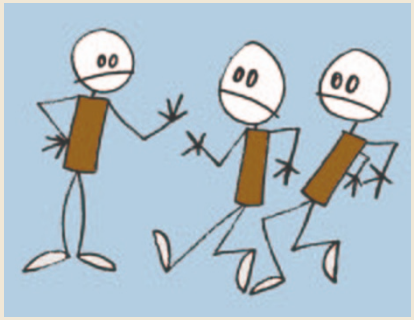
NATURAL KILLER CELLS

Maintaining tolerance



According to the 'missing-self' hypothesis, natural killer (NK)-cell tolerance is maintained by the interaction of inhibitory NK-cell receptors with MHC class I molecules expressed at the surface of autologous cells. However, NK cells from MHC-class-I-deficient humans maintain self-tolerance — so how does this occur? Megan McNerney and colleagues now show that there is another system for controlling NK-cell tolerance, in which engagement of 2B4 (also known as CD244) at the surface of mouse NK cells by CD48 at the surface of autologous cells provides a 'stop' signal for NK-cell cytotoxicity.

Previous studies have shown that engagement of 2B4 can inhibit NK-cell responses to tumour cells. In this study, the authors first asked whether both Ly49 molecules and 2B4 (which are inhibitory NK-cell receptors in mice) are required for the inhibition of NK cells or whether either system alone is sufficient. In NK-cell cytotoxicity assays, maximal cytotoxicity was detected in the absence of both inhibitory systems, showing that they are non-redundant for protection against NK-cell cytotoxicity.

So, is 2B4 responsible for maintaining NK-cell tolerance in the absence of MHC class I expression: for example, in β_2-microglobulin (β_2m)-deficient mice? In cytotoxicity assays carried out in the absence of 2B4–CD48-mediated inhibition, $\beta_2m^{-/-}$ NK cells had a higher lytic capacity, indicating that the 2B4–CD48 system normally operates in the absence of MHC class I expression. Similar results were obtained in the reverse situation, using NK cells from C57BL/6 mice that lack all known MHC-class-I-engaging inhibitory receptors but retain expression of 2B4 (and express MHC class I molecules).

The authors then investigated the role of 2B4 in an *in vivo* situation, by looking at the effect of 2B4 on the elimination of syngeneic cells in bone-marrow transplants. Wild-type and *2b4*$^{-/-}$ mice were injected with mixed bone marrow containing labelled β_2m-deficient bone-marrow cells from C57BL/6 mice, as well as wild-type C57BL/6 bone-marrow cells labelled with a different dye. Spleens were isolated 2 days later, and the remaining donor cells were counted. Compared with wild-type mice, *2b4*$^{-/-}$ mice showed greater rejection of transplanted $\beta_2m^{-/-}$ cells.

These results show that 2B4–CD48 interactions are an additional system for controlling NK-cell tolerance.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER McNerney, M. E., Guzior, D. & Kumar, V. 2B4 (CD244)–CD48 interactions provide a novel MHC class I-independent system for NK cell self-tolerance in mice. *Blood* 3 May 2005 (doi:10.1182/blood-2005-01-0357)

FURTHER READING Kumar, V. & McNerney, M. E. A new self: MHC-class-I-independent natural-killer-cell self-tolerance. *Nature Rev. Immunol.* **5**, 363–374 (2005)

INNATE IMMUNITY

A new ligand for TLR11

It is now well established that Toll-like receptors (TLRs) are crucial for the recognition of bacteria and viruses, but their roles in innate responses to parasitic infections are less well known. Now, reporting in *Science*, Yarovinsky *et al.* identify a ligand derived from the protozoan parasite *Toxoplasma gondii* that is recognized by TLR11, contributing to resistance to infection with this parasite.

Previously, it has been shown that interleukin-12 (IL-12) is essential for host resistance to *T. gondii* and that parasite-induced IL-12 production requires the TLR adaptor MyD88 (myeloid differentiation primary-response gene 88). So, the authors set out to identify the parasitic component and the TLR that might be involved.

Using gel filtration, the authors fractionated STAg, a soluble extract of the tachyzoite stage of *T. gondii*, and identified a low-molecular-weight protein that stimulated the production of high levels of IL-12 by dendritic cells (DCs). This protein had marked sequence homology to profilin proteins present in other protozoa. Consistent with the known MyD88 dependence of *T. gondii*-induced IL-12 production, DCs from *Myd88*$^{-/-}$ mice had impaired IL-12 responses to the recombinant *T. gondii* profilin.

So far, only two TLRs have been shown to recognize microbial-protein ligands — TLR5 (flagellin) and TLR11 (uropathogenic-bacteria-derived protein) — so the authors tested these TLRs for their ability to recognize *T. gondii* profilin. Indeed, TLR11 transfectants, but not TLR5 (or other TLR) transfectants, displayed dose-dependent activation of nuclear factor-κB when stimulated with profilin. Moreover, TLR11-deficient DCs failed to produce IL-12 in response to profilin, whereas DC populations from other TLR-deficient mice had no marked cytokine defects, indicating a role for a profilin–TLR11 interaction in IL-12 production *in vitro*.

Next, the authors showed that the profilin–TLR11 interaction is important for resistance to infection with *T. gondii*, as TLR11-deficient mice developed more brain cysts in the chronic phase of infection than did wild-type animals. This was accompanied by reduced levels of IL-12 and interferon-γ, as observed for *Myd88*$^{-/-}$ mice. The fact that the TLR11-deficient mice survived acute infection with *T. gondii*, unlike *Myd88*$^{-/-}$ mice, indicates that other MyD88-dependent TLR-family members might also be involved in resistance to infection with *T. gondii*.

Future studies aim to identify whether *T. gondii* profilin homologues from other related parasites are also recognized by TLR11 and whether they are important in protective responses.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Yarovinsky, F. *et al.* TLR11 activation of dendritic cells by a protozoan profilin-like protein. *Science* 28 Apr 2005 (doi:10.1126/science.1109893)