dots at 84, 143 indicate the position of the Tyr-Thr hydrogen bond conserved in class I, and a potential salt bridge, semi-conserved in class II and implicated in resistance to IDDM (see text)[49,50]. Xs mark class I RFDS-like sequences[47] (see text). Shaded loops contain similar residues in class I and class II: S1–S2 (Pro and Gly), S2–S3 (two acids), S1′–S2′ (class I Pro, Gly; class II Asn, Gly), S3′–S4′ (126, 130, 133 conserved hydrophobics), H1′–H2′ (conserved 147 Trp, 154 Glu). Deletions and insertions in class II sequences relative to class I occur in loops S1–S2, S2–S3, S3–S4, H1′–H2′, and at the N- and C-terminals of both α_1 and β_1 domains. CHO (residue 86) is the common carbohydrate attachment site. The second class II CHO site (105–107) is found in the shaded loop after 103.

has space to accommodate an α-helical or extended conformation, or a mixture of both, and therefore leaves open many possibilities[17]. In cases where the conformation of a bound peptide can be proposed from other data or where contacts between the peptide and specific residues on the histocompatibility antigens can be identified, the number of degrees of freedom may be reduced enough to allow specific models of the complex to be proposed. The hen egg-white lysozyme peptide binding to I-A^k is such a case[31]. HEL (46–61) binds to I-A^k but not to I-A^d [13,29]. In the 10-mer HEL(52–61), three 'MHC-contact' and three 'T-cell contact' residues segregate on the opposite sides of the bound peptide if it binds as an α-helix[31]. Because Asp52 is 2.5 turns from Arg61 on an ideal helix, it is possible that one residue contacts the helix of the α_1 domain and the other contacts the helix of the β_1 domain[17]. By sliding this 2.5 turn helix in the site, two ways are found which both stabilize the charged peptide residues by oppositely charged I-A^k helix residues and keep the 'T-cell contact' residues pointing up (Fig. 3*b*,*c*). Both models also result in the third defined I-A^k 'contact residue', Ile58, contacting Phe26 from the β-sheet and Gly66 from the helix. Differences between I-A^k and I-A^d at residues 26 and/or 151 could account for the absence of binding to I-A^d (see legend to Fig. 3*b*,*c*). The dotted rectangle on Fig. 3*b* represents the area of an Fab-antigen interface[51–53], to indicate that the T-cell receptor, if it binds like an Fab with which it has sequence homology[54], could recognize both the Ia molecule and the peptide simultaneously.

In two other studies of peptide-MHC interaction [OVA (323–339)[32], PCC (93–104)[33]] no simple conformation could be deduced, but the data did not favour an α-helix. These peptides were shown to contain many positions with both MHC and T-cell contact residue characteristics. Such dual character could be expected for some peptide residues, given the structure of the binding site, but it could also arise from reorientation of single substituted peptides within the binding site, thereby obscuring any structural pattern. However, if the actual bound state of these peptides is as conformationally complex as these studies imply, then more detailed structural restrictions on peptide binding are a prerequisite to modelling.

Whereas the above studies locate those peptide residues that contact the MHC molecule, a recent study[22] has implicated I-E^k residue Val114 in contacting the PCC peptide and not the T cell. This is consistent with the model in Fig. 3*a*, since position 114 points up to the site from the β-sheet region and is probably inaccessible to direct interaction with the T-cell receptor[17]. A study showing Lys103 of PCC to contact only the MHC and not the T cell[33], suggests that PCC 103 may contact the β-sheet region of the site.

The hypothetical model for a class II foreign antigen binding site may be useful for formulating testable hypotheses about foreign antigen and T-cell binding. We note, however, that significant shifts in the direction (up to 30°) and location (up to 7 Å) of α-helices and β-strands (20°, 2 Å) have been observed in the X-ray structures of the very closely related members of both the globin and the IgG families[56,68]. Therefore any hypothetical model derived from even closely related sequences may differ from the true structure in important details and should be thought of only as an imperfect guide for experiments.

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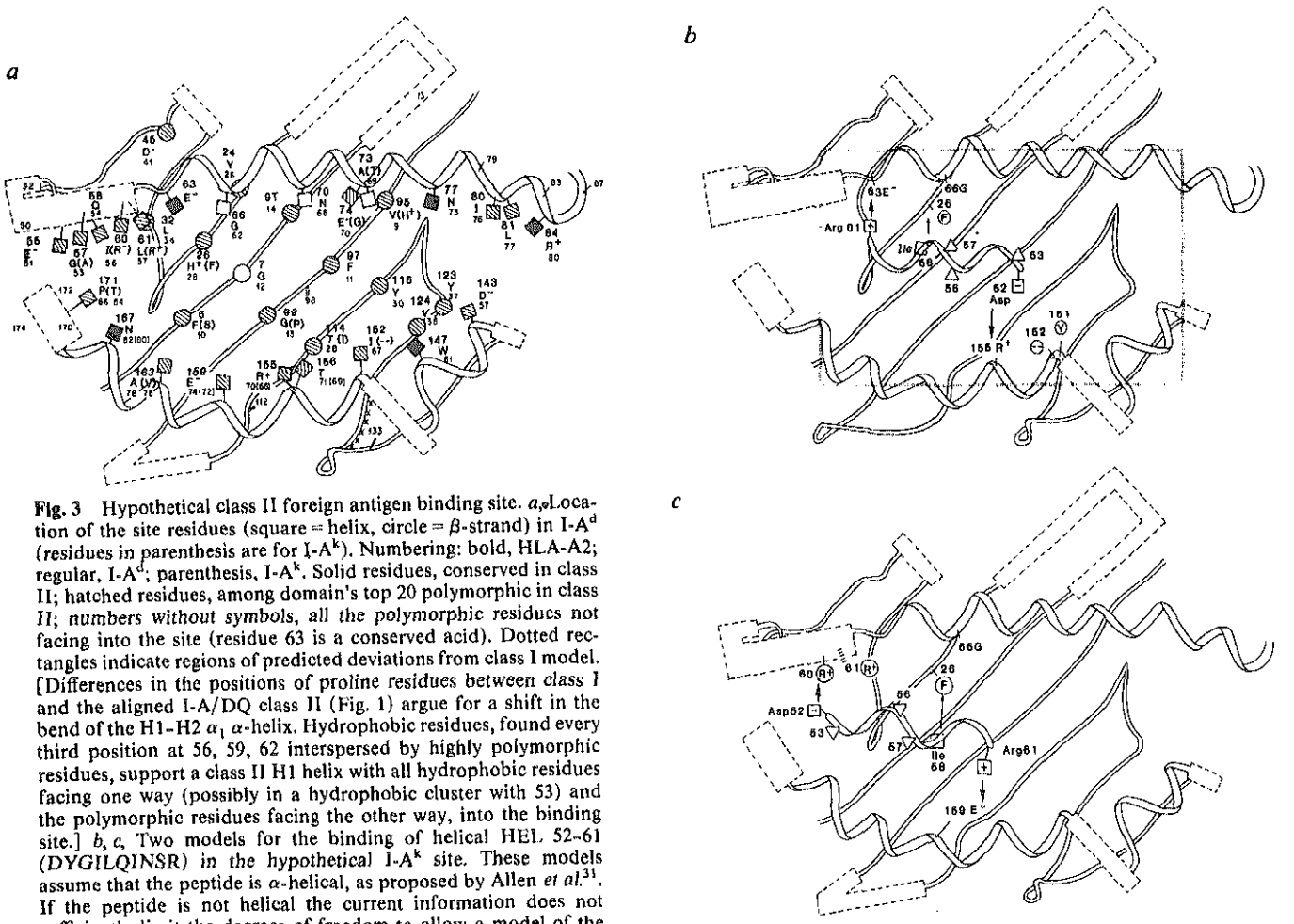

Fig. 3 Hypothetical class II foreign antigen binding site. *a*, Location of the site residues (square = helix, circle = β-strand) in I-A^d (residues in parenthesis are for I-A^k). Numbering: bold, HLA-A2; regular, I-A^d; parenthesis, I-A^k. Solid residues, conserved in class II; hatched residues, among domain's top 20 polymorphic in class II; numbers without symbols, all the polymorphic residues not facing into the site (residue 63 is a conserved acid). Dotted rectangles indicate regions of predicted deviations from class I model. [Differences in the positions of proline residues between class I and the aligned I-A/DQ class II (Fig. 1) argue for a shift in the bend of the H1–H2 α_1 α-helix. Hydrophobic residues, found every third position at 56, 59, 62 interspersed by highly polymorphic residues, support a class II H1 helix with all hydrophobic residues facing one way (possibly in a hydrophobic cluster with 53) and the polymorphic residues facing the other way, into the binding site.] *b*, *c*, Two models for the binding of helical HEL 52–61 (*DYGILQINSR*) in the hypothetical I-A^k site. These models assume that the peptide is α-helical, as proposed by Allen *et al.*[31]. If the peptide is not helical the current information does not sufficiently limit the degrees of freedom to allow a model of the complex to be proposed. Squares represent the peptide residues proposed[31] to be involved in 'MHC-contact'; triangles are the peptide's proposed 'T-cell-contact' residues[31]. I-A^k residues are indicated using the single letter code. Bold lines indicate potential salt bridges (see text). Circled residues are different in the non-responder I-A^d allele and may be responsible for lack of binding of the peptide to I-A^d. [For example Phe26 which is near peptide Ile58 is His in I-A^d, introducing a polar residue into a hydrophobic contact. And positions corresponding to 151 and 152 (HLA-A2) change from Tyr in I-A^k to Glu-Ile in I-A^d (the largest insertion in the site). In I-A^d the glutamic acid may form a salt bridge with Arg155 (151 and 155 are within hydrogen bonding distance in HLA-A2); this might eliminate Arg 155 as a potential partner to salt bridge to the peptide.] In the context of this hypothetical binding model, other non-responder alleles could result from other substitutions in the vicinity of the peptide.

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