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INNATE LYMPHOID CELLS

Support for indie B cells

Reporting in *Nature Immunology*, Magri *et al.* identify a key role for innate lymphoid cells (ILCs) in regulating T cell-independent (TI) B cell responses in the spleen. They show that a population of ILCs expressing retinoid acid receptor-related orphan receptor-γt (RORγt; which is encoded by *RORC*) interacts with stromal cells and neutrophils to promote TI antibody production by marginal zone B cells (MZ B cells).

Recent studies have shown that ILCs regulate various immune and non-immune cell populations by producing effector cytokines, and ILCs have been reported to support the production of TI antibodies at mucosal surfaces. The authors therefore suspected that ILCs may also regulate TI B cell responses in the spleen. In initial experiments, they identified cells in the human spleen that lacked expression of lineage markers, but expressed the interleukin-7 (IL-7) receptor, CD117 and natural killer cell-related molecules that are associated with mucosal ILC3s (which produce T helper 17-type cytokines). Gene expression analyses showed that splenic ILCs also expressed the transcription factors *RORC*, *AHR* and *ID2*, and the cytokines *IL22*, *IL26*, lymphotoxin-α (*LTA*), *LTB* and tumour necrosis factor (*TNF*), but that they did not express *IL17* or interferon-γ (*IFNG*). Notably, these ILCs localized to the marginal zone of the spleen, where innate-like B cell populations are found.

> “crosstalk between ILCs, stromal cells and neutrophils in the marginal zone of the spleen helps to promote MZ B cell responses to TI antigens”

The authors showed that the recruitment and survival of splenic ILCs in humans is supported by marginal reticular cells (MRCs), a specialized population of stromal cells in the marginal zone. MRCs were found to upregulate survival and recruitment factors for ILCs in response to ILC-derived lymphotoxin and TNF. Furthermore, both ILCs and MRCs supported innate-like B cell responses in *in vitro* assays. In co-culture assays, splenic ILCs promoted the survival, proliferation, IgM secretion and plasmablast differentiation of MZ B cells, but not of follicular B cells. Notably, MZ B cells showed greater levels of IgM secretion and plasmablast differentiation when they were cultured with both splenic ILCs and MRCs. Splenic ILCs were found to support MZ B cell responses by expressing B cell-activating factor (BAFF), CD40L and the Notch ligand delta-like ligand 1 (DLL1). Interestingly, human splenic ILCs were also shown to produce factors that recruit neutrophils to the spleen and enhance the capacity of these neutrophils to support innate-like antibody responses.

To further explore the function of splenic ILCs *in vivo*, the authors turned to mouse models. They found that RORγt-deficient mice had markedly fewer splenic ILCs compared with wild-type controls, and had decreased production of the TI antibody IgG3. This suggests that splenic ILCs promote TI B cell responses in mice, as well as in humans. In further support of this, antibody-mediated depletion of ILCs impaired IgG3 antibody responses following immunization of mice with TI antigens. Similarly to their counterparts in humans, mouse splenic ILCs expressed DLL1 and they also promoted the survival of splenic neutrophils that support TI antibody responses. However, unlike human ILCs, splenic ILCs in mice did not express BAFF and CD40L, but they did express a proliferation-inducing ligand (APRIL), a BAFF-related molecule that promotes plasmablast survival.

In summary, this study shows that crosstalk between ILCs, stromal cells and neutrophils in the marginal zone of the spleen helps to promote MZ B cell responses to TI antigens. A better understanding of these interactions could aid the development of vaccines targeting microbial TI antigens.

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ORIGINAL RESEARCH PAPER Magri, G. *et al.* Innate lymphoid cells integrate stromal and immunological signals to enhance antibody production by splenic marginal zone B cells. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2830 (2014)