IMMUNE REGULATION

Take two for Notch

Previous studies have indicated that signalling through Notch proteins is involved in the differentiation of $CD4^+$ T cells into T helper (T_H) cells, although whether these signals are required for differentiation into T_H1 cells, T_H2 cells or both was not clear. But now, in a paper published in *The Journal of Experimental Medicine*, Notch signalling in mature $CD4^+$ T cells is shown to be required for T_H2-cell-mediated immunity.

Notch signalling that depends on the transcription factor CSL (also known as RBP-Jκ) requires the transcription cofactor mastermind-like 1 (MAML1). So, to study the role of Notch signalling in $CD4^+$ T cells, Tu *et al.* generated mice (denoted as CCD mice) in which a green-fluorescent-protein-tagged, dominant-negative form of MAML1 was expressed only by $CD4^+$ T cells.

Importantly, T-cell development — in terms of the cellularity of the thymus, the proportion of $CD4^+$ and $CD8^+$ T cells, and the expression of cell-surface markers of activation — was normal in these mice. However, when $CD4^+$ T cells from these mice were cultured under T_H2-cell-polarizing conditions, the proportion of cells that produced interleukin-4 (IL-4), and the amount of IL-4 that they produced, was markedly lower than in control-cell cultures. By contrast, normal numbers of interferon-γ-producing cells were generated after culture under T_H1-cell-polarizing conditions.

Consistent with a role for CSL-dependent Notch signalling in optimal differentiation into T_H2 cells, CCD mice failed to generate a protective T_H2-cell response after infection with *Trichuris muris*. By contrast, CCD mice infected with *Leishmania major* generated a protective T_H1-cell response similar to that generated by control animals.

This study indicates that CSL-dependent Notch signalling is required for generation of a protective T_H2-cell response *in vivo*. The authors suggest that targeting this signalling pathway could potentially be used to treat T_H2-cell-mediated diseases such as asthma.

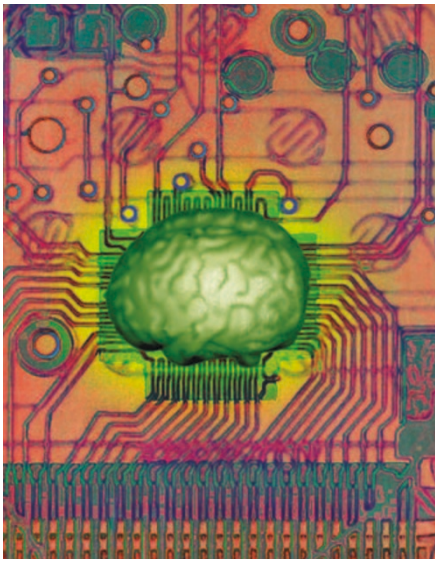
Karen Honey

References and links

ORIGINAL RESEARCH PAPER Tu, L. *et al.* Notch signaling is an important regulator of type 2 immunity. *J. Exp. Med.* **202**, 1037–1042 (2005)

IMMUNE RESPONSES

Shuttling serotonin: not just in our heads



Serotonin is generally thought of as a neurotransmitter that is passed between neurons at neuronal synapses for the regulation of appetite, mood and pain. Now, Peta O'Connell and colleagues report that serotonin might be delivered from dendritic cells (DCs) to T cells across the immunological synapse in a manner similar to that which occurs between neurons. They propose that this is a new form of rapid communication between DCs and T cells and that this might have important implications for the regulation of T-cell responses.

A role for serotonin in the immune response has previously been reported: serotonin has been shown to be a mediator that is released by mast cells and platelets in response to injury or pro-inflammatory signals. In this study, the authors show that, although DCs cannot themselves synthesize serotonin, they express the serotonin transporter SERT (also known as SLC6A4). Cell-surface expression of SERT by DCs was increased following activation and maturation, and this enabled the cells to take up serotonin from their microenvironment. Presumably, mature DCs could acquire serotonin from platelets or mast cells at inflammatory sites, but the authors show that activated T cells can synthesize serotonin for uptake by mature DCs.

Serotonin taken up by activated DCs was stored in vesicular compartments and not degraded by the serotonin catabolic enzymes monoamine oxidase A (MAOA) and MAOB, owing to downregulation of expression of these enzymes after DC activation. By loading DCs with radiolabelled serotonin, the authors next showed that stored serotonin is rapidly released, through exocytosis, in the presence of extracellular ATP, which induces the mobilization of intracellular calcium as occurs in DCs on interaction with T cells.

The authors then asked what effect serotonin might have on T cells. Treatment of T cells with exogenous serotonin reduced the concentration of the intracellular-signalling molecule cyclic AMP (cAMP), which inhibits T-cell proliferation at high concentrations, indicating that serotonin might terminate the initial increase in cAMP concentration that occurs after T-cell-receptor ligation and therefore promote T-cell activation.

Given these data, the authors suggest that DCs shuttle serotonin, possibly synthesized by activated T cells, to the synaptic space between a DC and a naive T cell. This allows localized delivery of a high concentration of this labile molecule, which is required for activating the naive T cell.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER O'Connell, P. J. *et al.* A novel form of immune signaling revealed by transmission of the inflammatory mediator serotonin between dendritic cells and T cells. *Blood* 13 Oct 2005 (doi:10.1182/blood-2005-07-2903)