LYMPHOCYTE DEVELOPMENT

Signalling identity

Developing thymocytes can differentiate into either αβ or γδ T cells, but how do they decide which path to take? Two papers in *Immunity* provide evidence that the key determinant in the αβ/γδ lineage-fate decision is the strength of the signal transmitted by the T-cell receptor (TCR).

Thymocytes at the $CD4^-CD8^-$ (double negative, DN) stage of development can express either the γδ-TCR or the pre-TCR (which consists of a complex of the TCR β-chain and the invariant pre-TCR α-chain). Although it is clear that the TCR is important in αβ/γδ lineage commitment, its exact role in this process remains controversial. Recent data show that both the αβ-TCR and the γδ-TCR can promote cross lineage development, which is inconsistent with models stating that the specific TCR isoform (pre-TCR or γδ-TCR) only directs development or promotes survival along its respective lineage. This, together with speculation that the pre-TCR provides a weaker signal than the γδ-TCR, led both groups to ask whether TCR signal strength is an important factor.

To manipulate TCR signalling potential, both groups used γδ-TCR-transgenic mice crossed with mice that are deficient in various molecules involved in either ligand recognition or TCR signal transduction. In γδ-TCR-transgenic mice, thymocyte development results not only in γδ T-lineage cells, which remain DN, but also in αβ T-lineage cells, which can be detected as $CD4^+CD8^+$ (double positive, DP) cells. Haks *et al.* used mice transgenic for the KN6 γδ-TCR crossed onto the recombination-activating gene (RAG)-deficient background to prevent expression of other TCR isoforms (the pre-TCR or αβ-TCR). In these mice, almost all thymocytes expressed the γδ-TCR. They then showed that backcrossing these mice onto the β_2-microglobulin-deficient background (which lacks the KN6 ligand) or the tyrosine kinase LCK-deficient background markedly reduced the number of mature γδ T cells but allowed the generation of a substantial population of DP thymocytes with the hallmarks of αβ T-lineage cells. This indicates that interfering with ligand binding or limiting downstream signalling enables a γδ-TCR to efficiently promote the development of αβ, rather than γδ, T-lineage cells.

In the model used by Hayes *et al.*, reducing γδ-TCR cell-surface expression resulted in a significant increase in the number of DP thymocytes and a corresponding decrease in $\gamma\delta\text{-TCR}^+$ thymocyte numbers. Because TCR signalling is coupled to ITAMs (immunoreceptor tyrosine-based activation motifs) in the TCR-associated CD3 ζ-chain, genetic reconstitution of γδ-TCR-transgenic, CD3ζ-deficient mice with transgenes encoding CD3ζ molecules that had between zero and three ITAMs enabled the authors to show that attenuation of the γδ-TCR signal favoured αβ T-cell development. Conversely, increasing γδ-TCR cell-surface expression or removing a negative regulator of signalling, CD5, favoured γδ T-cell development. So, in these experiments, reducing the signal strength resulted in more αβ T-lineage cells at the expense of γδ T-lineage cells, whereas increasing the signal strength had the converse effect.

Importantly, both groups showed, in non-transgenic mice, that $\gamma\delta\text{-TCR}^+$ thymocytes have higher levels of activated intracellular-signalling molecules than do pre-TCR^+ thymocytes. Taken together, these data are consistent with a model in which $\gamma\delta\text{-TCR}^+$ thymocytes that receive a 'strong' signal develop into γδ T-lineage cells, whereas $\gamma\delta\text{-TCR}^+$ or pre-TCR^+ thymocytes that receive a 'weak' signal develop into αβ T-lineage cells.

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References and links

ORIGINAL RESEARCH PAPERS Haks, M. *et al.* Attenuation of γδTCR signaling efficiently diverts thymocytes to the αβ lineage. *Immunity* **22**, 595–606 (2005) | Hayes, S. M., LiQi, L. & Love, P. E. TCR signal strength influences αβ/γδ lineage fate. *Immunity* **22**, 583–593 (2005)

IN BRIEF

INFLAMMATION

Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury.

Thiel, M. *et al. PLoS Biol.* **3**, e174 (2005)

This study looks at the clinical implications of a recently described hypoxia-driven anti-inflammatory mechanism for patients with acute respiratory distress syndrome (ARDS) who are treated by mechanical ventilation with high oxygen concentrations. In several models, accumulation of adenosine in hypoxic conditions induces a physiological tissue-protective pathway through adenosine receptors (A2ARs). The authors confirm that oxygenation can exacerbate inflammatory lung damage by blocking the A2AR pathway in several *in vivo* mouse models of lung disease. Lung inflammation could be prevented by the addition of an A2AR agonist. They suggest that ventilation of patients with ARDS can cause an iatrogenic exacerbation of lung inflammation that could be treated with A2AR agonists or other anti-inflammatory drugs.

IMMUNE REGULATION

Negative feed back regulation of T helper type 1 (T_H1)/T_H2 cytokine balance via dendritic cell and natural killer T cell interactions.

Minami, K. *et al. Blood* 10 May 2005 (doi:10.1182/blood-2004-12-4738)

This study describes how interactions between dendritic cells (DCs) and natural killer T (NKT) cells can regulate the T helper 1 (T_H1)/T_H2-cytokine balance. DCs can stimulate NKT cells by CD1d-restricted presentation of α-galactosylceramide (α-GalCer), but the NKT-cell response seems to be influenced by extracellular stimuli received by the DC. Indeed, pretreatment of α-GalCer-loaded DCs with T_H1 or T_H2 cytokines *in vitro* led to increased NKT-cell production of T_H2 or T_H1 cytokines, respectively, indicating that the NKT cells might provide a negative-feedback mechanism to maintain the cytokine balance. α-GalCer has been shown to have antitumour effects that require NKT-cell production of interferon-γ. So, by pretreating tumour-bearing mice with a T_H2 cytokine, interleukin-4, the authors could enhance the α-GalCer-induced antitumour response and reduce tumour metastases.

AUTOIMMUNITY

Initiation and exacerbation of autoimmune demyelination of the central nervous system via virus-induced molecular mimicry: implications for the pathogenesis of multiple sclerosis.

Croxford, J. L. *et al. J. Virol.* **79**, 8581–8590 (2005)

Viral infections are suspected of triggering various autoimmune diseases, but proving this has proved controversial. This study shows that infection with a non-pathogenic variant of Theiler's murine encephalomyelitis virus (TMEV) expressing a *Haemophilus influenzae*-encoded peptide that mimics a self-myelin epitope induces and exacerbates disease in a mouse model of multiple sclerosis. The disease is mediated by cross-activation of autoreactive T cells and was shown to depend on processing of the mimic from the native *H. influenzae* protein and on virus-activated innate immune signals.