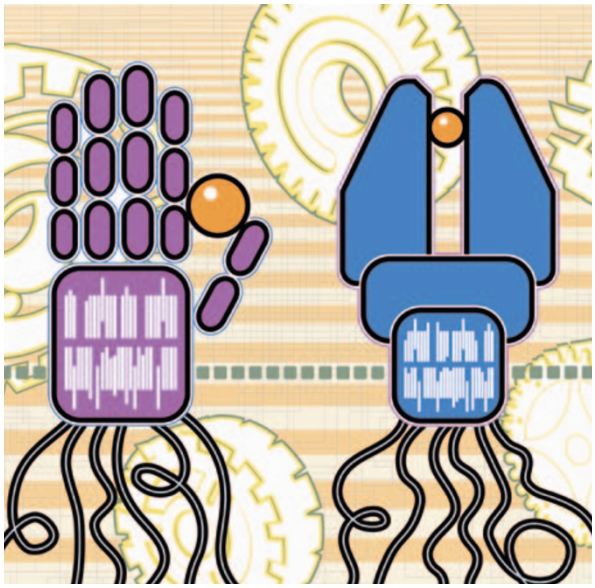
T CELLS

Selecting skin T cells

Although the steps involved in the selection of αβ T cells in the thymus have been elucidated in superb detail, the proposed thymic development of γδ T cells has, until now, remained a black box. Robert Tigelaar and colleagues now provide direct evidence that the development of a subset of skin-resident intraepithelial lymphocytes (IELs) expressing an oligoclonal γδ T-cell receptor (TCR) depends on positive selection in the thymus.



IELs are well known to have very limited antigen-receptor diversity. One such IEL population in the skin consists of dendritic epidermal T cells (DETCs), which express an oligoclonal γδ TCR (Vγ5Vδ1) detectable with the monoclonal antibody 17D1. Indeed, in the skin of most mouse strains, 17D1 binds 95% of DETCs. However, the authors have identified a mouse substrain, named FVB-Tac, that has a heterogeneous repertoire of DETCs, with very few cells expressing the Vγ5Vδ1 TCR. Nevertheless, these mice have normal γδ TCR repertoires of IELs in other tissues, including the intestine and reproductive tract. This indicates that FVB-Tac mice lack a crucial factor that is specifically involved in generating the usually homogeneous DETC repertoire.

An important functional role for the presence of a homogeneous 17D1-reactive DETC repertoire was illustrated by the fact that FVB-Tac mice developed spontaneous ear inflammation, as well as more severe dermatitis following contact with an irritant than control animals.

Further analysis of the defect in FVB-Tac mice showed that the maturation of DETC precursors in the fetal thymus at embryonic days 15 to 17 was defective. That is, the precursors failed express appropriate levels of maturation markers such as CD45RB and CD122 and chemokine receptors that are required for thymic emigration. Moreover, this maturation defect was concomitant with increased apoptosis of the DETC precursors, indicating an association between maturation and selection.

To determine whether the defect in FVB-Tac mice lies in the haematopoietic ($CD45^+$) or stromal ($CD45^-$) components of the fetal thymus, the authors used reaggregated thymic organ cultures (RTOCs). Notably, RTOCs

ASTHMA AND ALLERGY

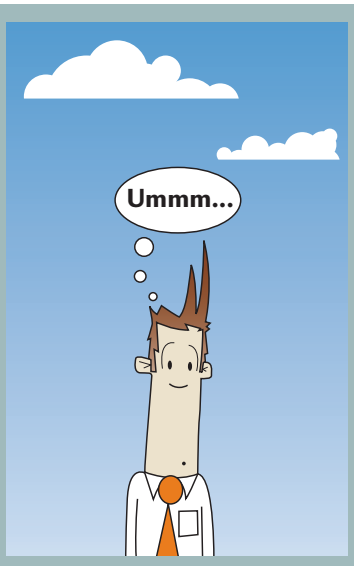
TSLP aids memory

It has been suggested that memory T helper 2 (T_H2) cells are the principal cell population responsible for the maintenance of chronic allergic inflammation. However, the mechanism by which these memory cells are maintained and reactivated remains elusive, in part owing to a lack of specific cell markers. Now, new research shows that $CD4^+$ T cells that express CRTH2 (chemoattractant-receptor homologous molecule expressed by T_H2 cells) are T_H2-type central memory cells. Wang *et al.* also found that dendritic cells (DCs) that have been activated by thymic stromal lymphopoietin (TSLP, a crucial factor in the development of allergic inflammation) promote the expansion and reactivation of these cells while maintaining their central memory T_H2-cell phenotype.

> "TSLP-activated DCs maintained both the central memory and T_H2-associated phenotypes of the expanded $CRTH2^+CD4^+$ T cells"

Previous studies have shown that CRTH2 is the most reliable marker for circulating human $CD4^+$ T_H2 cells. Therefore, Liu and colleagues examined the phenotype and molecular signature of these $CRTH2^+CD4^+$ T cells using various techniques. They found that these T cells are a unique subset of central memory T cells that have T_H2-cell characteristics, making them distinct from naive T cells, $CRTH2^-$ central memory T cells and effector memory T cells.

TSLP is produced by epithelial cells during allergic inflammation, leading to the pathogenesis associated with atopic dermatitis and asthma. The authors examined the ability of DCs that were activated by various stimuli, including TSLP, to expand $CRTH2^+CD4^+$ T cells *in vitro*. DCs that were stimulated with TSLP, or with the homeostatic cytokines interleukin-15 (IL-15) or IL-15 plus IL-7, induced the expansion of this cell population. However, only TSLP-activated DCs maintained both the central memory



and T_H2-associated phenotypes of the expanded $CRTH2^+CD4^+$ T cells. In contrast, DCs that were activated with IL-15 or IL-15 plus IL-7 induced $CRTH2^+CD4^+$ T cells to differentiate into effector memory T cells.

Interestingly, TSLP-activated DCs induced the expression of several

generated with CD45$^+$ cells from FVB-Tac mice and CD45$^-$ cells from control mice showed normal DETC maturation, as evidenced by co-expression of Vγ5Vδ1 and CD45RB. By contrast, RTOCs generated with FVB-Tac CD45$^-$ cells and wild-type CD45$^+$ cells contained very few CD45RB^{hi}Vγ5Vδ1$^+$ cells, indicating that the defect in FVB-Tac mice is intrinsic to stromal cells.

Last, the authors confirmed that the delivery of signals through the Vγ5Vδ1 TCR by thymic stromal cells was important for the maturation of DETC precursors, as the maturation defect could be rescued by the presence of 17D1 in the RTOCs.

This study highlights the importance of thymic development for a subpopulation of IELs, as well as an important and often overlooked role for these cells in physiological responses.

Lucy Bird

ORIGINAL RESEARCH PAPER Lewis, J. M. *et al.* Selection of the cutaneous intraepithelial γδ$^+$ T cell repertoire by a thymic stromal determinant. *Nature Immunol.* 9 July 2006 (doi:10.1038/ni1363)

pro-allergic genes by CRTH2$^+$CD4$^+$ T cells, such as those encoding cystatin A and prostaglandin D_2 synthase, which might further promote allergic inflammation by central memory T_H2 cells. T-cell accumulation at the inflammatory sites of atopic dermatitis is associated with high levels of TSLP expression. T cells were found colocalized with activated DCs at these sites, and an examination of these T cells showed that most expressed CRTH2. By contrast, T cells in lesional skin sections from T_H1-cell-mediated inflammatory diseases, such as psoriasis vulgaris, did not express CRTH2.

So, these data indicate that TSLP-activated DCs might have an important role in the maintenance and reactivation of central memory T_H2 cells in allergic disease.

Olive Leavy

ORIGINAL RESEARCH PAPER Wang, Y-H. *et al.* Maintenance and polarization of human T_H2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. *Immunity* **24**, 827–838 (2006)

AUTOIMMUNITY

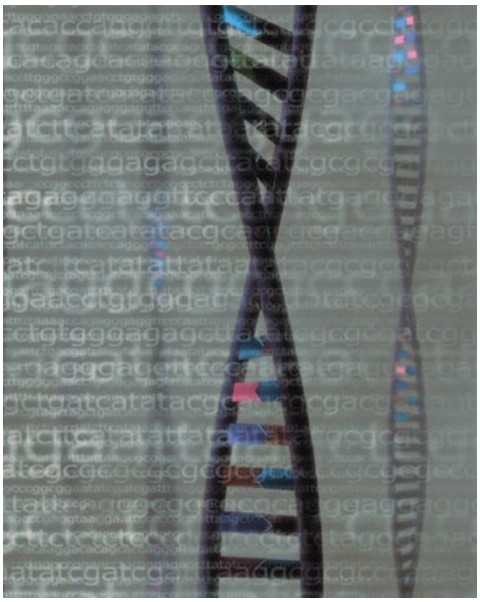
Defective genes at checkpoints

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by the presence of antibodies specific for self nucleic acids or proteins associated with these nucleic acids. For several decades, researchers have been trying to pin down the precise means by which tolerance to self molecules breaks down in individuals with SLE and to identify the various genes and proteins that underlie this disorder. In both mice and humans, SLE seems to be polygenic, and it is known to be associated with more than 12 genetic loci. Now, two papers published in *Science* explain the contribution of several loci to SLE in mice; together with previous findings, these results provide a potential explanation for the pathogenesis of SLE.

During B-cell development in the bone marrow, a diverse repertoire of B-cell receptors (BCRs) is generated through the random rearrangement of immunoglobulin gene segments. Many of these rearrangements result in BCRs that bind self antigens. However, such autoreactive B cells do not usually reach the periphery, because intracellular signalling through a self-reactive BCR results in cell death, anergy or receptor editing (in which new rearrangements generate a modified BCR).

To study how these tolerance mechanisms might break down and lead to SLE, Kumar *et al.* investigated the *Sle1* locus, which is known to be an SLE-susceptibility locus in mice and has an orthologue in humans. The authors show that inherited differences in one of the genes encoded in this region, *Ly108*, result in variations in BCR signalling: the presence of *Sle1b^z*, an allele that is present in a strain of SLE-prone mice, reduces the ability of self-reactive B cells to undergo anergy or receptor editing and therefore increases the number of self-reactive B cells in the periphery.

Pisitkun *et al.* studied another SLE-susceptibility locus in mice, the well-known Y-chromosome-linked autoimmune accelerator (*Yaa*) locus. They found that *Yaa* is a result of duplication of a segment of the X chromosome that has been transposed to the Y chromosome and contains the Toll-like receptor 7 (*Tlr7*) gene. Consequently, the B cells of *Yaa* mice express double the amount of TLR7 and are twice as sensitive to TLR7 ligands as are B cells from wild-type mice. Because TLR7 is present in the endosome, it would normally come into contact only with microbial nucleic acids, but mammalian nucleic acids can bind TLR7 if they are delivered to the endosome through internalization of cell-surface BCR. In addition, the phenotypic effects of *Yaa*



are known to be modified through interactions with other genes. The authors show that the presence of an SLE-associated allele of the inhibitory receptor FcγRIIb, together with *Yaa*, increases the severity and incidence of SLE symptoms.

Because of the polygenic nature of SLE, these findings, taken together with those from previous studies, indicate that self-tolerance is likely to be broken by a succession of defective checkpoints (see Further reading). First, B cells might have a defect in the induction of anergy and receptor editing (as exemplified by *Sle1b^z*), thereby increasing the pool of self-reactive B cells in the periphery. Second, peripheral B cells might have a defect in the inhibitory signalling that normally opposes BCR signalling (as in the case of loss of FcγRIIb function). Last, peripheral B cells might have a defect in discrimination between self and microbial nucleic acids by TLRs (as in the case of *Yaa* mice), thereby inducing the proliferation of self-reactive B cells. Each successive defect therefore removes any redundant controls in the system and compounds the problem, allowing T-cell-independent proliferation and autoantibody production by B cells.

Davina Dadley-Moore

ORIGINAL RESEARCH PAPERS Kumar, K. R. *et al.* Regulation of B cell tolerance by the lupus susceptibility gene *Ly108*. *Science* **312**, 1665–1669 (2006) | Pisitkun, P. *et al.* Autoreactive B cell responses to RNA-related antigens due to *TLR7* gene duplication. *Science* **312**, 1669–1672 (2006)
FURTHER READING Goodnow, C. C. Discriminating microbe from self suffers a double Toll. *Science* **312**, 1606–1608 (2006)