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► **COVER:** 'Tipping point' by Simon Bradbrook, is inspired by our article on page 767. Flicks of cigar ash set off a sequence of events that eventually open the window; similarly, minuscule changes in the BCR initiate signalling cascades that culminate in full B cell activation.



LUCY BIRD



KIRSTY MINTON



OLIVE LEAVY



YVONNE BORDON

Three Reviews in this issue consider how immune responses are influenced by the way in which immune cells 'see' antigens. The article by Angus Thomson and Percy Knolle (p753) describes how the various antigen-presenting cells in the liver ensure that T cells remain tolerant to innocuous antigens, such as gut-derived nutrients. This tolerogenic nature of the liver is largely the result of its unique anatomy and a microenvironment rich in immunoregulatory factors that inhibit the full activation of local antigen-presenting cells under steady-state conditions.

By contrast, prophylactic vaccines are designed to induce productive adaptive immune responses that are broadly reactive and long-lasting. On page 787, Martin Bachmann and Gary Jennings review the vaccine antigen delivery systems that are currently being developed to optimize vaccine-induced immune responses. In particular, they describe how the immune system responds best to vaccines that mimic the features of viruses, such as their size (to ensure efficient delivery to the lymph nodes), the repetitive organization of antigens (to facilitate B cell activation) and the presence of stimulators of the innate immune system.

In a Review on page 767, Susan Pierce and Wanli Liu describe in detail the immediate events that follow the binding of antigen to the B cell receptor (BCR), resulting in signalling cascades that activate the B cell. The authors explain that antigens in solution must crosslink the BCR to generate BCR microclusters, which are necessary for the activation of signalling cascades. However, when monovalent antigen is presented on a cell surface, signalling-competent BCR microclusters can form without the need for physical BCR crosslinking. This again highlights the importance of antigen context for the induction of appropriate immune responses.

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