Structure watch

HOW THE PRE-TCR SELF-ASSOCIATES

Unlike the αβ-T cell receptor (αβTCR), the pre-TCR does not need to be ligated to induce dimerization and signalling. By analysing the structure of the pre-TCR, this study shows how ligand-independent dimerization occurs and how this allows the invariant pre-TCR α-chain (pre-Tα) to sense the correct folding of its various partner TCR β-chains.

In the crystal structure, a cluster of hydrophobic residues on the pre-Tα forms an extensive interface with the TCR β-chain, similar to the mode of association in the αβTCR. The pre-TCR autonomously forms heterodimers with a head-to-tail orientation, made possible by the hydrophobic and flat 'top' of the pre-Tα and by occlusion of an otherwise surface-exposed hydrophobic patch on the Vβ domain. Importantly, this orientation enables the pre-Tα to interact, through various conserved residues, with both the variable domain and the joining region of the β-chain, which suggests that the pre-Tα acts as a chaperone that senses the correct folding of the TCR β-chain. Analysis of the effect of mutation of the conserved residues on pre-TCR dimerization in solution and at the cell surface confirmed that the head-to-tail configuration supports the function of the pre-TCR in quality control during T cell development.

ORIGINAL RESEARCH PAPER Pang, S. S. *et al.* The structural basis for autonomous dimerization of the pre-T-cell antigen receptor. *Nature* **467**, 844–848 (2010)

IMMUNORECEPTOR COMPLEX ASSEMBLY

Many activating immunoreceptor complexes are composed of an extracellular receptor and an intracellular signalling module: for example, the T cell receptor (TCR)–CD3 complex, the natural killer group 2 member D (NKG2D)–DAP10 complex and numerous activating receptors that form complexes with the dimer DAP12. These complexes assemble through interactions between the intramembrane domains of the proteins, but little is known about the exact structural nature of these interactions.

Using nuclear magnetic resonance and *in vitro* functional mutagenesis, the authors of this study examined the heterotrimeric complex formed by the transmembrane portion of NKG2C ($NKG2C_{TM}$) and the transmembrane portion of DAP12 ($DAP12_{TM}$). It is known that the aspartic acid residue at position 16 of $DAP12_{TM}$ is necessary for complex formation. In addition to this residue, it was shown that a threonine residue at position 20 is necessary. These four residues in the $DAP12_{TM}$–$DAP12_{TM}$ homodimer function together to guide the interaction with a basic lysine residue in $NKG2C_{TM}$. Analysis of the TCR–CD3 and NKG2D–DAP10 complexes identified a similar electrostatic network containing a polar five-amino-acid transmembrane motif that is important for complex assembly.

So, a DXXXT/S (in which T/S indicates a threonine or serine) motif is conserved in the transmembrane portion of several intracellular signalling proteins and is involved in the assembly of many immunoreceptor complexes.

ORIGINAL RESEARCH PAPER Call, M. E., Wucherpfennig, K. W. & Chou, J. J. The structural basis for intramembrane assembly of an activating immunoreceptor complex. *Nature Immunol.* 3 Oct 2010 (doi:10.1038/ni.1943)