NATURAL KILLER T CELLS

Switching on human NKT cells

The identification of lysophosphatidylcholine (LPC) as a self antigen for human natural killer T (NKT) cells indicates that these cells might be stimulated by physiological lipid signalling pathways to carry out their homeostatic immunoregulatory functions.

The semi-invariant T cell receptors of NKT cells recognize lipid and glycolipid antigens presented by the MHC-like molecule CD1d. Unlike conventional T cells, NKT cells are selected to recognize self, as well as foreign, antigens and their self-activation in the absence of an external challenge is important for their immunomodulatory functions. The glycolipid isoglobotrihexosylceramide (iGb3), which is generated in lysosomal compartments, has been identified as a self antigen for mouse NKT cells, but iGb3 is not produced by human cells and human NKT cell responses to self antigens do not require lysosomal processes.

The authors looked at the ability of lipids that were previously identified as ligands of human CD1d molecules to stimulate cytokine secretion by human NKT cell clones. LPC elicited the strongest and most consistent NKT cell responses and was identified as a weak to moderate agonist compared with the positive control α-galactosylceramide. Control experiments showed that the NKT cell response to LPC was not a result of direct stimulation and required CD1d-restricted presentation. LPC-reactive NKT cells also responded to lysosphingomyelin (although higher concentrations were required), which indicates that specificity might be for the shared choline head group. Finally, polyclonal NKT cells from the peripheral blood of a healthy volunteer also responded to LPC as an antigenic ligand.

Non-antigenic CD1d ligands could also have an important role in NKT cell stimulation by modulating the loading of antigenic lipids. However, a 1/1 molar ratio of LPC to CD1d was sufficient to replace approximately 30% of the trisialoganglioside GT1b from GT1b–CD1d complexes, showing that the loading of antigenic LPC would not be prevented by more abundant endogenous non-antigenic ligands. In further experiments, it was shown that extracellular LPC could compete with endogenous ligands for presentation on cell surface CD1d. Human peripheral blood monocytes, which constitutively express CD1d and can stimulate NKT cells, are a possible physiological source of extracellular LPC; indeed, monocytes pre-treated with a blocking antibody specific for secreted phospholipase A2 (which produces LPC) stimulated significantly less cytokine production by NKT cells.

The stimulation of human NKT cells by LPC, the production of which is known to be upregulated during inflammation, helps to explain the pro-inflammatory and adjuvant properties of this lipid.

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