The peptide-binding strategy of the MHC class II I-A molecules

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Despite the importance of murine major histocompatibility complex (MHC) class II I-A molecules for immunological research, the overall peptide-binding specificities of I-A and the homologous human HLA-DQ molecules remain unresolved. Here, Boris Reizis and colleagues review current evidence suggesting that DQ/I-A molecules bind peptides with a different hierarchy of anchor positions than has been found in the well-characterized DR/I-E proteins.

The allele-specific peptide-binding motifs of major histocompatibility complex (MHC) proteins, originally discovered by pool sequencing of MHC class I-bound peptides[1], provide a biochemical basis for the phenomenon of MHC restriction of T-cell responses. However, the analysis of class II peptide motifs has proved difficult due to the heterogeneity in peptide length[2–4]. This problem has been overcome using several approaches to characterize the binding motifs of human HLA-DR class II proteins (reviewed in Ref. 5). The understanding of the specificity of peptide–MHC class II interactions was greatly facilitated by the three-dimensional structures of HLA-DR1 (Ref. 6) and of its complex with a peptide[7]. Similar to class I molecules, the HLA-DR structure revealed pockets in the peptide-binding groove accommodating several 'anchor' residues in a peptide. The specificity of these pockets is influenced by polymorphic residues, resulting in allele-specific class II motifs.

The consensus core sequence of peptides binding to HLA-DR appears to be a nonamer with anchor residues at positions 1, 4, 6 and 9 (Ref. 5). Position 1 (P1) appears critical for binding and is invariably occupied by either aromatic or aliphatic residues. In addition, the murine class II I-E molecules, which are closely homologous to HLA-DR, were shown to be similar in their structure[8] and binding motifs[9,10]. The amino acid usage at the anchor positions in DR/I-E motifs seems to be more flexible than in class I motifs, allowing several possible residues at each position. Nevertheless, the overall combination of several positions results in a stringent binding motif.

In contrast to the well-characterized DR/I-E motifs, the peptide-binding specificity of human HLA-DQ and particularly of the murine H-2A (I-A) MHC class II proteins is controversial.

The elusive MHC class II I-A-binding specificity

The crystal structures of HLA-DR1 suggest that the general principles of peptide binding to class II proteins are very similar for different species and different class II molecules[7]. Indeed, the residues forming hydrogen bonds to the peptide backbone in HLA-DR1 are conserved in all class II proteins, implying similar polyproline type II helical conformation, N-to-C-terminal orientation and spacing of anchor residues in the bound peptides. Furthermore, the recent finding that the class II-associated invariant chain peptide (CLIP) can bind different class II molecules using the same set of anchor residues (reviewed in Ref. 11) supports the concept of a common organization of class II binding motifs.

Nevertheless, another family of class II gene products, the murine I-A molecules, has been resistant to characterization of peptide-binding motifs. I-A molecules are important because they are involved in many model immune responses and, in particular, in experimental autoimmune diseases. Moreover, it is the I-A molecules that were used in the seminal studies on the isolation of natural peptide ligands from class II proteins[2,3]. Indeed, binding motifs have been suggested for several I-A alleles[12,13], but these motifs appear very different both from one another and from the general pattern of HLA-DR/I-E motifs. Thus, a general picture of I-A peptide-binding motifs is lacking, despite extensive information regarding natural peptide ligands, peptide binding and T-cell epitopes of I-A molecules. In particular, a moot point is whether DQ/I-A motifs are organized like DR/I-E motifs, or whether they use a substantially different mode of peptide binding.

The controversy over I-A motifs can be illustrated by studies on the I-A^{g7} molecule expressed by nonobese diabetic (NOD) mice. At least four I-A^{g7} motifs have been proposed, which differ substantially in length and/or in the number and specificity of anchor residues[14–17]. This situation demonstrates not only the confusion about particular I-A motifs, but also the lack of agreement about what I-A motifs should look like in general.

Binding motifs of I-A molecules: recent progress

To uncover the general rules for I-A binding specificity, peptide binding to several murine I-A molecules has been studied[16–22]. Importantly, these studies suggest a strong similarity in the organization of

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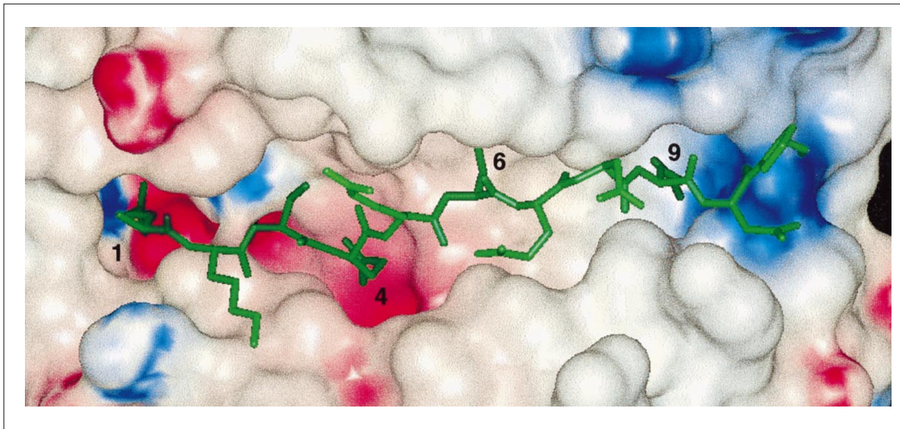

Fig. 1. *Predicted structural features of the interaction between the rat major histocompatibility complex class II I-A molecule RT1.B^l and peptide 74–84 of guinea-pig myelin basic protein (MBP), corresponding to bovine MBP 72–84 (QKSQRSQDENP). The structure was modeled by homology to the crystal structure of an HLA-DR1–peptide complex using HOMOLOGY program (Biosym/MSI, San Diego, CA). The solvent-accessible surface of RT1.B^l is colored according to the predicted electrostatic potential (calculated using Delphi, Biosym/MSI), with positive and negative potentials shown in blue and red, respectively. Note the presence of both a positive and a negative charge in pocket 1 and a large, flat pocket 4 extending beneath the β-chain α-helix.*

I-A motifs and those of DR/I-E. The proposed I-A motifs have a typical nonameric structure with the same spacing of anchor positions as described for DR/I-E motifs.

An important difference between I-A and DR/I-E, however, can be found in the nature and relative importance of particular anchor positions. In all DR/I-E motifs described so far, P1 is strongly conserved and usually serves as the primary anchor position. By contrast, P1 appeared relatively degenerate and was not particularly important for the binding of peptides to I-A molecules RT1.B^l or I-A^{g7} (Refs 16, 20). Instead, positions P4 and P9 seemed to contribute substantially to peptide binding, while other positions such as P6 further restricted the specificity of binding. The degeneracy of the N-terminal P1 anchor position makes the alignment of peptides particularly difficult, contributing to the elusive nature of I-A motifs. Furthermore, the minor role of P1 might explain the apparently short (6–7 residues) minimal core sequences of peptides binding to I-A molecules[12,23,24].

Notably, some I-A alleles do have a more restricted, although not necessarily hydrophobic, P1. Thus, preferences for negatively charged and aromatic residues at P1 were observed in I-A^k (Refs 19, 22) and I-A^b (Ref. 18) molecules, respectively. On the basis of their results, Nelson *et al.*[19] predicted that P1 might show more variability between different I-A alleles than it does between DR/I-E alleles. However, the specificities of P1 in I-A^k and I-A^b are apparently determined by rare residues at position 52 of the MHC α-chain (α52) (Ref. 25). These results suggest that some I-A alleles are similar to DR/I-E in the conserved nature of P1, although this specificity might be caused by unusual sequence features of particular alleles.

In addition, multiple non-anchor positions of low specificity, such as P5 and P7 in I-A^{g7} (Ref. 16), appear to affect peptide binding to I-A proteins. These auxiliary positions might be particularly important in the absence of strong 'consensus' anchor residues. Obviously, such minor preferences further complicate the characterization of I-A binding motifs. In general, therefore, the overall stringency of I-A motifs might result from a combination of more positions, each of lower specificity, than are present in DR/I-E motifs.

The emerging general picture of peptide binding to I-A molecules can be illustrated by computer modeling of I-A proteins and their peptide complexes. Figure 1 shows a model of the complex between the Lewis rat I-A molecule, RT1.B^l, and the immunodominant peptide (72–84) of the autoantigen myelin basic protein (MBP). The modeled peptide-binding groove of RT1.B^l appears very similar to that of DR1, with four prominent pockets (1, 4, 6 and 9) conserved in its structure. However, unlike DR, pocket 1 is polar rather than hydrophobic, and thus can accommodate a broad range of residues[20]. In addition, pocket 4, which favors aromatic residues in RT1.B^l (Ref. 20), is larger than pocket 1 and can potentially contribute more energy for the interaction with a peptide.

Suggested binding motifs for I-A^d and I-A^s molecules

The emerging general features of I-A specificity can be used to delineate new binding motifs from the existing data, as proposed here for two I-A alleles, I-A^d and I-A^s (Table 1). For comparison, the alignment of I-A^{g7}-binding peptides[16] is also shown. Most importantly, P1 appears degenerate in all three molecules. In I-A^s, a conserved Asn residue at α69 is substituted for Thr, probably abolishing a hydrogen bond with the amino group of residue 9 in a bound peptide[7]. Thus, the α69 Asn → Thr substitution might confer the observed strong preference at P9 for proline residues, which cannot donate a hydrogen bond from their amino groups. Aliphatic residues are favored at P6, while P4 appears more degenerate, accommodating aliphatic, polar and positively charged residues.

A stretch of 6–7 small and/or hydrophobic residues was originally observed in the peptides binding to I-A^d (Ref. 23). These observations can now be incorporated into a nonameric I-A^d motif with degenerate P1 and strongly conserved anchors P4 (aliphatic), P6 (small) and P9 (small). Notably, the specificities of P4 and P6 but not of P9 appear similar to those in the closely homologous I-A^{g7} allelic product[16]. Recently, Bartnes *et al.* suggested a nonameric I-A^d motif and demonstrated the degeneracy of P1 in I-A^d (Ref. 26). Although these proposed motifs are probably incomplete and require further testing and refinement, they emphasize the general similarity and different hierarchy of anchor positions in I-A and DR/I-E motifs.

The peptide-binding specificity of HLA-DQ molecules

The dissection of the peptide binding to human DQ molecules is particularly important in view of the close association of some DQ

Table 1. The alignment[a] of peptides binding to I-A^{s} and I-A^{d} compared with I-A^{g7}

Protein	Epitope		Sequence		Refs
			1 4 6 7 9		
I-A^{s}					
PLP	139–51	H	C L G K W L G H P	DKF	24
Collagen	675–86	EA	I Q P G C I G G P	K	27
MBP	81–98	NPVVHFF	K N I V T P R T P	PP[b]	28, 29
		NPVV	H F F K N I V T P	RTPPP	28, 29
Ovalbumin	271–85	NVME	E R K I K V Y L P	RM	30
Myoglobin	110–20	AI	I H V L H S R H P		30
PLP	178–91	NTW	T T C Q S I A F P	SK	30
Nuclease	101–20	EALVRQGL	A K V A Y V Y K P	NNT	30
HSVgd	245–60	A	P Y T S T L L P P	ELSETP	30
MLV	255–69	IRLK	I T D S G P R V P	IG[c]	13
IgG2a	194–210	WQSQ	S I T C N V A H P	ASST[c]	13
Unknown		xPYM	F A D K V V H L P	GSQ[c]	13
I-A^{d}					
Ovalbumin	323–35	I	S Q A V H A A H A	EIN	23
Myoglobin	108–18	S	E A I I H V L H S	R	21, 31
HA	131–42	N	T N G V T A A S S	HE	31
Ovalbumin	312–22		L S G I S S A E S	LK	32
Ovalbumin	317–27	S	A E S L K I S Q A	V	32
HSP60	443–54	AL	L R C I P A L D S	L[d]	
Cys-C	40–55	DAYH	S R A I Q V V R A	RKQ[e]	3
I-E$^{d}\alpha$	52–68	ASFEA	Q G A L A N I A V	DK[e]	3
TFR	442–59	VPQLNQ	M V R T A A E V A	GQX[e]	3
Apo-E	268–83	WANL	M E K I Q A S V A	TNP[e]	3
I-A^{g7}					
MSA	560–74	KPKAT	A E Q L K T V M D	D	14
hnRNP B1	31–43	ETT	E E S L R N Y Y E	Q	14
Hsp60	170–80	Q	V A T I S A N G D	K	16
TCR Vβ8	104–15	GH	G T K L S V L E D	L	16

Abbreviations: Apo-E, apolipoprotein E; Cys-C, cystatin C; HA, hemagglutinin; hnRNP, heterogeneous nuclear ribonucleoprotein; Hsp60, heat shock protein 60; HSVgd, herpes simplex virus glycoprotein D; MBP, myelin basic protein; MSA, mouse serum albumin; MLV, murine leukemia virus; PLP, proteolipid protein; TCR, T-cell receptor; TFR, transferrin receptor.

[a]Peptides are aligned according to the proposed anchor positions (bold). The reported core epitope sequences are underlined. Consensus residues are in red; tolerated residues are in blue; residues shown to be involved in the binding to MHC are in green. For comparison, several I-A^{g7}-binding peptides aligned to the proposed I-A^{g7}-binding motif[16] are shown.

[b]MBP peptide 81–98 was shown to contain two overlapping epitopes, which can be distinguished by the truncation of Pro96 (Ref. 28).

[c]These are natural peptide ligands of I-A^{s} (Ref. 13). Two other reported peptides could not be aligned according to the proposed motif.

[d]B. Reizis, unpublished.

[e]These are natural peptide ligands of I-A^{d} (Ref. 3). Another reported peptide (Apo-E 237–252) was shown to contain multiple overlapping epitopes[3] and could not be aligned according to the proposed motif.

alleles with susceptibility or resistance to several autoimmune diseases. Notwithstanding previously proposed DQ motifs[33–35], the overall binding specificity of HLA-DQ has been obscure. Moreover, a recent study suggested that peptide binding to DQ molecules is fundamentally different from that of DR molecules, depending mostly on inhibitory residues rather than on 'DR-type' anchors in a peptide[36].

Nevertheless, the reported binding motifs of several DQ alleles appear to be consistent with the principles outlined above for I-A molecules. Indeed, the peptide motifs of DQ3.2 (Ref. 37) and DQ2 (Refs 38, 39) comprise nine amino acids with prominent anchor positions 1, 4, 6 and 9. In DQ3.2, P1 appears relatively degenerate, accommodating all except positively charged residues[37]. In DQ2, P1 was found to favor hydrophobic residues[38,39]; nevertheless, the alignment of DQ2-binding peptides shows that P1 is less conserved than other anchor positions such as P7 and P9 (Ref. 38). Although more DQ alleles need to be analyzed for a comprehensive picture of peptide binding, these initial results suggest a common organization of the DQ/I-A binding motifs.

The role of position β57 in peptide binding

Position 57 of the DQ/I-A β-chain (β57) has drawn special consideration because of its association with autoimmune diabetes. In different MHC class II alleles, this position is occupied either by Asp or by non-Asp (Ala, Val or Ser) residues. The presence of non-Asp residues at β57 in both DQ and DR was found to correlate with susceptibility to type I diabetes in mice and humans[40] and was shown to affect the overall specificity of peptide binding[41]. Recent studies suggest a molecular basis for the effects of polymorphism at β57 on binding specificity. Indeed, the analysis of peptide binding to I-A^{g7} (Refs 14, 16), DRB1*0405 (Ref. 42), DRB1*0801 (Ref. 43), DQ3.2 (Ref. 37) and RT1.B^{l} (Ref. 20), all having a non-Asp residue at β57, showed a specific preference for negatively charged residues at P9 in the corresponding peptide motifs (see Table 1). Instead of a negatively charged residue at P9, Harrison *et al.* have concluded that the P9 anchor position of I-A^{g7} accommodates hydrophobic or positively charged residues[17]. However, this discrepancy could be explained by a mistaken assignment of anchor positions: the 'P6' (aliphatic residues) and 'P9' positions of Harrison *et al.* might actually correspond to the P4 and P7 positions of the I-A^{g7} motif[16] (see Table 1). However, some DQ/I-A proteins show a different specificity of P9 despite the presence of non-Asp residues at β57. Thus, DQ2, which features Ala at β57 (β57Ala), was convincingly shown to favor large hydrophobic rather than negatively charged side chains at P9 (Refs 38, 39).

The structures of class II molecules have revealed that β57Asp forms a salt bridge with a conserved α76Arg residue at the

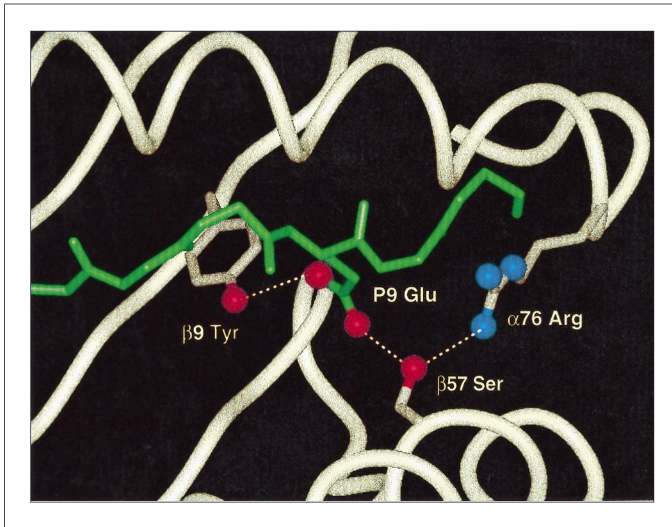

Fig. 2. *The predicted features of pocket 9 in major histocompatibility complex class II alleles having a non-Asp residue at position 57 of the β-chain (β57). The modeled interactions of the Glu residue in pocket 9 of the RT1.B^l–peptide complex shown in Fig. 1 are depicted. Oxygen atoms are in red, nitrogen atoms are in blue, peptide is in green; broken lines represent hydrogen bonds.*

C-terminal end of the groove. Therefore, it was originally proposed that the non-Asp residues at β57 'expose' the positive charge of α76Arg, which is then free to interact with negatively charged residues at P9 in a bound peptide[14,44]. Moreover, computer modeling of molecules containing a non-Asp residue at β57 suggests that α76Arg contributes a positive charge to the wall of pocket 9, thereby favoring negatively charged residues at P9 (Fig. 1). However, the α76Arg residue is probably too far from the P9 side-chain to form a direct interaction (Fig. 2). Rather, other MHC residues delineating pocket 9 might be critical for the specificity of P9. Thus, β57Ser itself, and other MHC residues such as β9Tyr in RT1.B^l, may form hydrogen bonds with negatively charged P9 residues in a peptide (Fig. 2). In the absence of such auxiliary residues in pocket 9 of the MHC, the exposed α76Arg residue alone might be insufficient to form a strong interaction with the acidic residue in a peptide. These considerations might explain the hydrophobic nature of P9 in the DQ2-binding motif. Indeed, the only apparent difference in the residues predicted to delineate pocket 9 in DQ2 compared with DQ8 is the Tyr→Ile substitution at β37, which could abolish a hydrogen bond formed with the P9 side chain in a peptide.

Thus, non-Asp residues at β57 appear to change dramatically the specificity of P9 in a corresponding motif, in most but not all cases conferring a preference for negatively charged residues at this position. However, this influence might be quite complex, depending on the nature of β57 itself (Ser versus Ala or Val) and the other residues forming pocket 9 in the groove.

Concluding remarks

Many DQ/I-A alleles are positively or negatively associated with various autoimmune diseases. These associations are likely to reflect distinct binding preferences of I-A alleles, as illustrated by the rare P9 specificity of the diabetes-associated I-A^{g7} (Refs 14, 16) and DQ3.2 (Ref. 37) molecules. Further characterization of I-A/DQ binding motifs might provide clues to the association of particular alleles with susceptibility or protection against autoimmune diseases.

The existence of two separate families of class II molecules (DR/I-E and DQ/I-A) increases the diversity of peptides available to any individual. However, despite the advantage of peptide diversity, class II molecules must accommodate common pathways of antigen presentation and a common mode of recognition by the T-cell receptor and co-receptors. Such a balance is apparently achieved by the two MHC families binding peptides in essentially a similar way, albeit with a different hierarchy of anchor positions and anchor specificities.`

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