B-CELL DEVELOPMENT

Heads or tails?

Some people rely on the roll of a dice or the toss of a coin to make decisions. But, how does an immature, transitional B cell in the spleen decide whether to develop into a follicular B cell or a marginal-zone (MZ) B cell? Reporting in *Nature Immunology*, Tanigaki and colleagues now show that Notch–RBP-J signalling is required for this cell-fate decision.

Notch signalling, of which the DNA-binding protein RBP-J is a key mediator, regulates cell-fate decisions in various lineages. RBP-J deficiency results in embryonic lethality in mice, thereby precluding the study of B-cell development in these animals. Here, the authors used conditional mutagenesis to generate mice that selectively lacked B-cell expression of RBP-J (*RBP-J$^{f/f}$× Cre* mice), so that they could investigate the function of Notch–RBP-J in B-cell differentiation.

Anti-CD21 and anti-CD23 antibodies were used to discriminate between immature B cells, follicular B cells and MZ B cells in the spleens of *RBP-J$^{f/f}$× Cre* mice. Flow-cytometric analysis showed that MZ B cells were absent in these mice. Higher numbers of follicular B cells were observed in *RBP-J$^{f/f}$× Cre* mice compared with wildtype mice, which indicates that Notch–RBP-J signalling might normally act to promote MZ B-cell fate at the expense of follicular B-cell fate. RBP-J deficiency caused no defects in B-cell maintenance, survival or activation, or plasma-cell differentiation.

The lack of MZ B cells in the *RBP-J$^{f/f}$× Cre* mice might indicate a role for RBP-J in the maintenance of these cells, rather than a role in lineage commitment. To address this, the authors crossed the *RBP-J$^{f/f}$* mice with mice that carry the *Cre* transgene under the control of an interferon-inducible promoter, and they induced the deletion of RBP-J in adult mice. If RBP-J is required for the specific localization or survival of MZ B cells, then inducible deletion of RBP-J would result in the rapid disappearance of MZ B cells. If, however, RBP-J is required for the lineage commitment of MZ B cells, then the MZ B cells with the deleted allele would remain in their original location and gradually decrease in number with their natural lifespan. Induced deletion of RBP-J in adult mice caused a slow reduction in the number of MZ B cells, which confirms that RBP-J signalling is required to regulate a cell-fate decision between follicular and MZ B cells.

Does the loss of MZ B cells in the *RBP-J$^{f/f}$× Cre* mice affect their immune responses? Tanigaki and colleagues immunized these mice with Ficoll, lipopolysaccharide or chicken γ-globulin, and showed that the antibody responses to these antigens were normal. By contrast, these mice were more susceptible to infection with intravenously administered *Staphylococcus aureus*, which indicates that MZ B cells are important for the clearance of blood-borne bacterial infections.

As well as providing useful insights into the molecular mechanisms of MZ B-cell differentiation and function, the *RBP-J$^{f/f}$* mice will be important for future studies of Notch signalling in other tissues.

Jenny Buckland

References and links

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MUCOSAL IMMUNOLOGY

Location is everything

If you have ever spent time house-hunting, it is likely that you will have heard the old adage — location is everything. The same principle applies to the immune system. Now, reporting in *Immunity*, McSorley *et al.* show that T-cell responses to *Salmonella* in mice are limited to mucosal sites, despite the existence of a disseminated infection.

Salmonella bacteria can cause a range of symptoms, from food poisoning to typhoid fever. Mouse models of infection have been valuable for our understanding of the immune response to *Salmonella*, but several questions remain unanswered. For example, it is not clear where naive *Salmonella*-specific T cells first encounter antigen or whether these T cells migrate to the liver, which is one of the main sites of infection. To address such questions, McSorley and colleagues developed an adoptive transfer system, which permits the tracking of *Salmonella*-specific CD4$^+$ T cells *in vivo*. Transgenic *Salmonella*-specific SM1 T cells were transferred into congenic wild-type mice; this mimics the natural situation in which *Salmonella*-specific T cells compete with T cells of other specificities. Differences in the expression of CD90 alleles between donor and host enabled the tracking of donor T cells in the recipient mice.

McSorley *et al*. found that SM1 T cells in the Peyer's patches responded to *Salmonella* bacteria within three hours of oral infection. The rapidity of this response indicates that it is not necessary for antigen-presenting cells (APCs) to migrate to the mesenteric lymph nodes to initiate T-cell responses; rather, it seems that dendritic cells in the Peyer's patches can acquire antigen rapidly and stimulate nearby T cells. The clonal expansion of SM1 T cells was restricted to mucosal lymphoid tissues, despite the presence of bacterial infection in other organs, such as the spleen and liver. The authors speculate that splenic SM1 T cells are unresponsive because APCs and T cells are anatomically separated in the spleen — preliminary data show that bacteria are located in the red pulp and T cells in the white pulp early after infection. But, an alternative explanation (see Further Reading) is that although the bacterial load in the spleen is high, the antigenic load might be low. SM1 T cells are specific for a flagellin epitope, and the expression of flagellin in systemic bacteria, which can switch off expression of certain genes, might be lower than in mucosal bacteria.

Elaine Bell

References and links

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