G-PROTEIN-COUPLED RECEPTORS

Putting the brake on inflammation

Chronic or inappropriate inflammation is characteristic of many disorders, such as rheumatoid arthritis and asthma. Although many drugs can reduce inflammation, current treatments merely ameliorate these diseases, a reflection of the fact that the body's own mechanism for controlling inflammation and the accompanying tissue damage is poorly understood. Now, writing in *Nature*, Akio Ohta and Michail Sitkovsky report that A_{2A} adenosine receptors are crucially involved in the limitation and termination of inflammatory responses.

Noting that extracellular adenosine accumulates in inflamed and damaged tissues, and the immunosuppressive properties of adenosine A_{2A} receptors on immune cells, the authors hypothesized that adenosine acting at the A_{2A} receptor could be the key signal that limits inflammation. To test this theory, they used mice deficient for the A_{2A} receptor, and exposed them to concanavalin A, which is a well-characterized inducer of inflammatory tissue damage in the liver, with the damage being mediated by T cells, macrophages and pro-inflammatory cytokines, such as tumour-necrosis factor (TNF)-α and interferon (IFN)-γ. The receptor-deficient mice all showed extensive tissue damage, and some died, in contrast to normal mice exposed to the same inflammatory stimulus, which only showed minimal tissue damage or were unaffected. Moreover, excessive and prolonged accumulation of TNF-α and IFN-γ was observed in the serum of the receptor-deficient mice, but not in that of normal mice. Ohta and Sitkovsky further confirmed the tissue-protecting properties of A_{2A} receptors in other models of inflammatory damage and systemic inflammation. The striking phenotypes observed in all the experiments indicate that no other mechanism for limiting inflammation can compensate fully for the loss of A_{2A} receptors on immune cells.

Before this report, A_{2A} receptors were just one of many candidates for the role of damping inflammation to prevent excessive tissue damage *in vivo*; other G_s-protein-coupled receptors were known to block inflammation when activated pharmacologically. The demonstration of the physiological role of A_{2A} receptors in the downregulation of acute inflammation is a key conceptual advance that could stimulate the development of novel therapeutic approaches for controlling excessive inflammation. Furthermore, modulation of A_{2A} receptors could be a new strategy for enhancing inflammatory responses when desirable; for example, to improve the immune defence in immunosuppressed patients or to increase inflammatory damage to cancer tissue.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Ohta, A. & Sitkovsky, M. Role of G-protein-coupled receptors in downregulation of inflammation and protection from tissue damage. *Nature* **414**, 917–920 (2001)

IN BRIEF

INFECTIOUS DISEASE

Plasmodium falciparum phospholipase C hydrolysing sphingomyelin and lysocholinephospholipids is a possible target for malaria chemotherapy

Hanada, K. *et al. J. Exp. Med.* **195**, 23–34 (2002)

The emergence of resistance in *Plasmodium falciparum* to drugs such as chloroquine highlights the need to develop new approaches to treating malaria. During the development of malaria parasites within erythrocytes, lipid metabolism rises dramatically, providing a possible therapeutic target. Hanada *et al.* have identified, cloned and characterized the parasite sphingomyelinase (SMase), an important enzyme in lipid metabolism. An inhibitor of SMase caused severe impairment of intra-erythrocytic parasite development.

PHARMACOGENETICS

Population distribution of human flavin-containing monooxygenase form 3: gene polymorphisms

Cashman, J., Zhang, J., Leushner, J. & Braun, A. *Drug Metab. Dispos.* **29**, 1629–1637 (2001)

Flavin-containing monooxygenase 3 (FMO3) is involved in the biotransformation of many drugs and chemicals. Cashman *et al.* report a statistically significant heterogeneity among ethnic subdivisions at three variable DNA sites in the *FMO3* gene, which accounts for much of its variability of action. This indicates that individuals could be genetically screened to determine the *FMO* alleles that they express, in order to optimize the therapeutic dosages of drugs that are metabolized by FMOs.

NEURODEGENERATIVE DISEASE

Chaperone suppression of α-synuclein toxicity in a *Drosophila* model for Parkinson's disease

Pavan, K. *et al. Science* 2001 Dec 20; [epub ahead of print]

Overexpression of α-synuclein, a protein that has been implicated in the onset of Parkinson's disease, in *Drosophila melanogaster* causes dopamine neuron loss, and thus provides a model of the human disease. Pavan *et al.* show that directed expression of the molecular chaperone HSP70 can prevent α-synuclein-induced neuron loss in *Drosophila*, and that neurotoxicity is accelerated by the loss of endogeneous chaperone activity. So, chaperone activation might be an effective therapeutic approach in humans.

RATIONAL DRUG DESIGN

Protection against anthrax: identification of a site for rational drug design

Glick, M., Grant, G. H. & Richards, W. G. *Nature Biotechnol.* (in the press)

Many will be familiar with the project started by Graham Richards' group, which uses 'spare' time on computers spread worldwide to screen virtual libraries for potential anti-cancer drugs. An analogous project screening for molecules that could bind to a ligand-binding site identified on a component of anthrax toxin and thus inhibit assembly of the toxin complex is now being initiated.