# Recognition of microbial and self-lipid antigens by invariant natural killer T cells

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The evolutionary conservation of the iNKT cell TCR indicates it has an extraordinarily useful specificity. This TCR responds to some glycosphingolipids with alpha-branched sugars produced by environmental microbes, such as *Sphingomonas* bacteria, and there are even antigens in some house dust extracts, although their structure(s) are unknown. Therefore, stimulatory compounds for iNKT cells are very widespread in the external environment. Antigens are present inside the body as well, as we found that stimulatory glycosphingolipids similar to the prototypical antigen, GalCer, are found in *Bacteroides fragilis,* a common organism in the mouse intestinal flora. Consistent with the presence of antigens in commensal microbes that might be engaging iNKT cells, the phenotype and responsiveness of iNKT cells is altered in germ free mice.

In addition to glycosphingolipids, iNKT cells recognize glycosylated diacylglycerol (DAG) antigens derived from pathogenic microbes, including *Borrelia burgdorferi*, which causes Lyme disease, *Streptococcus pneumoniae* and group B streptococcus. Mice deficient for iNKT cells are highly susceptible to these infections. Structural studies have elucidated how the different microbial glycolipids bind to CD1d, and how the TCR causes a significant structural accommodation of both the bound antigen and CD1d in order to attain a fixed orientation.

iNKT cells are also stimulated by cytokines such as IL-12 and IL-18, even without TCR engagement, as in the response to mouse cytomegalovirus. However, they are also truly self-reactive cells, although the nature of the self-antigens has been a source of controversy. Structural analyses show that interaction of the TCR with CD1d is dominant over interactions with the bound CD1d-bound antigen, in terms of the area of contact. We now show that exposure to cytokines unleashes the largely CD1d-dependent auto reactivity of iNKT cells, allowing them to detect diverse self-lipids. After TCR activation and cytokine exposure, the threshold for CD1d reactivity is decreased, in part by down regulation of the expression of inhibitory receptors and

phosphatases. When the threshold is lowered, iNKT cells can respond to autologous DC and even to high concentrations of insect cell-derived CD1d coated on microwells.

We conclude that the iNKT cell TCR is conserved because it is capable of recognizing essential glycolipid structures from a number of pathogenic microbes, and also, because the CD1d-dominant interactions of this TCR allow it to detect many types of lipid antigens in an inflammatory context.