Published in final edited form as:

Nat Immunol. 2018 February ; 19(2): 102–103. doi:10.1038/s41590-017-0031-9.

Trials and Tribulations of tissue T_{RM} cells

Jun Siong Low and Susan M. Kaech*

Department of Immunobiology, Yale School of Medicine, New Haven, CT, USA.

Abstract

CD8⁺ tissue-resident memory T cells (T_{RM} cells) in two mucosal tissues, the skin and the female reproductive tract, proliferate in situ to generate a secondary pool of T_{RM} cells that does not exit into the circulation.

An effective memory T cell response is based on tiered layers of defense that often begin with locally poised CD8⁺ T_{RM} cells. In this issue of *Nature Immunology*, Beura et al.¹ and Park et al.² describe the early and late effects of secondary infection on pre-existing T_{RM} cell pools in two mucosal tissues, the skin and the female reproductive tract (FRT), and show that CD8⁺ T_{RM} cells proliferate in situ to generate a secondary pool of T_{RM} cells that does not exit into the circulation. Although CD8⁺ memory T cells recruited from the circulation (T_{CIRC} cells) may also take up residence in the reinfected tissue, they do not outcompete the pre-existing T_{RM} cell population^{1,2}.

CD8⁺ memory T cells are a heterogeneous population of cells that can be conceptually segregated on the basis of their functional and spatial properties. Three memory T cell populations have been shown to circulate between the blood and organs: central memory T cells (T_{CM} cells), characterized by their high expression of lymph node (LN)-homing receptors, regenerative potential and interleukin 2 (IL-2) production; effector memory T cells (T_{EM} cells), distinguished by low expression of LN-homing receptors and high expression of CX3CR1, and which predominantly survey the blood and exert immediate cytotoxic functions; and peripheral memory T cells (T_{PM} cells), which are CX3CR1^{int} and preferentially patrol peripheral tissues via a distinct pattern of migration from blood to tissue to lymph. A fourth population of CD8⁺ memory T cells, the T_{RM} cells, derived from CX3CR1^{lo/int} and KLRG1^{lo} effector T cells and commonly distinguished by their increased expression of CD69 and CD103, do not recirculate in the host, but rather dwell long-term within tissues to provide rapid local protection. Such spatial compartmentalization of memory T cells provides a shield of protective immunity acting both outside-in and inside-out.

Poised at the front lines of defense, often within epithelial barriers, CD8⁺ T_{RM} cells serve as motile sentinels that patrol the tissue microenvironment for reinfection³ (Fig. 1). Intravital imaging by Park et al.² and Beura et al.¹ revealed different rates of motility of T_{RM} cells in

* Susan.Kaech@yale.edu.

Competing interests

The authors declare no competing financial interests.

the skin and FRT, with mean velocities of $2 \mu\text{m min}^{-1}$ and $10 \mu\text{m min}^{-1}$, respectively. Notably, in the FRT, CD8^+ T cell velocity is slower down in the collagen-rich perimetrium than in the myometrium¹, possibly because of the unique tissue architectures and densities of the two regions. This is akin in some ways to the situation in the skin, where CD8^+ T cell velocities are significantly faster in the dermis than in the epidermis³. Given the seemingly random motion of these motile CD8^+ T_{RM} cells, it will be informative to learn whether they preferentially interact with cells that express survival-cue proteins such as IL-15 and TGF- β .

A body of literature has informed on how T_{CM} cells and T_{EM} cells respond during secondary infection, but less is known about how T_{RM} cells respond in situ. The prevailing idea in the field was that T_{RM} cells had little self-renewal potential at steady state, and that upon reinfection T_{CM} cells dominated the recall response owing to their increased proliferative capacity. By elegantly delineating the responses of T_{CIRC} cells and T_{RM} cells, Park et al.² and Beura et al.¹ demonstrate that pre-existing T_{RM} cells undergo local proliferation in situ during reinfection. Whether there is a distinct subpopulation of T_{RM} cells with regenerative capacity remains to be explored. Importantly, the secondary pool of T_{RM} cells after reinfection is generated predominantly from the pre-existing, proliferating T_{RM} cells, rather than from the circulating memory T cells recruited into the inflamed tissue. One notable finding by Park et al.² is that homologous reinfection did not significantly boost the number of pre-existing T_{RM} cells, which suggests a numerically stable pool of T_{RM} cells that is robustly maintained, at least in the skin. Although there is evidence that CD103^+ gut T_{RM} cells can circulate and acquire properties of splenic memory when adoptively transferred and restimulated⁴, the present data suggest that when reactivated in situ, T_{RM} cells maintain their cell fate identity and do not re-enter the circulation. Perhaps this occurs because the T_{RM} cells further upregulate CD69 after reactivation, thereby preventing S1P-mediated egress into the blood or lymph. As prior work has demonstrated that secondary or tertiary ‘experienced’ T_{CIRC} cells can become qualitatively different with each successive round of infection^{5,6}, it will be interesting to further investigate the quality, longevity and function of these secondary T_{RM} cells compared with those of primary T_{RM} cells.

Comprehensive studies are beginning to discern the tissue-specific requirements for T_{RM} cell formation and maintenance. For instance, T_{RM} cells in the skin, salivary gland and kidney require IL-15 for their homeostatic maintenance, whereas those in the FRT or small intestine do not^{7,8}. Additionally, T_{RM} cells in the lung and brain require cognate antigen for their establishment^{9,10}, unlike T_{RM} cells in skin, FRT and nasal tissue, where topical application of the skin irritant DNFB² and prime-and-pull strategies¹¹ are sufficient to stimulate circulating CD8^+ T cells to adopt T_{RM} -cell-like phenotypes. Although Park et al. and Beura et al. both demonstrate that bystander CD8^+ cells recruited during reinfection adopt tissue residency, the acquisition of CD103 expression on the infiltrating bystander cells occurred only in the skin^{1,2}. Perhaps such tissue-specific effects stem from differences in the bioavailability of TGF- β , a hallmark cytokine for the induction of CD103 expression^{8,12}.

The mucosal tissues are constantly exposed to different environmental challenges. Secondary heterologous infection in the lung can drive the migration of pre-existing CD8^+ memory T cells into the bronchoalveolar spaces¹³. Whether these recruited memory T cells

belong to lung T_{RM} cells or T_{CIRC} cells remains to be investigated, but this observation raises the question of whether successive waves of heterologous infection and inflammation can cause the pre-existing pool of T_{RM} cells to shrink, expand or change qualitatively. In a series of heterologous rechallenges via varying infection routes, Park et al. observed that despite the influx and seeding of new T_{RM} cells, the number of pre-existing T_{RM} cells remained mostly unaltered², which indicates that T_{RM} cells persist long-term and that the entire T_{RM} cell pool is expandable within tissues. This is consistent with previous observations that the memory T_{CIRC} cell population is a flexible compartment that can accommodate increased numbers of CD8⁺ memory T cells after heterologous prime-boost vaccinations¹⁴. Together, these results imply that the encounter of various pathogens throughout life contributes to the development of a diverse repository of T_{RM} cells, a goal that should be achieved by future vaccination strategies. ■

References

1. Beura LK et al. *Nat. Immunol* 10.1038/s41590-017-0029-3 (2018).
2. Park SL et al. *Nat. Immunol* 10.1038/s41590-017-0027-5 (2018).
3. Gebhardt T et al. *Nature* 477, 216–219 (2011). [PubMed: 21841802]
4. Masopust D, Vezys V, Wherry EJ, Barber DL & Ahmed RJ *Immunol* 176, 2079–2083 (2006).
5. Nolz JC & Harty JT *Immunity* 34, 781–793 (2011). [PubMed: 21549619]
6. Fraser KA, Schenkel JM, Jameson SC, Vezys V & Masopust D *Immunity* 39, 171–183 (2013). [PubMed: 23890070]
7. Schenkel JM et al. *J. Immunol* 196, 3920–3926 (2016). [PubMed: 27001957]
8. Mackay LK et al. *Nat. Immunol* 14, 1294–1301 (2013). [PubMed: 24162776]
9. Takamura S et al. *J. Exp. Med* 213, 3057–3073 (2016). [PubMed: 27815325]
10. Wakim LM, Woodward-Davis A & Bevan MJ *Proc. Natl. Acad. Sci. USA* 107, 17872–17879 (2010). [PubMed: 20923878]
11. Shin H & Iwasaki A *Nature* 491, 463–467 (2012). [PubMed: 23075848]
12. Mohammed J et al. *Nat. Immunol* 17, 414–421 (2016). [PubMed: 26901152]
13. Ely KH et al. *J. Immunol* 170, 1423–1429 (2003). [PubMed: 12538703]
14. Vezys V et al. *Nature* 457, 196–199 (2009). [PubMed: 19005468]

Fig. 1 | Effects of secondary infection on a pre-existing T_{RM} cell population.

$CD8^+ T_{RM}$ cells (green) are motile sentinels that patrol and survey their tissue microenvironments for reinfection. When they recognize their target antigen (Ag) during reinfection, $CD8^+ T_{RM}$ cells arrest and undergo in situ proliferation to generate a secondary pool of T_{RM} cells that does not exit into the circulation. Antigen-specific (purple) and bystander (blue) $CD8^+ T_{CIRC}$ cells are also recruited into the infected tissue and adopt long-term tissue residency without displacing the pre-existing T_{RM} cells, thereby increasing the number and repertoire of T_{RM} cells in the tissue. Credit: Marina Spence/Springer Nature