

T cell traffic signals

In 1990, Charles Mackay and colleagues combined classical physiology with modern molecular biology to provide the first concrete evidence that naive and memory T cells follow distinct migratory routes out of the bloodstream—a discovery that helped invigorate the field of lymphocyte homing.

Decades of research have uncovered the complex rules that govern the recirculation of specific T cell subsets. Today we appreciate that memory and naive T cells (and subsets of these cells) differentially express homing receptors that control cellular traffic into distinct tissues and lymphoid organs. But a mere 15 years ago, the migration patterns of naive and memory T cells had yet to be mapped out.

T cells stay true to their roots

Before the late 1960s, it was generally believed that lymphocytes circulated randomly throughout the body. Among the first observations that hinted otherwise were those of James Gowans and E. Julie Knight (Oxford University) and Robert Taub and Eugene Lance (National Institute for Medical Research, London, UK), who noted that lymphocytes that were recovered from the lymph node or spleen of rats or mice would faithfully migrate back to their site of origin if transferred into another animal (1, 2).

These data were later confirmed in sheep by Ross Cahill's team (Basel Institute for Immunology, Switzerland). The sheep model allowed Cahill to access populations of T cells from distinct lymph nodes and lymphatic vessels—a feat not possible in rodents or humans. The team found that T cells from the intestinal lymph duct made their way back to the intestine upon transfer into another sheep. T cells from peripheral (nonintestinal) nodes also returned to their origins (3). Cahill's group thus proposed that the pool of recirculating T cells consisted of two major subsets: an intestinal pool and a nodal pool. Other groups performed similar experiments with activated T cells (immuno-

blasts) and reached similar conclusions (reviewed in reference 4).

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The mark of memory

Among the first hints that naive and memory T cells navigated differently probably came from Cahill's group, who showed that the pool of intestine-homing lymphocytes was absent from "immunologically virgin" fetal lambs (5). They concluded that the subpopulation of intestine-seeking cells only appears after birth, possibly as a result of antigen exposure. Although this interpretation turned out to be correct, defining the precise homing patterns of naive and memory T cells required a foolproof way to distinguish these subsets in vivo. In the late 1980s, groups led by Stephen Shaw, Peter Beverley, H. Robson MacDonald, and others identified adhesion molecules and integrins, including CD2, CD11a (LFA-1), CD44 (Pgp-1), and CD45RO, that were expressed on human and mouse memory T cells but not on naive cells.

Combining forces

A few years later, Mackay and colleagues at the Basel Institute for Immunology combined the sheep model with these molecular markers of T cell subsets. "We put a lot of effort into making antibodies to all these markers in the sheep, at a time when the field of lymphocyte homing was one of the least fashionable in immunology," says Mackay. His experimental design hinged primarily on an isoform of the CD45 molecule (CD45R) that his group

had previously shown to be expressed only on naive sheep T cells. Mackay used immunofluorescent staining and flow cytometry to show that memory T cells preferentially accumulated in the afferent lymph, indicating that they had migrated from the blood across the endothelium of peripheral tissues. Naive T cells, however, congregated in the efferent lymph, suggesting that they had entered the lymph nodes directly from the blood via the high endothelial venules. "It was a solid result," recalls Mackay. "It seemed to make so much sense that naive cells with a low frequency of antigen-specific cells would go through the node," where primary immune responses are initiated. In 1990, he published these data in the *Journal of Experimental Medicine* (6).

Memory T cells have since been divided into effector and central memory cells, which themselves have distinct homing patterns. In retrospect, Jonathan Sprent (Scripps, La Jolla, CA) notes that Mackay likely lumped central memory cells into his naive cell population. Nevertheless, Sprent feels that "the Mackay paper was indeed important in focusing attention on naive versus memory T cells." The precise traffic signals that guide these cells along the appropriate route have also been illuminated, largely by Eugene Butcher and colleagues at Stanford University (reviewed in reference 3), who discovered the majority of the adhesion molecules and integrins that allow cells to access particular tissues and lymphoid compartments.

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