Nature **401,** 659–660; 1999

Dual personality of memory T cells

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A newly identified chemokine receptor can identify two types of memory T cell with different migration preferences. Their existence may explain how memory cells initiate the rapid and effective secondary response to antigens.

Often, when a pathogen first infects the body, nothing happens — at least, not for several days. But when the same pathogen is encountered a second time, the response is rapid and vigorous. This phenomenon, known as immunological memory, is the basis for vaccination, yet very little is understood about how it protects the entire body so effectively. On page 34 of this supplement, Sallusto *et al.*[1] report that a newly identified cell-surface marker — the chemokine receptor CCR7 — can distinguish two subsets of T cells that carry immunological memory. These two subsets apparently circulate around the body by different pathways, and mediate the memory response in different ways. The results provide a new insight into the memory response, one that is relevant to basic immunology, as well as to vaccination strategies and the development of immunosuppressive therapies.

The immune system responds slowly to newly encountered pathogens owing to the relative lack of antigen-specific cells. New pathogens must first be transported to nearby lymphoid tissue, where the primary immune response develops and where naive lymphocytes and antigen-presenting cells interact. Two clonally expanded populations emanate from this primary response: 'effector' cells, which combat spread of the pathogen; and 'memory' cells, which guard against subsequent infections. Effector and memory cells are thought to be distributed to all tissues in the body, particularly epithelial surfaces (such as the skin and gut) where pathogens are likely to be re-encountered, so lymphocyte migration facilitates systemic immunological memory.

How can we tell the difference between naive, memory and effector T cells? This has been an elusive goal. In humans, isoforms of CD45 (a phosphatase involved in cell signalling) seemed able to distinguish naive and memory T cells. Any cell expressing the CD45RO isoform was regarded as a memory T cell, based on the fact that $CD45RO^+$ (memory) T cells — but not $CD45RA^+$ (naive) T cells — can respond vigorously *in vitro* to previously encountered antigens. Moreover, whereas $CD45RA^+$ T cells migrate almost exclusively through lymphoid tissue[2], $CD45RO^+$ T cells migrate throughout the body, including epithelial surfaces. The rationale is that a naive T cell has such a low probability of seeing its specific antigen that it needs to travel through the lymph nodes, which are designed for massive migration of lymphocytes and antigen sampling[2]. In contrast, memory or effector cells migrate mainly to peripheral tissues, providing protection at sites vulnerable to challenge by pathogens. But the problem with this system was that both memory and effector cells express CD45RO, so there was still no way to distinguish between the two.

Sallusto *et al.*[1] have now used a monoclonal antibody that recognizes the chemokine receptor CCR7 to discriminate between the two subsets of $CD45RO^+$ T cells. The $CCR7^-$ subset has many characteristics of effector cells. For example, these cells rapidly produce effector cytokines such as interferon-γ, interleukin-4 and interleukin-5, or they express perforin granules (a feature of cytotoxic cells). Cells in the $CCR7^+$ subset, on the other hand, behave more like true memory cells — they lack effector function, but the authors found that these cells could differentiate to $CCR7^-$ effector cells after being stimulated with antigen. So, expression of CCR7, in conjunction with CD45RO, distinguishes memory cells from effector cells.

Many cells that migrate to the lymph nodes, such as naive T cells and antigen-presenting cells, express CCR7. Moreover, the chemokines that bind to CCR7 (MIP-3β and secondary lymphoid chemokine; SLC) are both constitutively expressed in lymph nodes. For example, SLC is produced by specialized blood vessels in the lymph nodes and provides the entry cue for $CCR7^+$ cells circulating in the blood[3]. And the lymphocytes in mice that lack CCR7 or SLC migrate poorly through the lymph nodes[4,5]. But

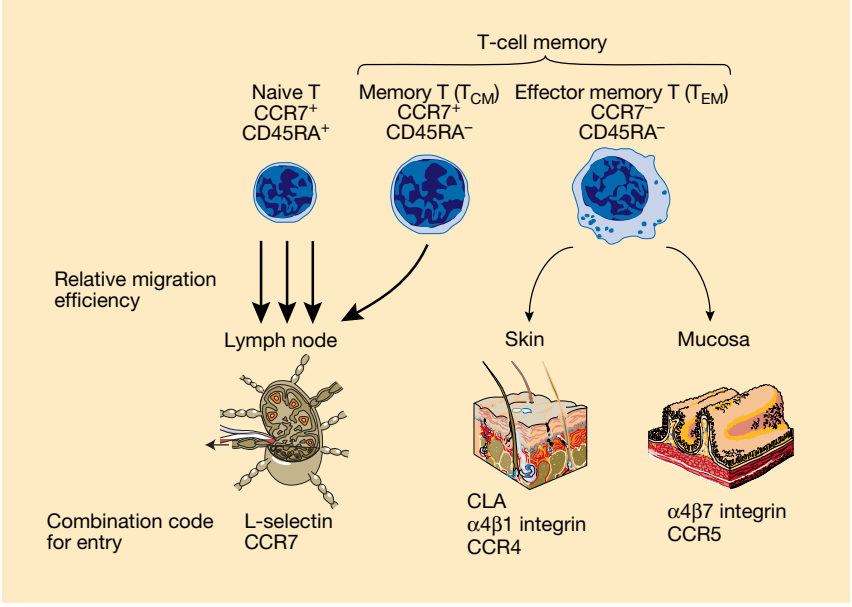

Figure 1 **Two types of memory T cell with different migration preferences. Expression of CCR7 and the CD45RA isoform distinguishes three subsets of T cells: naive T cells ($CCR7^+$ $CD45RA^+$); a new subset, which Sallusto *et al.*[1] term central memory T cells (T_{CM}: $CCR7^+$ $CD45RA^-$); and effector memory T cells (T_{EM}: $CCR7^-$ $CD45RA^-$). Naive T cells migrate very efficiently through lymph nodes using a 'combination code' of L-selectin (an adhesion molecule) and CCR7 (a chemokine receptor). Central memory T cells probably migrate through lymph nodes, whereas effector memory T cells migrate through peripheral tissues such as the skin and mucosa. There are likely to be many combination codes for homing of T cells to the skin and mucosal tissues. CLA, cutaneous lymphocyte antigen.**

CCR7 is only half the story, because cells first adhere to the walls of the lymph-node vessels using a molecule called L-selectin. So, the 'combination code' for entry of T cells to normal lymph nodes is L-selectin binding, followed by CCR7 signalling through SLC. This code is expressed by naive T cells and $CCR7^+$ memory T cells (Fig. 1), but not by certain cells that do not recirculate, such as neutrophils or monocytes. Trafficking experiments show[2,6] that a subset of memory T cells does indeed enter lymph nodes, although we cannot yet say whether these are Sallusto and colleagues' $CCR7^+$ memory T cells.

The traffic of T cells through peripheral sites differs fundamentally from that through lymph nodes. So-called 'inflammatory' chemokines and receptors are involved, together with adhesion molecules that are upregulated by inflammatory cytokines. The T cells recruited to peripheral tissues are usually very distinctive, and include $CD45RO^+$ T cells expressing chemokine receptors such as CCR5, CCR2 or CCR3 (ref. 7). But Sallusto *et al.*[1] show that these T cells, which are the effector-type cells, do not express CCR7. CCR5 is a particularly good marker for a subset of effector T cells, and T cells expressing CCR5 are prominent in inflammatory disease and at mucosal surfaces[7] (a feature that may relate to the transmission of HIV-1). In fact, it is likely that the T cells that show a degree of tissue-selective migration — preferential migration through the skin, say, rather than the gut — are effector-type T cells. For instance, the skin-homing subset of effector T cells expresses cutaneous lymphocyte-associated antigen and the chemokine receptor CCR4 (ref. 8).

The basis of immunological memory has long been contentious. According to one theory, the long-lived, recirculating memory T cells differentiate quickly to effector cells when they re-encounter an antigen. Another theory holds that constant exposure to the antigen is needed to maintain memory. Sallusto and colleagues now show that both $CCR7^+$ (memory) and $CCR7^-$ (effector) cells from people immunized with tetanus toxoid respond well to subsequent challenge with the toxoid *in vitro*. That is, toxoid-specific effector T cells remain alive and well, years after an initial immunization. The implication is that immunological memory is carried by both classical-type memory T cells (which Sallusto *et al.* term central memory T cells, T_{CM}) and effector T cells (now referred to as effector memory T cells, T_{EM})[2].

So what is the precursor–product relationship between the central memory T cell and the 'effector' memory cell? Sallusto *et al.* propose that the naive T cell differentiates to a central memory T cell and, finally, to an effector memory cell. A more conventional idea is that effector cells are the precursors of memory cells[9]. Whatever the case, the existence of two types of memory cell with different migration pathways makes a lot of sense. Effector memory cells provide immediate front-line protection, particularly at epithelial surfaces. The central memory cells are the reserves, which can differentiate rapidly to effector memory cells in the lymph nodes in response to antigen. In conclusion, Sallusto and colleagues' study illustrates an important principle — the relationship between the functional activity of lymphocytes and their migration properties. For this reason, the chemokine receptors are proving to be excellent markers for various subsets of immune cells. ■

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