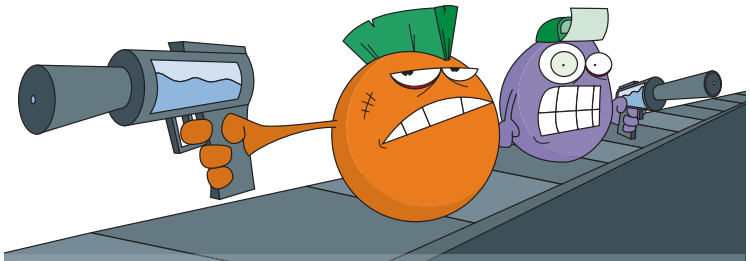

AUTOIMMUNITY

Cytokine partnership to destruction

Researchers reporting in *The Journal of Experimental Medicine* have identified the mechanism behind a form of spontaneous autoimmune arthritis that occurs in mice with a mutation in the interleukin-6 (IL-6) receptor subunit gp130. Intriguingly, it turns out that signalling by this mutant IL-6 receptor in non-haematopoietic cells results in increased production of IL-7 by these cells. This, in turn, drives hyperproliferation of $CD4^+$ T cells, contributing to arthritis.

To reach this conclusion, the authors first asked what cell population — haematopoietic or non-haematopoietic — might be responsible for disease in mice that have a single amino-acid change in gp130, termed $gp130^{F759/F759}$ mice. This mutation disrupts only one IL-6-receptor signalling pathway (the SH2 (SRC-homology 2)–MAPK (mitogen-activated protein kinase) pathway) and results in increased signalling through the STAT3 (signal transducer and activator of transcription 3) pathway. Surprisingly, lethally irradiated wild-type mice that received bone marrow from $gp130^{F759/F759}$ mice did not develop arthritis. By contrast, $gp130^{F759/F759}$ mice that received wild-type bone marrow did develop arthritis as normal, indicating that the disease was due to the mutation in non-haematopoietic cells. However, this did not preclude a role for haematopoietic cells in the disease process, as $gp130^{F759/F759}$ mice that lacked $CD4^+$ T cells did not develop disease.

Next, on observing that $gp130^{F759/F759}$ mice had enlarged lymph nodes and spleens, the authors tested whether homeostatic proliferation of T cells might be involved, as has been described in other models of autoimmune disease. Indeed, after irradiation or neonatal thymectomy, homeostatic proliferation of $CD4^+$ T cells was increased and more rapid in the mutant mice than in wild-type controls. Notably, thymectomized $gp130^{F759/F759}$ mice developed arthritis earlier than sham-operated $gp130^{F759/F759}$ mice, suggesting a role for increased homeostatic proliferation in the disease.

So, how does the non-haematopoietic-cell mutation in the IL-6 receptor induce $CD4^+$ T-cell hyperproliferation? The authors showed that the expression of IL-7, which is known to be involved in T-cell proliferation, was markedly increased in $gp130^{F759/F759}$ non-haematopoietic cells. Moreover, treatment of these cells with IL-6, or other IL-6-family cytokines that also bind receptors that contain gp130, led to increased IL-7 production. Because the STAT3 pathway is functional in $gp130^{F759/F759}$ cells, the authors hypothesized that signalling through this pathway induced IL-7 production. Accordingly, conditional knockout of *Stat3* in non-haematopoietic cells impaired IL-6-driven IL-7 production.

Finally, the important role for IL-7-mediated homeostatic proliferation of $CD4^+$ T cells in the disease was confirmed by showing that *in vivo* depletion of IL-7 by treatment with specific antibody suppressed homeostatic proliferation and disease development in thymectomized $gp130^{F759/F759}$ mice.

This study provides the first evidence of a partnership between IL-6 and IL-7 in driving T-cell proliferation. Whether such a mechanism occurs in the joints of patients with rheumatoid arthritis, which have been shown to contain increased amounts of IL-6, will be the subject of future studies.

Lucy Bird

ORIGINAL RESEARCH PAPER Sawa, S. *et al.* Autoimmune arthritis associated with mutated interleukin (IL)-6 receptor gp130 is driven by STAT3/IL-7-dependent homeostatic proliferation of $CD4^+$ T cells. *J. Exp. Med.* **203**, 1459–1470 (2006)

IN BRIEF

IMMUNOTHERAPY

Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing $CD4^+CD25^-LAP^+$ T cells.

Ochi, H. *et al. Nature Med.* **12**, 627–635 (2006)

The induction of regulatory cells is a principal goal of immunotherapy for autoimmune disease. A new study shows that oral administration of CD3-specific antibody suppresses autoimmune encephalomyelitis, when given at the peak of disease but also before induction of the disease. Unlike parenteral administration of CD3-specific antibody, oral administration did not deplete T cells or induce T-cell division, even at high doses. The suppression of disease by orally administered CD3-specific antibody was through the induction of transforming growth factor-β-dependent regulatory T cells that express surface latency-associated peptide (LAP). These results indicate that oral administration of CD3-specific antibody might provide a signal to T cells in the gut that is not strong enough to induce cell division or cell deletion, but can enhance the regulatory function of $CD4^+CD25^-LAP^+$ T cells.

IMMUNE REGULATION

SOCS-3 negatively regulates innate and adaptive immune mechanisms in acute IL-1-dependent inflammatory arthritis.

Wong, P. K. K. *et al. J. Clin. Invest.* **116**, 1571–1581 (2006)

The suppressor of cytokine signalling (SOCS) proteins are important negative regulators of cytokine signalling, but their role in disease is not well understood. Using $Socs^{-/\Delta vav}$ mice, which lack SOCS3 in haematopoietic and endothelial cells, Wong *et al.* examined the function of endogenous SOCS3 during interleukin-1 (IL-1)-dependent inflammatory arthritis. The absence of SOCS3 was associated with particularly severe arthritis, which was characterized by an increased number of infiltrating neutrophils in the synovium, increased osteoclast generation and bone destruction. $Socs^{-/\Delta vav}$ mice produced higher levels of granulocyte colony-stimulating factor (G-CSF) and IL-6 than wild-type mice did. In the absence of SOCS3, antigen-specific T-cell proliferation was also increased in both the draining and non-draining lymph nodes, and IL-17 production was higher. Therefore, endogenous SOCS3 might be a potent negative regulator of multiple inflammatory pathways in arthritis.

IMMUNE REGULATION

Collagens are functional, high affinity ligands for the inhibitory immune receptor LAIR-1.

Lebbink, R. J. *et al. J. Exp. Med.* **203**, 1419–1425 (2006)

Collagens are the principal proteins of the extracellular matrix (ECM) and have a crucial role in maintaining the integrity of various tissues. Lebbink *et al.* have shown that collagens are functional ligands for the widely expressed immune inhibitory receptor LAIR1 (leukocyte-associated immunoglobulin-like receptor 1) and can directly inhibit the activation of immune cells *in vitro*. They showed that LAIR1 binds to a common collagen motif in a hydroxyproline-dependent manner and is directly crosslinked by collagens, thereby downregulating the immune response. The binding of ECM collagens to an inhibitory immune receptor is a novel mechanism of peripheral immune regulation. The authors note that all ligands for inhibitory immune receptors known so far have been membrane molecules, which could indicate that these receptors have a regulatory role in cell–cell interactions.