NATURAL KILLER T CELLS

Limiting B cell autoimmunity

The production and deposition of autoantibodies by B cells is a cardinal feature of systemic lupus erythematosus (SLE). Defective apoptotic cell clearance, as well as decreased numbers of invariant natural killer T (iNKT) cells, has been described in patients with SLE; however, whether these two observations are linked — and if so, how — is not known. Karlsson and colleagues now describe a role for iNKT cells in limiting autoantibody production in response to increased numbers of apoptotic cells.

iNKT cells express an invariant Vα14–Jα18 T cell receptor chain and recognize lipid antigen presented by the MHC class I-like molecule CD1d. Given that the cell membrane lipid bilayer is disrupted and modified during apoptosis, the authors investigated whether iNKT cells have a role in regulating autoimmunity to apoptotic cells. Mice lacking iNKT cells (*Cd1d*$^{-/-}$ or *Ja18*$^{-/-}$ mice) developed higher levels of autoantibodies and IgG-containing immune complex deposition in the kidneys following injection of syngeneic apoptotic cells compared with control mice, but transfer of iNKT cells to *Ja18*$^{-/-}$ mice ameliorated the autoimmune response.

iNKT cells from wild-type mice injected with apoptotic cells produced lower levels of interferon-γ but higher levels of interleukin-10 following *ex vivo* stimulation compared with iNKT cells from untreated mice, indicating that iNKT cells directly respond to apoptotic cells by altering their cytokine production.

But which cells express the CD1d molecule required for iNKT cell activation? Loss of CD1d expression on B cells resulted in increased autoantibody production, suggesting that a direct iNKT cell–B cell interaction is needed to limit B cell autoreactivity. This CD1d-mediated tolerance checkpoint probably occurs before B cells enter the germinal centre, as a higher proportion of *Cd1d*$^{-/-}$ B cells had a germinal centre phenotype compared with wild-type B cells in mixed chimeric mice injected with apoptotic cells, and B cells in wild-type mice decrease CD1d expression on entering the germinal centre.

So, iNKT cells have an important role in regulating CD1d^{+} B cell autoreactivity to increased numbers of circulating apoptotic cells that, if impaired, results in an SLE-like phenotype.

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ORIGINAL RESEARCH PAPER Wermeling, F., Lind, S. M., Jordö, E. D., Cardell, S. L. & Karlsson, M. C. I. Invariant NKT cells limit activation of autoreactive CD1d-positive B cells. *J. Exp. Med.* **207**, 943–995 (2010)