AUTOIMMUNITY

NKT cells linked to immune tolerance breakdown

Primary biliary cirrhosis (PBC) is a chronic lethal autoimmune disease in humans characterized by the destruction of small bile ducts in the liver and the presence of autoantibodies directed against mitochondrial pyruvate dehydrogenase complex E2 (PDCE2). These autoantibodies crossreact with a homologous enzyme found in ubiquitous commensal α-proteobacteria such as *Novosphingobium aromaticivorans*, suggesting a link between antimicrobial immunity and liver pathology. Consistent with this, new research shows that activation of natural killer T (NKT) cells by *N. aromaticivorans* initiates autonomous, liver-specific autoimmunity.

Mattner *et al.* first showed that infection of several common mouse strains with *N. aromaticivorans* led to the production of PBC-associated antibodies against microbial and mitochondrial PDCE2 and also to liver pathology. Because the *N. aromaticivorans* cell wall lacks the Toll-like-receptor ligand lipopolysaccharide and instead contains glycosphingolipids, the authors reasoned that CD1d-restricted invariant NKT cells might be important in microbial detection through the recognition of CD1d–glycosphingolipid complexes. Indeed, after *N. aromaticivorans* infection, CD1d-deficient mice had reduced PDCE2-specific IgG titres compared with wild-type mice, and mixed chimaera experiments revealed that CD1d-dependent cognate interactions between invariant NKT cells and B cells promoted antibody class switching.

Closer examination of the liver in mice after infection with *N. aromaticivorans* indicated massive lymphocyte infiltration, granuloma formation and severe bile duct damage, similar to that seen in patients with PBC. Interestingly, the inflammatory process was mainly confined to the liver, where NKT cells and *N. aromaticivorans* are known to accumulate, and was shown to require NKT cells.

The observation that the liver disease could be ameliorated by early but not late treatment with antibiotics suggested that the chronic phase of the disease was independent of microbial persistence. Support for this was shown by the ability to initiate disease in uninfected wild-type or CD1d-deficient recipients through the transfer of liver lymphocytes from donor animals with liver disease. This supports a model in which early activation of invariant NKT cells by *N. aromaticivorans* glycosphingolipids causes a breakdown in immune tolerance that results in liver damage mediated by chronic effector T- and B-cell responses.

Lucy Bird

ORIGINAL RESEARCH PAPER Mattner, J. *et al.* Liver autoimmunity triggered by microbial activation of natural killer T cells. *Cell Host Microbe* **3**, 304–315 (2008)
FURTHER READING Joyce, S. & Van Kaer, L. Invariant natural killer T cells trigger adaptive lymphocytes to churn up bile. *Cell Host Microbe* **3**, 275–277 (2008)