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T Cell Receptor–MHC Interactions up Close

Minireview

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In the last four years, the atomic structures of more than a half-dozen of the intercellular recognition complexes, formed by αβT cell receptors (αβTCR) on cytotoxic T lymphocytes (CTL) or T helper cells and MHC/peptide complexes on antigen presenting cells, have been visualized by X-ray crystallography (Figure 1A). These molecular complexes are the common recognition component in a diverse set of cell–cell encounters that activate the T cell receptor both during development of the repertoire of T cells within an individual organism (positive selection; negative selection; peripheral survival) and during the control (T helper) and effector stages (T killer) of an immune response. In the adaptive immune response, antigens are recognized by hypervariable molecules, antibodies or T cell receptors, which are expressed with sufficiently diverse structures to be able to recognize any protein antigen. Antibodies can bind to any part of the surface of a protein antigen. The receptors on T cells, however, are restricted to sensing the presence of protein antigens by binding to short peptides from the antigens that are presented on the surface of other cells bound to class I or class II molecules of the major histocompatibility complex (MHC). The crystallographic studies of TCR/peptide/MHC complexes have shown examples of viral antigen recognition, agonist and antagonist ligand recognition, and the allorecognition of graft rejection. Some induced fitting at the TCR interface is observed upon peptide/MHC binding, but no global conformational change has been observed that could initiate a signal or determine the different signals associated with agonist and antagonist ligands. All TCRs studied have been found to bind to peptide/MHC complexes in a similar way, positioned across the MHC/peptide surface at an angle between 45° and 80° (Figure 1B). This similarity in binding mode is apparently achieved without using conserved contacts which may suggest its importance for initiating signals within T cells.

The T cell receptor is composed of two membrane anchored polypeptides, α and β (red and blue in Figure 1A), that each contain one constant (C) and one variable (V) domain. The V domain is encoded by assembled segments of genes, similar to antibodies. The complementarity determining regions (CDRs) are the hypervariable loops at one end of the TCR (red and blue in Figure 1B) that recognize the composite antigenic surface made from the jaws of an MHC molecule (gray in Figure 1B) and a bound peptide (yellow in Figure 1B). On class I MHC molecules the peptide, usually derived from proteins in the cytoplasm of any cell, is generated by the proteasome, transported into the endoplasmic reticulum, loaded onto MHC molecules, and presented on the cell surface to the surveillance system of circulating CTL. TCR recognition of such peptide/MHCI complexes usually triggers a cytotoxic response killing the virally infected or otherwise abnormal cell. On class II MHC molecules the peptide, usually derived from extracellular antigens, is generated by endosomal proteolysis of proteins after they are endocytosed by specialized antigen presenting cells such as dendrocytes or B cells. TCR recognition of such peptide/MHCII complexes usually triggers the release of cytokines that regulate inflammation and the response of other cells, such as signaling for the secretion of antibodies.

Although both self- and non-self-peptides are presented on MHC molecules, many mechanisms, collectively called immune tolerance, exist to avoid TCR reactions with self-peptide/MHC complexes. These mechanisms involve, for example, the regulation of when and how much peptide is presented, the elimination or control of self-reactive T cells, the upregulation by inflammation of costimulatory molecules on antigen-presenting cells that can provide a second signal, and generally the requirement for more than just a good fit between TCR and a peptide/MHC complex to initiate T cell activation. Occasionally breakdowns in immune tolerance result in autoimmune disorders.

TCRs Bind Very Similarly to Peptide/MHC Complexes

The X-ray structures of both human and murine αβTCR/peptide/MHC complexes from different TCR bound to both MHCI/peptide and MHCII/peptide complexes show a similar binding mode. The CDR2 loops of α and β contact only the MHC molecules, while the CDR1 and CDR3 loops contact both peptide and MHC atoms (Figure 1B). Furthermore, the Vα domain is always closer to the N-terminal end of the bound peptide (left in Figures 1A–1C) and the Vβ domain to the C-terminal end, with the TCR taking an angled path across the MHC binding site. In 4 TCR/peptide/MHCI complexes, the angle between the peptide direction and the long axis of the αβTCR interface is between 45° and 70°, while the two TCR/peptide/MHCII structures are at one end of the range, 70° and 80° (Figure 1C). Because the CDR3 loops are the most variable, being encoded by D and J gene segments, it was anticipated that they would contact the most diverse part of the peptide/MHC complex, the peptide. There are only about 50 TCR Vα and 50 Vβ genes, which encode the CDR1 and CDR2 loops in the germline.

The surface of the TCR that contacts peptide/MHC is relatively flat, sometimes with a central cavity. The MHC surface by contrast contains two high peaks (symbolized by large zigzag in Figure 2C). To achieve a large interface (1500 to 2200 Å^2 of buried solvent-accessible surface area), the TCR apparently binds between these two highpoints on the MHC/peptide surface as predicted from mutagenesis experiments (reviewed in Bjorkman, 1997). The TCR footprints on the MHC/peptide

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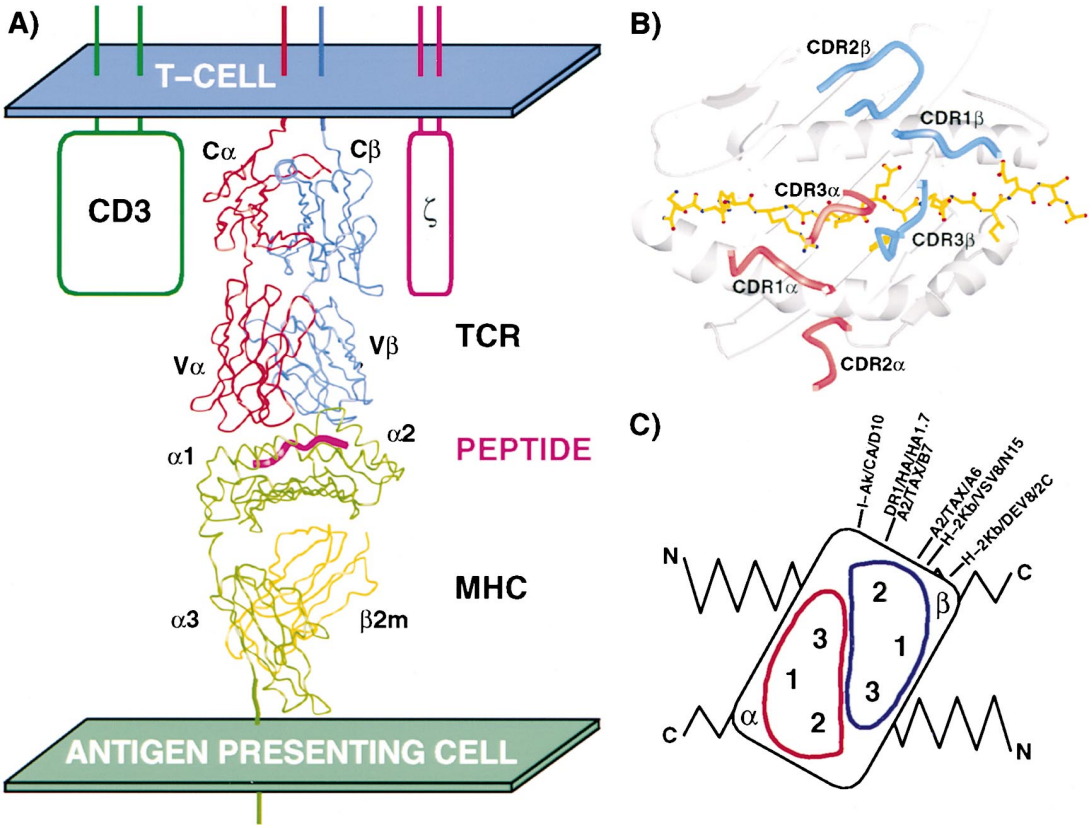

Figure 1. TCR/Peptide/MHC Complexes

(A) Overall view between cells (Garcia et al., 1998). (B) CDR placement over the peptide/MHC surface (Reinherz et al., 1999). (C) Range of TCR binding modes in TCR/peptide/MHC complexes. Short lines by the TCR labels indicate the angles at which each TCR binds across the peptide/MHC surface. (TCR counterclockwise: Garcia et al., 1998; Teng et al., 1998; Ding et al., 1998; Garboczi et al., 1996; Hennecke et al., 2000; Reinherz et al., 1999).

vary considerably with the ratio of the surface buried by Vα and Vβ domains ranging from 2:1 to 1:2. However, the location and size of the CDR1, 2, and 3 footprints of Vα vary much less than the footprints of Vβ, giving the impression that different TCRs pivot about contacts made by the CDR1 and CDR2 of Vα (lower left in Figure 1C).

Of the 31 MHC amino acid positions contacted in at least one of the known TCR/peptide/MHC structures, only a subset of about 1/2 of those are actually contacted in each complex. Even contacts to the same peptide/MHC complex by two different TCRs can share as few as one conserved atomic interaction (Garboczi et al., 1996; Ding et al., 1998). Which of these residues are contacted depends on global parameters like the twist, tilt, and shift of the TCR over the pMHC surface (Teng et al., 1998), the different angles found between the Vα and Vβ domains, and the conformation and length of the CDR loops. At present, there is no simple code for predicting these global parameters or the details of binding from the sequence of a TCR and the peptide/MHC antigen, although one contact is conserved in the two complexes with class II MHC molecules (Reinherz et al., 1999; Hennecke et al., 2000).

The lack of conserved contacts between all TCRs and the conserved residues on the MHC molecules presents an apparent paradox. How do TCRs bind similarly if contacts are not conserved? Because there are many conserved MHC residues and about 50 Vα and Vβ genes, the binding mode might have been preserved by a combinatorial mechanism where different TCRs contact a different subset of MHC residues, but even TCRs with identical CDR1 and CDR2 loops in one V domain can interact very differently with MHC molecules, as illustrated by the different binding of 2C TCR to H-2K^b/DEV8 and D10 TCR to I-A^k/CA (references in Figure 1). An alternative is that the coevolution of TCRs with MHC molecules in a species has only selected for TCRs that can initiate a signal (e.g., during positive selection). Any binding mode consistent with signaling would have been preserved, irrespective of the conservation of particular atomic contacts.

The existence of an approximately conserved TCR orientation might be important for the recognition of the TCR/peptide/MHC complex by coreceptor molecules on the T cell surface like CD4 or CD8 or to facilitate a proposed association of TCR/peptide/MHC complexes into oligomers to initiate signaling within the T cell.

Recognizing Foreign Antigens

Only one-third of the surface of peptides bound to MHC molecules is unoccluded and available to be recognized by contacts to a TCR. TCRs contact from 5 to 7 of a span of 8 residues of MHCI bound peptides (8-mers and

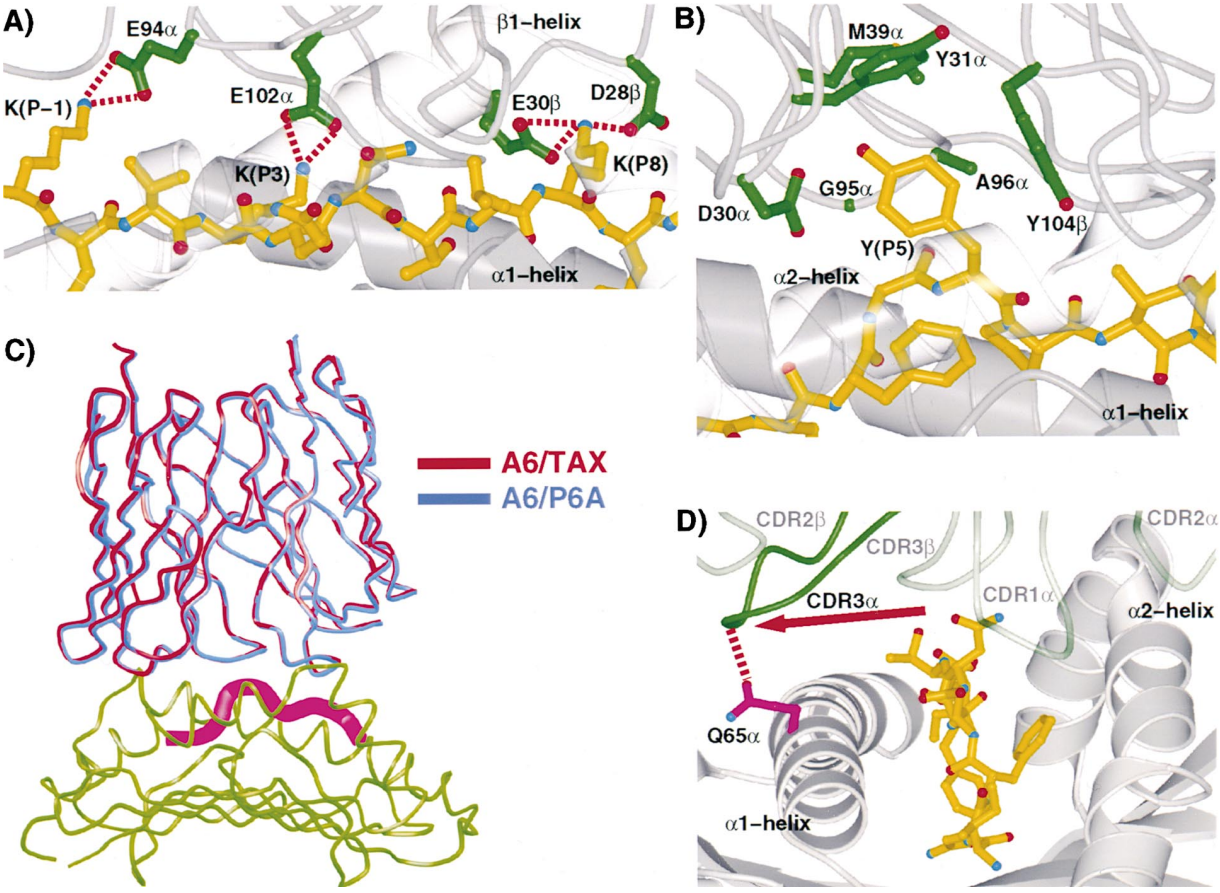

Figure 2. TCR–Peptide/MHC Interfaces

(A) A TCR with flat (green) surface contacting projecting peptide (yellow) sidechains (Hennecke et al., 2000). (B) A TCR with a deep pocket between CDR3 loops (green) engulfing a peptide tyrosine sidechain (yellow) (Garboczi et al., 1996). (C) The A6-TCR bound to an agonist Tax peptide (red TCR) and an antagonist, singly substituted (P6A) peptide (blue TCR) have almost identical bound conformations but initiate very different signals (Ding et al., 1999). (D) An allo-complex, between a TCR and a mismatched MHC molecule, has an unusual CDR3α conformation (green arrow) extending away from the peptide but initiates a strong agonist signal (Reiser et al., 2000).

9-mers) and from 6 to 7 of a span of 9 residues of MHCII bound peptides (13-mers and 16-mers). In some cases a relatively flat surface of a TCR (green in Figure 2A) contacts the projecting sidechains from a bound peptide (yellow in Figure 2A). In other cases the central peptide residue (yellow tyrosine in Figure 2B) is completely surrounded by a deep pocket in the TCR surface formed primarily by the two CDR3 loops (green in Figure 2B). The interfaces sometimes contain water molecules and by one measure of complementarity they score below interfaces within oligomeric proteins but near the range of Fab/antigen complexes (Garcia et al., 1999).

The number of contacts between TCR and peptide is limited, suggesting that crossreactivity in which more than one peptide sequence can fit between a given TCR/MHC pair will occur, as has been observed in functional experiments. Although in crossreactions different peptides can generate the same activation signal, in other cases TCR signaling can be exquisitely sensitive to peptide sequence. Single amino acid substitutions in peptides, even in residues not directly contacted by the TCR, can convert a strong agonist peptide/MHC ligand into a weak agonist or even an antagonist. (Antagonist ligands do not activate T cells, instead they bind TCR, cause some hypophosphorylation, and inhibit T cell responses by agonist ligands.) Such peptides are called altered-peptide-ligands (APL) (reviewed in Sloan-Lancaster and Allen, 1996). One structural study of three TCR/APL/MHC complexes showed that some peptide substitutions could be accommodated by very minor readjustments in the TCR/peptide interface (induced fit), which did not propagate to the outer surface of the TCR (Ding et al., 1999). Furthermore there was no correlation between the minor structural refitting and the signaling outcome. Very minor refitting resulted in an antagonist (compare red and blue TCR conformations in Figure 2C with a peptide Pro-6 to Ala substitution.), whereas on another APL a more extensive refitting diminished signaling only to a weak agonist (producing full activation but at much higher peptide concentration). A comparison of the structures of a weak and a strong agonist peptide also showed only minor adjustments in the TCR/peptide/MHC interface (Degano et al., 2000). This lack of correlation between the structure and the signal generated is consistent with suggestions that tightness or duration of TCR binding causes different signals (Davis

et al., 1998), not different conformations of the TCR/peptide/MHC complex.

Induced Fit in TCR/Ligand Binding, but No Global Conformational Changes

The structure of a murine TCR has been determined both unliganded and bound to a peptide/MHC complex (reviewed in Garcia et al., 1999). A comparison indicates induced fitting of the TCR CDR loops to accommodate the ligand with differences in structure ranging from 4 to 6 Å. These conformational differences do not appear to propagate away from the TCR/peptide/MHC interface to the outer surface of the TCR. Because the induced fit is only local, no conformational change of the TCR that might signal to the cytoplasm that a ligand has been engaged has been discovered. This again suggests signaling models based on the affinity or the kinetic lifetime of the complex.

Graft Rejection—Alloreactivity

The immune reaction to the introduction of cells expressing a foreign MHC molecule into an MHC mismatched host, an alloreaction (*allos*, Greek for other), is particularly severe. Up to 10% of peripheral T cells respond to such an allo-challenge, while less than 1% respond to a typical viral challenge (reviewed in Kranz, 2000). Two models have been proposed to account for the high reactivity. In one, the TCR might bind to the allo-MHC/peptide complex primarily to the polymorphic and conserved MHC residues of the allo-MHC molecule. Alternatively, because the allo-MHC can bind a new constellation of self-peptides, many peptide/MHC ligands would be generated for which T cells would not have been eliminated by tolerance mechanisms like negative selection. The X-ray structure of a murine TCR bound to an allo-MHC/peptide complex showed that both peptide and MHC residues were contacted by TCR and that the binding mode was like that of other TCR/peptide/MHC complexes (Reiser et al., 2000). The structure of this allo-complex adds evidence to the latter proposal, namely, that allo-recognition is very similar to other TCR reactions, but there are just more novel complexes generated by peptide/allo-MHC interactions. Hypothetical molecular models constructed of other allo-complexes suggest the same conclusion (Speir et al., 1998; Reinherz et al., 1999).

The X-ray structure of the murine allo-complex had an unusually positioned CDR3α loop (green in Figure 2D) that is folded back away from the peptide and only in contact with one MHC residue (arrow in Figure 2D). As a result of the unusual position of the CDR3 loop there are fewer TCR/peptide contacts in this complex, rendering this particular TCR/MHC interaction less peptide sequence–dependent (Reiser et al., 2000). The interface also contains a large cavity estimated to contain 30 solvent molecules.

Summary

X-ray crystal structures of $\alpha\beta$TCRs bound to MHCI and MHCII molecules with bound antigenic peptides reveals the atomic contacts upon which MHC restricted T cell recognition is based. Very different signals can result from very similar structures and identical signals can result from different structures (Figures 2C and 2D). An important caveat is that the CD3 and zeta chains of the TCRs and all of the transmembrane anchors and cytoplasmic segments were absent from all of the crystal studied to date. The possibility, for example, that the cell surface TCR contains two $\alpha\beta$TCR units (Fernandez-Miguel et al., 1999) suggests that until the full TCR with CD3 and zeta chains is assembled and crystallized, choosing among signal initiation mechanisms involving oligomerization or allosteric switches will be difficult.

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