ARTHRITIS

Oxygen burst may be crucial

A naturally occurring polymorphism in the protein neutrophil cytosolic factor (Ncf1) regulates the severity of arthritis through a previously unknown mechanism involving arthritogenic T cells, explains an article published in the January issue of *Nature Genetics*. Holmdahl and colleagues used positional cloning to identify the *Ncf1* gene in a particular locus that is associated with arthritis severity. Ncf1, also known as phagocyte oxidase, is a component of the nicotinamide adenine dinucleotide phosphate oxidase (NADPH) complex, which produces reactive oxygen species (ROS). The authors went on to show that pharmacological treatment with drugs that activated the NADPH oxidase complex, thereby producing higher levels of ROS, were able to ameliorate arthritis in rats. Arthritis in the rat model is very similar to rheumatoid arthritis (RA) in humans, so this work suggests new therapeutic pathways to target.

RA is a chronic inflammatory disease that affects peripheral joints; synovial inflammation in these joints leads to cartilage destruction, bone erosion and ultimately joint deformity and loss of joint function. Inheritance of RA is polygenic and influenced by environmental factors. The authors have found, using the rat arthritis model, that different gene regions control different phases of the disease, such as the onset, and severity of the acute and chronic phases.

Ncf1 is expressed in all phagocytic cells, and following phosphorylation it forms part of the NADPH oxidase complex in the cell membrane. This complex has a central role in host defence against bacterial infections through the production of ROS. Holmdahl and colleagues showed that the Ncf1 disease-related polymorphism led to differences in enzyme activity, rather than to quantitative differences in expression, and to a lower oxygen burst, which resulted in more severe arthritis.

High levels of ROS in the joints are believed to be involved in inflammation-mediated joint destruction; however, the possibility that these high ROS levels might actually reduce arthritis severity through earlier events is not usually considered. The authors showed that Ncf1 is involved in the early phase of arthritis due to the generation of disease-causing autoimmune arthritogenic T helper cells. Furthermore, T cells originating from a rat with the disease-related polymorphism could transfer severe arthritis to rats without the Ncf1 polymorphism.

The involvement of Ncf1 in the generation of arthritogenic T cells explains the paradox that a decreased, rather than an increased, oxygen burst is associated with arthritis. Activation of the NADPH oxidase complex is characteristic of activated macrophages and other immune cells that trigger T cells into action. The authors speculate that the production of ROS during T-cell interaction with another immune cell induces apoptosis, which limits the expansion of T cells responding to self-components; a reduction in the ROS allows arthritogenic T cells to escape death.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Olofsson, P. *et al* Positional identification of *Ncf1* as a gene that regulates arthritis severity in rats. *Nature Genet.* **33**, 25–32 (2003)

FURTHER READING Feldman, M. Development of anti-TNF therapy for rheumatoid arthritis. *Nature Rev. Immunol.* **2**, 364–371 (2002) | Pope, R. M. Apoptosis as a therapeutic tool in rheumatoid arthritis. *Nature Rev. Immunol.* **2**, 527–535 (2002) | Lu, S., *et al.* Both common and unique susceptibility genes in different rat strains with pristane-induced arthritis *Eur. J. Hum. Genet.* **10**, 475–483 (2002)

WEB SITES

Holmdahl's laboratory: http://net.inflam.lu.se/

Encyclopedia of Life Sciences: http://www.els.net Rheumatoid arthritis

IN BRIEF

LEAD DISCOVERY

Virtual screening to enrich hit lists from high-throughput screening: a case study on small-molecule inhibitors of angiogenin.

Jenkins, J. L., Kao, R. Y & Shapiro, R. *Proteins* **50**, 81–93 (2003)

Hit lists from high-throughput screening (HTS) often contain a large proportion of false positives, which means that follow-up assays are needed to find the truly active compounds. Consequently, there has been growing interest in integrating virtual screening (VS) with HTS with the aim of improving the quality of the hit-lists. Application of such a VS/HTS approach to the discovery of leads against the enzyme angiogenin leads to a sixfold enrichment in the hit rate compared with HTS alone.

GENOMICS

The protein kinase complement of the human genome.

Manning, R. *et al*. *Science* **298**, 1912–1934 (2002)

Using public and proprietary genomic, complementary DNA and expressed sequence tag sequences, the authors identify 518 putative protein kinases in the human genome, providing a starting point for comprehensive analysis of protein phosphorylation in normal and disease states.

HORMONE RECEPTORS

Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids.

Limbourg, F. P. *et al. J. Clin. Invest.* **110**, 1729–1738 (2002)

Classically, steroids hormones act by modulating gene expression, with effects occuring over hours to days. However, growing evidence indicates that important effects of steroids are mediated through rapid nontranscriptional mechanisms. Limbourg *et al.* show that the neuroprotective effects of corticosteroids are mediated through rapid non-nuclear activity of the glucocorticoid receptor (GR), suggesting that drugs that selectively activate the nontranscriptional actions of GR might be beneficial in stroke.

GENE THERAPY

Inhibiting HIV-1 infection in human T cells by lentiviral-mediated delivery of small interfering RNA against CCR5.

Qin, X.-F. *et al*. *Proc. Natl Acad. Sci. USA* **100**, 183–188 (2003)

The use of small interfering RNA (siRNA) to reduce expression of specific genes has great therapeutic potential, but a key challenge is delivering siRNA into the target cells. By using a lentiviral vector derived from HIV-1, Qin *et al.* introduced siRNA against the chemokine receptor CCR5 — a necessary co-receptor for infection by HIV-1 — into T cells, which led to up to 10-fold reduction in CCR5 expression, and a 3–7 fold reduction in the number of T cells infected after challenge with HIV-1.