

Editorial: Pulmonary resident memory CD8 T cells: here today, gone tomorrow

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Infection with influenza A virus can result in the establishment of cross-reactive protective immunity against subsequent exposure to influenza A viruses of a distinct serotype. This phenomenon, termed heterosubtypic immunity, is conferred by the adaptive arm of the immune system and is predominantly attributed to T cell detection of shared viral protein epitopes. Paradoxically, heterosubtypic immunity to influenza virus wanes over time [1], despite the fact that long-lived, influenza-specific memory T cells persist within secondary lymphoid organs (Fig. 1A).

For some time, memory T cells have been characterized as T_{CM}, which recirculate among blood, lymph, and secondary lymphoid organs, or T_{EM}, which were all thought to recirculate among blood, lymph, and nonlymphoid tissues. Recently, a nonrecirculating subset of memory T cells that resides permanently in nonlymphoid tissues has been described in several organs, including the skin, intestine, kidney, brain, lung, and female reproductive tract [2]. This subset is most often referred to as T_{RM} cells, which have been shown to protect against viral infections in the skin [3, 4] and lung [5] and precipitate local inflammatory cascades that recruit circulating T cells to sites of infection [6]. It has been noted that T_{RM} cells often express the C-type lectin CD69, as well as the $\alpha_E\beta_7$ integrin heterodimer (which is most often identified by staining cells with antibodies specific for α_E , otherwise known as CD103) [2]. CD69 may be associated with retention of T_{RM}, as expression antagonizes S1P responsive-

ness, and S1P promotes egress of lymphocytes into the circulation. $\alpha_E\beta_7$ may also contribute directly to the local maintenance of T_{RM} by anchoring T lymphocytes to epithelial cells through interactions with E-cadherin. However, many critical questions remain: what induces CD69 and CD103 expression among T cells in different tissue compartments? What is the longevity of T_{RM} within different locations? How are T_{RM} established within a particular location? Under what conditions do T_{RM} contribute to protection?

In this issue of the *Journal of Leukocyte Biology*, Wu and colleagues [7] help address these questions by revisiting an old mystery: the enigma that heterosubtypic immunity to respiratory influenza challenge is not long-lasting. Heterosubtypic immunity was examined using two serologically distinct recombinant strains of influenza virus that express chicken ovalbumin (WSN-OVA_I and X31-OVA), as well as transgenic CD8 T cells (OT-I) expressing a TCR that recognizes the OVA-derived SIINFEKL peptide when it is presented by H-2K^b-bearing cells. One month after challenging mice with WSN-OVA_I via the respiratory route, but not the i.p. route, OT-I cells were found in the epithelial layer lining the large lung airways. This demonstrated that the site of primary challenge impacted the establishment of T cell memory in the lung. Additionally, many memory T cells in the airway epithelium expressed CD103, consistent with the phenotype of T_{RM}. Further analysis revealed that mice challenged only a month earlier with WSN-OVA_I exhibited much more rapid control upon a subsequent heterosubtypic challenge with X31-OVA. In fact, a significant reduction in X31-OVA titers preceded the recruitment of CD8 T cells from outside of the lung. This implies that T_{RM}

within the lung, rather than recirculating memory T cells, were most responsible for viral control. This interpretation was supported by the observation that CD103⁺ CD8 T cells in the lung epithelium dissipated within 7 months, and it was their loss that correlated with the waning of heterosubtypic immunity.

However, many questions remain. Why is local infection important for the establishment of T_{RM} within the lung epithelium? Is this a result of programming of a homing phenotype during priming, or is the infectious milieu of an infected lung driving recruitment? More importantly, what is regulating the short-term maintenance of local T_{RM} and the subsequent attrition? Interestingly, T_{RM} do not appear to wane significantly in the skin and intestinal mucosa [3, 4, 8], suggesting that the lung is unique in this regard. Why is the lung different, teleologically and mechanistically?

One possible difference between tissues is in the regulation of CD103 itself. Many studies implicate a role for TGF- β in driving CD103 expression. TGF- β is constitutively expressed in the small intestinal mucosa, where CD103 is maintained on virtually all memory CD8 T cells within the epithelium, and interfering with TGF- β signaling or CD103 expression results in a gradual loss of intestinal intraepithelial memory CD8 T cells [9–11]. In contrast, CD103 is expressed by only a minority of CD8 T cells in the lung, and many of these cells are lost over time. Perhaps TGF- β is also the driver of CD103 expression in the respiratory tract, but available

Abbreviations: S1P=sphingosine-1 phosphate, T_{CM}=central memory CD8 T cells, T_{EM}=effector memory CD8 T cells, T_{RM}=resident memory CD8 T cells

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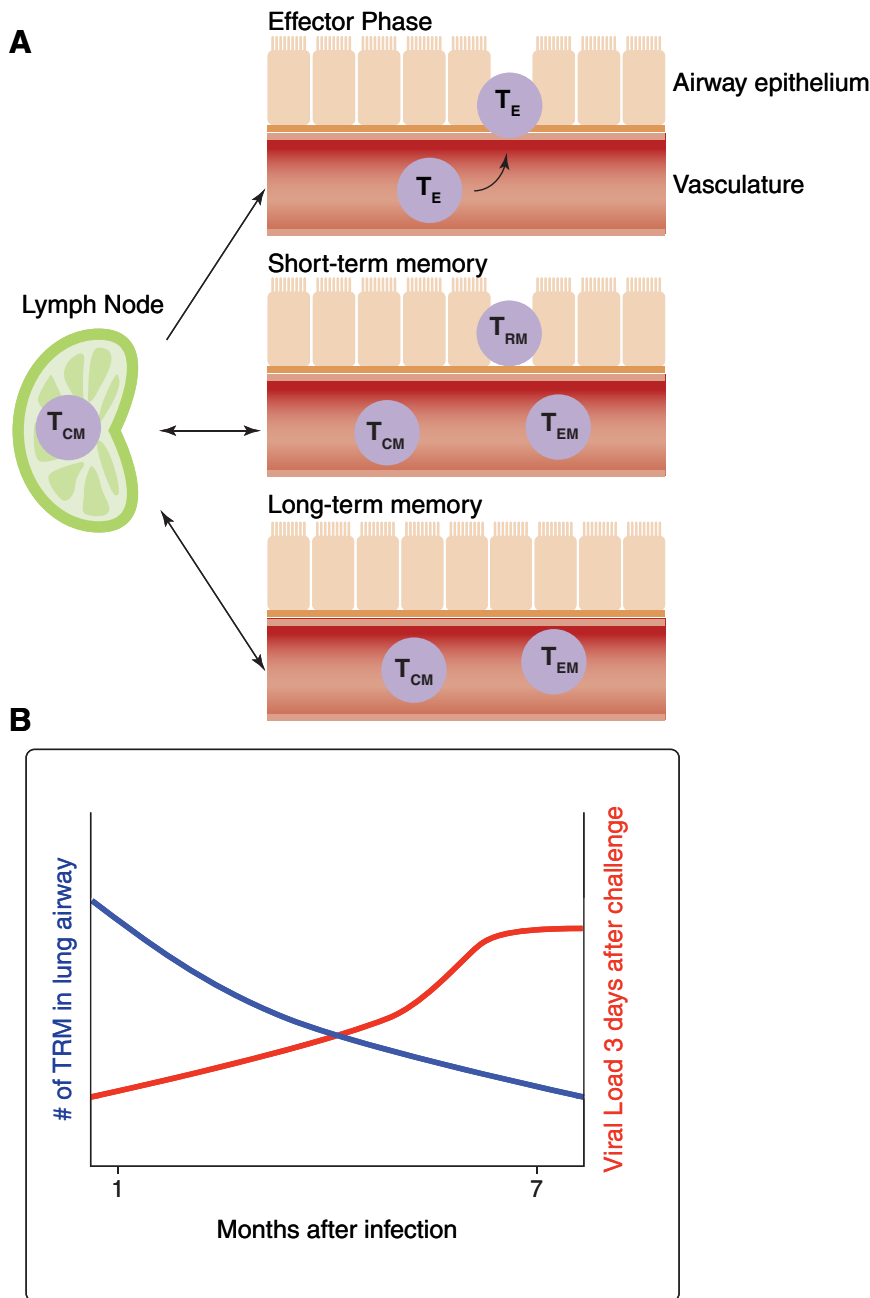


Figure 1. The loss of short-lived T_{RM} in the lung correlates with the erosion of heterosubtypic immunity against influenza virus. (A, top) Effector CD8 T cells (T_E) enter the lung epithelium during the course of respiratory influenza virus infection. (Middle) Early after the infection is cleared, T_E cells in the lung epithelium differentiate into a specialized population of T_{RM} that remain in the tissue without recirculating. The lung epithelium is not under routine surveillance by recirculating T_{EM} and T_{CM} . (Bottom) Unlike longer-lived memory CD8 T cell subsets, T_{RM} CD8 T cells gradually wane within the lung epithelium. (B) One month after primary infection, when T_{RM} in the lung epithelium are abundant, the host exhibits rapid control against a heterosubtypic influenza rechallenge. Seven months after priming, the number of T_{RM} in the lung airways is reduced greatly, which correlates with a pronounced reduction in heterosubtypic protection at this time-point. This suggests that the maintenance of T_{RM} is critical for optimal interception of influenza virus at the primary site of secondary infection.

TGF- β is maximal only for transient periods after infection. Indeed, loss of CD103+ T_{RM} parallels the gradual loss of

prolonged antigen presentation and the loss of PD-1 expression (which may reflect recent TCR engagement) that occurs within

a few months after influenza virus infection [7, 12–14]. This issue merits further investigation, and other factors may regulate T_{RM} maintenance within the respiratory mucosa.

We also have no definitive teleological explanation of why local memory in the lung wanes. Why would the host not be better served by maintaining protective immunity at this site indefinitely? Perhaps there is a cost to such a strategy. Indeed, unlike the gut or skin, the lung is a particularly inflammation-intolerant organ, given the delicate architecture necessary for efficient respiration. Once influenza has truly been cleared, and the innate antiviral state wanes, exuberant reactivation of local memory T cells, however helpful for eliminating infected host cells, may also be harmful by promoting excessive inflammation and pathology. If that is the case, then it is imperative to understand the possible pathological consequences of retaining T_{RM} in the lung indefinitely. This will, in turn, allow us to identify strategies that strike a balance necessary for optimizing host fitness in the face of reinfection of the respiratory mucosa: maintaining critical contributors to heterosubtypic protection without compromising host-lung function. The observations by Wu et al. [7] raise intriguing questions about this delicate equilibrium.

As direct contact between antigen-specific T cells and the virally infected epithelial cells is likely required for their function, the ratio of antigen-specific cytotoxic cells to target cells becomes an important consideration. How many antigen-specific T_{RM} are needed in the lung epithelium for considerable protection? Under physiological conditions that experience exposure to a wide variety of pathogens (when a plethora of antigen specificities are needed), how does the frequency of T_{RM} affect lung function? Questions regarding the threshold of T_{RM} cells required to enhance heterosubtypic protection optimally remain to be addressed (Fig. 1B).

Perhaps one of the most interesting questions raised by Wu and colleagues [7] revolves around the mechanism by which T_{RM} in the lung epithelium provide protection. It has been shown that memory CD4 T cells in the lung induce innate responses upon reactivation, which helps control influenza infection [15]. Control of influenza A virus infections also depend on Fas and perforin-

dependent cytotoxic processes [16], but T cells in the lung airways may have reduced cytolytic function [17, 18]. It has been speculated that this reduced cytotoxic functionality may be a mechanism for reducing excessive pathology in a vital, yet delicate, organ. Perhaps a compromise between maintaining local cell-mediated protection against pathogens and the need for preserving lung function may be related to the gradual waning of T_{RM} numbers in the lung.

The investigators have raised several exciting questions with respect to the establishment, regulation of longevity, and the protective role of memory T cells in the lung. Local T_{RM} cells promote rapid viral control at the point of viral exposure. Although the gradual disappearance of this protective population diminishes their potential for long-term protection against future infections, additional work may address whether the longevity of this memory population can be enhanced. Additionally, as T_{RM} are critical players in rapid pathogen clearance against heterosubtypic challenges, vaccines may be designed that optimize their generation. An improved understanding of the contribution of T_{RM} to protection during heterosubtypic viral challenges has the potential to advance our application of this new knowledge to the fight against respiratory infections.

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Editorial: Bone marrow progenitors share their experiences with their offspring

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One of the key differences between the innate and adaptive immune responses is the ability of the adaptive immune system to

establish long-term immune memory via the maintenance of antigen-specific lymphocyte populations. Attempts have been made to draw parallels between this mechanism and demonstrations that the function of innate immune cells, such as macrophages, DCs, and NK cells, is impacted by prior encoun-

ters that prime or tolerize subsequent responses [1, 2]. However, such innate immune cell training effects, even if

Abbreviations: HSC=hematopoietic stem cell, HSPC=hematopoietic stem and progenitor cell

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