

NKT cells sense bacterial infection and recognize bacterial glycolipids

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Natural Killer T (NKT) cells are highly conserved T lymphocyte subpopulation that has been implicated in host defense against various microbial infections. NKT cell express an invariant TCR α chain and they recognize self and foreign glycolipids presented by CD1d. NKT cells respond to IL-12 and IL-18 produced by APC that have been activated by LPS or TLR7 or TLR9 ligands. As a result, NKT cells rapidly produce IFN γ . This IFN γ stimulates the innate immune response to microbial products, which is greatly reduced in mice that lack NKT cells. By responding to activated APC, NKT cells can amplify the innate immune response to many different microbes.

We reported that the invariant TCR expressed by mouse and human NKT cells recognizes glycosphingolipids with α branched sugars, which are unique to *Sphingomonas* bacteria. This provides a direct mechanism for microbial recognition by NKT cells, as opposed to the indirect mechanism described above. The NKT cell response to *Sphingomonas* is driven by TCR recognition rather than APC-derived cytokines, and mice that lack NKT cells have reduced bacterial clearance, especially in the liver. *Sphingomonas* are not highly pathogenic, however, and it remained unknown if NKT cells can recognize other classes of glycolipids derived from pathogenic microbes. We show that mouse and human NKT cells with an invariant TCR recognize glycosyl diacylglycerols from *Borrelia burgdorferi*, which causes Lyme disease. Interestingly, the response to these compounds was highly dependent on the nature of the aliphatic chains, with the addition of a single unsaturated bond having an enormous influence on antigenic potency. The responses of mouse and human NKT cells differ, because the human CD1d groove preferentially presents lipids that have more unsaturated bonds. NKT cells are activated during *B. burgdorferi* infection, and the glycolipid from *B. burgdorferi* stimulated NKT cell cytokine release. This response required TCR recognition and was independent of MyD88 activation of APC. These data provide evidence that NKT cells recognize a new category of microbial glycolipids, diacylglycerols, which is more broadly distributed in pathogenic microbes, and they suggest that this TCR-mediated recognition provides protection from microbial pathogens.

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