INNATE IMMUNITY

Chemokine mimic is STAg's secret ingredient

Activation of cell-mediated immunity by the protozoan intracellular parasite *Toxoplasma gondii* is essential for control of infection and long-lived immunity. Now researchers have identified what seems to be a crucial initiator of this response — a parasite protein that can activate dendritic cells (DCs) through a chemokine receptor.

Infection with *T. gondii* is widespread throughout the world and, although it can cause devastating encephalitic disease in immunosuppressed individuals, it is usually asymptomatic. Infection leads to the rapid induction of interleukin-12 (IL-12) production by DCs, which triggers a T helper 1 (T_H1) response that controls the acute infection but then subsides, allowing the maintenance of inactive parasites in tissue cysts, often for the life of the host.

Tachyzoites — the parasite stage that multiplies and destroys host cells — are known to produce IL-12-inducing soluble factors but, until now, the specific molecule(s) had not been characterized. To pinpoint this factor(s), Julio Aliberti and colleagues fractionated tachyzoite supernatant (instead of the more complex and more commonly used soluble tachyzoite extract, known as STAg). A single protein with IL-12-inducing activity was isolated and identified as a cyclophilin known as C18.

Cyclophilins are peptidyl propyl isomerases that are thought to be involved in protein folding; C18 is the first cyclophilin reported to have immunostimulatory properties. Notably, cyclophilins from the related malaria parasite *Plasmodium falciparum* and from humans did not share the potent IL-12-inducing capacity of C18. Although C18 was less potent than STAg or tachyzoite supernatant in inducing the production of IL-12 by DCs, C18-specific antibodies almost completely inhibited STAg-induced IL-12 production by DCs.

Previously, this group had shown that MYD88, an adaptor of Toll-like receptor (TLR) signalling, and the chemokine receptor CCR5 were required for the maximal induction of IL-12 production by STAg. To find out whether C18 engages these pathways, DCs from MYD88- or

NATURAL KILLER T CELLS

Can an NKT cell change its spots?

The answer to this question seems to be yes … if the natural killer gene complex (NKC) is involved. A study published in *Immunity* by Diana Hansen, Louis Schofield and colleagues indicates that CD1d-restricted natural killer T (NKT) cells can contribute to either protection against or susceptibility to malaria depending on the host genetic background.

Plasmodium berghei **ANKA mouse malaria is an accepted model of the cytokine-dependent pro-inflammatory cascade that develops in human malaria. However, whereas C57BL6 mice, which have a genetic bias to T helper 1 (T_H1) responses, are susceptible to disease, BALB/c mice, which have a genetic bias to T_H2 responses, are resistant to disease. As high-level cytokine production occurs early in infection, it has been suggested that progress of the mouse disease involves non-conventional lymphocytes of innate immunity.**

To investigate the possible role of CD1d-restricted NKT cells, the authors compared *Cd1d*$^{-/-}$ and wild-type mice on both backgrounds in terms of percentage death and histological markers of infection. On the BALB/c background, NKT cells seem to be protective, as *Cd1d*$^{-/-}$ BALB/c mice are more susceptible than wild-type BALB/c mice to disease. By contrast, NKT cells are moderately disease promoting on the C57BL6 background as *Cd1d*$^{-/-}$ C57BL6 mice are partially protected against disease. Serum levels of interferon-γ (IFN-γ) were increased in susceptible *Cd1d*$^{-/-}$ BALB/c mice compared with resistant wild-type mice, whereas levels of IFN-γ were decreased in partially resistant *Cd1d*$^{-/-}$ C57BL6 mice compared with susceptible wild-type mice. By looking at the cytokine production of isolated CD4$^+$ T cells from infected wild-type and knockout mice, the authors were able to show that in BALB/c mice, the function of NKT cells promotes a switch from high-level IFN-γ production (T_H1 response) to interleukin-4 production (T_H2 response), which is protective. The opposite is true for C57BL6 mice, in which NKT cells promote sustained IFN-γ production.

What are the host genetic factors responsible for the different roles of NKT cells in the different mouse strains? The authors used congenic mice to investigate the role of differences in expression of NKC loci between BALB/c and C57BL6 mice. For example, BALB.B6-Cmv1^r mice, which contain the NKC from susceptible C57BL6 mice on a resistant BALB/c background, are susceptible to disease compared with non-congenic BALB/c mice. The expression of C57BL6 NKC loci leads to increased levels of IFN-γ production.

So, not only is this one of the first reports of a clear role for NKT cells in infection, but it also shows that the exact role of these cells is more flexible than previously imagined. The response of the same type of cell to the same pathogen can vary as a result of host genetic factors such as NKC polymorphisms.

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References and links

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