NATURAL KILLER T CELLS

More help for B cells

Invariant natural killer T (iNKT) cells have previously been shown to provide cognate help for lipid-specific B cells. Two new studies provide further details of the long-term outcome of this help and describe a population of iNKT cells that resemble follicular helper T (T_{FH}) cells.

The lipid antigen α-galactosylceramide (αGalCer) binds to CD1d and is a potent activator of iNKT cells. To assess the outcome of cognate iNKT cell help for B cell responses, King *et al.* immunized B1-8 mice — in which ~5% of B cells express a B cell receptor specific for the hapten NP (4-hydroxy-3-nitrophenylacetyl) — with the haptenated lipid antigen NP–αGalCer. NP–αGalCer induced the early formation of extrafollicular foci in the spleen and the expansion of NP-specific plasmablast populations. These responses are similar to those induced by T cell-independent antigens. However, in contrast with T cell-independent responses, the response to NP–αGalCer also involved germinal centre formation. Furthermore, NP–αGalCer induced modest antibody affinity maturation after two immunizations, whereas the T cell-independent antigen NP–Ficoll did not.

Interleukin-21 (IL-21) production by T_{FH} cells has an important role in T cell-dependent B cell responses. King *et al.* showed that iNKT cell-derived IL-21 has a role in the induction of early NP-specific IgG antibody production following immunization with NP–αGalCer. However, unlike T cell-dependent antigens, NP–αGalCer did not initiate an enhanced B cell memory response. So, these data suggest that cognate iNKT cell help for lipid-specific B cells induces a unique response that has characteristics of both T cell-dependent and T cell-independent B cell responses.

Chang *et al.* also found that immunization of mice containing hen egg lysozyme (HEL)-specific B cells with HEL conjugated to αGalCer (HEL–αGalCer) induced the rapid formation of germinal centres. Germinal centre formation was dependent on the expression of CD1d by the HEL-specific B cells, indicating that the help provided by iNKT cells was a result of cognate interactions between iNKT cells and B cells. Indeed, imaging studies showed that, in response to HEL–αGalCer immunization, HEL-specific B cells and iNKT cells formed stable interactions that promoted B cell activation.

Do these iNKT cells have a phenotype similar to that of T_{FH} cells? In αGalCer-immunized mice, ~3% of iNKT cells isolated from the spleen and lymph nodes expressed high levels of the T_{FH} cell-associated markers CXCR5 and PD1. In addition, ~10% of iNKT cells from human tonsil tissue were $CXCR5^{hi}PD1^{hi}$. Similarly to T_{FH} cell development, the development of 'follicular helper' iNKT cells in mice was shown to require the expression of the transcriptional repressor BCL-6, co-stimulation through CD28 and the presence of B cells. However, unlike T_{FH} cells, follicular helper iNKT cells developed independently of IL-21. Similarly to King *et al.*, Chang *et al.* identified a role for IL-21 in the formation of germinal centre B cells and plasmablasts in response to HEL–αGalCer. However, follicular helper iNKT cells promoted only limited antibody affinity maturation and did not induce long-lived plasma cells.

So, these studies describe a population of iNKT cells with phenotypical and developmental characteristics similar to those of T_{FH} cells. Furthermore, iNKT cells can provide cognate help for germinal centre formation, although these germinal centres do not seem to support the formation of memory.

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ORIGINAL RESEARCH PAPERS Chang, P.-P. *et al.* Identification of Bcl-6-dependent follicular helper NKT cells that provide cognate help for B cell responses. *Nature Immunol.* 27 Nov 2011 (doi:10.1038/ni.2166) | King, I. L. *et al.* Invariant natural killer T cells direct B cell responses to cognate lipid antigen in an IL-21-dependent manner. *Nature Immunol.* 27 Nov 2011 (doi:10.1038/ni.2172)

FURTHER READING McHeyzer-Williams, M. *et al.* Molecular programming of B cell memory. *Nature Rev. Immunol.* **12**, 24–34 (2012)