MACROPHAGES

Amazing architecture

The architecture of the spleen — with specialized regions containing subsets of B cells, T cells and antigen-presenting cells (APCs) — is designed to ensure a rapid and efficient response to blood-borne pathogen antigens. A new study in *The Journal of Experimental Medicine* shows that a specialized subset of macrophages might be the architects responsible for careful planning of the marginal zone of splenic white pulp.

The marginal zone contains a population of B cells (MZBs) and specialized marginal-zone macrophages (MZMs), which are defined in part by expression of the scavenger receptor Marco. Mice that lack the inositol polyphosphate phosphatase Ship have splenomegaly and disruption of this marginal-zone architecture, with the loss of MZBs and the redistribution of Marco$^+$ MZMs to the red pulp. As Ship is expressed by almost all haematopoietic cells, the authors conditionally disrupted Ship in macrophages and showed that the disrupted marginal-zone phenotype can be attributed to a primary macrophage defect. This was confirmed by the injection of Ship-deficient and wild-type bone marrow into irradiated wild-type recipients; both types of bone marrow contributed equally to the MZB population, which shows that Ship-deficient B cells can still give rise to MZBs.

Ship is known to be a negative regulator of cell signalling. In B cells, it achieves this by inhibiting the association of the Tec-family kinase Btk with the cell membrane, which raises the threshold for stimulation. As Btk is also expressed by macrophages, is the increased activity of Btk as a result of Ship deficiency in MZMs responsible for the disrupted architecture? Mice that were deficient for both Ship and Btk had a normal marginal-zone structure, which indicates that although other Tec-family kinases are also expressed by macrophages, the specific inhibition of Btk by Ship is essential for the white-pulp organization.

MZMs, but not other types of macrophage and APC, were preferentially depleted from the spleen. This resulted in a reduction in the number of MZBs in the marginal zone. Marco has a domain that has been proposed to bind to activated B cells, so the authors looked at whether Marco can bind to MZBs. The extracellular domains of Marco were used to stain splenic populations and maximal staining occurred for MZBs. Furthermore, injection of a Marco-specific antibody in wild-type mice disrupted the marginal zone. Therefore, the Marco–MZB interaction is a mechanism for the retention of MZBs in the marginal zone by MZMs.

So, just as there would be no Eiffel Tower without Gustave Eiffel, this study shows that without Marco$^+$ MZMs, there is no splenic marginal zone containing specialized B cells ready to respond to pathogen antigens.

Kirsty Minton

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WEB SITE

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VACCINES

Time runs out for Ebola

Ebola virus causes an untreatable haemorrhagic fever, which is fatal in 90% of cases. Now, the production of a vaccine that can confer protection against Ebola virus in macaque monkeys only 28 days after immunization could mean that a vaccine can be administered in outbreak situations.

The Ebola virus glycoprotein (GP) — an envelope protein — is the main pathogenic determinant during infection. Previously, immunization with a DNA vaccine containing genes encoding GP from several Ebola virus serotypes and nucleoprotein (NP), followed by a booster with a recombinant adenovirus vector containing GP from the Zaire Ebola virus subtype — a 'prime–boost' strategy — generated protective cellular and humoral immunity in macaques. But the prime–boost regime took six months to administer. Now, Sullivan *et al.* have developed a vaccine that contains an equal mixture of recombinant adenovirus vectors encoding Ebola virus (Zaire and Sudan serotypes) GP and NP. One shot of this vaccine protects against Ebola virus challenge in macaques 28 days after immunization. With the one-shot vaccine, protection was achieved against low and high challenge doses of Ebola virus — both of which were lethal for saline-injected control macaques. Protection correlated with the generation of Ebola-virus-specific CD8$^+$ T-cell and antibody responses.

Intriguingly, Ebola-virus-specific immune responses did not increase markedly after a second round of vaccination, probably because of anti-vector immunity. Adenovirus is one cause of the common cold — and 45% of the United States population have adenovirus-specific antibodies. The authors speculate that using different adenovirus serotypes as vaccine vectors could help to overcome potential problems with resistance to these vaccines. Because Ebola virus typically causes outbreaks that are spread in healthcare settings, this new vaccine could help to control outbreaks if it proves to be similarly effective in humans.

Susan Jones, Associate Editor,
Nature Reviews Microbiology

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