DENDRITIC CELLS

Intracellular trafficking, IRF7 and type-I-IFN responses

Two papers from Tadatsugu Taniguchi's laboratory that were recently published in *Nature* reveal the importance of the transcription factor interferon (IFN)-regulatory factor 7 (IRF7) in the regulation of type I IFN (IFN-α and IFN-β) responses.

In the first paper, the authors generated IRF7-deficient mice and studied the induction of expression of type I IFNs in these mice. The results showed that IRF7 is essential for the systemic induction of type-I-IFN expression during innate antiviral immune responses (which occurs through a MyD88 (myeloid differentiation primary-response protein 88)-independent signalling pathway), as well as for the local induction of type-I-IFN expression by plasmacytoid DCs (pDCs), which influences $CD8^+$ T-cell-mediated adaptive immune responses (and occurs through the Toll-like receptor (TLR)-activated, MyD88-dependent signalling pathway).

A typical feature of pDCs is their ability to robustly produce large amounts of type I IFNs in response to viruses. But how pDCs, but not conventional DCs (cDCs), can achieve this level of IFN production in response to the same TLR stimuli is not clear. In the second paper, the authors report that this is achieved by spatio-temporal regulation of the MyD88–IRF7-signalling pathway.

To study the cell-type-specific induction of type-I-IFN expression, the authors used confocal microscopy to examine intracellular trafficking of labelled synthetic oligodeoxynucleotides (ODNs). Two different ODNs containing unmethylated CpG motifs were used, CpG-A and CpG-B; both of these signal through TLR9, but they elicit different responses. CpG-A induces a more efficient type-I-IFN response by pDCs than does CpG-B. Using markers to label different cellular compartments, the microscopy results showed that CpG-A is retained for long periods within endosomal vesicles in pDCs, in which MyD88 and IRF7 are co-localized, and this results in sustained activation of the TLR9–MyD88–IRF7-signalling pathway. By contrast, CpG-A in cDCs and CpG-B in pDCs are rapidly transferred to lysosomal vesicles. This endosomal-trafficking model was verified by showing that robust induction of expression of IFN-α and IFN-β could be achieved in cDCs by manipulating the trafficking of CpG-A so that it was similar to that of CpG-A in pDCs. Similarly, it was possible to manipulate CpG-B trafficking in pDCs so that it was retained in endosomal vesicles and could induce robust type-I-IFN production.

Together, these results reveal the importance of IRF7 in the induction of all type-I-IFN responses, and they show that it might be possible to manipulate IFN responses in clinical situations, using compounds that target specific cellular compartments or that alter cellular trafficking.

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References and links

ORIGINAL RESEARCH PAPERS Honda, K. *et al*. IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature* **434**, 772–777 (2005) | Honda, K. *et al*. Spatiotemporal regulation of MyD88–IRF-7 signalling for robust type-I interferon induction. *Nature* **434**, 1035–1040 (2005)

IN BRIEF

LYMPHOCYTE MIGRATION

Intravascular immune surveillance by $CXCR6^+$ NKT cells patrolling liver sinusoids.

Geissmann, F. *et al*. *PLoS Biol.* **3**, e113 (2005)

Dan Littman and colleagues have used intravital fluorescence microscopy to look at the behaviour of natural killer T (NKT) cells in the liver, which comprise up to 30% of the lymphocytes found in this organ. NKT cells that were labelled with green fluorescent protein (GFP) — by replacing the gene encoding the chemokine receptor CXCR6 with cDNA encoding GFP — were shown to actively patrol the liver sinusoids without extravasating into the tissue, with a random motion that was independent of the direction of blood flow. The NKT cells underwent rapid arrest after activation through their T-cell receptor. The authors also looked at the role of CXCR6 expression by NKT cells, and they showed that this was required for cell survival but not for the crawling behaviour. This intravascular search for antigen by NKT cells is unprecedented for lymphocyte populations, which are normally sheltered in specialized compartments in the lymph nodes and spleen.

DENDRITIC CELLS

Immunological role of neuronal receptor vanilloid receptor 1 expressed on dendritic cells.

Basu, S. & Srivastava, P. *Proc. Natl Acad. Sci. USA* **102**, 5120–5125 (2005)

Vanilloid receptor 1 (VR1) is expressed by sensory neurons and has been shown to convey a sense of pain in response to capsaicin, a component of chillies. In support of the known overlap between neural and immune signalling pathways, this paper now shows that VR1 is also expressed by dendritic cells (DCs) and that receptor ligation can induce a pro-inflammatory response, involving the maturation of immature DCs *in vitro* and their migration to draining lymph nodes *in vivo*. In a T-cell-receptor-transgenic mouse model, the proliferation of ovalbumin-specific T cells in response to their cognate antigen was increased when capsaicin was injected with the antigen. It is therefore possible that other neuroactive ligands might also have immunological effects.

INFECTIOUS DISEASE

Ipr1 gene mediates innate immunity to tuberculosis.

Pan, H. *et al*. *Nature* **434**, 767–772 (2005)

Only some individuals who are infected with *Mycobacterium tuberculosis* develop an active infection, and this innate susceptibility is thought to be genetically controlled. However, deciphering the genetic basis of susceptibility has proven challenging. Now, Pan *et al*. report the identification of a gene, intracellular-pathogen resistance 1 (*Ipr1*), that controls susceptibility to tuberculosis in mice. *Ipr1* expression is lacking in susceptible macrophages, and these cells die by necrosis after infection. By contrast, *Ipr1* is expressed by resistant macrophages, in which it is linked to the induction of apoptotic cell death following infection. Expression of *Ipr1* also restricted replication of the bacterium *Listeria monocytogenes*, indicating that this could be a common innate defence mechanism against intracellular bacteria.