Milestone 17

An elegant defence

Decades of immunological research had seemed to paint a clear picture of how T cells respond to microbial infection in vivo: microorganism-derived antigens are captured in tissue-draining lymph nodes and presented to T cells, which, once activated, home to the infected tissue to counter any microbial threats. In other words, most of the early T cell action was thought to occur in lymphoid tissues (Milestone 7). However, a series of pioneering studies in 2001 added an important twist to the story of T cell behaviour. Working in the lab of Leo Lefrançois, David Masopust and colleagues used mouse models of systemic viral and bacterial infection to show that pathogen-specific T cells migrated to several tissues including bone marrow, lung, gut and kidney. Interestingly, these pathogen-specific T cells could remain within tissues as highly functional effector memory cells for many months. In the same year, David Woodland's group published a pair of papers showing that both $CD4^+$ and $CD8^+$ antigen-specific mouse T cells accumulated in the lung after a respiratory virus infection. These T cells were maintained in the lung tissue as effector cells for extended periods. Notably, the transfer of the lung-resident $CD4^+$ T cells could protect naive recipients from respiratory virus. Collectively, these three studies suggested that T cells can remain at the site of an infection long after it had been cleared.

Subsequent work from Rachel Clark and colleagues extended these findings to the human setting. They identified a large population of T cells present within normal human skin at steady state — so large that it numerically outweighed the number of those in the blood. The T cells were primarily of an effector memory helper T cell 1 (T_H1) phenotype (Milestone 11) but regulatory T cells were also present (Milestone 15). Another human study, this time from the group of Donna Farber, used material from human organ donors to find T cells in tissues throughout the body. The stable presence of tissue T cells therefore seemed to be a widespread physiological phenomenon.

In 2009, Thomas Gebhardt and colleagues were arguably the first to coin the term 'tissue-resident memory T cells' (T_{RM} cells) — a nomenclature that has now been universally adopted. But what were these T_{RM} cells doing?

"T_{RM} cells… represent an elegant defense system that provides a rapid response during the earliest stages of infection."

Using a model of herpes simplex virus infection, these authors showed that once recruited to tissues, the T cells stayed put and provided a lasting defence at sites of pathogen entry. Another important finding of this work was that the T_{RM} cells constitutively expressed the cell-surface molecules CD69 and CD103.

The developmental pathway of T_{RM} cells was the next question addressed through a series of papers by Laura Mackay and colleagues. They first found that instead of just being key markers, CD69 and CD103 were in fact important for the optimal generation and/or survival of skin T_{RM} cells. CD69 seemed to be essential for enforced retention of T_{RM} cells in tissues. Furthermore, T_{RM} cells originated from precursors outside of tissues and lacked expression of the effector T cell marker KLRG1. Once within tissues and via the combined action of the IL-15 and TGF-β cytokines, the T cells differentiated into fully-fledged and long-lived T_{RM} cells. The T_{RM} cells were also transcriptionally distinct from their conventional memory T cell (Milestone 3) counterparts in lymphoid tissues. The related transcription factors HOBIT and BLIMP1 were found to instruct the tissue-residency program of not only T_{RM} cells but also other tissue-resident cells such as natural killer T cells (Milestone 14) in the liver.

T_{RM} cells are therefore a universal feature at barrier sites throughout the body, and represent an elegant defence system that provides a rapid response during the earliest stages of infection. Understanding how these cells can be harnessed for vaccines and cancer therapies, or how their activity can be regulated in autoimmune diseases, is likely to be an area of great interest in the future.

Zoltan Fehervari
Senior Editor, *Nature*

Milestone studies

Masopust, D., Vezys, V., Marzo, A. L. & Lefrançois, L. Preferential localization of effector memory cells in nonlymphoid tissue. *Science* **291**, 2413–2417 (2001) | Hogan, R. J. et al. Protection from respiratory virus infections can be mediated by antigen-specific $CD4^+$ T cells that persist in the lungs. *J. Exp. Med.* **193**, 981–986 (2001) | Hogan, R. J. et al. Activated antigen-specific $CD8^+$ T cells persist in the lungs following recovery from respiratory virus infections. *J. Immunol.* **166**, 1813–1822 (2001).

Further reading

Please visit the online article for a full list of further reading.