Milestone 7

How T cells navigate

In the 1950s, T cells were yet to be described and the functions of lymphocytes were unknown. But animal experiments had shown that each day, enough lymphocytes enter the blood from the main lymphatics to replace all of the blood lymphocytes many times over. Where did all of the lymphocytes go?

One theory proposed that lymphocytes were primitive stem cells, another that they were end-stage cells that soon died. In 1959, James Gowans solved the 'mystery of the disappearing lymphocytes', showing that lymphocytes continuously recirculate from the blood to lymphoid organs and back again. In further seminal studies, Gowans, Knight and colleagues tracked radioactively labelled lymphocytes. They found that lymphocytes 'home' to lymph nodes by crossing specialized post-capillary high endothelial venules (HEVs), then pass through the lymph node cortex into lymph sinuses and eventually return to the blood via the thoracic duct lymph. Moreover, these studies and others, such as from Griscelli et al., provided evidence that subsets of lymphocytes show distinct patterns of migration. Therefore, lymphocyte migration was not random or passive, but controlled by active mechanisms.

In 1977, Cahill et al. reported that the migration of small thymus-derived (T) lymphocytes in sheep is not uniform. When they isolated T lymphocytes from the efferent lymph of peripheral lymph nodes (PLNs) or from intestinal lymph, labelled the cells and reinfused them into animals, the T lymphocytes were twice as likely to return to the tissue location that they originally came from. Soon after, in 1980, Butcher et al. used the adhesion assay developed by Stamper and Woodruff to show that biased homing to PLNs or to the gut-associated Peyer's patches was mediated by lymphocyte interactions with 'organ-specific determinants' on HEVs. However, the identity of these determinants was unknown.

A key breakthrough came in 1983, when Gallatin, Weissman and Butcher isolated a monoclonal antibody, MEL-14, which bound to an undefined antigenic target on T cells and B cells. Treatment of lymphocytes with MEL-14 specifically blocked their binding to PLN HEVs, but did not alter their binding to Peyer's patch HEVs. This was the first direct evidence that antigenically distinct receptors expressed by T cells could guide their entry into peripheral versus intestinal lymphoid tissues.

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The field progressed at breakneck speed throughout the late 1980s and 1990s, with a flurry of papers from Butcher's group and others identifying key homing receptors and vascular 'addressins' that guide T cell trafficking. LFA1 (the αLβ2 integrin) had been identified in the context of T cell killing responses (Milestone 2), but it was soon realized to mediate binding of activated lymphocytes to endothelium via interaction with ICAM1. Another lymphocyte-expressed integrin, α4β7, was found to interact with MADCAM1 to promote recruitment to mucosal tissues, and VCAM1 (a ligand for α4β1 integrin) was upregulated on activated endothelium to promote T cell recruitment to inflamed sites. The CLA–E-selectin adhesion pathway was shown to promote lymphocyte homing to the skin.

Studies from Charles Mackay and others confirmed that naive and memory T cells have distinct trafficking patterns, recirculating from the blood to lymph nodes or from the blood to tissue, respectively. Crucially, it was realized that these unique patterns of migration are intimately linked to T cell function — recirculation of naive T cells through lymph nodes optimizes their chance of encountering rare cognate antigens on dendritic cells, while targeting of memory T cells to peripheral tissues ensures that they are in the right location to mediate their protective functions. Sallusto et al. also described distinct populations of 'central' and 'effector' memory T cells (Milestone 3), which preferentially migrated to PLNs or inflamed tissues, respectively.

Butcher's group defined the famous 'multistep adhesion cascade' for cell extravasation from the blood. Briefly, naive T cells first use L-selectin (the molecular target of MEL-14) to tether and 'roll' on HEVs, then undergo integrin activation to firmly adhere on endothelium and then transmigrate across the endothelium to enter PLNs. Variations on this cascade mediate the recruitment of specific T cell populations to other sites, such as the intestinal mucosa or inflamed tissues.

Another layer of control was added by the discovery of the expansive chemokine (chemotactic cytokine) family. Different chemokines produced in response to homeostatic or inflammatory tissue signals were shown to guide leukocyte migration, for example by inducing integrin activation or by acting as direct chemoattractants for cells. Certain chemokine receptors were linked with the tissue-specific migration of T cells; for instance, CCR4 and CCR10 were shown to be associated with homing to the skin. And tissue-specific factors were identified that act via dendritic cells to 'imprint' T cells with particular homing properties; for example, retinoic acid promotes the upregulation of gut homing receptors. Other studies elucidated T cell 'exit' signals to add to the growing list of 'entry' ones, with T cell egress from lymph nodes and tissues found to be driven by sphingosine-1-phosphate receptor 1.

In the past few decades, advanced real-time imaging techniques and the study of migration at the single-cell level has shown how diverse chemical and biophysical cues combine to help T cells traverse tissues. Our growing understanding of T cell migration could be useful therapeutically, for instance to enhance T cell homing to tumours (Milestone 20).

Yvonne Bordon Senior Editor,
Nature Reviews Immunology

Milestone study

Gallatin, W. M., Weissman I. L. & Butcher E. C. A cell-surface molecule involved in organ-specific homing of lymphocytes. *Nature* **304**, 30–34 (1983)

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