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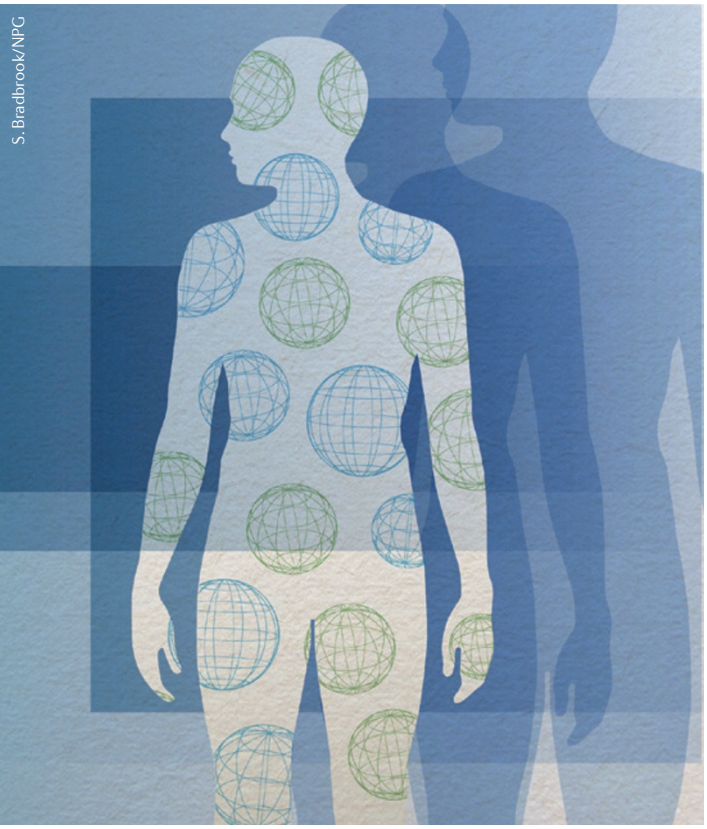
B CELL MEMORY

Making sense in humans

In human peripheral blood there are two main B cell populations: a naive IgM$^+$CD27$^-$ population that has unmutated immunoglobulin genes and a class-switched memory IgG$^+$CD27$^+$ population. IgM$^+$CD27$^+$ memory B cells have also been identified, but the generation and immunological function of these cells are poorly understood. Now, Ralf Küppers and colleagues report that human IgM$^+$ memory B cells are more similar to IgG$^+$ memory B cells than to naive B cells. Human IgM$^+$ memory B cells can re-enter germinal centre (GC) reactions upon antigen re-encounter and they can interact with neutrophils in early inflammatory responses *in vitro*.

> IgM$^+$ memory B cells have chemotactic activity



S. Bradbrook/NPG

To characterize different human B cell subsets, the authors compared the transcriptional expression profiles of IgM$^+$CD27$^-$, IgG$^+$CD27$^+$ and IgM$^+$CD27$^+$ B cells. The two CD27$^+$ memory B cell subsets showed substantial similarities and were clearly different from the naive CD27$^-$ B cells. Gene set enrichment analysis identified shared gene signatures that were associated with a memory B cell phenotype, including genes associated with enhanced antigen responsiveness and plasmablast differentiation.

Next, the authors investigated differences between IgG$^+$ and IgM$^+$ memory B cells; pairwise gene comparisons revealed more than 400 genes with at least a twofold difference in expression between the two B cell subsets. They identified genes encoding key molecules that have specific functions in IgM$^+$ memory B cells, including carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) and CC-chemokine receptor 2 (CCR2). *In vitro* chemotactic assays with soluble CEACAM8 (sCEACAM8) and CC-chemokine ligand 2 (CCL2) showed that IgM$^+$ memory B cells have chemotactic activity towards both ligands. Furthermore, IgM$^+$ memory B cells differentiated more readily into antibody-secreting cells than IgG$^+$ memory B cells and naive B cells in response to sCEACAM8 stimulation. Thus, by expressing different surface receptors, IgM$^+$ memory B cells can respond to stimulation by specific signals, which can lead to increased migratory capacity and differentiation into antibody-secreting cells.

Interestingly, both sCEACAM8 and CCL2 are known to be secreted by neutrophils in early phases of inflammatory responses and these molecules help to recruit leukocytes. Co-cultures of neutrophils and IgM$^+$ memory B cells showed that activated neutrophils could stimulate IgM$^+$ memory B cells to differentiate and secrete IgM or class switch to IgG2.

Finally, the authors investigated whether human IgM$^+$ and IgG$^+$ memory B cells show a distinct memory response to antigen recall. IgM$^+$ memory B cells showed greater migration towards signals that direct homing to B cell follicles than naive and IgG$^+$ memory B cells, whereas the naive and IgG$^+$ B cell subsets preferentially migrated towards signals that direct plasma cell homing. This result suggests that IgM$^+$ memory B cells can re-enter GC reactions. Indeed, they found that human IgM$^+$ memory B cells upregulated the expression of the GC-associated transcription factor B cell lymphoma 6 (BCL-6), which indicates that IgM$^+$ memory B cells preferentially adopted a pre-GC B cell phenotype. However, following T cell-independent antigen stimulation, IgM$^+$ memory B cells also differentiated into plasma cells, as they adopted plasma cell morphology and downregulated their expression of BTB and CNC homologue 2 (BACH2). By contrast, human IgG$^+$ memory B cells primarily differentiated into plasma cells following re-encounter with either T cell-dependent or T cell-independent antigen.

Together, these results increase our understanding of human peripheral blood IgM$^+$ memory B cells and reveal the unexpected functional plasticity of these cells.

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