LYMPHOCYTE SIGNALLING

Isoform isolated

Phosphatidylinositol 3-kinases (PI3Ks), a family of p85–p110 heterodimeric lipid kinases, are important regulators of cell signalling. But, do the three isoforms of the catalytic p110 subunit (p110α, -β and -δ) have distinct biological roles? Okkenhaug and colleagues report in *Science* that B-cell receptor (BCR) and T-cell receptor (TCR) signalling is impaired in p110δ-mutant mice, which indicates that p110δ has a specific role in immunity.

Previous studies of the PI3Ks have been complicated by the fact that altering the level of expression of one subunit can affect the expression of the others. To avoid this, rather than generating *p110δ*-knockouts, the authors generated mice that express an inactivated, point-mutated p110δ protein ($p110\delta^{D910A}$) at normal levels.

B-cell development was affected in these mice: their bone marrow contained reduced numbers of B-cell progenitors; the ratio of pre- to pro-B cells was altered; their spleens contained 50% fewer B cells than in wild-type mice; and marginal-zone B cells were undetectable. T-cell development was normal with respect to CD4/CD8 profiles, but the level of expression of CD44 by peripheral T cells (a marker that is associated with a memory, rather than naive, phenotype) was reduced.

In addition to this role in the development of B and T cells, further experiments showed that p110δ is required for the function of these cells. BCR signalling and B-cell proliferation in response to anti-IgM antibodies was reduced, and the $p110\delta^{D910A}$ mice had lower levels of serum immunoglobulin and defective humoral responses, and they failed to form germinal centres in the spleen. TCR signalling and T-cell proliferation in response to anti-CD3 antibodies or antigen was also defective. Taken together, these results indicate that p110δ has a unique role in antigen-receptor signalling.

The $p110\delta^{D910A}$ mice also developed a mild inflammatory bowel disease (IBD). This is interesting because the human p110δ gene (*PI3KCD*) maps to the IBD7 susceptibility locus, and, as the authors propose, further investigations might show that *PI3KCD* is a human IBD-susceptibility gene.

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References and links

ORIGINAL RESEARCH PAPER Okkenhaug, K. *et al.* Impaired B- and T-cell antigen receptor signaling in p110δ PI3-kinase mutant mice. *Science* July 18 2002 (DOI 10.1126/science.1073560)

FURTHER READING Cantley, L. C. The phosphoinositide 3-kinase pathway. *Science* **296**, 1655–1657 (2002)

ANTIGEN RECOGNITION

TCR docking

What are the physical properties of T-cell receptors (TCRs) that can account for their inherent cross-reactivity with many different peptide–MHC combinations? Mark Davis' group have analysed the residues that are involved in initial binding and in stable interactions between TCRs and peptide–MHC complexes. The results, reported in *Nature*, indicate that TCR binding is a two-step process, in which initial docking on the MHC molecule is essentially a peptide-independent process.

The TCR molecule is a dimer composed of an α- and a β-chain, each of which consists of constant and variable immunoglobulin-like domains. The regions within the variable domains that comprise the peptide–MHC-binding interface are known as the complementarity-determining regions (CDRs). CDR1 and CDR2 seem to be positioned over the MHC molecule, whereas CDR3 seems to be positioned over the peptide.

Using the well-characterized TCR 2B4, which interacts with the moth cytochrome C (MCC)–IE^k peptide–MHC complex, Wu and colleagues analysed the contribution of individual residues in the MCC–IE^k complex to TCR binding by alanine-scanning mutagenesis and assessed binding affinity using surface plasmon resonance. Mutagenesis of the TCR-contact residues in MCC markedly disrupted binding, which indicates that peptide residues are important for the stable interaction of TCR and peptide–MHC.

Next, the authors analysed the contribution of individual residues in the MCC–IE^k complex during the initation phase of the interaction. In this phase, residues in the MHC helices contributed most to the TCR interaction.

These data indicate that TCR interactions with peptide–MHC complexes occur by a two-step process. First, the CDR1 and CDR2 loops of the TCR chains dock on the MHC helices, then an induced-fit mechanism allows CDR3 to interact specifically with the peptide in the MHC groove.

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References and links

ORIGINAL RESEARCH PAPER Wu, L. C., Tuot, D. S., Lyons, D. S., Garcia, K. C. & Davis, M. M. Two-step binding mechanism for T-cell receptor recognition of peptide–MHC. *Nature* **418**, 552–556 (2002)

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