Activation and immunoregulatory function of type II natural killer T lymphocytes

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av
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Avhandlingen baseras på följande arbeten:

I. Maria Blomqvist*, Sara Rhost*, Susann Teneberg, Linda Löfbom, Thomas ∅sterbye, Manfred Brigl, Jan-Eric Månsson and Susanna L. Cardell. **Multiple tissue-specific isoforms of sulfatide activate CD1d-restricted type II NKT cells.** *Eur. J. Immunol. 2009, 39, 1726-1735*

II. Sara Rhost, Linda Löfbom, Britt-Marie Rynmark, Bo Pei, Jan-Eric Månsson, SusannTeneberg, Maria Blomqvist and Susanna L. Cardell. **Identification of novel glycolipid ligands activating a sulfatide-reactive, CD1d-restricted, type II natural killer T lymphocyte.** *Eur. J. Immunol. 2012, 42, 2851-60*

III. Sara Rhost, Linda Löfbom, Jan-Eric Månsson, Maria Blomqvist and Susanna L. Cardell. **Administration of sulfatide to ameliorate type 1 diabetes in non-obese diabetic mice.** *Manuscript*

IV. Jakub Kwiecinski*, Sara Rhost*, Linda Löfbom, Maria Blomqvist, Jan-Eric Månsson, Susanna L. Cardell and Tao Jin (2013). **Sulfatide attenuates experimental *Staphylococcus aureus* sepsis through a CD1d-dependent pathway.** *Infection and Immunity, 2013, 81, 1114-20*

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Natural killer T (NKT) lymphocytes make up a potent immunomodulatory subset of innate-like lymphocytes. NKT cells are activated by self-lipids presented by the unconventional MHC class I-like molecule CD1d, resulting in the rapid production of a range of different cytokines, that modulate innate and adaptive immunity. NKT cells possess regulatory properties in several immune setting such as autoimmunity, infection and cancer. However, the activation of NKT cells is not fully understood. In this thesis, we have addressed the role of self-lipids for type II NKT cell activation and autoreactivity, and employed self-lipids to investigate the immunoregulatory function of type II NKT cells in murine disease models.

The glycosphingolipid (GSL) sulfatide has previously been shown to be a stimulatory self-ligand for type II NKT cells. Sulfatide exists naturally as a mixture of different isoforms and is abundant in organs such as the central nervous system, gastrointestinal tract, kidneys and the pancreas where it has important functions. We demonstrate that naturally existing isoforms, including C24:1 sulfatide and lyso-sulfatide, activate type II NKT cells. Organ specific isoforms in particular, but not non-physiological isoforms, of sulfatide induced efficient activation of type II NKT cells. Despite the potent activation of NKT cells by natural sulfatide isoforms, the autoreactivity of the type II NKT cells to CD1d-expressing cells was not dependent on sulfatide production by the stimulatory cells, demonstrating that other self-lipids were causing autoreactivity. In a search for such lipids, isolated from stimulatory cells, we identified two novel NKT cell activating self-GSLs, β-glucosylceramide and β-galactosylceramide and defined their stimulatory isoforms. However, by using antigen presenting cells deficient in all GSLs we could demonstrate that the autoreactivity of the type II NKT cells did not require GSLs. In summary, we demonstrate that natural isoforms of sulfatide, β-glucosylceramide and β-galactosylceramide are ligands for type II NKT cells, suggesting that they may play a role to activate type II NKT cells upon increased exposure in autoimmunity or tumor immunity. We also find that the CD1d-dependent natural autoreactivity of the type II NKT cells depends on lipids other than GSLs.

Sulfatide is present in pancreatic β-cells that are targets for autoimmune destruction in type I diabetes (T1D). We demonstrate immune reactivity to sulfatide in non-obese diabetic mice that spontaneously develop TID. However, treatment of these mice with sulfatide, to activate immunomodulatory type II NKT cells, did not confer protection from TID. In contrast, we found that sulfatide treatment significantly improved the survival rate of mice with *Staphylococcus aureus* sepsis. The protective effects mediated by sulfatide required CD1d but not type I NKT cells, suggesting that activated type II NKT cells ameliorated sepsis development. Protection was associated with reduced serum levels of pro-inflammatory cytokines and improved platelet counts.

In conclusion, our results provide novel information on the activation of type II NKT cells, and expands our understanding of their immunomodulatory capacity to improve disease outcome.

Keywords: NKT cells, GSL, Activation, T1D, *S. aureus* sepsis
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