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Review

Three-Dimensional Structures of MHC Class I-Peptide Complexes: Implications for Peptide Recognition

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Abstract. Over the last decade, the number of crystal structures of major histocompatibility complex (MHC) class I-peptide complexes has increased rapidly. These studies have provided unique and fascinating insights into the structural basis of MHC-peptide interactions and the specificity of peptide recognition by MHC class I molecules.

Key words: MHC class I; peptide binding; protein crystallography.

Introduction

Major histocompatibility complexes (MHC) are membrane-anchored glycoproteins that are expressed on practically all nucleated cells. Their function is to bind and present peptides to other molecules of the immune system. The peptides that are presented are generally fragments of degraded proteins derived from cytoplasmic self proteins and proteins of viral and bacterial origin. There are two kinds of MHC complexes, class I and class II, that interact with different subsets of T cell receptors, class I with cytotoxic T cells and class II with helper T cells. Both classes are heterodimers, the class I molecules consist of a membrane associated heavy chain and a soluble β2-microglobulin (β2m) subunit while the class II molecules are formed by two membrane-anchored chains, α and β.

Presentation of a foreign peptide by a MHC class I molecule is a signal to the cytotoxic T cells that the presenting cell is infected and must be eliminated. If the MHC molecule is binding a self-derived peptide the T cells will in contrary recognise the cell as healthy and no action will be taken. The interaction between T cells and MHC class I bearing cells is one of the best studied mechanisms of the immune system and two of the pioneers in this field, Doherty and Zinkernagel, were rewarded with the Nobel prize in physiology or medicine in 1996. Despite the vast amount of data available there are still many questions that remain to be answered, for instance how T cells can distinguish between self and non-self peptides.

In recent years it has become clear that the MHC class I molecules also interact with natural killer (NK) cells. While the interaction of MHC presenting foreign peptides with T cell receptors will trigger lysis of the target cell the interaction between MHC and inhibitory NK cell receptor will, in contrary, protect the cell from being killed. The NK receptors are of two different types. One class of receptors belongs to the immunoglobulin superfamily, of the type I integral membrane proteins, having two or three extracellular immunoglobulin domains.

The other class belongs to the type II integral membrane proteins that are members of the C-type lectin

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superfamily. The lectin-like receptors are homo-, or heterodimers where the subunits are linked via disulphides. To date, the NK cell receptors that interact with human MHC class I molecules are all of the immunoglobulin family while the NK receptors interacting with mouse MHC class I molecules are of the C-type lectin superfamily.

The Overall Structure of MHC Class I Complexes

MHC class I molecules are heterodimers that consist of a variable heavy chain and an invariant β2m subunit (Fig. 1). The heavy chain is built up from two domains, α1/α2 and α3. Both the α3 domain and β2m exhibit immunoglobulin folds, a four stranded anti-parallel β-sheet packing against a three-stranded anti-parallel sheet. The α1 and α2 subdomains are encoded on different exons and contribute equally to the α1/α2 domain with a helical segment and a four stranded β-sheet each. The two sheets together form a floor of eight β-strands that is lined by the helical segments on each side. The helices are running antiparallel to each other and are separated by a long groove that constitute the binding cleft where peptides, usually 8–11 residues long, are bound (Fig. 2). The heavy chain also contains a short transmembrane anchor and a small cytoplasmic domain. There is one conserved glycosylation site in the human heavy chain (Asn86) and two in the murine (Asn86 and Asn176).

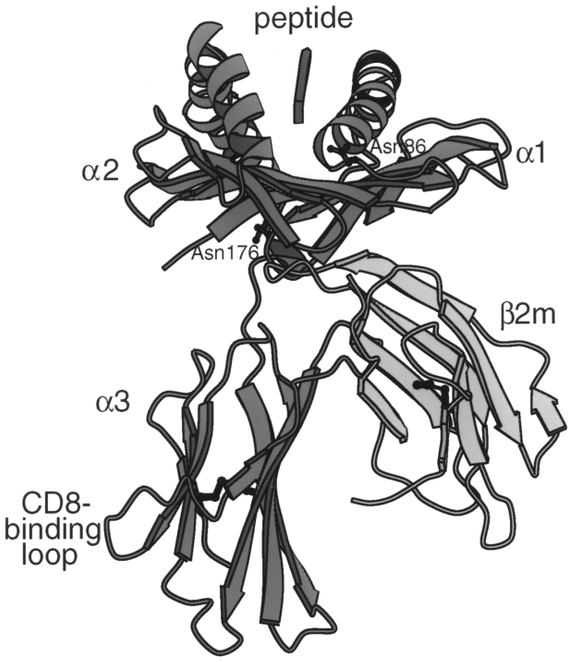

Fig. 1. Schematic cartoon showing the structure of a MHC class I molecule with a peptide bound in the cleft between the α1 and α2 subdomains. The arrows indicate those parts of the polypeptide chain, which form β-strands. The CD8-binding loop and the murine glycosylation sites Asn86 and Asn176 are indicated. Disulphide bonds are shown in black

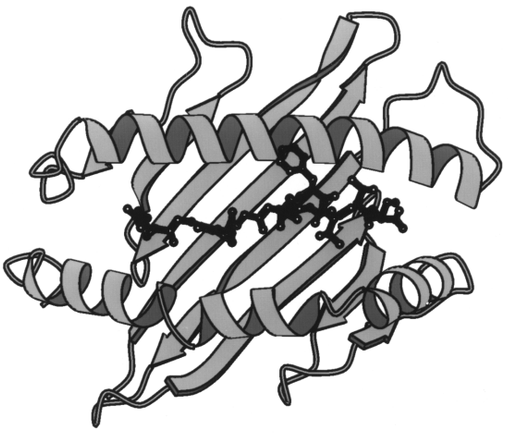

Fig. 2. View of the peptide binding groove of H-2D^d, formed by the α1 and α2 subdomains, with bound peptide shown as a ball-and-stick model. The floor of the groove is formed by eight β-strands and the walls by two α-helices, running anti-parallel

The first crystal structure of a MHC class I molecule to be determined was HLA-A2 in complex with a mixture of peptides[5, 6]. Later, a protocol for expressing the MHC heavy and β2m chains separately in *E. coli* followed by renaturation in presence of single peptides was developed[20]. This method has enabled the structure determination of a large number of murine and human MHC class I molecules in complex with single peptides which has enhanced the understanding of peptide binding and selectivity. There are now more than 30 crystal structures of MHC class I-peptide complexes deposited in the Protein Data Bank (Tables 1–3).

The Interaction with the T Cell Receptor

Knowledge of the structural basis of the interactions between MHC class I and other molecules of the immune system has been further refined by the structure determination of the T cell receptor (TCR). First, fragments of the receptor were determined[4] followed by the intact TCR[21] and TCR in complex with MHC class I and peptide[19].

These were soon followed by several structures of both human and murine TCRs complexed with different MHC-peptide complexes, recently reviewed by

Table 1. Crystal structures of human MHC class I-peptide complexes

Molecule	Peptide	Comments	PDB code	Reference
HLA-A2	mixture		1hla	5
			3hla	42
	ILKEPVHGV		1hhj	33
	LLFGYPVYV		1hhk	
	GILGFVFTL		1hhi	
	TLTSCNTSV		1hhg	
	FLPSDFFPSV		1hhh	
	MLLSVPLLLG	C-term. ext.	2clr	12
	GILGFVFTA			7
	XILGFVFTA	X=methyl		
	GILGFVFTX	X=methyl	1b0r	
	GILGFVFTX	X=methyl		
	ALWGFFPVL		1b0g	54
HLA-Aw68	mixture		2hla	22
	KTGGPIYKR			43
	mixture		1hsb	25
	EVAPPEYHRK	α3 deleted	1tmc	11
HLA-B27	mixture	Arg at P2	1hsa	34
HLA-B8	GGRKKYKL		1agb	39
	GGKKKYQL		1agc	
	GGKKKYKL		1agd	
	GGKKKYRL		1age	
	GGKKRYKL		1agf	
HLA-B35	VPLRPMTY		1a1n	45
	LPPLDITPY		1a9e	35
HLA-B53	KPIVQYDNF		1a1o	44
	TPYDINQML		1a1m	
HLA-Cw4	QYDDAVYKL		1qqd	14

GARBOCZI and BIDDISON[18]. The structures have revealed that TCR binds diagonally over the MHC α1/α2 domain and interacts with the exposed peptide residues. The interaction between the MHC class I molecule and TCR is stabilised by the co-receptor CD8. The crystal structure of CD8 in complex with a human MHC molecule[17] has given further insights into this complex molecular interplay.

Non-Classical MHC and Molecules with MHC-Like Folds

The non-classical MHC molecules (for recent reviews see O'CALLAGHAN and BELL[36], BRAUD et al.[8]) are, in human, HLA-E, -F, and -G. These molecules are structurally very similar to the classical MHC complexes and most of them exhibit the same conserved disulphide pair, the conserved glycosylation site and the highly conserved CD8-binding loop (Fig. 1). They are, however, contrary to the classical molecules, relatively non-polymorphic, and very restrictive in peptide binding and are expressed in lower amounts.

Table 2. Crystal structures of murine MHC class I complexes

Molecule	Peptide	Comments	PDB code	Reference
H-2K^b	RGYVYQGL		2vaa	15
	FAPGNYPAL		2vab	
	RGYVYQGL		2mha	53
	SIINFEKL		1vac	16
	SRDHSRTPM		1vad	
	RGYLYQGL		1osz	23
		glycopeptide	1kbg	46
H-2D^b	ASNENMETM		1hoc	51
	FAPGNYPAL		1ce6	24
	FAPGSYPAL	glycopeptide		
	FAPSNYPAL	glycopeptide		
	FAPGVFPYM		1bz9	54
H-2L^d	YPNVNIHNF		1ld9	2
	QLSPFPFDL	Mix. w.APAAAAAAM	1ldp	47
H-2D^d	RGPGRAFVTI		1bii, 1ddh	1, 30

Table 3. Crystal structures of non-classical MHC class I molecules and MHC-like molecules

Molecule	Comments	PDB code	Reference
HLA-E	Binds leader peptide from other MHC class I	1mhe	37
HFE	No peptide. Involved in iron metabolism	1a6z	29
C1d1	Binds lipids and hydrophobic peptides	1cd1	52
H2-M3	Formylated peptides	1mhc	49
FcRn	Neonatal Fc receptor	3fru	48
ZAG	Fat depleting factor, does not bind β2m	1zag	41
MIC-A	Does not bind peptide or β2m	1b3j	31

The binding cleft of HLA-E is predominantly hydrophobic and binds the leader signal cleaved off from classical MHC heavy chains. HLA-E in complex with the leader peptide is a ligand for the NK cell receptor CD94/NKG2 and inhibits killing of targets. The crystal structure of HLA-E, complexed with a leader peptide, revealed that the overall structure is very similar to the classical MHC. However, in HLA-E peptide residues are tightly bound in all binding pockets contrary to the more flexible binding in the classical MHC class I molecules[37].

Other MHC homologues are mouse H2-M3 that binds formylated peptides, usually of mitochondrial or bacterial origin, and the CD1 molecules that bind lipids in their extremely hydrophobic binding groove instead

of peptides. The crystal structures of H2-M3 and CD1d1 have been determined[49, 52]. MICA and MICB are MHC homologues, expressed mainly in the gastrointestinal epithelium. They are recognised by a certain subset of T cells and are independent of β2m. The crystal structure of MICA has recently been determined[31]. The neonatal Fc-receptor is a protein with a fold very similar to the MHC class I molecules and is important for the transmission of maternal IgG to the foetus to provide the new-born with a functional immune system. The structure of the class I-like neonatal Fc-receptor has been solved[9, 48]. Another structurally similar complex is the hemochromatosis protein HFE[29]. This complex does not bind peptides and is instead involved in iron metabolism and is known to interact with the transferrin receptor [38]. Zn-α2-glycoprotein (ZAG) is a MHC class I like protein, not associated with β2m, which stimulates the degradation of lipids. In contrary to MHC, ZAG is a soluble protein and is present in most body fluids. The structure of ZAG was solved recently[41]. Crystal structures of non-classical MHC and MHC-like proteins are listed in Table 3.

Recognition of Peptides by MHC Class I Molecules

The class I molecules usually bind peptides 8–11 residues long in their binding groove. The binding cleft is blocked at the ends, which forces longer peptides to either zig-zag or bulge out in the middle. The dilemma about peptide binding is that the MHC molecule has to bind the peptide antigen tightly, but at the same time it also has to be able to bind thousands of different peptides with similar affinity, therefore the binding cannot be too specific. Still, each allelic form of MHC prefers certain residues at some positions of the peptide. These peptide residues are termed anchors and fit the binding pockets of the MHC groove. Other peptide residues are very polymorphic and usually bind the groove via main chain interactions[3, 28, 32, 50].

Conserved binding at the N-, and C-terminus

MHC molecules and in particular the α1/α2 domain are, as mentioned above, extremely polymorphic[26]. Still, there are several highly conserved residues at both ends of the peptide binding groove that are present in both human and murine MHC. Three conserved tyrosines, Tyr7, Tyr59 and Tyr171, bind the free amino group of the N-terminal peptide residue P1. Another conserved tyrosine, Tyr159, interacts with the carbonyl oxygen of the same residue. Thus, conserved residues from both α1 and α2 participate in peptide binding.

A cluster of invariant residues also binds the C-terminal part of the peptide. Tyr84, Thr143 and Lys146 bind to the terminal carboxylate group and Trp147 forms a hydrogen bond to the carbonyl oxygen of the penultimate residue of the peptide. Most class I molecules also have a conserved Asp77 that interacts via a hydrogen bond with the amino group of the last residue.

The binding of the peptide at the N-, and C-termini is identical in almost all the MHC class I-peptide complexes determined. However, there are exceptions from this rule. In the crystal structure of HLA-A2 in complex with a decameric peptide, the final residue, a glycine, extends from the C-terminal pocket[12]. The binding pocket was significantly rearranged leaving only one of the standard hydrogen bonds, between Thr143 and one of the carboxylate oxygen atoms, unaltered. Also the peptide bound to the non-classical H2-M3 extends from the C-terminal pocket with several residues[49]. In the H2-M3 molecule Trp147 is replaced by Leu, which makes the binding pocket wider.

Also at the N-terminal alterations from the standard binding mode have been reported. In the complex between HLA-B35 and an octameric peptide the N-terminal does not reach to the classical N-terminal pocket. Instead, a water molecule mediates hydrogen bonds between the main chain amino group of the first peptide residue and the regular MHC residues[45]. Altered binding at the N-terminal is also the case in H2-M3, discussed above, where the N-terminal peptide residue is formylated. In H2-M3, leucine and phenylalanine replace consensus Trp167 and Tyr171. The presence of a leucine at position 167 makes the binding pocket smaller than the regular pocket as the leucine projecting down the groove contrary to the usual Trp167 that is point up.

Classification of binding pockets

Most of the strongest interactions are independent of the peptide sequence and are only mediated via its main chain atoms. Still, each allelic form has preferences for certain peptide residues in the different binding pockets of the groove. The preferred sequences can be determined by the analysis of naturally bound peptides eluted from the complexes. The tight binding of anchors to the specific pockets has been confirmed by the many crystal structures determined. Six binding pockets were originally termed A, B, C, D, E and F, (Fig. 3), based on the structure of HLA-A2[42]. However, it should be noted that all the pockets are not necessarily used for peptide binding in every allelic MHC form.

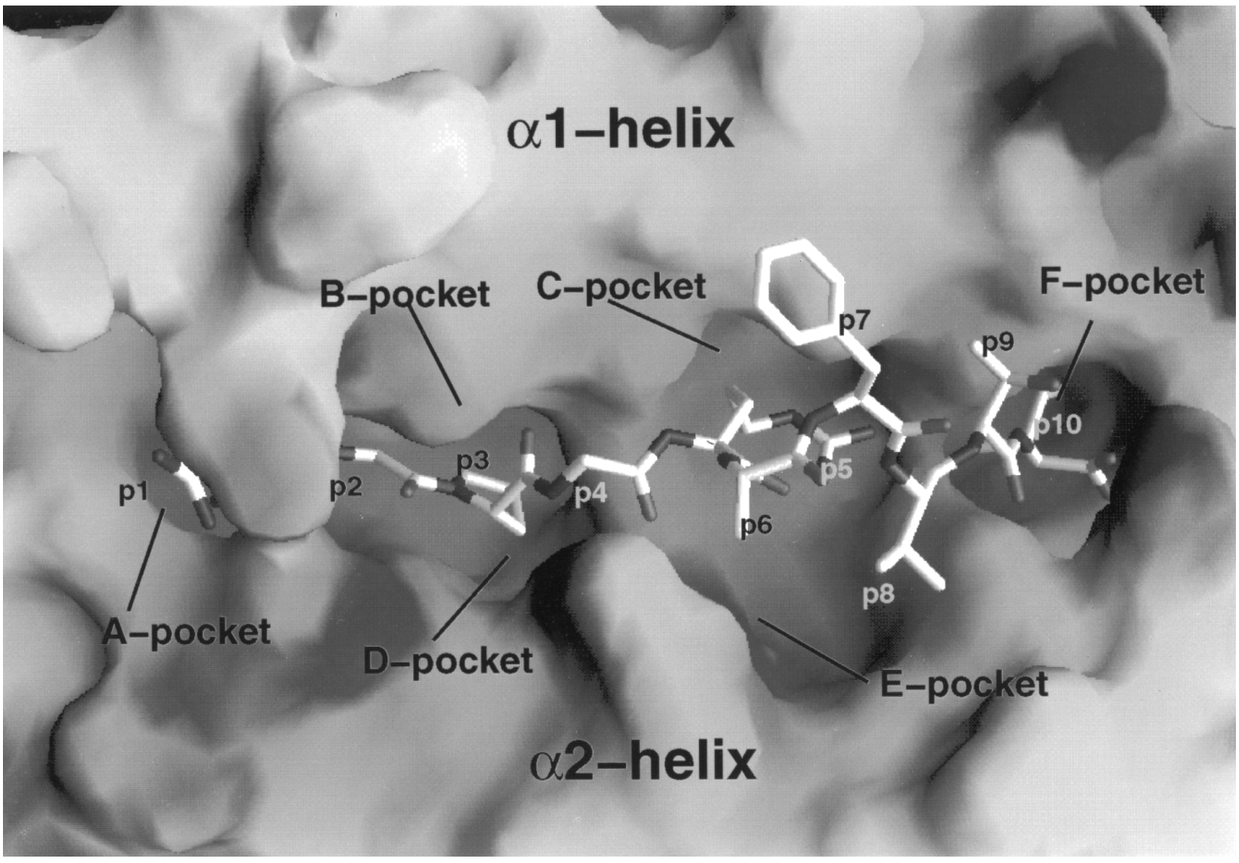

Fig. 3. Surface representation of the peptide binding groove of H-2D^d with bound peptide included as a ball-and-stick model. The six binding pockets, responsible for peptide selectivity, are indicated

The A-pocket (Fig. 4a) is binding the N-terminal, as discussed above, and is generally very flexible concerning the side chain, which is facing the solvent. The C-terminal pocket (Fig. 4b) is termed F and is usually more restrictive in which side chain to bind. The C-terminal peptide side chain is deeply buried while the main chain is more exposed to solvent than in the N-terminal. The C-terminal side chain is the most strongly binding anchor residue, and is restricted by the size, shape and charge of the F-pocket. The C-terminal peptide residues in structures determined to date are basic (in HLA-A68 and--B27) or hydrophobic (in HLA-A2, -B35, B-53 and-B8, HLA-Cw4 and all the murine MHC class I complexes).

The pocket B is, in the human MHC class I molecules, a deep pronounced indentation under the α1-helix that accommodates an anchor residue at position P2. The pocket is formed by the polymorphic residues 9, 24, 45, 67 and 99. The sequence of these residues dictates the shape and charge of the pocket and thus the characteristics of the peptide anchor. The B pocket has preference for small uncharged residues in HLA-A2 (Leu and Ile) and in HLA-A68 (Val and Thr), or basic residues (Arg in HLA-B27). HLA-B35 and -53 have strong preference for Pro at this position, while the B-pocket of HLA-Cw4 is highly specific for tyrosine. Some of the murine complexes also have anchor residues bound at position P2, e.g. H-2L^d that has a consensus proline anchor at position 2. In H-2K^d, of which the structure is not yet determined, the anchor residue binding to the B-pocket is a tyrosine[40]. H-2D^d has a very strong double anchor at position 2 and 3 with an absolute preference for glycine followed by a proline. The crystal structure revealed that Arg66 of the α1 domain pointing down the groove, thus filling the B-pocket. This arrangement makes the passage so narrow that nothing but a glycine can fit at this position[1].

Some of the murine molecules do instead bind anchors in the centre of the groove, in the C-pocket. The C-pocket comprises the residues around 9, 97 and 99 and is also located between the α1-helix and the β-sheet floor. The anchor residues are Phe and Tyr in H-2K^b and Asn in H-2D^b.

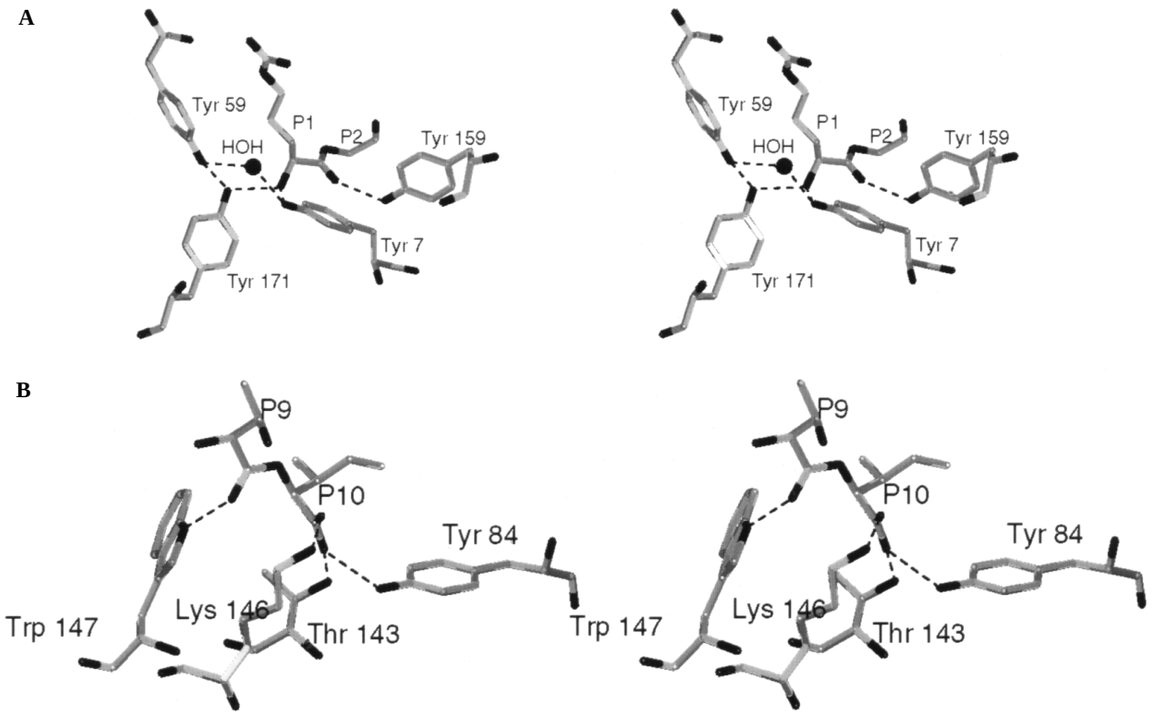

Fig. 4. A – stereoview of the A-pocket, which anchors the N-terminal amino acid of the peptide through hydrogen bonds (indicated by dashed lines) to MHC side chains. P1 and P2 denote peptide residues 1 and 2 and HOH represents a bound water molecule. **B** – stereoview of the F-pocket, responsible for binding of the C-terminal amino acid of the peptide. P9 and P10 denote peptide residues 9 and 10. Note the tight interaction of the C-terminal carboxyl group of the peptide with protein side chains via three hydrogen bonds

Secondary anchors are peptide residues that contribute to the affinity between the peptide and the MHC molecule, but are not as invariant as the primary anchors. Secondary anchor residues are often bound in the D and E-pockets. The D-pocket is, in the human molecules, generally hydrophobic and binds the side chain P3. There is a preference for large hydrophobic residues, but almost any other residue can bind, as shown for HLA-B27[27]. The D-pocket is positioned towards the α2-helix, adjacent to the E-pocket. However, there are examples of secondary anchor residues that do not bind to any binding pocket. Peptides binding to H-2D^d have very strong secondary anchors at position 5 (Arg, Lys or His), and in the complex between H-2D^d and the viral peptide P18-I10 the arginine at position 5 rests on the hydrophobic floor of the groove and is not bound to any pocket.

Length of peptides

The peptides binding to MHC class I are normally 8–11 residues long, although there are examples of longer peptides that have been eluted from the peptide pools of e.g HLA-A2[10]. It is believed that the final residues can extend out from the cleft at the C-terminal, with some loss of binding energy, similar to the peptide discussed above[12]. However, the peptides are most often limited by the N-, and C-terminal pockets and their conformations are dictated by the architecture of the binding groove. While the shorter peptides bind to the binding groove in an extended conformation longer peptides have to loop out, leaving the central residues of the peptide exposed to solvent. This is usually performed by a kink in the backbone in the middle part of the peptide. Peptides bulging out have been observed in the HLA-Aw68 in complex with decameric peptides[25] and in H-2D^{d1}. In the latter case, a type I' reverse turn, formed by residues 5–8 of the peptide, stabilizes the conformation of the bound peptide.

Another way of accommodating a long peptide in the binding cleft is to let it zig-zag along the cleft, with every second residue facing α1 and α2, respectively, as in the complex between HLA-A2 and a hepatitis B nucleocapsid 10-mer[33].

Water in the binding cleft

Water molecules in the peptide-binding groove contribute to the flexibility of the MHC-peptide interaction. Some of these water molecules are more or less conserved, and found in most of the crystal structures, e.g.

a water molecule that links the conserved Tyr59 with the other conserved tyrosines (Tyr7 and Tyr171) that are binding the N-terminus of the peptide. Water often mediates hydrogen bonds between peptide and MHC, stabilising and, as discussed above, even maintaining the hydrogen bonding pattern of a peptide not reaching to the end of the binding cleft[45]. Also, water molecules optimise the fit between the binding groove and the peptide by filling cavities and pockets not filled by peptide residues[16, 44].

Conclusions

The availability of a large number of crystal structures of MHC class I-peptide complexes has enabled structural biologists to extract a number of more general features employed in the recognition of peptides by MHC molecules. These insights provide the basis for the prediction of peptide-MHC interactions in structurally not characterized complexes. Nevertheless, there are still surprises ahead as shown in the case of H-2D^d. In this complex the peptide binds in a completely different manner[1] than predicted from modelling studies[13]. Further studies of peptide-MHC complexes are therefore required to be able to predict peptide binding in a more reliable manner.

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