Chapter 2

IMGT Standardization for Molecular Characterization of the T Cell Receptor/Peptide/MHC Complexes

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Abstract. One of the key elements in the adaptive immune response is the presentation of peptides by the major histocompatibility complex (MHC) to the T cell receptors (TR) at the surface of T cells. The characterization of the TR/peptide/MHC trimolecular complexes (TR/pMHC) is crucial to the fields of immunology, vaccination, and immunotherapy. In order to facilitate data comparison and cross-referencing between experiments from different laboratories whatever the receptor, the chain type, the domain, or the species, IMGT®, the international ImMunoGeneTics information system (http://imgt.cines.fr), has developed IMGT-ONTOLOGY, the first ontology in immunogenetics and immunoinformatics. In IMGT/3Dstructure-DB, the IMGT three-dimensional structure database, the molecular characterization of the TR/pMHC is made according to the IMGT Scientific chart rules that are based on the IMGT-ONTOLOGY concepts. IMGT/3Dstructure-DB provides the standardized IMGT gene and allele names (CLASSIFICATION), the standardized IMGT labels (DESCRIPTION), and the IMGT unique numbering (NUMEROTATION). As the IMGT structural unit is the domain, amino acids at conserved positions always have the same number in the IMGT® databases, tools, and Web resources. For the TR α and β chains, the amino acids in contact with the peptide/MHC (pMHC) are defined according to the IMGT unique numbering for V-DOMAIN. The MHC chain cleft that binds the peptide is formed by two groove domains (G-DOMAIN), each one comprising four antiparallel β strands and one α helix. The IMGT unique numbering for G-DOMAIN applies both to the first two domains (G-ALPHA1 and G-ALPHA2) of the MHC class I α chain, and to the first domain (G-ALPHA and G-BETA) of the MHC class II α chain and β chain, respectively. Based on the IMGT unique numbering, we defined 11 contact sites for the analysis of the pMHC contacts. The TR/pMHC contact description, based on the IMGT numbering, can be queried in the IMGT/StucturalQuery tool, at http://imgt.cines.fr.

2.1 Introduction

T cells are implicated in the specific immune response against a stress of viral, bacterial, fungal, or tumoral origin. They identify antigenic peptides presented by the major histocompatibility complex (MHC) cell surface glycoproteins. The recognition is

carried out by the T cell receptor complex (TcR), a multisubunit transmembrane surface complex made up of a T cell receptor (TR) and of the CD3 chains, that is associated, in the immunological synapse, to the CD4 or CD8 coreceptors, to the CD28 and CTLA-4 costimulatory proteins, to the CD2 adhesion molecule, and to intracellular kinases (Lefranc and Lefranc 2001). The TR directly binds the peptide/MHC complex (pMHC), and activates the T cell through interactions with the CD3 and other components of the TcR (Vasmatzis, Cornette, Sezerman, and DeLisi 1996a; Sim, Zerva, Greene, and Gascoigne 1996; Kjer-Nielsen, Clements, Purcell, Brooks, Whisstock, Burrows, McCluskey, and Rossjohn 2003). Three-dimensional (3D) structures of the TR, pMHC, and TR/pMHC complexes provide an atomic description of their interactions (Kaas, Ruiz, and Lefranc 2004; Kaas and Lefranc 2005).

Since 1989, IMGT®, the international ImMunoGeneTics information system® (Lefranc, Giudicelli, Kaas, Duprat, Jabado-Michaloud, Scaviner, Ginestoux, Clément, Chaume, and Lefranc 2005c), http://imgt.cines.fr, has offered standardized genetic and structural data on immunoglobulins (IG), TR, and MHC, and on related proteins of the immune system (RPI) that belong to the immunoglobulin superfamily (IgSF) and to the MHC superfamily (MhcSF). In order to facilitate data comparison and cross-referencing between experiments from different laboratories whatever the receptor, the chain type, the domain, or the species, IMGT® has developed IMGT-ONTOLOGY (Giudicelli and Lefranc 1999), the first ontology in immunogenetics and immunoinformatics.

Based on the IMGT-ONTOLOGY concepts, the IMGT Scientific chart provides the controlled vocabulary and the annotation rules necessary for the identification, the description, the classification, and the numbering of the IG, TR, MHC, and RPI (Lefranc 2004a; Lefranc, Giudicelli, Ginestoux, Bosc, Folch, Guiraudou, Jabado-Michaloud, Magris, Scaviner, Thouvenin, Combres, Girod, Jeanjean, Protat, Monod, Duprat, Kaas, Pommié, Chaume, and Lefranc 2004b; Lefranc, Clément, Kaas, Duprat, Chastellan, Coelho, Combres, Ginestoux, Giudicelli, Chaume, and Lefranc 2005a). The IDENTIFICATION concept refers to the IMGT standardized keywords that are essential for the sequence and 3D structure assignments. The DESCRIPTION concept provides the IMGT standardized labels used to describe structural and functional regions that compose IG, TR, MHC, and RPI sequences and 3D structures. Standardized labels have also been defined to characterize the three-dimensional assembly of domains and chains. The CLASSIFICATION concept provides immunologists and geneticists with a standardized nomenclature per locus and per species. The human IG and TR gene nomenclature elaborated by IMGT was approved by the Human Genome Organisation (HUGO) Nomenclature Committee, HGNC (Wain, Bruford, Lovering, Lush, Wright, and Povey 2002), in 1999. The mouse IG and TR gene names with IMGT reference sequences were provided by IMGT to HGNC and to the Mouse Genome Database (MGD; Blake, Richardson, Bult, Kadin, and Eppig 2003) in July 2002. The NUMEROTATION concept provides the IMGT unique numbering for the IG and TR V-DOMAIN and the V-LIKE-DOMAIN of the IgSF proteins other than IG or TR (Lefranc, Pommié, Ruiz, Giudicelli, Foulquier, Truong, Thouvenin-Contet, and Lefranc 2003b), and for the IG and TR C-DOMAIN and the C-LIKE-DOMAIN of the IgSF proteins other than IG or TR (Lefranc, Pommié, Kaas, Duprat, Bosc,

Guiraudou, Jean, Ruiz, Da Piedade, Rouard, Foulquier, Thouvenin, and Lefranc 2005d). An IMGT unique numbering has also been set up for the MHC G-DOMAIN and the G-LIKE-DOMAIN of the MhcSF proteins other than MHC (Lefranc, Duprat, Kaas, Tranne, Thiriot, and Lefranc 2005b).

The IMGT standardization has allowed the construction of a unique frame for the comparison of the TR, peptide, and MHC interactions in the different resources provided by the IMGT® information system. IMGT/3Dstructure-DB (Kaas et al. 2004), the IMGT structural database, is used with the IMGT sequence databases, IMGT/LIGM-DB (Lefranc 2003a; Giudicelli, Ginestoux, Folch, Jabado-Michaloud, Chaume, and Lefranc 2006) and IMGT/MHC-DB (Robinson, Waller, Parham, de Groot, Bontrop, Kennedy, Stoehr, and Marsh 2003); the IMGT gene database, IMGT/GENE-DB (Giudicelli, Chaume, and Lefranc 2005); the IMGT tools for sequence analysis, IMGT/V-QUEST (Giudicelli, Chaume, and Lefranc 2004), IMGT/JunctionAnalysis (Yousfi Monod, Giudicelli, Chaume, and Lefranc 2004); and the IMGT tool for 3D structure analysis, IMGT/StructuralQuery (Kaas et al. 2004), to explore the TR and MHC conserved structural features. In this paper, we describe the IMGT standardized rules that have been set up for the molecular characterization of the TR/pMHC complexes. Coordinate files are from IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr, with original crystallographic data from the Protein Data Bank, PDB (Berman, Westbrook, Feng, Gilliland, Bhat, Weissig, Shindyalov, and Bourne 2000). Eleven IMGT pMHC contact sites were defined (C1 to C11) which can be used to compare pMHC interactions (Kaas and Lefranc 2005).

2.2 T Cell Receptor/Peptide/MHC 3D Structures and IMGT Standardization

IMGT/3Dstructure-DB (Table 1) contains 18 TR/pMHC structures: 14 (12 TR/pMHC-I and 2 TR/pMHC-II) with complete extracellular regions of the α-β TR (TR-ALPHA_BETA) and 4 structures with an Fv variable fragment (FV-ALPHA_BETA). The α-β TR chains, TR-ALPHA and TR-BETA, are described with standardized IMGT labels in Fig. 1.

The references for the 18 TR/pMHC 3D structures are: 1ao7 (Garboczi, Ghosh, Utz, Fan, Biddison, and Wiley 1996), 1qrn, 1qse, 1qsf (Ding, Baker, Garboczi, Biddison and Wiley 1999), 1bd2 (Ding, Smith, Garboczi, Utz, Biddison, and Wiley 1998), 1oga (Stewart-Jones, McMichael, Bell, Stuart, and Jones 2003), 1mi5 (Kjer-Nielsen et al. 2003), 1lp9 (Buslepp, Wang, Biddison, Appella, and Collins 2003), 1g6r (Degano, Garcia, Apostolopoulos, Rudolph, Teyton, and Wilson 2000), 1jtr, 1mwa (Luz, Huang, Garcia, Rudolph, Apostolopoulos, Teyton, and Wilson 2002), 2ckb (Garcia, Degano, Pease, Huang, Peterson, Teyton, and Wilson 1998), 1fo0 (Reiser, Darnault, Guimezanes, Gregoire, Mosser, Schmitt-Verhulst, Fontecilla-Camps, Malissen, Housset, and Mazza 2000), 1nam (Reiser, Darnault, Gregoire, Mosser, Mazza, Kearney, van der Merwe, Fontecilla-Camps, Housset, and Malissen 2003), 1kj2 (Reiser, Gregoire, Darnault, Mosser, Guimezanes, Schmitt-Verhulst, Fontecilla-Camps, Mazza, Malissen, and Housset 2002), 1fyt (Hennecke, Carfi, and

Wiley 2000), 1j8h (Hennecke and Wiley 2002), 1d9k (Reinherz, Tan, Tang, Kern, Liu, Xiong, Hussey, Smolyar, Hare, Zhang, Joachimiak, Chang, Wagner, and Wang 1999).

Table 1. TR/peptide/MHC complexes in IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. Sp, species; Hs, *Homo sapiens*; Mm, *Mus musculus*; L, length in amino acids. Fourteen 3D structures (12 TR/pMHC-I and 2 TR/pMHC-II) correspond to TR receptors (TR-ALPHA_BETA). Four 3D structures (1d9k, 1fo0, 1kj2, and 1nam) correspond to an Fv variable fragment (FV-ALPHA_BETA). Gene and allele names are according to IMGT/GENE-DB (Giudicelli et al. 2005) for human and mouse TR, to IMGT/HLA-DB (Robinson et al. 2003) for human MHC, and to IMGT for mouse MHC. Amino acid sequences of the TR V-DOMAINs and MHC G-DOMAINs are reported in Figs. 3 and 4, respectively. H2-K1*01 encodes H2-K1b, H2-AB*02 and H2-AA*02 encode I-Abk and I-Aak, respectively. Lengths of the CDR-IMGT are according to Lefranc et al. (2003b).

(A) TR/pMHC-I

	T cell receptor				Peptide		MHC
3D	Name	Sp.	V-DOMAIN genes	CDR-IMGT	Sequence	L	Gene and allele
1ao7	A6	Hs	TRAV12-2-TRAJ24	[6.6.11]	LLFGYPVYV	9	HLA-A*0201
			TRBV6-5-TRBD2-TRBJ2-7	[5.6.14]			
1qrn	A6				LLFGY<u>A</u>VYV	9	
1qse	A6				LLFGYP<u>R</u>YV	9	
1qsf	A6				LLFGYPV<u>A</u>V	9	
1bd2	B7	Hs	TRAV29/DV5-TRAJ54	[6.6.10]	LLFGYPVYV	9	HLA-A*0201
			TRBV6-5-(TRBD2)-TRBJ2-7	[5.6.13]			
1oga	JM22	Hs	TRAV27-TRAJ42	[5.6.10]	GILGFVFTL	9	HLA-A*0201
			TRBV19-(TRBD2)-TRBJ2-7	[5.6.11]			
1mi5	LC13	Hs	TRAV26-2-TRAJ52	[7.4.14]	FLRGRAYGL	9	HLA-B*0801
			TRBV7-8-(TRBD2)-TRBJ2-7	[5.6.11]			
1lp9	12.2	Mm	TRAV12D-2-TRAJ50	[6.6.13]	ALWGFFPVL	9	HLA-A*0201
			TRBV13-3-(TRBD2)-TRBJ2-7	[5.6.11]			
1g6r	2C	Mm	TRAV9-4-TRAJ35	[6.7.10]	SIYRYYGL	8	H2-K1*01
			TRBV13-2-(TRBD2)-TRBJ2-4	[5.6.9]			
1jtr	2C				EQYKFYSV	8	
2dkb	2C				EQYKFYSV	8	
1mwa	2C				EQYKFYSV	8	

	T cell receptor				Peptide		MHC
3D	Name	Sp.	V-DOMAIN genes	CDR-IMGT	Sequence	L	Gene and allele
1fo0	BM3.3	Mm	TRAV16-TRAJ32	[7.7.14]	INFDFNTI	8	H2-K1*01
			TRBV1-TRBD1-TRBJ1-3	[6.6.12]			
1nam	BM3.3				RGYVYQGL	8	
1kj2	KB5-C20	Mm	TRAV14-1-TRAJ15	[6.6.11]	KVITFIDL	8	H2-K1*01
			TRBV1-TRBD2-TRBJ2-3	[6.6.16]			

(B) TR/pMHC-II

	T cell receptor				Peptide		MHC
3D	Name	Sp.	V-DOMAIN genes	CDR-IMGT	Sequence	L	Gene and allele
1fyt	HA1.7	Hs	TRAV8-4-TRAJ48	[6.7.13]	PKYVKQNT LKLAT	13	HLA-DR A *0101
		Hs	TRBV28-TRBD1-TRBJ1-2	[5.6.12]			HLA-DR B1*0101
1j8h	HA1.7				PKYVKQNTL KLAT	13	HLA-DR A*0101
							HLA-DR B1*0401
1d9k	D10	Mm	TRAV14D-2-TRAJ4	[6.6.10]	GNSHRGAIE WEGIESG	16	H2-AA *02
			TRBV13-2-TRBD2-TRBJ2-1	[5.6.11]			H2-AB *02

Each complete TR chain comprises an extracellular region made up of a variable domain and a constant domain (V-ALPHA and C-ALPHA for the α chain, V-BETA and C-BETA for the β chain) (Fig. 1), a connecting region, a transmembrane region, and a very short intracytoplasmic region. The MHC-I is formed by the association of a heavy chain (I-ALPHA) and a light chain (β-2-microglobulin B2M, Fig. 1). The MHC-II is a heterodimer formed by the association of an α chain (II-ALPHA) and a β chain (II-BETA). The I-ALPHA chain of the MHC-I, and the II-ALPHA and II-BETA chains of the MHC-II comprise an extracellular region made of three domains for the MHC-I and of two domains for the MHC-II, a connecting region, a transmembrane region, and an intracytoplasmic region. The I-ALPHA chain comprises two groove domains (G-DOMAIN), G-ALPHA1 [D1] and G-ALPHA2 [D2], and a C-LIKE domain [D3]. The B2M corresponds to a single C-LIKE domain. The II-ALPHA chain and the II-BETA chain each comprise two domains, G-ALPHA [D1] and C-LIKE [D2],

and G-BETA [D1] and C-LIKE [D2]. Only the extracellular region that corresponds to these domains has been crystallized (Fig. 1). The TR V-DOMAINs and MHC G-DOMAINs that are directly involved in TR/pMHC interactions are described in the next sections.

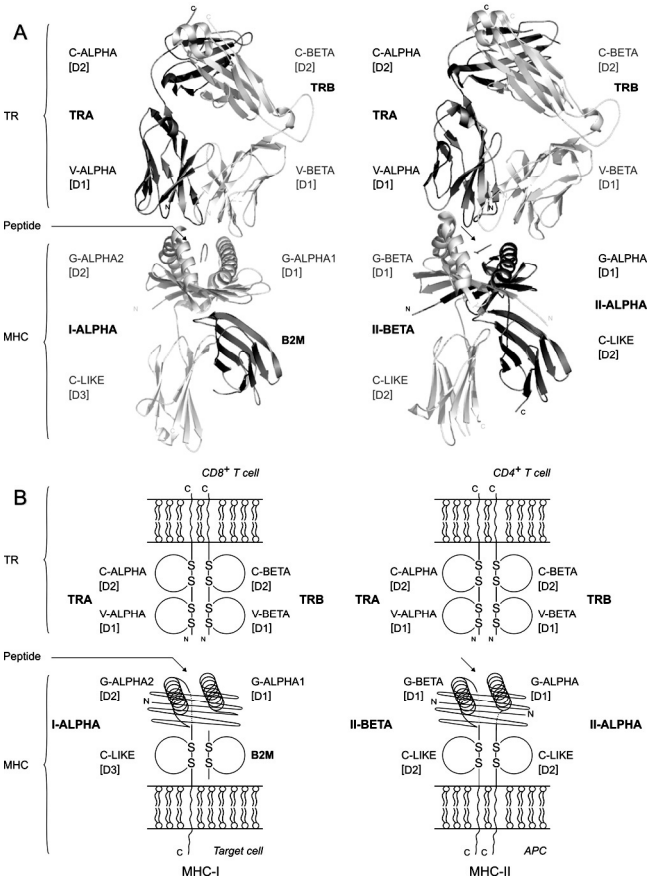


Fig. 1. T cell receptor/peptide/MHC complexes with MHC class I (TR/pMHC-I) and MHC class II (TR/pMHC-II). [D1], [D2] and [D3] indicate the domains. (A) 3D structures of TR/pMHC-I (1oga) and TR/pMHC-II (1j8h). (B) Schematic representation of TR/pMHC-I and TR/pMHC-II. The TR (TR-ALPHA and TR-BETA) chains, the MHC-I (I-ALPHA and β-2-microglobulin B2M) chains and the MHC-II (II-ALPHA and II-BETA) chains are shown with the extracellular domains (V-ALPHA and C-ALPHA for the TR-ALPHA chain; V-BETA and C-BETA for the TR-BETA chain; G-ALPHA1, G-ALPHA2 and C-LIKE for the I-ALPHA chain; C-LIKE for B2M; G-ALPHA and C-LIKE for the II-ALPHA chain; II-BETA and C-LIKE for the II-BETA chain), and the connecting, transmembrane and cytoplasmic regions. Arrows indicate the peptide localization in the G-DOMAIN groove. The MHC G-DOMAINs and TR V-DOMAINs are likely to be in a diagonal rather than in a vertical position relative to the cell surface (Wang, Meijers, Xiong, Liu, Sakihama, Zhang, Joachimiak and Reinherz 2001; Wang and Reinherz 2002).

2.2.1 TR V-DOMAINs

The V-DOMAINs have an immunoglobulin fold, that is an antiparallel β sheet sandwich structure with nine strands (Lefranc et al. 2003b; Lesk and Chothia 1982), the A, B, E, and D strands being on one sheet, and the G, F, C, C', and C" strands on the other sheet. These strands are indicated in the IMGT Colliers de Perles (Fig. 2) and in the IMGT Protein displays (Fig. 3).

IMGT Colliers de Perles are IMGT 2D graphical representations based on the IMGT unique numbering. The IMGT Colliers de Perles of TR V-DOMAINs are based on the IMGT unique numbering for V-DOMAIN and V-LIKE-DOMAIN (Lefranc et al. 2003b) and can be displayed on one layer or on two layers. IMGT Colliers de Perles of the V-ALPHA and V-BETA domains from 1ao7 (Garboczi et al. 1996) are shown as examples in Fig. 2. The IMGT Protein display (Fig. 3) shows the amino acid sequences of the different V-ALPHA and V-BETA domains found in TR/pMHC (Table 1).

The V-ALPHA and V-BETA domains share main conserved characteristics of the V-DOMAIN which are the disulfide bridge between cysteine 23 (1st-CYS) and cysteine 104 (2nd-CYS), and the other hydrophobic core residues tryptophan 41 (CONSERVED-TRP) and leucine (or hydrophobic) 89 (Lefranc et al. 2003b) (Figs. 2 and 3). The A strand comprises positions 1 to 15, B strand positions 16 to 26, C strand positions 39 to 46, C' strand positions 47 to 55, C" strand positions 66 to 74, D strand positions 75 to 84, E strand positions 85 to 96, F strand positions 97 to 104, and G strand positions 118 to 128 (Lefranc et al. 2003b). Compared to the general V-DOMAIN 3D structure, the V-ALPHA domains have shorter C" and D strands at the C" D turn.

The three hypervariable loops or complementarity determining regions (CDR) of each V-DOMAIN are involved in the pMHC recognition. The CDR1-IMGT comprises positions 27 to 38, the CDR2-IMGT positions 56 to 65, and the CDR3-IMGT positions 105 to 117 (Lefranc et al. 2003b). The CDR3-IMGT corresponds to the junction resulting from the V-J and V-D-J rearrangement, and is more variable in sequence and length than the CDR1-IMGT and CDR2-IMGT that are encoded by the V-REGION only (Lefranc and Lefranc 2001). Lengths of the CDR-IMGT are shown separated by dots between brackets (Lefranc et al. 2003b). Lengths of the CDR-IMGT from available TR/pMHC 3D structures are reported in Table 1, together with the names of the V, D, and J genes (Lefranc and Lefranc 2001).

For example, 1ao7 [6.6.11] V-ALPHA means that in the V-ALPHA domain of 1ao7, CDR1-IMGT has a length of 6 amino acids, CDR2-IMGT a length of amino acids, and CDR3-IMGT a length of 11 amino acids. The V-ALPHA CDR3-IMGT results from the TRAV12-2–TRAJ24 rearrangement (Table 1, Fig. 3). In the same way, 1ao7 [5.6.14] V-BETA means that in the V-BETA domain of 1ao7, CDR1-IMGT, CDR2-IMGT, and CDR3-IMGT have a length of 5, 6, and 14 amino acids, respectively (Lefranc et al. 2003b). The V-BETA CDR3-IMGT results from the TRBV6-5–TRBD2–TRBJ2-7 rearrangement (Table 1, Fig. 3).

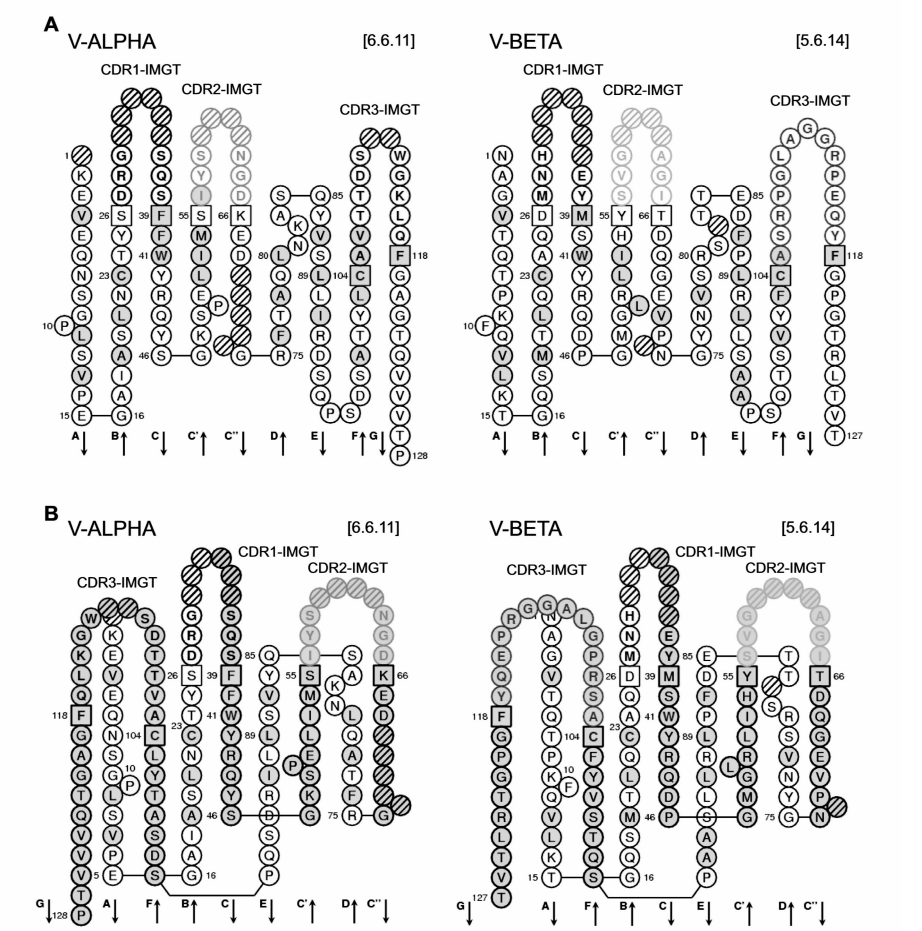
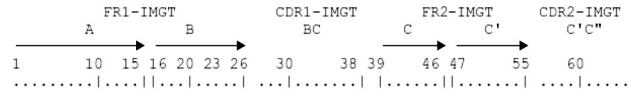


Fig. 2. IMGT Colliers de Perles of the V-ALPHA and V-BETA domains from 1ao7 (IMGT/ 3Dstructure-DB, http://imgt.cines.fr) (A) on one layer (B) on two layers. Amino acids are shown in the one-letter abbreviation. Hydrophobic amino acids (hydropathy index with positive value) and tryptophan (W) found at a given position in more than 50% of analysed IG and TR sequences are shown. The CDR-IMGTs are limited by amino acids shown in squares, which belong to the neighbouring FR-IMGT and represent anchor positions. Hatched circles correspond to missing positions according to the IMGT unique numbering (Lefranc et al. 2003b). Arrows indicate the direction of the β sheets.



V-ALPHA [D1]

Homo sapiens

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1ao7_D   .KEVEQNSGPLSVPEGAIASLNCTYS DRG......SQS FFWYRQYSGKSPELIMS IYS....NGD
1bd2_D   .QQVKQNSPSLSVQEGRISILNCDYT NSM......FDY FLWYKKYPAEGPTFLIS ISSI...KDK
1oga_D   .QLLEQSPQFLSIQEGENLTVYCNSS SVF.......SS LQWYRQEPGEGPVLLVT VVTG...GEV
1mi5_D   ..KTTQ.PNSMESNEEEPVHLPCNHS TISG.....TDY IHWYRQLPSQGPEYVIH GLT.....SN
1d9k_A   ..QVRQSPQSLTVWEGETTILNCSYE DST......FDY FPWYRQFPGKSPALLIA ISLV...SNK
1fyt_D   .QSVTQLGSHVSVSEGALVLLRCNYS SSV......PPY LFWYVQYPNQGLQLLLK YTSA..ATLV
Mus musculus
11p9_E   .DSVTQTEGLVTLTEGLPVMLNCTYQ STY......SPF LFWYVQHLNEAPKLLLK SFTD...NKR
1g6r_A   .QSVTQPDARVTVSEGASLQLRCKYS YSA......TPY LFWYVQYPRQGLQLLLK YYSG..DPVV
1fo0_A   .QKVTQTQTSISVMEKTTVTMDCVYE TQDS.....SYF LFWYKQTASGEIVFLIR QDSY..KKEN
1kj2_A   .QQVRQSPQSLTVWEGETAILNCSYE DST......FNY FPWYQQFPGEGPALLIS IRSV...SDK
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V-BETA [D1]

Homo sapiens

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1ao7_E   NAGVTQTPKFQVLKTGQSMTLQCAQD MNH.......EY MSWYRQDPGMGLRLIHY SVG....AGI
1bd2_E   NAGVTQTPKFQVLKTGQSMTLQCAQD MNH.......EY MSWYRQDPGMGLRLIHY SVG....AGI
1oga_E   DGGITQSPKYLFRKEGQNVTLSCEQN LNH.......DA MYWYRQDPGQGLRLIYY SQI....VND
1mi5_E   ..GVSQSPRYKVAKRGQDVALRCDPI SGH.......VS LFWYQQALGQGPEFLTY FQN....EAQ
1d9k_B   ..AVTQSPRNKVAVTGGKVTLSCNQT NNH.......NN MYWYRQDTGHGLRLIHY SYG....AGS
1fyt_E   ..KVTQSSRYLVKRTGEKVFLECVQD MDH.......EN MFWYRQDPGLGLRLIYF SYD....VKM
Mus musculus
11p9_F   EAAVTQSPRSKVAVTGGKVTLSCHQT NNH.......DY MYWYRQDTGHGLRLIHY SYV....ADS
1g6r_B   EAAVTQSPRNKVAVTGGKVTLSCNQT NNH.......NN MYWYRQDTGHGLRLIHY SYG....AGS
1fo0_B   VTLLEQNPRWRLVPRGQAVNLRCILK NSQ......YPW MSWYQQDLQKQLQWLFT LRS....PGD
1kj2_A   VTLLEQNPRWRLVPRGQAVNLRCILK NSQ......YPW MSWYQQDLQKQLQWLFT LRS....PGD
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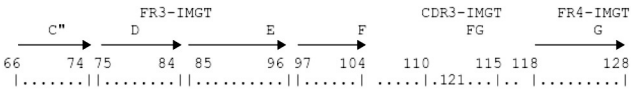

V-ALPHA [D1]

Homo sapiens

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1ao7_D   KED.....GRFTAQLNKASQYVSLLIRDSQPSDSATYLC AVTTDS.....WGKLQ FGAGTQVVVTP
1bd2_D   NAD.....GRFTVFLNKSAKHLSLHIVPSQPGDSAVYFC AAMEG......AQKLV FGQGTRLTINP
1oga_D   KKL.....KRLTFQFGDARKDSSLHITAAQPGDTGLYLC AGAGS......QGNLI FGKGTKLSVKP
1mi5_D   VNN.....RMASLAIAEDRKSSTLILHRATLRDAAVYYC ILPLAGG..TSYGKLT FGQGTILTVHP
1d9k_A   KED.....GRFTIFFNKREKKLSLHITDSQPGDSATYFC AATGS......FNKLT FGAGTRL....
1fyt_D   KGI.....NGFEAEFKKSETSFHLTKPSAHMSDAAEYFC AVSESPF...GNEKLT FGTGTRLTIIP
Mus musculus
11p9_E   PEH.....QGFHATLHKSSSSFHLQKSSAQLSDSALYYC ALFLASS...SFSKLV FGQGTSLSVVP
1g6r_A   QGV.....NGFEAEFSKSNSSFHLRKASVHWSDSAVYFC AVSGF......ASALT FGSGTKVIVLP
1fo0_A   ATV.....GHYSLNFQKPKSSIGLIITATQIEDSAVYFC AMRGDYG..GSGNKLI FGTGTLLSVKP
1kj2_A   KED.....GRFTIFFNKREKKLSLHITDSQPGDSATYFC AARYQG.....GRALI FGTGTTVSVSP
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V-BETA [D1]

Homo sapiens

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1ao7_E   TDQGEVP.NGYNVSRS.TTEDFPLRLLSAAPSQTSVYFC ASRPGLA..GGRPEQY FGPGTRLTVT.
1bd2_E   TDQGEVP.NGYNVSRS.TTEDFPLRLLSAAPSQTSVYFC ASSYPGG...GFYEQY FGPGTRLTVT.
1oga_E   FQKGDIA.EGYSVSRE.KKESFPLTVTSAQKNPTAFYLC ASSSRS.....SYEQY FGPGTRLTVT.
1mi5_E   LDKSGLPSDRFFAERP.EGSVSTLKIQRTQQEDSAVYLC ASSLGQ.....AYEQY FGPGTRLTVT.
1d9k_B   TEKGDIP.DGYKASRP.SQENFSLILELATPSQTSVYFC ASGGQG.....RAEQF FGPGTRLTVL.
1fyt_E   KEKGDIP.EGYSVSRE.KKERFSLILESASTNQTSMYLC ASSSTG....LPYGYT FGSGTRLTVV.
Mus musculus
11p9_F   TEKGDIP.DGYKASRP.SQENFSLILELASLSQTAVYFC ASSDWV.....SYEQY FGPGTRLTVL.
1g6r_B   TEKGDIP.DGYKASRP.SQENFSLILELATPSQTSVYFC ASGGG.......GTLY FGAGTRLSVL.
1fo0_B   KEVKSLPGADYLATRV.TDTELRLQVANMS..QGRTLYC TCSADR....VGNTLY FGEGSRLIV..
1kj2_A   KEVKSLPGADYLATRV.TDTELRLQVANMS..QGRTLYC TCSAAPDWGASAETLY FGSGTRLTVL.
```

Fig. 3. Protein display of the TR V-ALPHA and V-BETA domains found in the TR/pMHC complexes in IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. Amino acid sequences and gaps (shown by dots) are according to the IMGT unique numbering for V-DOMAIN (Lefranc et al. 2003b). The three additional positions in the CDR3-IMGT are 111.1, 112.2 and 112.1. Potential N-glycosylation sites are underlined. Assignments of the V, D and J genes are shown in Table 1.

2.2.2 MHC G-DOMAINs

The four G-DOMAINs, G-ALPHA1 and G-ALPHA2 of the MHC-I, and G-ALPHA and G-BETA of the MHC-II (Figs. 1, 4, and 5), have a similar groove 3D structure that consists of one sheet of four antiparallel β strands ("floor" of the groove or platform) and one long helical region ("wall" of the groove) (Lefranc et al. 2005b). For each G-DOMAIN (Figs. 4 and 5), the A strand comprises positions 1 to 14, B strand positions 18 to 28, C strand positions 31 to 38, and D strand positions 42 to 49 (Lefranc et al. 2005b). The helix (positions 50 to 92) seats on the β sheet and its axis forms an angle of about 40 degrees with the β strands. The helix is split into two parts separated by a kink, positions 58 of G-ALPHA1, 61 of G-ALPHA2, 63 of G-ALPHA, and 62 of G-BETA being the "highest" points on the floor groove. The G-ALPHA2 and G-BETA domains have a disulfide bridge between positions 11 and 74. The G-ALPHA1 and G-ALPHA domains have a conserved N-glycosylation site at position 86 (N-X-S/T, where N is asparagine, X any amino acid except proline, S is serine, and T is threonine), except for HLA-DMB and H2-DMB1. Asparagine 15 of the G-BETA domains also belongs to a conserved N-glycosylation site (Lefranc et al. 2005b).

2.3 TR/pMHC Contact Analysis

2.3.1 Peptide/MHC

The 3D structure of the MHC main chain is well conserved and the peptide binding groove specificity is due to side chain physicochemical characteristics (Reinherz et al. 1999). Both MHC-I and MHC-II grooves have pockets where side chains of bound peptides may anchor (Falk, Rotzschke, Stevanovic, Jung, and Rammensee 1991), the specificity of a peptide to a given MHC being controlled by the physicochemical properties of the pockets. Conversely, comparisons of peptide sequence alignments and pMHC 3D structures have revealed that some anchored peptide positions with conserved properties were needed to bind a peculiar MHC allele. Several databases, SYFPEITHI (Rammensee, Bachmann, Emmerich, Bachor, and Stevanovie 1999), JenPep (Blythe, Doytchinova, and Flower 2002), and MHCpep (Brusic, Rudy, and Harrison 1998), provide peptide sequences associated with MHC alleles together with anchor positions and experimental data on affinity. These observations have extensively been used in peptide/MHC binding prediction (Singh and Raghava 2003; Adams and Koziol 1995; Vasmatzis, Zhang, Cornette, and DeLisi 1996b). A list of prediction programs and servers is available at "The IMGT Immunoinformatics page" (http://imgt.cines.fr). Nevertheless, exceptions have been found (Mandelboim, Bar-Haim, Vadai, Fridkin, and Eisenbach 1997; Apostolopoulos, Yu, Corper, Teyton, Pieters, McKenzie, and Wilson 2002; Scott, Peterson, Teyton, and Wilson 1998) and it was noted that while only 30% of peptides with the expected pattern really bind, peptides without the expected pattern also bind (Gulukota, Sidney, Sette, and

```
                                    A                B           C            D
                        ------------->      ---------->   -------->   ------->
                        1        10  14    18        28  31      38   42 45  49
                  4321  | ......A..|...| ... |.........| .. |......| ... |..|...|
G-ALPHA1 [D1]
1ao7_A HLA-A*0201 (1)    (G)SHSMRY.FFTSVSR PGR GEPRFIAVGYV DD TQFVRFDS DAA SQRMEPRA
1g6r_H H2-K1*01   (2)    (G)PHSLRY.FVTAVSR PGL GEPRYMEVGYV DD TEFVRFDS DAE NPRYEPRA
1mi5_A HLA-B*0801        (G)SHSMRY.FDTAMSR PGR GEPRFISVGYV DD TQFVRFDS DAA SPREEPRA

G-ALPHA [D1]
1d9k_G H2-AA*02        IE(A)DHVGSYGITVYQSP ... .GDIGQYTFEF DG DELFYVDL D.. KKETVWML
1fyt_A HLA-DRA*0101    IK(E)EHVIIQ.AEFYLNP ... .DQSGEFMFDF DG DEIFHVDM A.. KKETVWRL
1j8h_A

G-ALPHA2 [D2]
1ao7_A HLA-A*0201 (1)    (G)SHTVQR.MYGCDVG SDW RFLRGYHQYAY DG KDYIALKE D.. LRSWTAAD
1g6r_A H2-K1*01   (2)    (G)SHTIQV.ISGCEVG SDG RLLRGYQQYAY DG CDYIALNE D.. LKTWTAAD
1mi5_A HLA-B*0801        (G)SHTLQS.MYGCDVG PDG RLLRGHNQYAY DG KDYIALNE D.. LRSWTAAD

G-BETA [D1]
1d9k_H H2-AB*02          (R)HFVHQF.QPFCYFT NGT QRIRLVIRYIY NR EEYVRFDS D.. VGEYRAVT
1fyt_B HLA-DRB1*01011    (P)RFLWQL.KFECHFF NGT ERVRLLERCIY NQ EESVRFDS D.. VGEYRAVT
1j8h_B HLA-DRB1*04011    (P)RFLEQV.KHECHFF NGT ERVRFLDRYFY HQ EEYVRFDS D.. VGEYRAVT

                                            Helix
                          ----------------------------------------------
                          50        60         70         80        90
                          |.........|.AB.......|..A.......|.........|..
G-ALPHA1 [D1]
1ao7_A HLA-A*0201 (1)     PWIEQEGPEYWD..GETRKVKAHSQ.THRVDLGTLRGYYNQSEA..
1g6r_H H2-K1*01   (2)     RWMEQEGPEYWE..RETQKAKGNEQ.SFRVDLRTLLGYYNQSKG..
1mi5_A HLA-B*0801         PWIEQEGPEYWD..RNTQIFKTNTQ.TDRESLRNLRGYYNQSEA..

G-ALPHA [D1]
1d9k_G H2-AA*02           PEFAQ....LRR..FEPQGGLQNIA.TGKHNLEILTKRSNSTPATN
1fyt_A HLA-DRA*0101       EEFGR....FAS..FEAQGALANIA.VDKANLEIMTKRSNYTPITN
1j8h_A

G-ALPHA2 [D2]
1ao7_A HLA-A*0201 (1)     MAAQTTKHKWEAA.HVAEQLRAYLEGTCVEWLRRYLENGKETLQRT
1g6r_A H2-K1*01   (2)     MAALITKHKWEQA.GEAERLRAYLEGTCVEWLRRYLKNGNATLLRT
1mi5_A HLA-B*0801         TAAQITQRKWEAA.RVAEQDRAYLEGTCVEWLRRYLENGKDTLERA

G-BETA [D1]
1d9k_H H2-AB*02           ELGRPDAEYWNK..QYLERTRAELDTVCRHNYEKTETPTSLRRLE.
1fyt_B HLA-DRB1*01011     ELGRPDAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRR...
1j8h_B HLA-DRB1*04011     ELGRPDAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRR...

(1) also in 1qrn, 1qse, 1qsf, 1bd2, 1oga, 1lp9
(2) also in 1jtr (G-ALPHA1 K89>A), 2ckb, 1mwa (G-ALPHA1 K89>A),1fo0, 1nam, 1kj2
```

Fig. 4. Protein display of the G-DOMAINs found in the TR/pMHC complexes in IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. Amino acid sequences and gaps (shown by dots) are according to the IMGT unique numbering for G-DOMAIN (Lefranc et al. 2005b). Amino acids resulting from the splicing with the preceding exon are shown within parentheses. Potential N-glycosylation sites are underlined. Positions 61A, 61B and 72A are characteristic of the G-ALPHA2 and G-BETA domains. The corresponding gaps in G-ALPHA1 and G-ALPHA shown in this IMGT Protein display are not reported in the IMGT Colliers de Perles as these gaps are shared by those two domains. H2-K1*01 encodes H2-K1b, H2-AB*02 and H2-AA*02 encode I-Abk and I-Aak, respectively.

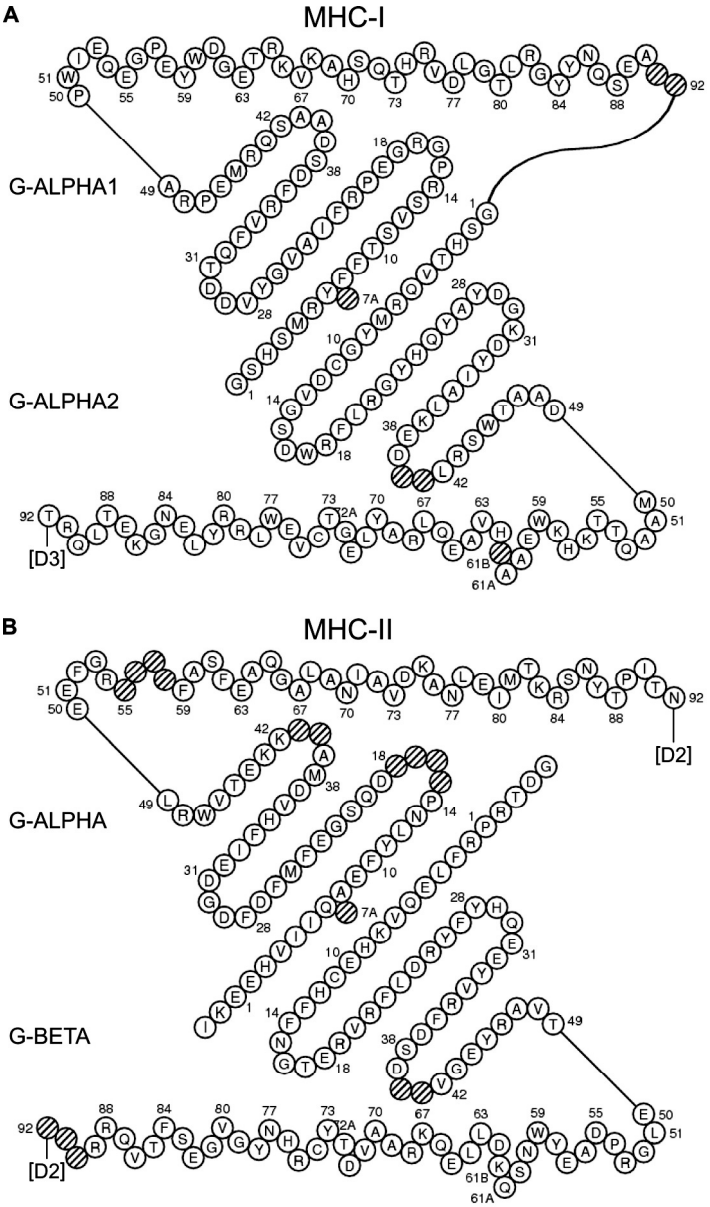

Fig. 5. IMGT Colliers de Perles of MHC G-DOMAINs. (A) MHC-I G-ALPHA1 and G-ALPHA2 domains from 1ao7 (B) MHC-II G-ALPHA and G-BETA domains from 1j8h (IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines). Amino acids positions are according to the IMGT unique numbering for G-DOMAIN (Lefranc et al. 2005b). Positions 61A, 61B and 72A are characteristic of the G-ALPHA2 and G-BETA domains (and are not reported in the G-ALPHA1 and G-ALPHA IMGT Colliers de Perles).

DeLisi 1997). Peptide/MHC binding prediction and epitope prediction remain a big challenge. In order to compare data from different MHC sequences and 3D structures, the IMGT unique numbering for G-DOMAIN has been set up (Lefranc et al. 2005b) (Figs. 4 and 5). This has allowed to graphically represent, in the IMGT Colliers de Perles for G-DOMAIN (Fig. 5), the MHC amino acid positions that have contacts with the peptide side chains. Eleven IMGT pMHC contact sites were defined (C1 to C11, in Figs. 6–8) which can be used to compare pMHC interactions (Kaas and Lefranc 2005). Examples of contact sites for an MHC-I binding an 8-mer peptide (1jtr), for an MHC-I binding a 9-mer peptide (1ao7), and for an MHC-II binding the nine amino acids of a peptide (1j8h) are shown in Figs. 6, 7, and 8, respectively.

In contrast to previous attempts to define pockets (Zhang, Anderson, and DeLisi 1998), structural data for defining the IMGT pMHC contact sites take into account the length of the peptides and are considered independently of the MHC class and sequence polymorphisms. The interactions between the peptide amino acid side chains and MHC amino acids were computed using an interaction scoring scheme based on true mean energy ratio (Kaas and Lefranc 2005). All direct contacts (defined with a cutoff equal to the sum of the atom van der Waals radii and of the diameter of a water molecule) and water-mediated hydrogen bonds were taken into account for the definition of the IMGT pMHC contact sites (Kaas and Lefranc 2005). The analysis was carried out for the pMHC available in IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. One hundred fourteen 3D structures with peptides of 8, 9, and 10 amino acids bound to MHC-I and forty-four 3D structures of pMHC-II were identified. The contact analysis was performed for the peptide amino acid side chains of the 9 amino acids located in the groove. Results for MHC-I with 8-amino acid peptides (30 pMHC-I 3D structures), MHC-I with 9-amino acid peptides (74 pMHC-I 3D structures), and MHC-II for the 9 amino acids located in the groove (44 pMHC-II 3D structures) are reported in Table 2 (the results for the 10 pMHC-I with 10-amino acid peptides are not shown). These "IMGT reference pMHC contact sites" are also available as IMGT Colliers de Perles. They will be updated as the number of 3D structures increases. IMGT Colliers de Perles for IMGT pMHC contact sites are provided for each individual pMHC and TR/pMHC entry in IMGT/3Dstructure-DB. They allow easy identification of the amino acid contacts between the MHC and the peptide amino acid side chains and comparison of them with the "IMGT reference pMHC contact sites".

C1 to C11 refer to the 11 IMGT pMHC contact sites (Kaas and Lefranc 2005). 1 to 9 refer to the numbering of the peptide amino acids in the groove. The peptide binding mode to MHC-I is characterized by the N and C peptide ends docked deeply with C1 and C11 contact sites that correspond to the two conserved pockets A and F, and by the peptide length that mechanically constrains the peptide conformation in the groove. There are no C2, C7, and C8 contact sites for MHC-I with 8-amino acid peptides and no C2 and C7 contact sites for MHC-I with 9-amino acid peptides. In contrast, for MHC-II, C2 is present but there are no C7 and C8. Whereas C1 and C11 correspond to the conserved pockets A and F, respectively, the correspondence between the other

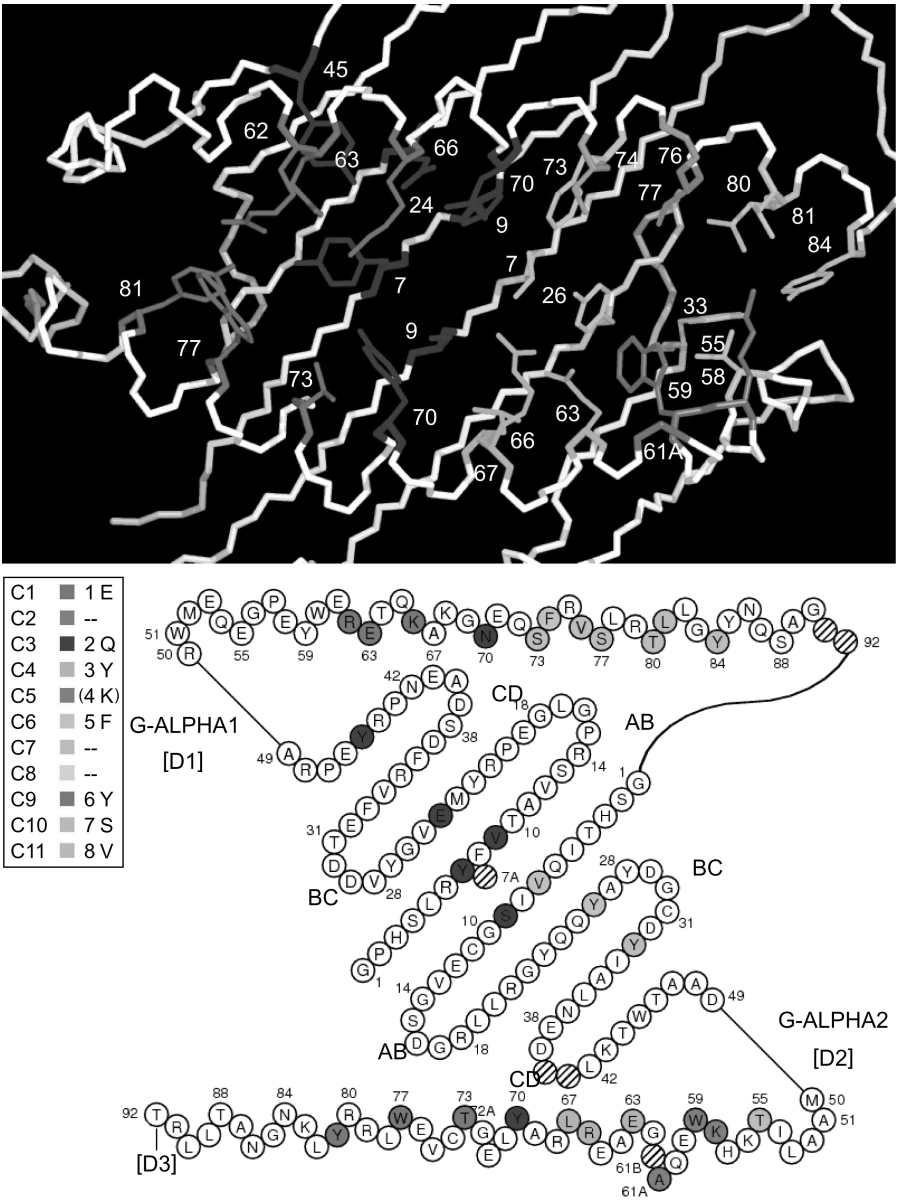

Fig. 6. IMGT pMHC contact sites of mouse H2-K1 MHC-I and a 8-amino acid peptide (1jtr). (A) 3D structure of the mouse H2-K1*01 groove. (B) IMGT pMHC contact sites IMGT Colliers de Perles. Both views are from above the cleft with G-ALPHA1 on top and G-ALPHA2 on bottom. In the box, C1 to C11 refer to contact sites (Kaas and Lefranc 2005), 1 to 8 refer to the numbering of the peptide amino acids P1 to P8. There are no C2, C7 and C8 in MHC-I 3D structures with 8-amino acid peptides. There is no C5 in this 3D structure as P4 does not contact MHC amino acids (4K is shown between parentheses in the box). (A color version of this figure appears between pages 76 and 77.)

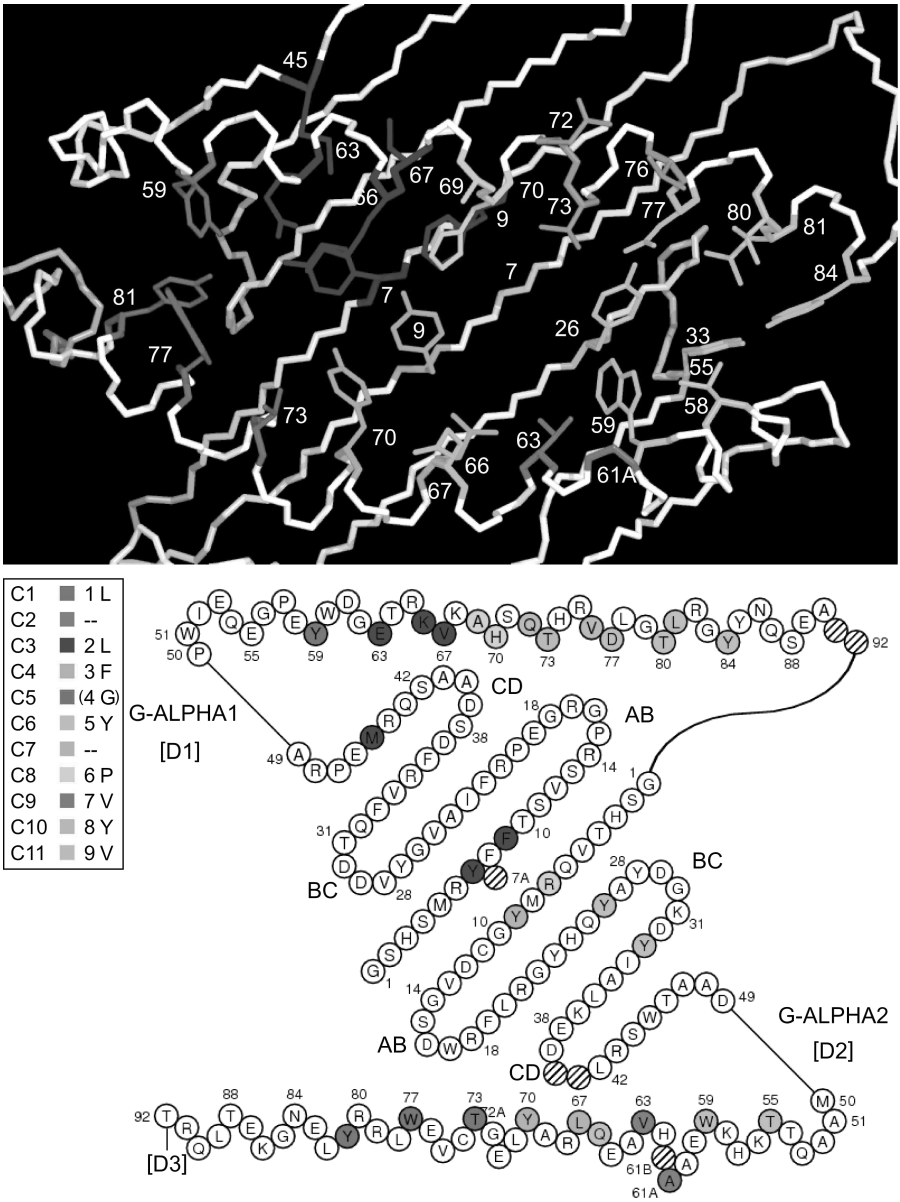

Fig. 7. IMGT pMHC contact sites of human HLA-A*0201 MHC-I and a 9-amino acid peptide (1ao7). (A) 3D structure of the human HLA-A*0201 groove. (B) IMGT pMHC contact sites IMGT Colliers de Perles. Both views are from above the cleft with G-ALPHA1 on top and G-ALPHA2 on bottom. In the box, C1 to C11 refer to contact sites (Kaas and Lefranc 2005). 1 to 9 refer to the numbering of the peptide amino acids P1 to P9. There are no C2 and C7 in MHC-I 3D structures with 9-amino acid peptides. There is no C5 in this 3D structure as P4 does not contact MHC amino acids (4G is shown between parentheses in the box). (A color version of this figure appears between pages 76 and 77.)

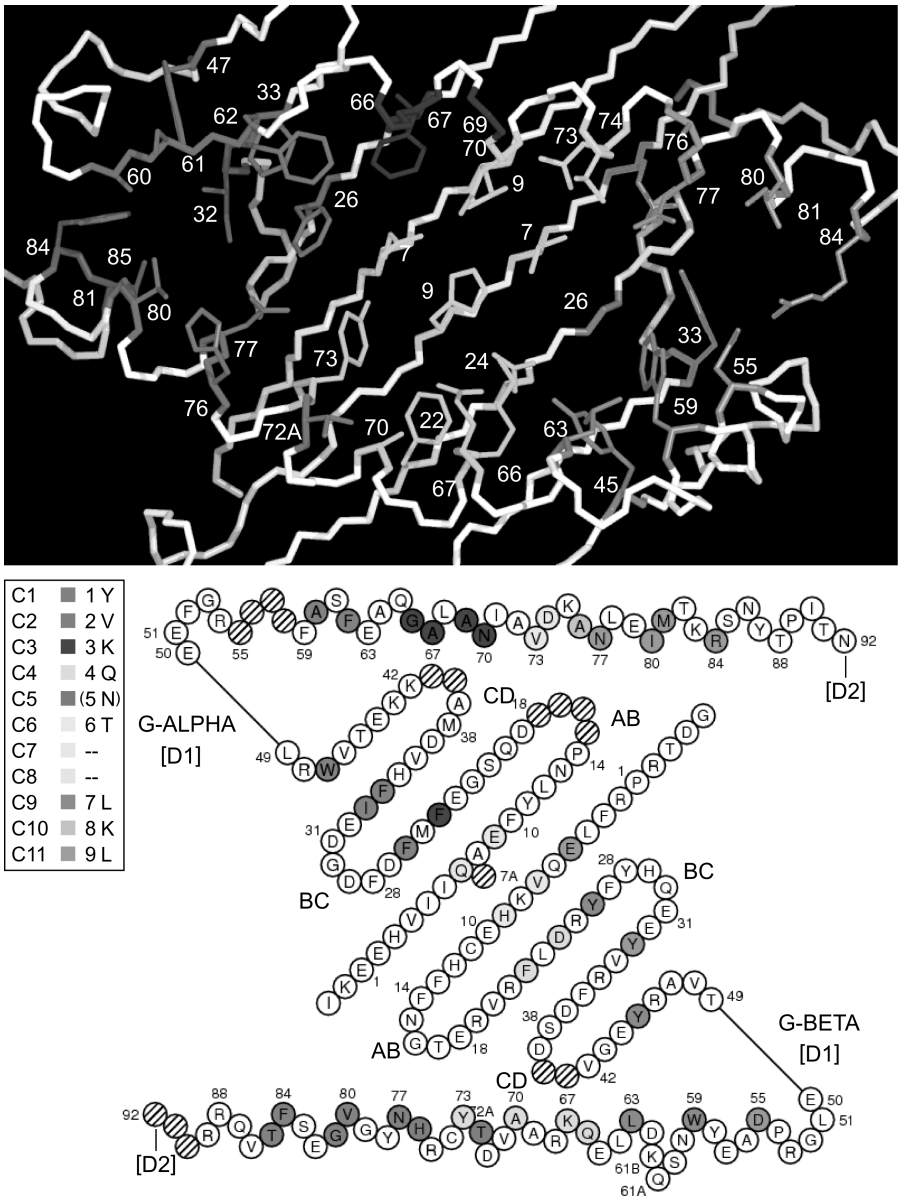

Fig. 8. IMGT pMHC contact sites of the human HLA-DRA*0101 and HLA-DRB1*0401 MHC-II and the peptide side chains (9-amino acids located in the groove). (A) 3D structure of the human HLA-DRA*0101 and HLA-DRB1*0401 groove (1j8h). (B) IMGT pMHC contact sites IMGT Colliers de Perles. Both views are from above the cleft with G-ALPHA on top and G-BETA on bottom. In the box, C1 to C11 refer to contact sites. 1 to 9 refer to the numbering of the peptide amino acids 1 to 9 located in the groove. There is no C5 and C7 in MHC-I 3D structures with 9-amino acid peptides. There is no C5 in this 3D structure as 5 does not contact MHC amino acids (5N is shown between parentheses in the box). (A color version of this figure appears between pages 76 and 77.)

contact sites and the previously defined pockets is more approximative. For MHC-I with a peptide of 8-amino acids, C3, C4, C6, and C9 correspond roughly to the B, D, C, and E pockets, and for MHC-I with a peptide of 9-amino acids C3, C4, and C9 correspond to the B, D, and E pockets.

Table 2. IMGT reference pMHC contact sites. (A) MHC-I. Results for 104 pMHC-I 3D structures (30 with 8-amino acid peptides and 74 with 9-amino acid peptides). (B) MHC-II. Results from 44 pMHC-II 3D structures with 9 amino acids in the groove.

(A) MHC-I			
8-amino acid peptides			
		G-ALPHA1	G-ALPHA2
C1	1	59 62 63 66	73 77 81
C3	2	7 24 45	9
C4	3		9 24 63 66 67 70
C5	4		
C6	5	7 9 22 70 74	7 9 24 26
C9	6		59 61A 63 66
C10	7	77 73 76	
C11	8	77 80 81 84	5 26 33 34 55 59
9-amino acid peptides			
		G-ALPHA1	G-ALPHA2
C1	1	5 59 62 63 66	73 77 81
C3	2	7 9 22 24 34 45 63 66 67 70	
C4	3		7 9 24 66 67 70
C5	4	65 66	66
C6	5	70 73 74	7 26 66 67
C8	6	66 69 70 73 74	7 24 62 66
C9	7		7 24 59 61A 63 66
C10	8	72 73 76 80	58
C11	9	77 80 81 84	5 26 33 34 55 59
(B) MHC-II			
		G-ALPHA	G-BETA
C1	1	26 33 34 47 60 61 62	77 80 81 82 84 85
C2	2		72A 73 76
C3	3	7 24 62 63 66 67 69	
C4	4	7	9 11 22 24 66 67 70 73 74
C5	5		66
C6	6	9 69 70 73 74	7 26
C9	7		24 26 45 59 63 66
C10	8	73 76	
C11	9	77 80 81 84	5 33 55

2.3.2 TR/pMHC

The analysis of the pairwise contacts that occur at the TR/MHC and TR/peptide interfaces was carried out using the IMGT unique numbering for V-DOMAINs (Lefranc et al. 2003b) for the TR, and the IMGT unique numbering for G-DOMAINs for the MHC (Lefranc et al. 2005b). Table 3 shows the interactions of the TR V-ALPHA and TR V-BETA with MHC-I and the peptide, in nine TR/pMHC-I 3D structures. Table 4 shows the interactions of the TR V-ALPHA and TR V-BETA with MHC-II and the peptide, in two TR/pMHC-II 3D structures. The results show that positions implicated in the binding are well conserved but not the pairwise interactions. The MHC contact positions belong to the G-DOMAIN helices. The TR positions that are involved in the contacts belong mostly to the CDR-IMGT and to anchor positions (shown by squares in Fig. 2). The FR-IMGT positions involved in the contacts are positions 84 and 84A that are located at the DE turn (designated as "hypervariable 4" or HV4). The contact analysis confirms that the V-ALPHA CDR2-IMGT seats on top of the G-ALPHA2 (MHC-I) or G-BETA (MHC-II) helices and that the V-BETA CDR2-IMGT seats on top of the G-ALPHA1 (MHC-I) or G-ALPHA (MHC-II) helices (Tables 3 and 4). This agrees with data (Sim et al. 1996) which showed that most of the TR/MHC specificity comes from the CDR1 and CDR2 because mutations in these CDRs are able to change specificity between MHC-I and MHC-II. V-ALPHA and V-BETA CDR3-IMGT usually follow the same G-DOMAIN contact preference as the CDR2-IMGT but they can also have contacts with the other G-DOMAINs. For example, in the 1oga 3D structure, position 66 of G-ALPHA2 is contacted by the V-ALPHA CDR3-IMGT but also by the V-BETA CDR3-IMGT.

The diagonal orientation of the TR/pMHC complex puts the TR in a globally conserved position for a peptide "read-out" (Buslepp et al. 2003). V-ALPHA is on top of the peptide N terminus while V-BETA is on top of the peptide C terminus. TR positions implicated in the peptide recognition are in CDR3-IMGT and generally to a lesser extent in V-ALPHA CDR1-IMGT (Tables 3 and 4). Nearly every 3D structure shows different CDR3 conformations and binding mode. In the JM22/peptide/HLA-A complex (1oga) (Stewart-Jones et al. 2003), the V-BETA CDR3-IMGT extensively contacts the peptide and G-ALPHA2 through hydrogen bonds (Table 3), by inserting itself between the peptide and the G-ALPHA2. In contrast, the 2C/peptide/H2-K1complex (1jtr) (Degano et al. 2000) has comparatively fewer contacts between the V-BETA CDR3-IMGT and the peptide and the MHC; however the V-BETA CDR1-IMGT has more contacts and hydrogen bonds with the peptide and G-ALPHA2.

The TR LC13 and 2C were crystallized both alone and in complex with a pMHC. The structural superimposition of both V-DOMAIN scaffold α carbons reveals large movements of the CDR3 and of the CDR1, respectively. The V-ALPHA domains of LC13, in the 1mi5 and 1kgc 3D structures, have 3.5 Å root mean square (RMS) between their CDR3. The V-ALPHA domains of 2C, in the 2ckb and 1tcr 3D structures, have 2.3 Å RMS between their CDR1. The TR A6 was crystallized in complex with the same MHC but with different peptides. In these structures, the V-BETA CDR3 adopt different conformations to adapt to the different peptides (Rudolph, Luz, and Wilson 2002). The CDR3 conformational change does not increase the binding surface but gives a better shape complementarity to the interface (Lawrence and Colman 1993).

Table 3. TR V-ALPHA and V-BETA CDR interactions with pMHC-I. TR positions in bold indicate hydrogen bonds. 3D structures are from IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. Lengths of the CDR-IMGT are shown within brackets. Amino acids are shown in the one-letter code. Sequences of the peptides are reported in Table 1, sequences of the TR V-ALPHA and V-BETA domains in Fig. 3 and sequences of the MHC-I G-ALPHA1 and G-ALPHA2 in Fig. 4. (A) V-ALPHA CDR-IMGT interactions. (B) V-BETA CDR-IMGT interactions. (C) V-ALPHA and V-BETA FR-IMGT interactions.

(A) V-ALPHA CDR-IMGT interactions

V-ALPHA CDR1-IMGT				
PDB	CDR1	G-ALPHA1	Peptide	G-ALPHA2
1ao7 [6.]	27_D	**58_E**		
	28_R	58_E		77_W 80_R
	29_G		1_L	77_W
	37_Q	66_K	1_L **2_L** 3_F 4_G 5_Y	70_Y 73_T
	38_S		5_Y	
1bd2 [6.]	28_S		1_L	76_E **77_W**
	29_M	58_E 59_Y 62_G 63_E 66_K	1_L	77_W
	37_D	66_K	4_G **5_Y**	66_Q 73_T
	38_Y		5_Y	66_Q
1oga [5.]	37_S			65_E 66_Q
1mi5 [7.]	29_S	62_R		
	30_G			69_A
	36_T		4_G	**66_Q** 70_Y 73_T
	38_Y		7_Y	$61A_A$ 62_R 63_V 64_A 65_E 66_Q
1lp9 [6.]	28_T			76_E
	29_Y			69_A $72A_G$ 73_T 76_E 77_W
	36_S			69_A
	38_F			65_E 66_Q 69_A
1g6r [6.]	27_Y	62_R		
	28_S	58_E **62_R**		
	29_A	62_R		
	36_T			76_E
	38_Y		3_Y 4_R	66_R
1jtr [6.]	27_Y	62_R		
	28_S	58_E 59_Y 62_R		
	29_A	62_R	1_E	77_W
	36_T		1_E	
	38_Y		3_Y 4_K	66_R
1fo0 [7.]	28_Q	58_E 62_R		
	29_D	62_R		
	30_S			**73_T**
	36_S			69_A
	38_F			66_R
1kj2 [6.]	27_D	58_E **62_R**		
	29_T	62_R	1_K	77_W
	37_N			73_T

(continued)

Table 3. (continued) V-ALPHA CDR2-IMGT

PDB	CDR2	G-ALPHA1	Peptide	G-ALPHA2
1ao7 [.6.]	57_Y			65_E 66_Q 69_A
	58_S			69_A
	63_N			76_E
1bd2 [.6.]	57_S			65_E 66_Q 69_A
	58_S			69_A 70_Y 73_T
	59_I			68_R 69_A 72_E $72A_G$
1oga [.6.]	57_V			62_H 65_E
1mi5 [.4.]	56_G			62_R
	57_L			65_E 66_Q 69_A
	58_T			65_E
	64_S			65_E
1lp9 [.6.]	57_F			$61A_A$ 62_H 65_E 66_Q
	58_T			62_H 65_E
	64_K			65_E
1g6r [.7.]	57_Y			66_R 69_A
	58_S			69_A $72A_G$ 73_T 76_E
1jtr [.7.]	57_Y			65_E 66_R 69_A
	58_S			69_A 76_E
1fo0 [.7.]	59_Y			62_G 65_E 66_R 69_A
	62_K			65_E
1kj2 [.6.]	57_R			69_A 72_E
	58_S			76_E
	59_V			72_E $72A_G$ 76_E

V-ALPHA CDR3-IMGT

PDB	CDR3	G-ALPHA1	Peptide	G-ALPHA2
1ao7 [.11]	108_T	$\mathbf{65}_R$ 66_K	4_G 5_Y	
	109_D	62_G $\mathbf{65}_R$ 66_K	4_G 5_Y	
	110_S		$\mathbf{4}_G$ 5_Y 6_P	
	113_W	65_R 68_K 69_A 72_Q		
	114_G	65_R		
1bd2 [.10]	107_M		5_Y	
	108_E	58_E 62_G $\mathbf{65}_R$ 66_K		
	109_G	65_R 66_K	4_G 5_Y	
	113_A		4_G 5_Y	
	114_Q	65_R 69_A		
	115_K	65_R		
1oga [.10]	107_A			66_Q
	108_G		5_F	66_Q
	109_S		4_G 5_F	66_Q
	113_Q	66_K	4_G 5_F	
	114_G		4_G 5_F	
1mi5 [.14]	108_L		6_A 7_Y	66_Q
	109_A	62_R		
	110_G	62_R 66_I		
	111_G	65_Q 66_I $\mathbf{69}_T$	4_G	

PDB	CDR3	G-ALPHA1	Peptide	G-ALPHA2
	112.1_T	62_R 65_Q 66_I 69_T		
	112_S	69_T	6_A	
	113_Y	69_T 72_Q	6_A	
1lp9 [.13]	107_F		5_F	66_Q
	109_A		3_W 4_G 5_F	66_Q
	110_S		2_L 3_W 4_G	66_Q 69_A 70_Y 73_T
	111_S	63_E $\mathbf{66}_K$	2_L 4_G	73_T 77_W
	112_S	66_K	4_G 5_F	
	113_F	65_R 66_K 69_A	4_G 6_F	
	114_S		$\mathbf{4}_G$ 5_F 6_F	
1g6r [.10]	107_S		$\mathbf{4}_R$	
	108_G		$\mathbf{4}_R$	
	109_F	62_R 65_Q 66_K	4_R	
	113_A		4_R	
	114_S		4_R	
1jtr [.10]	107_S		4_K	
	108_G		4_K	
	109_F	62_R 65_Q 66_K 69_G	4_K	
	113_A		$\mathbf{4}_K$	
	114_S		4_K	
1fo0 [.14]	110_Y	65_Q		
	111_G	65_Q		
	112.1_G	65_Q		
1kj2 [.11]	108_Y	62_R		
	109_Q	63_E $\mathbf{66}_K$	1_K $\mathbf{2}_V$ 3_I 4_T	70_Y 73_T
	110_G	66_K	4_T	
	114_R	$\mathbf{65}_Q$ 68_K 69_G 72_Q		

(B) V-BETA CDR-IMGT interactions

V-BETA CDR1-IMGT				
PDB	CDR1	G-ALPHA1	Peptide	G-ALPHA2
1ao7 [5.]	37_E		$\mathbf{8}_Y$	
1oga [5.]	37_D		$\mathbf{8}_T$	58_K
1mi5 [5.]	37_V	76_E 80_N		
	38_S	76_E		
1lp9 [5.]	37_D	$\mathbf{72}_Q$ 76_V		
	38_Y	69_A 73_T	6_F	
1g6r [5.]	28_N		6_Y	58_K
	29_H		6_Y	61_Q $61A_A$
	37_N		$\mathbf{6}_Y$ 7_G 8_L	58_K
	38_N		6_Y	
1jtr [5.]	27_N			61_Q
	28_N		6_Y	$\mathbf{58}_K$ 61_Q
	29_H		6_Y	58_K $61A_A$
	37_N		$\mathbf{6}_Y$ $\mathbf{7}_S$ 8_V	58_K
	38_N		6_Y	

(continued)

Table 3. (continued) V-BETA CDR1-IMGT

PDB	CDR1	G-ALPHA1	Peptide	G-ALPHA2
1fo0 [6.]	29_{2}	61_{2}		
	38_{W}	76_{V}	7_{T}	
1kj2 [6.]	29_{Q}			58_{K} 59_{W} 61_{Q} $61A_{A}$
	36_{Y}			$61A_{A}$
	37_{P}		7_{D}	
	38_{W}	69_{G} 72_{Q}		

V-BETA CDR2-IMGT

PDB	CDR2	G-ALPHA1	Peptide	G-ALPHA2
1bd2 [.6.]	65_{I}	72_{Q}		
1oga [.6.]	57_{Q}	69_{A}	$\mathbf{4}_{G}$ 5_{F} $\mathbf{6}_{V}$	
	58_{I}	69_{A} 72_{Q} 73_{T} 76_{V}	6_{V} 8_{T}	
	63_{V}	72_{Q} 76_{V}		
	64_{N}	72_{Q} 75_{R}		
	65_{D}	65_{R} 68_{K} 69_{A} 72_{Q}		
1mi5 [.6.]	57_{Q}	72_{Q} 75_{R} 76_{E}		
	58_{N}	$\mathbf{79}_{R}$		
	63_{E}	$\mathbf{79}_{R}$		
1lp9 [.6.]	57_{Y}	65_{R} 68_{K} 69_{A} 72_{Q}		
	58_{V}	72_{Q}		
	65_{S}	68_{K}		
1g6r [.6.]	57_{Y}	69_{G} 70_{N} 72_{Q} 73_{S} 76_{V}		
	58_{G}	76_{V}		
	63_{A}	76_{V} 79_{R}		
	64_{G}	79_{R}		
	65_{S}	76_{V}		
1jtr [.6.]	57_{Y}	69_{G} 72_{Q} 73_{S} 76_{V}	$\mathbf{7}_{S}$	
	58_{G}	76_{V}		
	63_{A}	76_{V} $\mathbf{79}_{R}$ 80_{T}		
	64_{G}	79_{R}		
	65_{S}	72_{Q} 76_{V} 79_{R}		
1fo0 [.6.]	57_{R}	76_{V} 79_{R} 80_{T}		
	58_{S}	76_{V} $\mathbf{79}_{R}$		
	63_{P}	79_{R}		
1kj2 [.6.]	57_{R}	72_{Q} 73_{S} 76_{V}	$\mathbf{7}_{\mathbf{D}}$	
	58_{S}	72_{Q}		
	65_{D}	72_{Q}		

PDB	CDR3	G-ALPHA1	Peptide	G-ALPHA2
1ao7 [.14]	107_R		5_Y	
	109_G		6_P	
	110_L	69_A 72_Q 73_T	6_P 7_V **8_Y**	
	111_A		7_V 8_Y	$61A_A$
	112_G		5_Y 7_V	**$61A_A$** 62_H 63_V **66_Q**
	112.1_G		5_Y 7_V	$61A_A$
	113_R		5_Y	**61_A** $61A_A$ 62_H 66_Q
	114_P		5_Y	66_Q
1bd2 [.13]	108_Y		8_Y	
	109_P		6_P 7_V	
	110_G		6_P 7_V **8_Y**	
	111_G		7_V 8_Y	$61A_A$
	112_G		7_V	$61A_A$
	114_Y		5_Y 7_V	$61A_A$ 63_V 66_Q
1oga [.11]	108_S			$61A_A$
	109_R		5_F 6_V 7_F	**$61A_A$** **62_H** 63_V **66_Q**
	110_S		5_F 6_V	66_Q
	113_S		5_F	66_Q
	114_Y			**61_A** $61A_A$ 62_H
1mi5 [.11]	108_L	76_E		58_K
	109_G	76_E		
	110_Q	69_T **72_Q** **73_T** **76_E**	5_R **6_A**	
	113_A		6_A 7_Y	
	114_Y	76_E	7_Y **8_G**	58_K 59_W $61A_A$
1lp9 [.11]	109_W		5_F 6_F 7_P 8_V	58_K 59_W $61A_A$ 63_V
	110_V		5_F	$61A_A$
	113_S		5_F	
	114_Y		5_F	61_A $61A_A$ 62_H 66_Q
1g6r [.9]	107_G		6_Y	
	108_G		6_Y	$61A_A$ 63_E
	109_G		4_R 6_Y	$61A_A$ 66_R
	114_G		4_R	66_R
	115_T			$61A_A$
1jtr [.9]	107_G		6_Y	
	108_G		6_Y	**63_E** 66_R
	109_G		4_K 6_Y	66_R
	115_T			61_A
1fo0 [.12]	108_A			58_K
	109_D		6_N **7_T**	58_K 59_W
	110_R	**69_G** 70_N 72_Q **73_S**	4_D **5_F** 6_N	
	112_V		4_D 5_F **6_N**	66_R
	113_G		6_N	
	114_N		6_N	$61A_A$
1kj2 [.16]	108_A		6_I	66_R
	109_A		4_T 6_I	66_R
	110_P		4_T	

(continued)

Table 3. (continued) V-BETA CDR3-IMGT

PDB	CDR3	G-ALPHA1	Peptide	G-ALPHA2
	111_{D}		4_{T}	66_{R}
	111.1_{W}			62_{G} 65_{E} 66_{R} 69_{A}
	112.1_{A}			$61A_{A}$
	112_{S}			61_{Q} $61A_{A}$
	114_{E}			69_{A}

(C) V-ALPHA and V-BETA FR-IMGT interactions

V-ALPHA FR-IMGT

PDB	Position	G-ALPHA1	Peptide	G-ALPHA2
1ao7	2_{K}	58_{E}		
	26_{S}	58_{E}		
	82_{K}			**73_{T}** **76_{E}**
1bd2	2_{Q}	58_{E} 65_{R}		
	82_{K}			$72A_{G}$ 73_{T}
1oga	84_{R}			65_{E}
1mi5	40_{H}		7_{Y}	
	52_{Y}			62_{R}
	55_{H}		7_{Y}	**$61A_{A}$** **62_{R}**
	66_{V}			62_{R}
1lp9	82_{K}			65_{E}
1g6r	2_{Q}		4_{R}	
	55_{K}			65_{E}
1kj2	82_{K}			76_{E}

V-BETA FR-IMGT

PDB	Position	G-ALPHA1	Peptide	G-ALPHA2
1bd2	55_{Y}	65_{R}		
	67_{D}	68_{K}		
1oga	67_{Q}	65_{R}		
1mi5	55_{Y}	72_{Q} 76_{E}		
	66_{L}	72_{Q} 75_{R}		
1lp9	55_{Y}	65_{R}		
	67_{E}	**65_{R}** 68_{K}		
1g6r	67_{E}	72_{Q}		
	84_{Q}			58_{K}
1jtr	67_{E}	72_{Q}		
	84_{Q}			**58_{K}**

Table 4. V-ALPHA and V-BETA CDR interactions with MHC-II. TR positions in bold indicate hydrogen bonds. Three dimensional (3D) structures are from IMGT/3Dstructure-DB (Kaas et al. 2004), http://imgt.cines.fr. Lengths of the CDR-IMGT are shown within brackets. Amino acids are shown in the one-letter code. Sequences of the peptides are reported in Table 1, sequences of the TR V-ALPHA and V-BETA domains in Fig. 3, and sequences of the MHC-II G-ALPHA and G-BETA in Fig. 4. (A) V-ALPHA CDR-IMGT interactions. (B) V-BETA CDR-IMGT interactions. (C) V-ALPHA and V-BETA FR-IMGT interactions.

(A) V-ALPHA CDR-IMGT interactions

V-ALPHA CDR1-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [6.]	28_S		2_K	76_H
	29_V		2_K 4_V	76_H
	36_P		4_V	$72A_T$ 76_H
	38_Y			$72A_T$
1d9k [6.]	27_D		3_S	
	28_S			$72A_T$ 76_H
	29_T		3_S 4_H $\mathbf{5}_R$	$72A_T$ 76_H
	36_F		5_R	$72A_T$
	37_D		$\mathbf{5}_R$ 8_I	$\mathbf{66}_R$ 69_A $72A_T$
	38_Y			66_R

V-ALPHA CDR2-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [.7.]	57_T			$\mathbf{65}_E$
	58_S			69_A $72A_T$
	59_A			65_E
1d9k [.6.]	57_S			65_E 66_R 69_A
	58_L			69_A 72_D $72A_T$
	59_V			65_E 66_R 68_R 69_A
	63_S			65_E

V-ALPHA CDR3-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [.13]	108_E	63_E	$\mathbf{2}_K$ 4_V	
	110_P		7_N	66_Q
	111_F		7_N 9_L	62_D 63_L 66_Q
	114_E	66_G 69_A 70_N	5_K	
1d9k [.10]	107_T			66_R
	108_G		5_R 8_I	66_R
	109_S	69_Q	8_I	66_R
	113_F	$\mathbf{69}_Q$ 73_T	8_I 9_E 10_W 11_E	63_Y 66_R
	114_N	69_Q		66_R
	115_K	65_Q		

(continued)

Table 4. (continued)

(B) V-BETA CDR-IMGT interactions

V-BETA CDR1-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [5.]	27_M		10_K	
	28_D	76_A	**10_K**	
	29_H		10_K	
	37_E	72_A 73_V 76_A	**10_K**	
	38_N	69_A		
1d9k [5.]	37_N	76_H		
	38_N	**69_Q**		

V-BETA CDR2-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [.6.]	57_Y	65_Q 66_G 68_L 69_A 72_A		
	58_D	68_L 72_A **75_K**		
	65_M	43_K 68_L		
1d9k [.6.]	57_Y	**65_Q** 66_G 68_L 69_Q 72_A		

V-BETA CDR3-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h [.12]	108_S	73_V	10_K	
	109_T	69_A 70_N 73_V	5_K 7_N 8_T	
	110_G	73_V	8_T 9_L **10_K**	
	112_L		10_K	58_Y
	113_P			$61A_Q$ 62_D 63_L
1d9k [.11]	108_G		11_E	
	109_Q		11_E	58_Y 63_Y
	110_G		10_W 11_E	**63_Y** 66_R
	113_R			61_K **62_Q** 63_Y 65_E 66_R
	114_A			66_R

(C) V-ALPHA and V-BETA FR-IMGT interactions

V-ALPHA FR-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h	55_K			62_D
1d9k	82_K			**72_D**

V-BETA FR-IMGT

PDB	Position	G-ALPHA	Peptide	G-BETA
1j8h	55_F	65_Q		
	66_K	43_K		
	67_E	**43_K** **65_Q**		
	84_K	72_A 76_A	10_K	
1d9k	55_Y	**65_Q**		
	66_T	**43_K**		
	67_E	**43_K** 65_Q 68_L		
	68_K	65_Q		

2.4 Conclusions

With only 18 TR/pMHC 3D structures, the atomic details of TR/pMHC interactions already show a great deal of variability. IMGT standardization is a step toward a better understanding of the mechanisms ruling TR/pMHC recognition. It will help comparing new experimentally resolved 3D structures with published data. However, the TR/pMHC interactions are far from being unravelled and the study of the TR/pMHC interactions with the other proteins of the immunological synapse will be crucial. For example, the interaction between an MHC and the CD4 considerably enhances the pMHC/TR sensibility (Irvine, Purbhoo, Krosgaard, and Davis 2002; Davis 2002). The understanding of the T cell triggering early events is subject to active studies.

Although the TR/pMHC binding represents a necessary step for the TR recognition, many factors, the TR affinity for the pMHC, the relocation of surface proteins such as CD4 or CD8 in the immunological synapse are necessary for generating the T cell activation signal. Each of these steps needs to be described and characterized so that data from different experiments can be integrated. IMGT standardization will be further extended on the IMGT Web site at http://imgt.cines.fr as new parameters become available.

2.5 Citing IMGT/3Dstructure-DB

Users are requested to cite IMGT/3Dstructure-DB (Kaas et al. 2004) and this article, and to quote the IMGT home page URL, http://imgt.cines.fr.

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