Like a circus performer in a high-wire act, the human immune system teeters on a precarious perch. It must continually balance an effective defense against microbial invaders with the need to avoid the kind of inappropriate immune activity that leads to autoimmune disease. The consequences of a misstep can be disastrous.

Natural killer T (NKT) cells, a specialized type of T cell, constitute one of the fulcrums upon which a functional and appropriate immune response balances. Although present in very small numbers in the body, NKT cells can produce large amounts of cytokines, thereby potently manipulating the activities of other cells of the immune system. However, the precise role of NKT cells in the immune response is unclear; in some circumstances, the cytokines made by NKT cells can prod a developing immune response into high gear to help fight off microbial invaders and cancer. But in other cases, NKT cells help prevent autoimmunity by strengthening immunosuppressive pathways. A better grasp of the functions of these enigmatic cells is essential to understanding the workings of the immune system.

One important question about NKT cells concerns the nature of the signals that are used in the body to regulate their development and function. NKT cells respond to glycolipids presented to them by other body cells (the glycolipids are presented in complexes with the CD1d protein, a relative of the major histocompatibility complex, [MHC] protein family). But just which glycolipids regulate NKT cell activity within the body? So far, the search for endogenous glycolipids that can activate NKT cells has turned up just one major contender: isoglobotrihexosylceramide (iGb3). This lipid is present in mice and can potently activate both mouse and human NKT cells. However, the idea that iGb3 has any role in NKT cell activation and human NKT cells is not all research has supported the role of iGb3 in NKT cell activation and human NKT cells. However, the recent studies into the significance of this glycolipid iGb3 (structure pictured above) in regulating natural killer cells in the human immune system.

Starting Over: The Search for Endogenous NKT Cell Ligands

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New evidence casts doubt on a role for glycolipid iGb3 (structure pictured above) in regulating natural killer cells in the human immune system.

molecule as an NKT cell ligand are warranted, it is becoming increasingly clear that the search for the endogenous glycolipid NKT ligand(s) must be re-started if we are to gain a better understanding of this cell type and its role in controlling the balance of immune function.

The absence of iGb3 in humans has other important physiological implications, beyond the control of NKT cells. For example, Christiansen and colleagues showed that humans actually make antibodies to iGb3 (presumably because iGb3 is not normally present in the body) and that these antibodies can cause the lysis of cells that express iGb3. This is potentially important for the field of transplantation biology, which has been increasingly looking to our mammalian cousins as potential sources for organ transplantation. For example, pigs can be genetically manipulated to be more similar to transplant recipients. However, because pigs express iGb3 and humans do not, any organs transplanted from pigs to humans might face antibody or NKT cell-mediated attacks against the iGb3 antigen.