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Structural Alterations in peptide–MHC Recognition by Self-reactive T cell Receptors

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summary

The crystal structures of five autoimmune T cell receptor (TCR)–peptide–MHC complexes reveal substantial structural alterations compared to anti-microbial TCRs. The two human TCRs bind their self-peptide–MHC ligands with an altered topology, while the three mouse receptors recognize a self-peptide that only partially fills the MHC binding groove. In most cases the peptide is contacted only by a subset of available TCR complementarity-determining loops and there is a paucity of hydrogen bonds from TCR to peptide. These suboptimal binding properties may have enabled escape from negative thymic selection. While only minute amounts of antigen are typically available for negative selection, the antigens recognized by many autoimmune TCRs are abundant in the target organ. Such compensatory mechanisms can allow self-reactive T cells with altered TCR binding properties to be pathogenic.

Introduction

Five structures of autoimmune TCRs bound to self-peptide–MHC class II ligands have now been determined. These are: 1) the complex between human TCR Ob.1A12 and myelin basic protein (MBP) 85–99 presented by HLA-DR2b (DRA*0101, DRB1*1501) [1]; 2) the complex between human TCR 3A6 and MBP 89–101 presented by HLA-DR2a (DRA*0101, DRB5*0101) [2]; and 3) the complexes between three mouse TCRs (172.10, 1934.4 and c119) and acetylated MBP 1–11 (MBP Ac1–11) presented by I-A^u [3,4]. TCRs Ob.1A12 and 3A6 were derived from multiple sclerosis (MS) patients, and humanized mice transgenic for the Ob.1A12 TCR and DR2b develop symptoms characteristic of experimental autoimmune encephalomyelitis (EAE) [5]. TCRs 172.10, 1934.4 and c119 were isolated from H-2^u mice with EAE; transfer of the corresponding T cell clones into mice induces EAE [6]. Importantly, all these autoimmune TCRs display striking alterations in the structure and/or stability of the TCR–peptide–MHC recognition unit compared to TCRs specific for foreign antigens. Some of these features have also been observed in the structure of a tumor-specific TCR (E8) bound to a mutant self-peptide presented by HLA-DR1 (altered self recognition) [7].

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In the following sections, we first discuss cases in which the autoreactive TCR engages peptide–MHC via altered docking modes (Ob.1A12, 3A6 and E8). We then discuss situations where the TCR binds self-peptide–MHC with conventional topology, but where the peptide–MHC ligand displays structural alterations (172.10, 1934.4 and cl19). In all these examples, the overall stability of the TCR–peptide–MHC recognition unit is markedly reduced (Table 1a), presumably allowing the autoreactive T cells to escape negative selection.

Altered topology of TCR binding to self-peptide–MHC ligands

Ob.1A12–MBP–DR2b complex

The structure of human autoimmune TCR Ob.1A12 bound to MBP–HLA-DR2b revealed a markedly different docking mode from those of all reported TCR–peptide–MHC complexes involving non-self ligands [1]. TCR Ob.1A12 exhibits a counterclockwise rotation relative to peptide–MHC compared to anti-foreign TCRs such as HA1.7, which recognizes an influenza hemagglutinin peptide presented by HLA-DR1 [8] (Figure 1a,b), resulting in a highly asymmetrical interaction with HLA-DR2b. As a consequence, the orientation angle of Ob.1A12 to peptide–MHC is 110° compared to 70° for HA1.7. This orientation angle is well outside the range for all known MHC class I- or class II-restricted TCRs (45–80°) [9], including autoimmune TCRs 3A6, 172.10, 1934.4 and cl19 [2–4]. In addition, the TCR is not centered over peptide–MHC and only contacts the N-terminal portion of the MBP self-peptide (Figure 1b). As expected for a TCR that has escaped thymic deletion, Ob.1A12 binds MBP–DR2b with low affinity [10].

Unlike other TCRs, which contact the MHC α -helices mainly through the germline-encoded CDR1 and CDR2 loops of $V\alpha$ and $V\beta$, most contacts to MHC made by Ob.1A12 are mediated by the more structurally variable CDR3 loops. Thus, CDR3 β straddles the peptide-binding groove and contacts both α -helices of HLA-DR2b (Figure 1b). Another feature that distinguishes the Ob.1A12–MBP–DR2b complex from complexes involving anti-foreign TCRs is a large, dome-shaped pocket, composed of the two CDR3 loops, that accommodates the P2 side chain of MBP, in addition to a side chain from HLA-DR2b (His81 β) (Figure 2b). By contrast, this pocket accommodates only a single peptide residue (P5) in MHC class II-restricted anti-foreign TCRs (Figure 2a) [8,11,12].

The distinctive offset position of the Ob.1A12 footprint on the MBP–DR2b self-ligand (Figure 1b) is maintained in a complex between Ob.1A12 and a cross-reactive peptide from *Escherichia coli* bound to HLA-DR2b [13]. This naturally processed microbial peptide, which is derived from the guanosine triphosphate-binding protein engA, shares limited sequence identity with MBP 85–99 [14]. Nevertheless, the engA peptide induced MS-like disease in humanized Ob.1A12–DR2b transgenic mice by cross-reacting with the TCR [13]. Comparison of the Ob.1A12–engA–DR2b and Ob.1A12–MBP–DR2b complexes showed that cross-reactivity is likely attributable to structural mimicry of a binding hotspot shared by the microbial and self-peptides. This hotspot comprises residues P2 His and P3 Phe, common to both peptides, which are key TCR–contacting residues in the two complexes [15].

The atypical docking mode of Ob.1A12 may not be restricted to this TCR, but could imply a wider range of possible TCR orientations on peptide–MHC than generally appreciated [9,16]. In support of this notion, another T cell clone derived from the same MS patient (Ob.2F3) that represented an *in vivo* expanded population exhibited a fine specificity very similar to Ob.1A12 with MBP residues P2 and P3 representing critical TCR contacts [14]. Moreover, computational docking of Ob.2F3 TCR onto MBP–DR2b suggested a similar binding topology as defined for Ob.1A12 TCR [17].

3A6–MBP–DR2a complex

The structure of autoimmune TCR 3A6 in complex with MBP–HLA–DR2a provides further evidence for altered TCR binding to self-peptide–MHC ligands. Similar to Ob.1A12 (Figure 1b), the CDR footprint of 3A6 on MBP–DR2a is displaced towards the N-terminus of the bound peptide, and towards the MHC β 1 α -helix, compared to the CDR footprint of HA1.7 on HA–DR1 (Figure 1c). In addition, 3A6 binds its self-ligand with very low affinity ($K_D > 200 \mu\text{M}$), like Ob.1A12 TCR [2]. Unlike Ob.1A12, however, 3A6 is positioned in a typical diagonal orientation over peptide–MHC, with an orientation angle of 65° relative to 110° for Ob.1A12.

Compared to HA1.7, substantial differences are observed in the placement of both CDR3 loops along the MBP peptide, such that the loops are centered over residue P2 rather than P5 (Figure 2a,c). Indeed, the broad pocket formed by CDR3 α and CDR3 β , which accommodates a single peptide side chain in other TCRs, envelopes residues P2 and P3 in 3A6. As noted above, a similar pocket in Ob.1A12 also accommodates two residues, P2 of MBP and His81 β of HLA–DR2b (Figure 2b). Remarkably, no hydrogen bonds or salt bridges are observed between the CDR loops of 3A6 and MBP, involving either main-chain or side-chain atoms of the TCR or peptide, in contrast to other TCR–peptide–MHC complexes [9]. Interactions between TCR and peptide are mainly restricted to van der Waals contacts, with poor fit. These factors likely contribute to the low affinity of 3A6 for MBP–DR2a, as well as to highly degenerate peptide recognition by this TCR [2].

It is striking that both 3A6 and Ob.1A12 primarily recognize the N-terminal, rather than central, portion of MBP, even though these TCRs bind peptide–MHC at very different orientation angles (Figure 1b,c). The N-terminal site may be intrinsically suboptimal for TCR binding, resulting in low affinities and favoring escape from negative selection. By contrast, anti-microbial TCRs attain higher affinities by focusing on the central, or occasionally C-terminal, portion of peptides [9,18], which are presumably more favorable sites for TCR binding. However, an interesting case of an MHC class I-restricted TCR (CF34) specific for an Epstein-Barr virus peptide presented by HLA-B8 was recently reported in which the TCR is shifted towards the N-terminus of the bound peptide in a manner reminiscent of 3A6 [19]. This TCR originated from a subject who expressed both HLA-B8 and HLA-B44 and was therefore self-tolerant toward HLA-B44. In contrast, a TCR from a subject who did not express HLA-B44 bound over the center/C-terminal part of the HLA-B8 bound EBV peptide and was alloreactive to HLA-B44. Hence, N-terminal docking footprints are not entirely restricted to autoimmune TCRs, but in the case of this anti-viral TCR this binding topology may also have emerged as a consequence of thymic selection.

E8–mutTPI–DR1 complex

Tumor-specific antigens arising from mutations in self-proteins are situated at the interface between truly self and foreign antigens. One such example is a unique HLA-DR1-restricted human melanoma antigen derived from the glycolytic enzyme triose phosphate isomerase (TPI), in which a naturally occurring point mutation resulted in the substitution of an isoleucine residue for threonine at position P3 of the epitope [7]. T cell recognition of the mutant TPI peptide (mutTPI) is enhanced 100,000-fold over the wild-type peptide, rendering the altered self-antigen visible to the immune system.

The structure of melanoma-specific TCR E8 in complex with mutTPI–HLA–DR1 has revealed a number of features intermediate between those of anti-foreign and autoimmune TCR–peptide–MHC class II complexes that may reflect the hybrid nature of altered self [7]. These include a displacement of E8 toward the N-terminus of the peptide compared to anti-foreign TCRs (Figure 2d), though not as far as for autoimmune TCRs Ob.1A12 and 3A6, while maintaining the diagonal docking orientation of anti-foreign TCRs (Figure 1d). Due to this

shift, the CDR3 loops of E8 are located directly over residue P3 of mutTPI (Figure 2d). This position is intermediate between those of the CDR3 loops of 3A6 (or Ob.1A12) and HA1.7, which converge on peptide residues P2 and P5, respectively (Figure 2a,c). In agreement with the hypothesis that the N-terminal portion of peptides is relatively unfavorable for TCR binding, E8 resembles autoimmune TCRs 3A6 and Ob.1A12 in engaging mutTPI–DR1 very weakly, although the affinity is increased by the mutation at TCR–contacting position P3 of TPI [7]. Also in common with 3A6 and Ob.1A12, the CDR3 loops of E8 form a dome-shaped pocket that accommodates two ligand residues (P3 and P5) (Figure 2d), whereas the corresponding, but narrower, pocket of anti-foreign TCRs generally contains only a single residue (P5). Significantly, the structure of a second melanoma-specific TCR (G4) bound to mutTPI–DR1 revealed a docking mode closely resembling that of E8, even though the two TCRs utilize different $V\alpha$ – $V\beta$ combinations (L Deng, SL Topalian and RA Mariuzza, unpublished results).

Defects in the peptide–MHC component of the recognition unit

TCR–MBP–I-A^u complexes

In the above examples, failure of negative selection may be attributed to reduced TCR affinity for self-peptide–MHC due to suboptimal docking topologies. However, escape from thymic deletion could also result from unusually weak binding of the self-peptide to MHC, which would effectively destabilize the complex with TCR. The structures of three autoimmune mouse TCRs (172.10, 1934.4 and cl19) bound to MBP Ac1–11 and I-A^u showed that they engage peptide–MHC in the canonical diagonal orientation, and that their CDR3 loops overlay the central region of the peptide-binding groove in the usual manner [3,4] (Figure 1e). Furthermore, TCRs 172.10, 1934.4 and cl19 bind MBP–I-A^u relatively tightly ($K_{DS} \sim 5 \mu\text{M}$) [20]. However, it is important to note that MBP Ac1–11 binds very weakly to I-A^u, and that TCR affinity measurements were conducted using an engineered version of MBP–I-A^u designed to stabilize this naturally short-lived ligand, and hence its interaction with TCR.

The MBP–I-A^u ligand is unusual in that the N-terminal one-third of the binding groove is empty (Figure 1e) [21]. The groove contains only the first seven residues of the MBP Ac1–11 peptide, leaving the P1 and P2 pockets of I-A^u unoccupied. In effect, the register of the MBP peptide is shifted by two residues, such that residue P1 resides where residue P3 is normally located in canonically registered peptide–MHC class II complexes [21]. The C-terminal portion of the MBP peptide (residues 8–11) lies outside the binding groove. Residue P4 is situated in an incompatible p6 pocket of I-A^u, which explains the short half-life of the MBP–I-A^u complex ($t_{1/2} < 15 \text{ min}$) [22].

Due to these structural defects in the self-ligand, TCRs 172.10, 1934.4 and cl19 recognize only six peptide residues of MBP (P3 to P8), compared to nine (P–1 to P8) in the case of HA1.7 [3,4]. Furthermore, interactions to peptide side chains are mediated by the CDR3 loops (Figure 2e), with no participation by germline-encoded $V\alpha$ or $V\beta$ residues, a feature shared with autoimmune TCR Ob.1A12. In other TCR–peptide–MHC complexes, by contrast, CDR1 α and/or CDR1 β also generally contact the peptide [9]. The insulin B chain 9–23 peptide that is important in the pathogenesis of type 1 diabetes in NOD mice is also a very low affinity binder for I-A^{g7} [23–25], suggesting that structural defects to the peptide–MHC component of the recognition unit are not restricted to the MBP Ac1–11 example.

Common features of autoimmune TCRs

The structural alterations observed in all five examined autoimmune TCRs (Table 1a) suggest that negative selection is quite efficient in eliminating those self-reactive CD4 T cells with optimal binding properties for self-peptide–MHC complexes. The I-A^u presented MBP Ac1–

11 peptide is the dominant MBP epitope in wild-type H-2^u mice, but in MBP-deficient mice immunized with MBP it represents a minor epitope, and the response is instead directed against the 121–150 region of the antigen. Peptides from the MBP 121–150 region form stable complexes with I-A^u, while the Ac1–11 peptide binds with very low affinity [22]. Negative selection thus eliminates most of these T cells, leaving T cells with a structurally altered recognition unit behind.

Four of the six CDR loops of the TCR are typically available for peptide recognition, the CDR3 and CDR1 loops [9,26]. A large number of TCRs specific for foreign peptides have been crystallized with their MHC class I or class II ligands and in most cases all four of these loops contribute to peptide recognition [9]. For the majority of studied autoimmune TCRs, peptide side chains are only contacted by the two CDR3 loops (Table 1b). This is caused by the altered binding topology of the human TCRs (Ob.1A12) or by the partial occupancy of the peptide binding groove in case of the three EAE TCRs (172.10, 1934.4, c119). Furthermore, for the majority of these TCRs there is a paucity of hydrogen bonds to peptide side chains, a feature that likely contributes to low affinity binding (3A6) and the observed cross-reactivity (3A6, Ob.1A12) of these TCRs [14,27].

How can TCRs with such structural alterations be pathogenic?

A crucial conceptual issue is the fact that the amount of antigen available for negative selection is very small for tissue-specific self-proteins relevant in autoimmune processes [28,29], but that many of these proteins are expressed at a high level in the target organ. Important examples are MBP (EAE, MS), insulin (NOD mouse model, type 1 diabetes) and type II collagen (collagen-induced arthritis model) [6,23,30]. Pathogenic T cells can thus take advantage of the low abundance of such antigens in the thymus to escape negative selection, but become sufficiently activated and cause disease when they encounter a much higher density of self-peptide/MHC complexes in the target organ due to high level expression of both antigen and MHC. Furthermore, antigen modification can be critical to increase the affinity for MHC binding and/or TCR recognition. Excellent examples are the acetylation of the N-terminal MBP 1–11 peptide [31], citrullination of arginine residues in HLA-DR4 binding peptides in a rheumatoid arthritis animal model [32], and deamidation of glutamine residues in gliadin peptides presented by HLA-DQ2 and HLA-DQ8 in celiac disease [33]. In the case of the MBP 1–11 peptide, the acetyl group is essential for T cell activation [31]. It is likely that other important compensatory mechanisms remain to be discovered.

Conclusions

The crystal structures of all autoimmune TCRs that have been defined to date show substantial structural alterations in the TCR–peptide–MHC recognition unit, including structural alterations in the peptide–MHC interaction (partial filling of binding site, low affinity), an altered topology of TCR binding and/or a low affinity of TCR binding to peptide–MHC (Table 1a). In each case studied so far, distinctive individual features are observed, and structural characterization of a large number of autoimmune TCRs is therefore required to identify the diversity in TCR interaction with self-peptide–MHC complexes. Which of the findings made for autoimmune CD4 T cells also extend to self-reactive CD8 T cells remains to be determined.

To be pathogenic, autoimmune T cells have to meet two competing requirements: they have to escape negative selection in the thymus but nevertheless signal with sufficient strength in the target organ to be pathogenic. Escape from negative selection is favored by suboptimal TCR binding to peptide–MHC in the thymus, but compensatory mechanisms must be in place to allow such T cells to be sufficiently activated by self-antigens.

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Figure 1.

Structural comparison of TCR-peptide-MHC class II complexes. (a) Upper panel: Top view of the human anti-microbial HA1.7-HA-DR1 complex (PDB accession code 1FYT). MHC α -chain is dark blue and β -chain is light blue; TCR α -chain is magenta and β -chain is yellow; peptide is an orange line. The peptide residue occupying the P5 position of the peptide-binding groove is shown as an orange sphere. Bottom panel: Positions of the V α and V β CDR loops (numbered 1–3) on the peptide-MHC surface. (b) The human autoimmune Ob.1A12-MBP-DR2b complex (1YMM). (c) The human autoimmune 3A6-MBP-DR2a complex (1ZGL). (d) The human anti-tumor E8-mutTPI-DR1 complex (2IAM). (e) The mouse autoimmune 172.10-MBP-I-A^u complex (1U3H). The comparison shows the shift of human self-reactive TCRs Ob.1A12, 3A6 and E8 towards the peptide N-terminus and the MHC class II β chain helix (light blue).

Figure 2.

Position of TCR CDR3 loops over foreign, self, or mutant self-peptide antigens in TCR–peptide–MHC class II complexes. Color codes for TCR, MHC and peptide are the same as in Figure 1. The peptide is drawn in ball-and-stick representation with carbon atoms in orange, oxygen atoms in red, and nitrogen atoms in blue. The residue located in the center of the pocket formed by the CDR3 α and CDR3 β loops is labeled. (a) The human anti-microbial HA1.7–HA–DR1 complex. (b) The human autoimmune Ob.1A12–MBP–DR2b complex. (c) The human autoimmune 3A6–MBP–DR2a complex. (d) The human anti-tumor E8–mutTPI–DR1 complex. (e) The mouse autoimmune 172.10–MBP–I-A^u complex. TCRs 1934.4 and c119 dock very similarly.

Table 1a

Structural defects of self-reactive TCRs

	Ob.1A12 Human MS3A6	Human MSE8	Human Melanoma	172.10 Mouse EAE	1934.4 Mouse EAE	Mouse EAE
Altered binding topology	✓	✓	✓			
Partial occupancy of peptide binding groove				✓	✓	✓
Recognition of peptide by CDR3 loops alone	✓			✓	✓	✓
Paucity of side chain specific hydrogen bonds between peptide and TCR		✓		✓	✓	✓
Low affinity binding	✓ ^a	✓ ^a	✓ ^a	✓ ^b	✓ ^b	✓ ^b

^aCaused by weak interaction between TCR and peptide-MHC.

^bCaused by weak interaction between peptide and MHC.

Table 1b

TCR loops contacting peptide side chains

	CDR1 α	CDR3 α	CDR3 β	CDR1 β
A. Self-reactive TCRs				
Ob.1A12		√	√	
3A6	√	√	√	√
E8	√	√	√	√
172.10		√	√	
1934.4		√	√	
cl19		√	√	
B. Anti-foreign TCRs				
HA1.7	√	√	√	√
DO11.10	√	√	√	