INFLAMMATION

Cooling the inflammatory response

Phosphoinositide 3-kinases (PI3Ks) are attractive therapeutic targets in various diseases, such as autoimmune and inflammatory disorders and cancer. However, a shortage of isoform-selective compounds has been an obstacle to therapeutically targeting these enzymes. Two papers in *Nature Medicine* support the promise of the PI3Kγ isoform as a viable therapeutic target.

PI3Ks are intracellular signalling enzymes that are involved in several fundamental biological processes, such as cell survival and proliferation, and vesicular trafficking. One of the drawbacks of disrupting the activity of the PI3Ks is that some isoforms are essential for these cellular processes; for example, knockouts of the genes encoding the ubiquitously expressed PI3Kα and PI3Kβ are embryonically lethal in mice. However, targeting the PI3Kγ and PI3Kδ isoforms would circumvent this problem because their expression is restricted to the haematopoietic system. Mice lacking the genes encoding these enzymes develop normally, although they do show defects in adaptive immunity, including activation of T and B cells. This suggests that PI3Kγ and PI3Kδ could be potential targets for diseases caused by inappropriate inflammatory responses, such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Indeed, PI3Kγ is known to have a key role in mediating the activation and migration of white blood cells (leukocyte chemotaxis), such as macrophages and neutrophils during an immune response, and neutrophil migration has been strongly implicated in the pathogenesis of rheumatoid arthritis.

Using an automated *in vitro* lipid-kinase assay, Camps *et al.* identified, and subsequently optimized, a series of small-molecule inhibitors of PI3Kγ. Crystallization of one of the compounds, AS-604850, with PI3Kγ facilitated the structure-based design of AS-605240, which was found to have a greater inhibitory potency towards PI3Kγ. After demonstrating the inhibitory effects of these compounds on several types of immune cells and chemokine ligands *ex vivo*, the authors tested the efficacy of AS-605240 in two distinct mouse models of rheumatoid arthritis. Oral administration of AS-605240 suppressed joint inflammation and damage in both models. Importantly, treatment with AS-605240 afforded the same protective effects that were observed in mice deficient in the gene encoding PI3Kγ.

The effect of inhibiting PI3Kγ-mediated inflammation in a model of the chronic inflammatory autoimmune disease SLE using AS-605240 was also investigated by Barber and colleagues. In MRL-*lpr* SLE-prone mice, AS-605240, as well as reducing inflammation of the glomeruli of the kidney (glomerulonephritis), which is a characteristic symptom of SLE, extended the lifespan of the mice and caused no adverse side effects.

The successful development of an orally active inhibitor that is selective for the PI3Kγ isoform strengthens the hypothesis that this enzyme represents a valid therapeutic target for disrupting leukocyte activation and migration in chronic inflammatory disorders.

Samantha Barton

References and links

ORIGINAL RESEARCH PAPERS Camps, M. *et al.* Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. *Nature Med.* 28 August 2005 (doi:10.1038/nm1284) | Barber, D. F. *et al.* PI3Kγ inhibition blocks glomerulonephritis and extends lifespan in a mouse model of systemic lupus. *Nature Med.* 28 August 2005 (doi:10.1038/nm1291)

FURTHER READING Smolen, J. S. & Steiner, G. Therapeutic strategies for rheumatoid arthritis. *Nature Rev. Drug Discov.* **2**, 473–488 (2003)