NATURAL KILLER T CELLS

New lipid ligand nourishes NKT-cell responses

Most natural killer T (NKT) cells express a semi-invariant T-cell receptor (TCR) α-chain (Vα14–Jα18 in mice and the homologous Vα24–Jα18 in humans). These NKT cells recognize endogenous lipid antigens presented by the MHC-class-I-like molecule CD1d; however, the identity of the natural CD1d-bound ligands has not been established. But now, a paper published in *Science* shows that a lysosomal glycosphingolipid, isoglobotrihexosylceramide (iGb3), stimulates both human Vα24$^+$ and mouse Vα14$^+$ NKT cells.

Previous studies have shown that presentation of natural CD1d-bound ligands requires lysosomal trafficking of CD1d molecules and several lysosomal proteins, including proteases and lipid-transfer proteins, leading to the hypothesis that the endogenous ligands might be lysosomal glycosphingolipids. So, Zhou *et al.* analysed mice deficient in the B subunit of the lysosomal-glycosphingolipid-degrading enzyme β-hexosaminidase (HEXB) and found that the number of Vα14$^+$ NKT cells was decreased by 95%. In addition, thymocytes that were isolated from HEXB-deficient mice could not stimulate interleukin-2 (IL-2) production by an autoreactive CD1d-restricted Vα14$^+$ NKT-cell hybridoma, indicating that HEXB-deficient cells have a specific defect in generating lysosomal Vα14$^+$ NKT-cell ligands.

HEXB-dependent enzymes remove the β-linked *N*-acetylgalactosamine (GalNAc) residues from several distinct types of glycosphingolipid, such as isogloboglycosphingolipids. However, Vα24$^+$ NKT cells present in freshly isolated peripheral-blood mononuclear cells (PBMCs) clonally expanded only in the presence of one of these glycosphingolipid types, iGb3. CD1d presentation of iGb3 also stimulated interferon-γ and IL-4 production by Vα24$^+$ NKT cells and IL-2 production by the Vα14$^+$ NKT-cell hybridoma. Furthermore, although HEXB-deficient bone-marrow-derived dendritic cells (BMDCs) presented iGb3 to the Vα14$^+$ NKT-cell hybridoma as efficiently as wild-type BMDCs, they could not present the iGb3 precursor iGb4, indicating that iGb4 processing by HEXB-dependent enzymes is required for iGb3 recognition by the Vα14$^+$ NKT cells.

Further evidence that iGb3 is a ligand for Vα14$^+$ and Vα24$^+$ NKT cells was provided by the observation that isolectin B4 (IB4) — a lectin isolated from *Griffonia simplicifolia* that binds the terminal Gal α1,3-Gal of iGb3 — impaired iGb3 stimulation of Vα24$^+$ NKT cells but not stimulation of Vα24$^+$ NKT cells by an unrelated ligand, α-galactosylceramide. IB4 also inhibited Vα24$^+$ NKT-cell recognition of natural CD1d ligands presented by PBMC-derived DCs.

This study defines iGb3 as an agonist ligand for Vα14$^+$ and Vα24$^+$ NKT cells, and the authors suggest that this might be the principal endogenous ligand for these cells that is expressed in non-diseased peripheral tissues, as well as the ligand responsible for Vα14$^+$ NKT-cell development. However, isogloboglycosphingolipids have not yet been biochemically identified in humans or mice, so further studies are required to confirm that iGb3 is indeed the principal self-antigen of Vα14$^+$ and Vα24$^+$ NKT cells.

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References and links

ORIGINAL RESEARCH PAPER Zhou, D. *et al.* Lysosomal glycosphingolipid recognition by NKT cells. *Science* **306**, 1786–1789 (2004).