B-CELL RESPONSES

TLRs are crucial for B cells too

A recent report in *Nature* provides the latest instalment in the popular Toll-like receptor (TLR) story and reveals an unexpected requirement of TLR signalling in B cells for optimal antibody responses to T-cell-dependent antigens.

It is now well established that TLRs induce the dendritic-cell maturation required for activation and differentiation of T helper (T_H) cells, which can then provide help to B cells for the generation of specific antibody responses. Indeed, the observation that mice deficient in the crucial TLR-signalling adaptor protein MyD88 (myeloid differentiation primary-response gene 88) have defective T-cell activation and impaired antibody responses to T-cell-dependent antigens favours this indirect role of TLRs in the induction of antibody responses. However, restoration of the T-cell defect in these MyD88-deficient mice did not restore the B-cell response. So, the authors set out to investigate whether TLRs expressed by B cells have a direct role in antibody responses.

To address this, B cells were transferred from wild-type, MyD88-deficient or TLR4-deficient mice to mice that lack mature B cells (μMT mice). Following immunization with a T-cell-dependent antigen (human serum albumin) and the TLR4 ligand lipopolysaccharide (LPS), $CD4^+$ T-cell responses were induced in all of the recipient μMT mice. Although mice that received wild-type B cells developed antigen-specific IgM and IgG responses, the production of antibodies was markedly impaired in mice that received TLR4- or MyD88-deficient B cells.

Next, the authors asked whether TLR signalling in B cells was also required to induce antibody responses to T-cell-independent antigen. For this, they used flagellin, which functions as both a T-cell-dependent antigen (to induce IgG1) and a T-cell-independent antigen (to induce IgG3), and also binds TLR5 on B cells. Accordingly, μMT mice that received wild-type B cells induced strong IgM, IgG1 and IgG3 responses to flagellin. However, μMT mice that received MyD88-deficient cells failed to induce IgM and IgG1, although their IgG3 response was comparable to that in the control mice, indicating that responses to T-cell-independent antigens do not require TLR signalling in B cells.

Further analysis was then carried out to determine at what stage in the B-cell response to T-cell-dependent antigen — antigen processing and presentation or B-cell differentiation into antibody-producing cells —TLR signalling is involved. Using B cells expressing a transgenic B-cell receptor (BCR) specific for hen-egg lysozyme (HEL), it was shown that BCR-mediated uptake of HEL was increased in the presence of LPS. In addition, differentiation into germinal-centre B cells also seemed to depend on TLR signalling, as 12 days after immunization, μMT mice that received MyD88- or TLR4-deficient B cells had fewer germinal-centre B cells than mice that received wild-type cells. This differentiation defect was also reflected in the mRNA levels of key regulators that are involved in B-cell differentiation, such as BCL-6 and BLIMP1 (B-lymphocyte-induced maturation protein 1).

So, TLR signalling affects multiple stages of B-cell activation and is required for optimal antibody responses to T-cell-dependent antigens. Such direct activation of B cells might have implications for autoimmune responses following inappropriate TLR-mediated activation of self-reactive B cells.

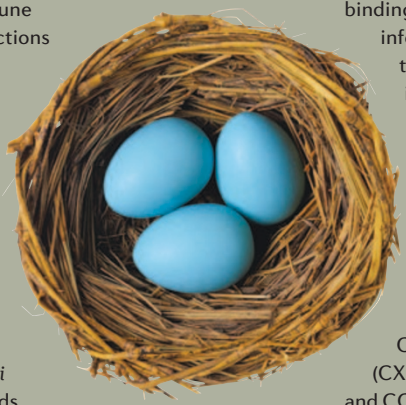
Lucy Bird

ORIGINAL RESEARCH PAPER Pasare, C. & Medzhitov, R. Control of B-cell responses by Toll-like receptors. *Nature* **438**, 364–368 (2005)

INFLAMMATION

An eggcellent way to avoid attraction

The parasite *Schistosoma mansoni* causes chronic infections in humans, because it can evade host immune defences long-term. Such infections alter the immune response in a manner that prevents the development of various immune-mediated diseases, indicating that molecules produced by schistosomes might be useful as immunomodulatory therapeutic agents. Now, a paper published in *The Journal of Experimental Medicine* shows that *S. mansoni* eggs secrete a protein that binds certain chemokines, and administration of this protein inhibits inflammation in several animal models of disease.



Because certain viruses have been shown to produce chemokine-binding proteins (CKBPs) and because infection with *S. mansoni* affects the local recruitment of immune cells, Philip Smith and colleagues examined whether *S. mansoni* produces CKBPs. Secretions from live eggs (produced by adult worms, which reside in the intestinal blood vessels of infected individuals) were shown to bind the chemokines CXC-chemokine ligand 8 (CXCL8; also known as IL-8) and CC-chemokine ligand 3 (CCL3). A single protein was found to provide this activity, and the gene that encodes this protein was cloned. A recombinant form of this novel CKBP was then shown not only to bind specific chemokines but also to prevent these chemokines from interacting with their receptors, thereby inhibiting the migration and activation of leukocytes that express the cognate chemokine receptors (particularly neutrophils, but also macrophages and eosinophils).

This is the first report of a human pathogen that produces a CKBP. The authors suggest that, because of its potent anti-inflammatory activity, *S. mansoni* CKBP has potential as a treatment for acute inflammation. This is supported by data from three *in vivo* models of acute inflammation that show that intravenous administration of recombinant *S. mansoni* CKBP suppresses leukocyte infiltration.

Davina Dadley-Moore

ORIGINAL RESEARCH PAPER Smith, P. *et al.* *Schistosoma mansoni* secretes a chemokine binding protein with antiinflammatory activity. *J. Exp. Med.* **202**, 1319–1325 (2005)

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