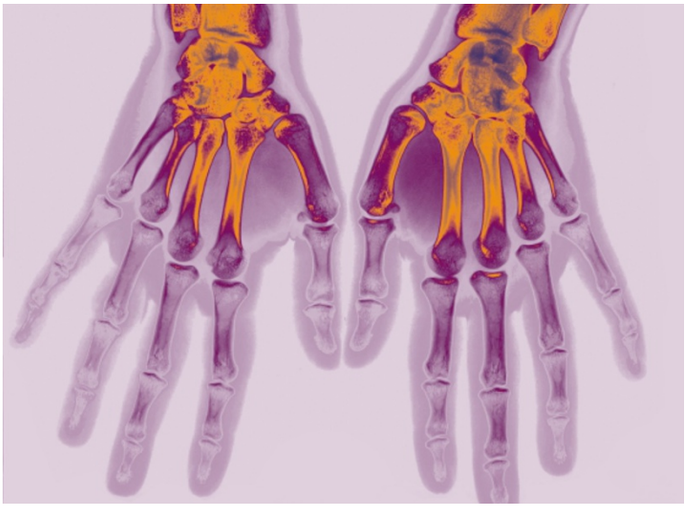

GENE THERAPY

Inflammation blockade

Rheumatoid arthritis (RA) is a disabling autoimmune disease of the synovial joints, characterized by chronic inflammation and the destruction of cartilage and bone. Proinflammatory cytokines, such as tumour-necrosis factor-α (TNF-α) and interleukin 6 (IL-6), have been implicated in the pathogenesis of this disease. Recent work by Shouda and colleagues in *The Journal of Clinical Investigation* shows that blocking cytokine signalling by inducing the expression of the cytokine signal regulator SOC3/CIS3 (suppressor of cytokine signalling 3/cytokine-inducible SH2 protein 3) effectively reduces bone destruction in mouse autoimmune arthritis, thus representing a possible new therapeutic target.

Earlier work, both *in vitro* and *in vivo*, established a role for IL-6 in the development of arthritis. IL-6 acts by activating Janus kinase (JAK) tyrosine kinases and the transcription factor STAT3(signal transducer and activator of transcription 3. SOCS3 was previously cloned by Shouda's group, and was shown to inhibit JAK kinases and to negatively regulate STAT3 functions. As SOCS3 is strongly induced by IL-6, the authors decided to investigate whether SOCS3 plays a negative regulatory role in the progression of RA.

To investigate the importance of STAT3 activation and SOCS3 induction in RA, adenoviral transfer was used to overexpress SOCS3 or a dominant negative form of STAT3 (dnSTAT3) in synoviocytes isolated from patients with RA. The proliferation of cells infected with either of these constructs was significantly reduced, as was the production of IL-6 and TNF-α. These results show that the proliferation and cytokine production of RA-synoviocytes *in vitro* is dependent on JAK/STAT3 signalling and that these processes can be inhibited by the expression of SOCS3 or dnSTAT3.

Do these constructs have any effect on the development of arthritis *in vivo*? Shouda and co-workers injected SOCS3 and dnSTAT3 adenovirus into the ankle joints of mice prone to antigen-induced arthritis (AIA) or collagen-induced arthritis (CIA). In the AIA model, both dnSTAT3 and CIS3 drastically reduced the severity of arthritis and joint swelling compared with control animals. However, in the CIA model the dnSTAT3 adenovirus was less effective than SOCS3, which significantly reduced the severity of arthritis. Finally, the SOCS3 adenovirus was also shown to be an effective treatment for established arthritis.

The authors conclude that adenovirus-mediated gene transfer of the *SOCS3* gene could represent a new approach for effectively blocking the pathogenesis of RA.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Shouda, T. *et al.* Induction of the cytokine signal regulator SOCS3/CIS3 as a therapeutic strategy for treating inflammatory arthritis. *J. Clin. Invest.* **108**, 1781–1788 (2001)

FURTHER READING Feldmann, M. *et al.* Cytokine blockade in rheumatoid arthritis. *Adv. Exp. Med. Biol.* **490**,119–127 (2001)

IN BRIEF

AUTOIMMUNITY

Association of BAFF/BLyS overproduction and altered B-cell differentiation with Sjögren's syndrome.

Groom, J. *et al. J. Clin. Invest.* **109**, 59–68 (2002).

Sjögren's syndrome (SS) is a chronic autoimmune disorder that causes a dry mouth and eyes. It is associated with B-cell hyperactivity and serum autoantibodies. BAFF-transgenic mice develop a lupus-like disorder. This paper shows that ageing BAFF-Tg mice develop a pathology that resembles SS. Marginal-zone-like B cells were identified in salivary glands of BAFF-Tg mice. Humans with SS have elevated levels of circulating BAFF, perhaps because of an imbalance in BAFF production.

INNATE IMMUNITY

Human macrophage activation programmes induced by bacterial pathogens.

G. J. Nau *et al. Proc. Natl Acad. Sci. USA* 22nd January 2002 (epub ahead of print).

Although the innate immune system is not 'specific', there are indications that it can differentiate between different classes of bacteria. Here, the responses of macrophages to three classes of bacteria (Gram-negative, Gram-positive and mycobacteria) were compared using genome-wide gene expression profiling. A common activation programme of gene expression (132 induced and 59 repressed genes) was identified. Pathogen-specific responses were also identified, such as the repression of IL-12 by *Mycobacterium tuberculosis*.

CYTOKINE SIGNALLING

Physical and functional interaction between GATA-3 and Smad3 allows TGF-β regulation of GATA target genes.

Blokzijl, A. *et al. Curr. Biol.* **12**, 35–45

GATA-3 is a master transcriptional activator of $CD4^+$ T_H2-cell differentiation. TGF-β has complex effects on T-cell differentiation and has been proposed to inhibit T_H2 differentiation by inhibiting GATA-3 production. Here, Blokzijl, A. *et al.* reveal a new interface between TGF-β and GATA-3. They show that smad 3 (a crucial TGF-β signal transducer) interacts physically with GATA-3 to form a complex that can regulate the transcription of T_H2 cytokine genes.

IMMUNE REGULATION

T_H2 response induction by dendritic cells: a role for CD40

MacDonald, A.S. *et al. J. Immunol.* **168**, 537–540 2002

Dendritic cells are thought to be key regulators of T_H1–T_H2 differentiation during $CD4^+$ T-cell priming. They interpret microbial signals and relay them to T cells through accessory molecules (such as CD40). However, most work has focused on the induction of T_H1 cells. By adoptive transfer of CD40-deficient dendritic cells that have been primed with T_H1- or T_H2-inducing microbial stimuli, MacDonald *et al.* shows a crucial role for CD40–CD40L interactions in the induction of T_H2, but not T_H1, responses.