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)

THYMOCYTE DEVELOPMENT

Thymic DCs improve their tolerance

A new study in *Nature* describes a role for medullary dendritic cells (DCs) in the positive selection of $CD4^+CD25^+$ regulatory T (T_{Reg}) cells in the thymus. This complicates the traditional view of central tolerance, in which epithelial cells in the cortex mediate positive selection of developing thymocytes, whereas DCs in the medulla mediate negative selection. The latter process ensures lack of reactivity to self-MHC plus self-peptide; now, this is joined by the positive selection of T_{Reg} cells as another central-tolerance mechanism mediated by DCs that prevents reactivity to self in the periphery.

Yong-Jun Liu and colleagues showed that human Hassall's corpuscles — which are groups of epithelial cells in the thymic medulla — express the interleukin-7-related cytokine thymic stromal lymphopoietin (TSLP). TSLP-expressing Hassall's corpuscles were colocalized with $CD11c^+$DC lysosomal-associated membrane protein $(DC\text{-}LAMP)^+$ DCs, with DC-LAMP being a marker of mature, activated DCs. In *in vitro* experiments, TSLP induced peripheral-blood and thymic $CD11c^+$ immature DCs to upregulate expression of DC-LAMP and other markers of maturation and activation, such as CD80, CD86 and MHC class II molecules. The authors therefore propose that Hassall's corpuscles express TSLP to activate immature DCs in the thymus.

DCs that are activated with TSLP (denoted TSLP-DCs) induced the proliferation of $CD4^+CD8^-$ thymocytes but not other thymocyte populations, *in vitro*, and resulted in a tenfold increase in the number of $CD25^+$ cells in this subset. This was a consequence of the proliferation of $CD4^+CD25^-$ cells and their differentiation into $CD4^+CD25^+$ cells, rather than of the proliferation of pre-existing $CD4^+CD25^+$ cells. The $CD4^+CD25^+$ cells that were induced by TSLP-DCs expressed *Foxp3* (forkhead box P3) mRNA and inhibited the proliferation of $CD4^+CD25^-$ thymocytes stimulated with CD3- and CD28-specific antibodies, showing that they have the characteristics of classical T_{Reg} cells. T_{Reg} cells in the thymus were shown to be present only in the medulla in close proximity to DC-$LAMP^+$ DCs and Hassall's corpuscles.

This new role for thymic DCs — after activation by TSLP produced by epithelial cells in Hassall's corpuscles — in the positive selection of T_{Reg} cells indicates another way in which DCs are involved in ensuring self-tolerance, by converting high-affinity autoreactive thymocytes into T_{Reg} cells rather than deleting them.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Watanabe, N. *et al.* Hassall's corpuscles instruct dendritic cells to induce $CD4^+CD25^+$ regulatory T cells in human thymus. *Nature* **436**, 1181–1185 (2005)