IMMUNE REGULATION

Driving DC differentiation

Little is known about the transcriptional control of dendritic-cell (DC) differentation, but a study reported in *Immunity* now shows that the lipid-activated transcription factor peroxisome proliferative activated receptor-γ (PPARγ) is upregulated early after DC differentiation from monocytes. This might be important to control the ability of DCs to stimulate invariant natural killer T (iNKT) cells, a population of autoreactive cells that seem to have a role in controlling the development of autoimmune disease.

The authors decided to investigate the role of PPARγ in DC differentiation because it is known to be expressed by both macrophages and DCs, and because PPARγ regulates the expression of CD36 — a surface receptor that mediates uptake of apoptotic cells. In this study, the role of PPARγ was examined using a human monocyte-derived DC system. PPARγ expression (at both the mRNA and protein levels) was found to be upregulated to a high level within a few hours of DC differentiation. Treatment of DCs with a PPARγ-specific agonist induced a phenotypic change in the DCs, including a decrease in the expression of CD1a, an increase in the expression of CD1d and an enhancement of endocytic activity. CD1 molecules are non-classical MHC-class-I-like molecules, and CD1d can present lipid or glycolipid antigens to iNKT cells. The results of this study show that CD1 expression during DC differentiation is coordinately regulated by activation of PPARγ, and DCs treated with the PPARγ agonist were able to activate iNKT cells more efficiently in the presence of α-galactosyl ceramide — which is presented by CD1d — than were untreated DCs.

What are the biological implications of this study? Reduced numbers of iNKT cells have been associated with the development of autoimmune diseases, and it might be possible to modify autoimmune diseases by enhancing CD1d expression and iNKT activation through the targeting of PPARγ.

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References and links

ORIGINAL RESEARCH PAPER Szatmari, I. *et al*. Activation of PPARγ specifies a dendritic cell subtype capable of enhanced induction of iNKT cell expansion. *Immunity* **21**, 95–106 (2004).

FURTHER READING Wilson, S. B. & Delovitch, T. L. Janus-like role of regulatory iNKT cells in autoimmune disease and tumour immunity. *Nature Rev. Immunol*. **3**, 211–222 (2003) | Daynes, R. A. & Jones, D. C. Emerging roles of PPARs in inflammation and immunity. *Nature Rev. Immunol*. **2**, 748–759 (2002).

WEB SITE

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IN BRIEF

T-CELL MEMORY

Serine protease inhibitor 2A is a protective factor for memory T cell development.

Liu, N. *et al*. *Nature Immunol*. 15 August 2004 (doi:10.1038/ni1107).

The mechanisms by which antigen-specific $CD8^+$ T cells escape programmed cell death (PCD) and become memory cells are not well established. Now, Liu *et al.* report a crucial protective role for serine protease inhibitor 2A (SPI2A), which inhibits PCD triggered by cathepsins. By screening for candidate genes, the authors showed that SPI2A expression was upregulated by memory T cells but not by naive T cells. Effector T cells from bone-marrow chimeric mice expressing a SPI2A transgene showed suppression of cathepsin B activity and induction of PCD. Accordingly, more virus-specific memory cells survived in these mice following viral infection, indicating that commitment to the memory lineage is facilitated by the upregulation of protective genes.

LYMPHOID ARCHITECTURE

Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5.

Allen, C. D. C. *et al*. *Nature Immunol*. 1 August 2004 (doi:10.1038/ni1100).

This study explores the mechanisms involved in segregating B cells to the dark and light zones of germinal centres (GCs), in which they carry out somatic hypermutation and antigen-driven selection, respectively. By generating fetal-liver chimeras, the authors show that deficiency in the chemokine receptor CXCR4 results in disrupted GC compartmentalization. Immunohistochemical analysis indicated that centroblasts undergoing somatic hypermutation expressed high levels of CXCR4 and localized to the dark zone, which is consistent with higher expression of the CXCR4 ligand CXCL12 in the dark zone compared with the light zone. By contrast, expression of CXCR5 and its ligand CXCL13 were concentrated in the light zone and contributed to recruitment of cells to this zone.

INFLAMMATION

Tumour necrosis factor (TNF) receptor shedding controls thresholds of innate immune activation that balance opposing TNF functions in infectious and inflammatory diseases.

Xanthoulea, S. *et al*. *J. Exp. Med.* **200**, 367–376 (2004).

Although the pro-inflammatory effects of tumour-necrosis factor (TNF) are beneficial to host defence, they can be harmful if not controlled. Proteolytic cleavage (shedding) of cell-surface TNF receptor p55 (TNFRp55) modulates TNF function, and in humans, impaired receptor shedding is linked to a group of autoinflammatory syndromes. In this study, knock-in mice heterozygous or homozygous for a non-sheddable TNFRp55 spontaneously developed TNF-dependent chronic inflammation of the liver and were increased in their susceptibity to TNF and lipopolysaccharide toxicity, as well as chronic inflammatory disease. By contrast, these animals showed increased resistance to infection with *Listeria monocytogenes*. These effects indicate a crucial role for TNFRp55 shedding in the regulation of the effects of TNF *in vivo*.