AUTOIMMUNITY

New drug for autoimmune diseases

Two papers published recently in *Nature Medicine* show that specific targeting of phosphatidylinositol 3-kinase-γ (PI3K-γ) with a drug can reduce the progression of disease in mouse models of rheumatoid arthritis and systemic lupus erythematosus (SLE).

For the treatment of chronic inflammatory diseases, specific targeting of PI3K-γ is thought to be crucial because, unlike class IA PI3Ks, which are ubiquitously expressed and are involved in numerous signalling pathways, PI3K-γ (a class IB PI3K) is expressed only by haematopoietic cells. Moreover, mice that lack PI3K-γ show impaired leukocyte migration and activation. Camps *et al.* identified two small-molecule inhibitors (AS-604850 and AS-605240) that are selective for PI3K-γ. *In vitro*, both compounds inhibited signalling triggered through PI3K-γ, as well as PI3K-γ-mediated chemotaxis of neutrophils and monocytes in response to several chemokines. Importantly, intracellular signalling and chemotaxis mediated by class IA PI3Ks were not affected by these inhibitors.

Because AS-605240 had the most potent inhibitory activity *in vitro*, the authors next tested whether AS-605240 could improve disease in two mouse models of rheumatoid arthritis. Indeed, paw swelling and joint inflammation induced by passive transfer of type-II-collagen-specific antibody were reduced by oral treatment with AS-605240 after the onset of arthritis. Similarly, oral administration of AS-605240 suppressed disease symptoms induced by immunization with type II collagen. In both models, the protective effect correlated with decreased neutrophil accumulation in the joints.

In the other paper, Barber *et al.* used the same inhibitor (AS-605240) and showed that it reduced the incidence and severity of glomerulonephritis and that it prolonged the lifespan of MRL-*lpr* mice, which are prone to an SLE-like disease.

Such developments provide hope for a new drug for the treatment of human autoimmune diseases.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Camps, M. *et al.* Blockade of PI3Kγ suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. *Nature Med.* **11**, 936–943 (2005) | Barber, D. F. *et al.* PI3Kγ inhibition blocks glomerulonephritis and extends lifespan in a mouse model of systemic lupus. *Nature Med.* **11**, 933–935 (2005)

FURTHER READING Ohashi, P. S. & Woodgett, J. R. Modulating autoimmunity: pick your PI3 kinase. *Nature Med.* **11**, 924–925 (2005)