T CELL MEMORY

A new resting place

Unlike memory CD8$^+$ T cells and plasma cells, which reside in bone marrow niches, it had been presumed that memory CD4$^+$ T cells constantly circulate in the body for surveillance. Now, Tokoyoda and colleagues show that memory CD4$^+$ T cells do in fact reside and rest in the bone marrow, where they associate with interleukin-7 (IL-7)-expressing stromal cells.

The authors tracked the tissue distribution of antigen-specific memory (CD44^{hi}CD62L$^-$) CD4$^+$ T cells in mice and found that 4 days after antigen immunization, activated antigen-specific CD44^{hi}CD4$^+$ T cells were only present in the spleen and draining lymph nodes. However, from day 60 onwards more than 80% of the antigen-specific memory CD4$^+$ T cells had relocated to the bone marrow, a process that depended on α2 integrin expression by the T cells. Unlike most spleen CD44^{hi}CD62L$^-$CD4$^+$ T cells, bone marrow CD44^{hi}CD62L$^-$CD4$^+$ T cells could be characterized by high expression levels of LY6C.

A comparison of the gene expression profile of spleen and bone marrow memory CD4$^+$ T cells showed that 96% of the genes that were differentially expressed were downregulated in bone marrow memory CD4$^+$ T cells. In addition, bone marrow memory CD4$^+$ T cells did not proliferate in the steady state, so together these observations indicate that these cells are in a resting state. Further analysis showed that ~95% of the antigen-specific memory CD4$^+$ T cells in the bone marrow colocalized individually with VCAM1$^+$ stromal cells that expressed IL-7, a cytokine that is essential for the maintenance of CD4$^+$ T cell memory. The authors estimated the capacity of the mouse bone marrow for memory CD4$^+$ T cells to be about 1% of the bone marrow cells, which corresponds to the percentage of VCAM1$^+$ IL-7-producing stromal cells in the bone marrow.

Finally, the authors showed that in a secondary immune response bone marrow memory CD4$^+$ T cells expressed interferon-γ and CD40 ligand faster and at higher levels than spleen memory CD4$^+$ T cells and that only bone marrow memory CD4$^+$ T cells could provide help for the production of high-affinity antibodies by B cells.

So, the data indicate that memory CD4$^+$ T cells reside in dedicated bone marrow survival niches in a resting state but can be quickly reactivated to provide fast and efficient help to B cells during secondary immune responses.

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