AUTOIMMUNITY

T cells escape deletion

Defects in thymic T-cell selection have long been suspected to lead to autoimmunity and now, Shimon Sakaguchi and colleagues describe a mouse model of autoimmune arthritis in which disease is caused by a single point mutation in the ζ -chain-associated protein 70 (*Zap70*) gene, altering the threshold of T-cell receptor (TCR) signalling and enabling autoreactive T cells to avoid deletion.

Sakaguchi *et al.* derived the SKG strain of mice from BALB/c animals and observed that they spontaneously developed a chronic arthritis that resembles rheumatoid arthritis in humans. Initial joint swelling was limited to finger joints of the forepaws, but progressed to the hindpaws, wrists and ankles and was accompanied by high titres of rheumatoid factor. Immunohistochemistry of the swollen joints revealed a marked cellular infiltration that included CD4⁺ T cells, and these cells were shown to mediate disease as they induced arthritis after transfer to T-cell-deficient recipients.

The *Skg* locus was mapped to a region of chromosome 1 that is known to include the *Zap70* gene and further analysis identified a single nucleotide substitution in *Zap70* of SKG mice, which altered the initial amino-acid residue of the carboxy-terminal Src homology 2 (SH2) domain. Transgenic expression of normal human ZAP70 by SKG mice prevented the development of arthritis, confirming the mutation as the cause of disease.

SKG T cells were shown to have a diminished proliferative response to specific peptide as well as polyclonal stimulation with CD3-specific antibodies, presumably as a result of the observed reduction in phosphorylation of key signalling molecules and the inability of Zap70 to associate with TCR- ζ .

Transgenic T cells expressing an MHC class-I-restricted TCR specific for the male H-Y antigen (HY-TCR) are efficiently selected in female mice,

but are negatively selected in males. However, the authors observed that after crossing these TCR-transgenic mice onto a homozygous SKG background, positive selection of HY-TCR⁺CD8⁺ T cells now occurred efficiently in male mice, indicating that the *Skg* mutation allows positive selection of T cells that are otherwise negatively selected. Further evidence for this was provided by the observation that SKG mice expressing an MHC class-II-restricted TCR have an increased population of transgenic-TCR^{low} CD4⁺ T cells that express an endogenous TCR- α chain compared with wild-type TCR-transgenic mice.

These results provide evidence that genetic mutations affecting the TCR-signalling pathway in such a way as to disrupt T-cell selection can cause autoimmunity in mice, and the authors suggest that similar mutations might prove to be important in the development of rheumatoid arthritis in some human patients.

Karen Honey

References and links
ORIGINAL RESEARCH PAPER Sakaguchi, N. *et al.* Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. *Nature* **426**, 454–460 (2003)

IN BRIEF

AUTOIMMUNITY

HSP70 promotes antigen-presenting cell function and converts T-cell tolerance to autoimmunity *in vivo*.

Millar, D. G. *et al.* *Nature Med.* 16 November 2003 (doi:10.1038/nm962)

Here, Millar *et al.* show that administration of HSP70 increases the stimulatory capacity of antigen-presenting cells (APCs) *in vivo*. Mice engineered to express the lymphocytic choriomeningitis virus glycoprotein (LCMV-GP) in pancreatic β -cells and in which CD8⁺ T cells are specific for LCMV-GP are tolerant when administered the immunodominant LCMV-GP-derived epitope gp33. HSP70 converts tolerance to autoimmunity when co-administered with gp33, rapidly inducing diabetes. HSP70 did not increase the expression of MHC class II molecules or CD80/CD86 by APCs, but its ability to induce diabetes was dependent on CD4⁺ T-cell help and CD40 expression by APCs. The authors, therefore, suggest that HSP70 partially activates APCs, but subsequent CD40 ligation is required for full activation and the onset of diabetes.

GENE REGULATION

A conserved signal-responsive sequence mediates activation-induced alternative splicing of CD45.

Rothrock, C. *et al.* *Mol. Cell* **12**, 1317–1324 (2003)

Alternative splicing generates the distinct CD45 isoforms expressed by naive and activated T cells. In this paper, Rothrock *et al.* identify a consensus sequence — the activation-responsive sequence (ARS) — that is required for the exclusion of exons 4, 5 and 6 from CD45 after stimulation with phorbol 12-myristate 13-acetate (PMA). The ARS within exon 4 was mapped and when compared with exons 5 and 6 for regions of sequence homology, a conserved imperfect repeat sequence was observed. ARS-homology regions were found and shown to mediate PMA-induced alternative splicing in other PMA-regulated genes, including cytotoxic T lymphocyte antigen 4 (*CTLA4*), Agrin (*AGRN*) and *FYN*. These studies indicate that a common pathway might regulate activation-induced alternative splicing of a large number of diverse genes.

HIV

Use of a small molecule CCR5 inhibitor in macaques to treat simian immunodeficiency virus infection or prevent simian–human immunodeficiency virus infection.

Veazey, R. S. *et al.* *J. Exp. Med.* **198**, 1551–1562 (2003)

Absence of the chemokine receptor CCR5 protects against HIV infection, and therapies for HIV based on CCR5-specific antibodies are being developed. In this study, the effects of a CCR5-specific receptor agonist CMPD167 on established simian immunodeficiency virus (SIV) infection were investigated. CMPD167 was shown to have antiviral activity against SIVmac251 and SIVB670 replication *in vivo*, resulting in marked decreases in plasma viraemia in six rhesus macaques, which was maintained in three animals. Vaginal administration of gel-formulated CMPD167 reduced the extent of viraemia after infection with SHIV-162P4, but was unable to prevent vaginal transmission.