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 C57BL/6 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 C57BL/6 background as *Cd1d*^{-/-} C57BL/6 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*^{-/-} C57BL/6 mice compared with 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

C57BL/6 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 C57BL/6 mice. For example, BALB.B6-Cmv1⁺ mice, which contain the NKC from susceptible C57BL/6 mice on a resistant BALB/c background, are susceptible to disease compared with non-congenic BALB/c mice. The expression of C57BL/6 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.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Hansen, D. S. *et al.* Regulation of murine cerebral malaria pathogenesis by CD1d-restricted NKT cells and the natural killer complex. *Immunity* **18**, 391–402 (2003)

FURTHER READING Kronenberg, M. & Gapin, L. The unconventional lifestyle of NKT cells. *Nature Rev. Immunol.* **2**, 557–568 (2002)

CCR5-deficient mice were stimulated with STAg or C18. Responses to STAg were reduced in both cases, but only CCR5-deficient DCs had defective responses to C18. This shows that C18 signals specifically through CCR5 and indicates the presence of at least one other IL-12-inducing factor that operates through a MYD88-dependent pathway. C18 was also shown to act as a chemoattractant for DCs both *in vitro* and *in vivo*.

The identity of the additional MYD88-dependent IL-12-inducing factor(s) is an important area for future study. In addition, it is possible that C18 requires a cofactor for full activity and the authors are now following up preliminary evidence that parasite-derived peptides might augment the IL-12-inducing capacity of C18.

Jennifer Bell

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ORIGINAL RESEARCH PAPER Aliberti, J. *et al.* Molecular mimicry of a CCR5 binding-domain in the microbial activation of dendritic cells. *Nature Immunol.* **4**, 485–490 (2003)

WEB SITES

Alan Sher's lab: <http://www.niaid.nih.gov/dir/labs/lpd/sher.htm>

The *Toxoplasma gondii* genome project: <http://www.tigr.org/tldb/e2k1/tga1/>

TRANSPLANTATION

A fine balance

Haematopoietic stem-cell transplantation (HCT) is a proven curative therapy for leukaemias and lymphomas, but tipping the balance towards a graft-versus-leukaemia (GVL) effect and away from the detrimental graft-versus-host disease (GVHD) has proven quite a challenge for immunologists. A new study from Megan Sykes' lab now shows that use of the immunosuppressive drug FTY720 — an agonist of the sphingosine-1-phosphate receptor family — might allow a reduction in GVHD but retain the GVL effect. At present, ~50% of patients who could benefit from HCT do not receive it because of the high incidence of GVHD in mismatched donors, but this new approach could pave the way for increased use of haplo-identical HCT.

Previous work from the Sykes lab showed that recipients who have undergone a T-cell-depleted bone-marrow transplant (BMT) — the T-cell depletion reduces the development of GVHD at the time of transplant — to achieve mixed haematopoietic chimerism, followed by delayed administration of donor lymphocyte infusions (DLIs), achieve GVL effects from the DLIs, without GVHD. The problem with this approach is that leukaemias can often progress rapidly, so it would be better to enhance the GVL effect closer to the time of transplant.

Sykes and colleagues hypothesized that the delay in administration of DLIs allows conditioning-induced inflammation in epithelial tissues — that are the target of GVHD — to subside, so that the GVHD-mediating T cells are not drawn from the lymphohaematopoietic tissues to these target tissues. As FTY720 can influence the migration of lymphocytes, the authors set out to test whether FTY720 might be beneficial in reducing GVHD even around the time of BMT when tissue inflammation is present.

Lethally irradiated mice were reconstituted with haplotype-mismatched, GVHD-inducing allogeneic bone-marrow cells or control syngeneic bone marrow, and spleen cells. Daily treatment with FTY720 resulted in decreased mortality and a marked decrease in GVHD in association with the allogeneic transplant. Histological analysis of tissues from the mice indicated that FTY720 treatment reduced the level of tissue infiltration by lymphocytes, macrophages and neutrophils, in the allogeneic transplanted mice.

To assess whether FTY720 treatment has a detrimental effect on the GVL effect, lethally irradiated mice received haplotype-mismatched allogeneic bone-marrow cells and spleen cells plus an inoculum of host-type T-cell leukaemia/lymphoma cells (EL4) on the same day as the BMT. Three out of 10 FTY720-treated mice that had received allogeneic transplants survived past day 100. By contrast, most untreated mice died by day 9 post-BMT, so it was not possible to assess an antitumour effect in these mice. To compare the GVL response in FTY720-treated and untreated mice, this experiment was repeated using a lower dose of spleen cells that did not cause lethal GVHD. In this case, EL4-induced mortality in allogeneic transplant mice was similar in the treated and untreated groups, indicating that FTY720 did not negatively affect the GVL response. Further experiments showed that FTY720 did not directly inhibit the proliferation or migration of EL4 tumour cells.

Together, these results illustrate the potential use of FTY720 in allowing the administration of DLIs at the time of BMT, and indicate that it is the ability of FTY720 to trap lymphocytes in the lymph nodes that prevents the GVHD-mediating T cells from reaching the target tissues.

Elaine Bell

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WEB SITE

Megan Sykes' lab: http://www.mghtbrc.org/about/staff_sykes.html