VACCINES

Amplifying with α-GalCer

CD8⁺ T-cell responses are the goal of vaccines against intracellular pathogens, such as HIV and malaria, as well as tumours. But, the vaccines and adjuvants that are currently in use work by inducing neutralizing antibodies and are poor stimulators of cellular immunity. Now, a study in the *Journal of Experimental Medicine* shows that α-galactosylceramide (α-GalCer), a glycolipid that was purified originally from a sea sponge, can be used with vaccines to promote protective T-cell responses.

Natural killer T cells (NKT cells) recognize α-GalCer in the context of the MHC-class-I-like molecule CD1. Although the number of NKT cells is small, they can produce large amounts of interleukin-4 (IL-4) or interferon-γ (IFN-γ) — cytokines that promote humoural or cellular immunity, respectively. Here, the authors tested whether α-GalCer could enhance antimalaria vaccines.

Irradiated malaria sporozoites and recombinant viruses that encode malaria antigens induce protective immunity and good CD8⁺ T-cell responses in a mouse model. In this study, mice were immunized with suboptimal doses of these vaccines with or without α-GalCer, then challenged with malaria. Strikingly, parasitaemia was ~10-fold lower in mice that received vaccine plus α-GalCer compared with those given the vaccine alone.

But, which branch of the immune response was enhanced? The authors compared the number of antigen-specific T cells and they found that α-GalCer induces up to a tenfold increase in the number of IFN-γ-producing CD8⁺ T cells and a less pronounced increase in the number of CD4⁺ T cells that produce IFN-γ. There was no increase in the number of IL-4-producing T cells or in antibody responses, and the immunomodulatory effects of α-GalCer were lost in mice deficient for the IFN-γ receptor, which confirms that IFN-γ mediates the adjuvant effects of α-GalCer.

Because α-GalCer activates human NKT cells also, it might prove to be a useful adjuvant for vaccines against malaria and other infections for which IFN-γ-mediated T-cell responses are protective.

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References and links

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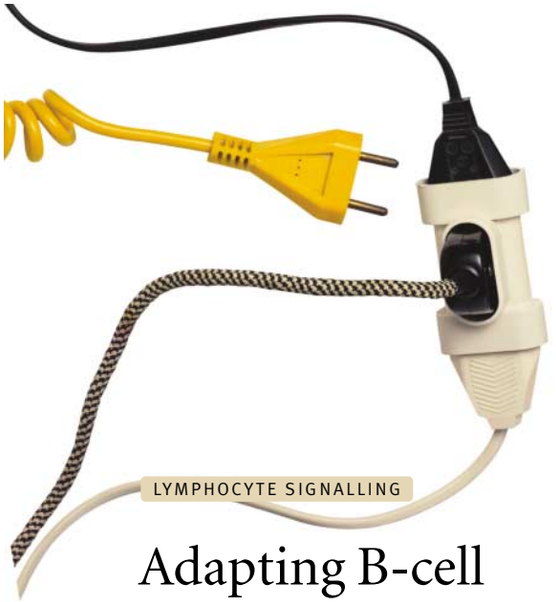

LYMPHOCYTE SIGNALLING

Adapting B-cell responses

B-cell receptor (BCR) signalling leads to various cellular responses, including survival, proliferation, differentiation and death. But, how is BCR signalling modulated to achieve the appropriate response? A study in the *Journal of Experimental Medicine* indicates that the recently discovered B-cell adaptor Bcap has a pivotal regulatory role.

Signalling adaptors are responsible for bringing together the BCR and the optimum combination of effector enzymes in the right place at the right time. Bcap has no obvious enzymatic domain, but it contains several potential tyrosine phosphorylation sites that might allow it to link to multiple signalling pathways. Bcap is known to bind phosphatidylinositol 3-kinase (PI3K), and recent experiments have shown that it regulates the activation of phospholipase C-γ2 (PLC-γ2) , but the *in vivo* role of this adaptor was not known.

Tetsuo Yamazaki and colleagues generated a *Bcap*-knockout mouse and found that B-cell development in the bone marrow was relatively normal, but the progression from $IgM^{hi}IgD^{lo}$ 'transitional' B cells to $IgM^{lo}IgD^{hi}$ 'mature' B cells in the spleen was partially blocked. Interestingly, the B1 B-cell compartment is almost non-existent in $Bcap^{-/-}$mice, but the marginal-zone B-cell compartment is unaffected. Together, these data support the idea that differences in BCR signalling direct maturing B cells into follicular, marginal-zone or B1 subcompartments.

The authors then looked at the responses of mature B cells. Antibody responses that were dependent on cognate T-cell interaction were normal, but T-cell-independent antibody responses were reduced in knockout mice. This might be due to the absence of B1 cells, which are important contributors to T-cell-independent responses. However, the *in vitro* responses of mature $Bcap^{-/-}$ B cells to various activating stimuli are impaired also.

What, then, is the basis of impaired B-cell signalling in the absence of Bcap? The BCR-induced Ca^{2+} flux — a central downstream event in BCR signalling — was found to be reduced in $Bcap^{-/-}$ B cells. This seems to be due to impaired PLC-γ2 activation, although conventional mechanisms of PLC-γ2 activation that involve protein tyrosine kinases or PI3K are unaffected. This is surprising, because PI3K is thought to have a key role in calcium flux, and previous studies in a B-cell line have shown that PI3K activation is diminished in the absence of Bcap.

The authors propose two alternative mechanisms by which Bcap might regulate PLC-γ2 activation. First, Bcap might be involved in targeting PLC-γ2 to membrane microdomains. Alternatively, Bcap might interact directly with PLC-γ2 to induce an activating conformational change.

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