HOST RESPONSE

How NKT cells detect microorganisms

Although natural killer T (NKT) cells that express a semi-invariant T cell receptor (TCR) α-chain (Vα14Jα18 in mice and the homologous Vα24Jα18 in humans) recognize glycolipid antigens presented by CD1d, it is unclear which ligands activate these cells during a microbial infection. Now, two papers published in *Nature* show that both mouse Vα14$^+$ and human Vα24$^+$ NKT cells recognize CD1d-presented glycosphingolipids from Gram-negative bacteria that lack lipopolysaccharide (LPS).

Previous studies have shown that Vα14$^+$ NKT cells are activated during microbial infection, but whether they are activated directly by TCR recognition of CD1d-presented microbial antigens or indirectly, by other immune cells responding to the pathogen, is a controversial issue that these two groups set out to investigate. Kinjo *et al.* showed that CD1d presentation of two distinct glycosphingolipid mixtures (GSL-1 and GSL-1′) purified from *Sphingomonas* species and CD1d presentation of GSL-1′sA and GSL-1′sB (which are synthetic versions of individual GSL-1′components) stimulated cytokine production by both human Vα24$^+$ T-cell lines and mouse Vα14$^+$ NKT cells, but not mouse T cells lacking the semi-invariant Vα14Jα18 TCR α-chain. In addition, GSL-1′sA-loaded CD1d multimers bound all the human Vα24$^+$ T cells and a proportion of liver mononuclear cells from wild-type mice, but not cells from mice lacking Jα18.

Activation of Vα14$^+$ NKT cells in the liver was also observed when wild-type mice were immunized with bone-marrow-derived dendritic cells pulsed with either GSL-1′sA or live *Sphingomonas yanoikuyae*. This *in vivo* activation did not depend on Toll-like receptor (TLR) activation of the antigen presenting cells (APCs) or APC secretion of interleukin-12. Functionally, *in vivo* Vα14$^+$ NKT-cell activation was associated with bacterial clearance.

In a similar study, Mattner *et al.* showed that heat-killed *Salmonella enterica* serovar Typhimurium (*S. typhimurium*), *Ehrlichia muris* and *Sphingomonas capsulata* all induced interferon-γ (IFN-γ) production by Vα14$^+$ NKT cells. Surprisingly, the response to *S. typhimurium* (an LPS-positive Gram-negative bacterium), but not the other two bacteria (both of which are LPS-negative Gram-negative bacteria), required TLR signalling by the APCs. In addition, if Vα14$^+$ NKT-cell recognition of the recently identified endogenous glycolipid ligand isoglobotrihexosylceramide (iGb3) was prevented, the response to *S. typhimurium*, but not the other two bacteria, was reduced; indicating that iGb3 activates Vα14$^+$ NKT cells following infection with *S. typhimurium*. By contrast, CD1d presentation of synthetic versions of glycosphingolipids from *Sphingomonas* species stimulated IFN-γ production by both mouse Vα14$^+$ and human Vα24$^+$ NKT cells. CD1d tetramers loaded with these compounds bound the human Vα24$^+$ T cells and a proportion of mouse Vα14$^+$ NKT cells, indicating that they are recognized directly by the NKT cells. In addition, although mice lacking Vα14$^+$ NKT cells showed impaired bacterial clearance after infection with *S. capsulata* compared with wild-type animals, they also showed reduced lethality after high dose infection, as they lack the NKT cell population that produces high levels of cytokines in response to microbial antigens.

These studies provide clear evidence that some microbial antigens can be directly recognized by NKT cells, whereas other microorganisms are sensed indirectly through the recognition of iGb3. The authors of both papers suggest that direct recognition of microbial antigens by NKT cells may be an innate immune mechanism for detecting microorganisms that lack TLR ligands.

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References and links

ORIGINAL RESEARCH PAPERS Kinjo, Y. *et al.* Recognition of bacterial glycosphingolipids by natural killer T cells. *Nature* **434**, 520–525 (2005) | Mattner, J. *et al.* Exogenous and endogenous glycolipid antigens activate NKT cells during microbial infection. *Nature* **434**, 525–529 (2005)