The Structural Basis of T-Cell Receptor Recognition

C.S. Clements and J. Rossjohn
Protein Crystallography Unit, Department of Biochemistry & Molecular Biology, Monash University, Clayton, Victoria, 3800, Australia

Recognition of antigens by T-cells bearing αβ T-cell receptors (TCR) is a central event in the immune response to pathogens. T-cells recognise and respond to antigens presented by major histocompatibility complex (MHC) proteins, a process known as MHC-restriction. The two major classes of T-cells, CD8 and CD4 T-cells, recognise peptide antigens in complex with MHC class I or class II respectively. This central recognition event has been studied intensely, providing a broad understanding of this interaction, yet the structural basis of MHC-restriction remains enigmatic.

The vast repertoire of TCRs is generated via gene rearrangement of exons that encode the variable region (V) of the TCR, in addition to random insertions and deletions at the junctions. This diversity is manifested in the Complementarity Determining Regions (CDR), three in each of the Vα and Vβ domains, which together define the antigen recognition site of the TCR.

MHC molecules are highly polymorphic with polymorphism generally focused in the antigen-binding cleft. The antigen-binding cleft of MHC-I and MHC-II comprises two α-helices and a β-sheet floor. The MHC-II cleft is open-ended allowing it to bind long peptides, whereas the MHC-I cleft is enclosed at each end generally constraining the length of MHC-I peptides to 8-10 residues. MHC-I can, however, present longer peptides that bulge out of the antigen-binding cleft [1, 2].

Although peptide-MHC-I and peptide-MHC-II are the prototypical TCR ligands, other antigens and antigen presenting molecules can elicit a T-cell response. MHC-Ib molecules are primarily involved in innate immunity, presenting self-peptides to Natural Killer cell receptors. Nevertheless, MHC-Ib presenting viral peptides can also be recognised by T-cells [4]. In addition, a semi-invariant TCR is capable of recognition of the MHC-like molecule CD1d presenting the glycolipid α-galactosylceramide [5].

As the number of TCR/MHC structures increases it is clear that although broad generalisations can be made, the interaction is both highly specific and versatile.

References

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[5] Borg et al (2007) Nature 448 44