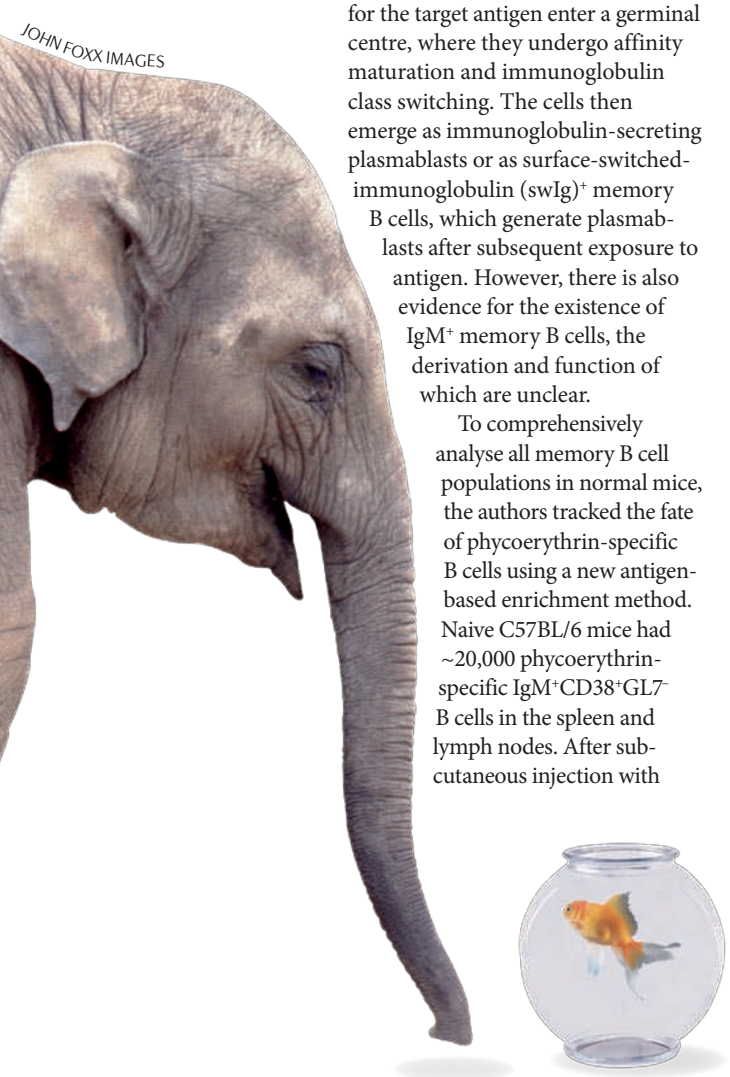
B CELLS

Short- and long-term memory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In a recent study in *Science*, Marc Jenkins and colleagues identify two populations of memory B cells that differ in terms of frequency, lifespan and activation potential.

In a classical primary immune response, naive IgM$^+$ B cells specific for the target antigen enter a germinal centre, where they undergo affinity maturation and immunoglobulin class switching. The cells then emerge as immunoglobulin-secreting plasmablasts or as surface-switched-immunoglobulin (swIg)$^+$ memory B cells, which generate plasmablasts after subsequent exposure to antigen. However, there is also evidence for the existence of IgM$^+$ memory B cells, the derivation and function of which are unclear.

To comprehensively analyse all memory B cell populations in normal mice, the authors tracked the fate of phycoerythrin-specific B cells using a new antigen-based enrichment method. Naive C57BL/6 mice had ~20,000 phycoerythrin-specific IgM$^+$CD38$^+$GL7$^-$ B cells in the spleen and lymph nodes. After subcutaneous injection with phycoerythrin plus adjuvant, the number of phycoerythrin-specific B cells increased markedly to a peak of ~10^6 cells by day 13 and then declined to a stable population of ~150,000 cells. At day 8 after antigen injection, the phycoerythrin-specific B cells could be divided into IgM$^+$ and swIg$^+$ populations, both of which contained plasmablasts with high intracellular immunoglobulin concentrations, CD38$^-$GL7$^+$ germinal centre cells and CD38$^+$GL7$^-$ memory cells.

The number of IgM$^+$ and swIg$^+$ plasmablasts and germinal centre B cells peaked around day 13 and then declined, but the memory B cells had different dynamics according to their immunoglobulin phenotype. swIg$^+$ memory B cells peaked on day 30 at ~60,000 cells and declined to very low numbers by day 450, whereas IgM$^+$ memory B cells peaked on day 10 at ~120,000 cells and the population then remained stable until at least day 450.

Adoptive transfer studies showed that both memory B cell populations in isolation could mount a memory response in recipient mice. However, different results were obtained when both memory B cell populations were present in mice that had been previously primed with phycoerythrin. On day 320 after priming, the mice contained 100,000 IgM$^+$ and 2,000 swIg$^+$ antigen-specific memory B cells. When these mice were rechallenged, the number of swIg$^+$ memory cells increased 150-fold to generate 25,000 swIg$^+$ plasmablasts (but no germinal centre cells), whereas the number of IgM$^+$ cells increased less than twofold. The poor secondary response of IgM$^+$ memory B cells was attributed to the presence during the challenge of phycoerythrin-specific antibody (produced by swIg$^+$ plasmablasts), which was shown to inhibit germinal centre formation by both naive B cells and IgM$^+$ memory B cells.

These results illustrate some analogies between how we think about humoral and neurological memories. In neuroscience, short-term memory is the capacity for holding a small amount of information in an active, readily available state for a short period of time. This is akin to the small number of short-lived but readily activated swIg$^+$ memory B cells. By contrast, long-term memories can be retained for much longer, akin to the IgM$^+$ memory B cells. The authors speculate that IgM$^+$ memory B cells do not contribute to the secondary response until the immunoglobulin levels produced by swIg$^+$ memory B cells have declined. As long-term memory is subject to fading, several recalls of memory might be required to prevent forgetting. In a similar manner, IgM$^+$ memory B cells can form germinal centres to repopulate the reservoir of humoral immune memory.

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ORIGINAL RESEARCH PAPER Pape, K. A. *et al.* Different B cell populations mediate early and late memory during an endogenous immune response. *Science* 10 Feb 2011 (doi:10.1126/science.1201730)