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Tissue resident memory T cells and viral immunity

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Abstract

Tissue resident memory T cells (T_{RM}) constitute a recently identified T cell lineage that is responsible for frontline defense against viral infections. In contrast to central and effector memory T cells, which constitutively recirculate between tissues and blood, T_{RM} reside permanently within tissues. As the main surveyors of non-lymphoid tissues, T_{RM} are positioned to rapidly respond upon reinfection at barrier sites. During a viral reinfection, T_{RM} trigger the local tissue environment to activate and recruit immune cells and establish an antiviral state. Consistent with this function, there is empirical evidence that T_{RM} accelerate control in the event of reinfection or possible reactivation of latent infections in solid organs and barrier tissues. Here we review recent literature highlighting the protective functions of T_{RM} in multiple viral challenge models and contextualize the implications of these findings for vaccine development.

Introduction

Tissue resident memory T cells (T_{RM}) constitute a recently identified T cell lineage that is responsible for frontline defense against viral infections. Prior to encountering cognate antigen, naïve T cells restrict trafficking to blood and secondary lymphoid organs (SLO) such as the spleen and lymph nodes (LN). Therefore, to prime a T cell response against a virus, antigens from viral infections occurring in peripheral tissues must reach SLOs, either directly or through migratory antigen presenting cells. Once activated, naïve T cells proliferate extensively to become numerically relevant and then must migrate to sites of infection. If the infection is cleared, an expanded memory cell population remains that can be found not only in blood and SLOs (like naïve cells) but also most tissues throughout the rest of the body. Thus, memory T cells are not only more abundant, but are also anatomically more broadly distributed than their naïve counterparts, enabling quicker and more effective protection against secondary infections that are initiated outside SLOs (e.g. by those pathogens encountered at barrier tissues such as the mucosae and skin).

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Pioneering work parsed memory T cells isolated from human blood into two lineages based on the expression of homing molecules [1]. Memory T cells that expressed SLO homing molecules, such as CCR7 and CD62L, were termed central memory T cells (T_{CM}). It was proposed that this population was specialized to recirculate among the T cell zones of SLOs, and in the event of viral antigen detection, proliferate vigorously and give rise to a second wave of effector T cell differentiation and migration. The second subset lacked SLO homing molecules, but expressed higher levels of integrins and chemokine receptors that were suggestive of nonlymphoid tissue (NLT) migration. These cells were termed effector memory T cells (T_{EM}) because they also expressed heightened levels of effector molecules, and they were proposed to be principal surveyors of NLTs. A common interpretation was that T_{EM} constitutively recirculated, meaning they routinely entered NLTs using blood as a conduit, then egressed from NLTs via the lymphatics on their way back to blood (Fig 1) [2–4].

This model has undergone significant revision. Evidence now suggests the existence of a third major T cell population that resides in tissues without recirculating through blood or lymph. These have been referred to as resident memory T cells (T_{RM}), and they constitute a transcriptionally and phenotypically unique T cell lineage. T_{RM} often express CD69 and sometimes express CD103 [5,6]. It should be noted that CD69 is transiently upregulated on T cells of any subset following restimulation [7], and CD103 may be expressed by regulatory T cells [8], and at low levels by recirculating naïve T cells. While imperfect, these markers are frequently used to identify T_{RM} when stringent migration studies are not feasible (reviewed in [6]). Transcription factors that regulate T_{RM} include Hobit, Blimp-1, KLF2, Tbet and Eomes, although many other factors may be involved in T_{RM} ontogeny and differentiation [9–11]. While uninfected specific pathogen free laboratory mice harbor few T_{RM} , mouse models of infection demonstrate that T_{RM} populate most, if not all, tissues [12,13]. Analyses of human cadavers confirm an abundance of T_{RM} phenotype cells in numerous tissues [14,15], and they may comprise the largest memory T cell lineage in free-living organisms with physiological infectious experience. Indeed, as a direct indication of T cell residency in humans, Clark et. al. demonstrated that Alemtuzumab, an anti-CD52 antibody, depleted circulating T cells in patients undergoing treatment for cutaneous T cell lymphoma. However, skin T cells were protected from depletion, supporting the hypothesis that they did not recirculate through blood and thus were resident [16]. Here we discuss the function and regulation of virus-specific T_{RM} and consider the implications for vaccination against viral pathogens.

T_{RM} provide rapid protection against viral reinfection

The control of secondary infection events by T_{RM} has been robustly demonstrated in numerous animal infection models. Here, we review key evidence of T_{RM} -mediated viral control to illustrate the breadth of relevant infectious contexts and anatomic locations surveyed by T_{RM} (Fig 2). Later in the review, we will discuss mechanisms of T_{RM} -mediated protection.

Many studies utilizing mouse models of cutaneous and intravaginal infection with herpes simplex virus (HSV) have demonstrated protective capabilities of T_{RM} at these barrier sites.

For example, intravaginal vaccination with an attenuated strain of HSV generated CD4+ T_{RM} in the female reproductive tract (FRT) capable of providing enhanced protection against a subsequent HSV challenge [17]. In addition to vaginal protection, virus-specific T_{RM} can also mediate cutaneous protection against HSV challenge. Cutaneous infection with HSV resulted in virus-specific CD8+ T_{RM} in the skin that were predominantly localized to the specific site of challenge and were absent at the opposite flank [18]. Importantly, immunized skin was protected against local HSV challenge compared to contralateral skin [18]. Experimental approaches for inducing site-specific T_{RM} include the generation of focal skin inflammation, which recruits recently activated CD8+ T cells that subsequently differentiate into T_{RM} upon migration into the epidermis. HSV-specific skin T_{RM} generated in this manner enhanced protection from local HSV challenge, as mice with circulating memory T cells alone supported high viral titers and skin lesions whereas in the presence of skin T_{RM}, there was no detectable infectious virus by day 6 and mice did not exhibit overt disease pathology [19]. Remarkably, in a skin smallpox reinfection model, circulating memory T cells took 26 days to completely eliminate virus compared to only 6 days when T_{RM} were present [20].

One postulated function of T_{RM} is to protect against local reactivation of latent viruses [21]. Studies using the herpesvirus murine cytomegalovirus (MCMV), which establishes latency in the salivary gland (SG), resulted in salivary gland T_{RM} that contribute to local viral control [22]. HSV establishes latency in the sensory ganglia and interestingly, human and mouse studies have found HSV-specific CD8+ T cells that reside in sensory ganglia and localize to latently infected neurons [23–25]. Moreover, these CD8+ T_{RM} can respond to and restrict HSV reactivation from latency in mice [25–27]. Consistent with this, human studies demonstrated that HSV-specific CD8+ T cells persisted in the genital skin and mucosa of patients who suffered from HSV lesions eight weeks prior. Notably, these CD8+ T cells were found to be positioned at the dermal-epidermal junction, likely poised to intercept reactivated HSV exiting axon terminals [28,29].

Many infections, including vesicular stomatitis virus (VSV), polyomavirus, and lymphocytic choriomeningitis virus (LCMV), result in T_{RM} positioned within the CNS; a compartment where successful pathogen control can come at the price of immunopathology [30–32]. For instance LCMV infection can result in T cell-induced cerebral meningitis in humans [33]. Likewise, circulating LCMV-specific memory T cells may trigger fatal immunopathology upon intracranial reinfection in mice [32,34]. Interestingly, however, LCMV-specific brain T_{RM} which were recently shown to be capable of protecting against reinfection without inducing immunopathology [32].

The lung presents an interesting case as the ontogeny and maintenance of lung T_{RM} remain not well defined. Nevertheless effective heterosubtypic protection against flu appears to be dependent upon pulmonary T_{RM} [35–37], and these results likely extend to other lung infections, including the mouse parainfluenza virus, Sendai [38,39]. Mechanistic studies have identified a role for flu-specific CD4+ T cells in the regulation of the induction of CD8+ T_{RM} within the pulmonary mucosae [40] and for direct control of reinfection [41]. Human lungs are abundantly populated with T cells bearing a T_{RM} phenotype [42] and particularly elegant work demonstrated that RSV infection of humans generated more

frequent RSV-specific CD8⁺ T cells in the lung airways than in the blood. Importantly, higher airway CD8⁺ T_{RM} correlated with reduced disease severity [43].

Mechanisms of T_{RM} protection

The eponymous function of cytotoxic CD8⁺ T lymphocytes is to kill infected target cells. Certain populations of T_{RM}, including those within the intestinal mucosa, constitutively express highly elevated levels of granzyme B [44], consistent with the hypothesis that T_{RM} may be poised for rapid lytic activity at frontline sites of pathogen exposure. While killing is difficult to assess in nonvascular compartments of nonlymphoid tissues in vivo, T_{RM} cytotoxicity has been demonstrated directly ex vivo in chromium release assays [44] (Fig 3).

One variable that likely regulates the efficiency of T_{RM} mediated immunosurveillance, target acquisition, and killing is cellular motility. Interstitial migration is likely to be tissue dependent, for instance, being significantly slower in skin epidermis compared to dermis [45,46]. Moreover, context matters. Indeed, during acute vaccinia virus or HSV infection within skin, evidence was provided that cytotoxic T cells migrate preferentially towards infected cells [47,48]. If generalizable, this important concept dramatically alters models of the efficiency of T cell immunosurveillance in tissues.

T_{RM} function, however, likely extends far beyond the mere capacity to kill infected host cells. Upon reactivation, T_{RM} orchestrate numerous changes within hours of cognate antigen recognition in the tissue, upregulating pro-inflammatory cytokines which work to activate and recruit immune cells, and establish an antiviral state [49–51] (Fig 3). LCMV-specific T_{RM} in the female reproductive tract (FRT) produced the cytokines IFN γ , IL-2 and TNF α upon recognition of cognate peptide [50]. This resulted in upregulation of adhesion molecules and chemokines, which promoted the recruitment of circulating memory T cells and B cells into the tissue; a process which was dependent on T_{RM}-derived IFN γ . Recruited memory T cells also exhibited signs of bystander activation as there was increased granzyme B expression [50]. Similar studies in the skin demonstrated that activated HSV-specific skin T_{RM} produced IFN γ resulting in interferon stimulated gene (ISG) expression in surrounding cells [49]. This is consistent with other infection models demonstrating IFN γ -dependent T_{RM} protection [32,38].

In addition to adaptive immune cells, T_{RM} activation may also activate leukocytes of the innate immune system. Granzyme B upregulation in NK cells was seen in the FRT after LCMV-specific T_{RM} reactivation and this was through an IL-2 β -dependent mechanism. Moreover, dendritic cell (DC) maturation occurred largely in a TNF α -dependent manner, marked by expression of CCR7 and upregulation of CD80 and CD86, molecules important for co-stimulation during T cell activation [50].

Notably, reactivation of T_{RM} only requires cognate peptide, and the immune response that is generated is capable of transiently protecting against antigenically unrelated pathogens, highlighting the potent capabilities of T_{RM} to establish an antiviral state in tissues [49,50]. In summary, T_{RM} protective functions likely rely on multiple mechanisms, including cytolytic activity and cytokine mediated alarm functions.

Regulation of T_{RM} establishment

Most activated T cells downregulate lymph node homing molecules and are transiently endowed with the capacity to enter nonlymphoid tissues. At this early point during the immune response, T cells entering tissues initially appear phenotypically similar to their counterparts in blood and SLOs. After migration into nonlymphoid tissues, however, KLRG1-T_{RM} precursors begin to take on characteristic markers of residence, supporting the hypothesis that the tissue environment promotes T_{RM} differentiation [10]. A well-studied example of this is the production of TGF β in certain tissues, which promotes CD103 expression. CD103 (α E) pairs with beta7, which together bind to E-cadherin and promote retention of T_{RM} within certain epithelial compartments, although this requirement remains incompletely characterized for many organs [10,52–54]. Other factors also play a role in T_{RM} establishment. For example, evidence indicates that down-regulation of KLF2 and SIP1 coupled with the transcription factors Hobit, Blimp-1, and surface expression of CD69 also enforces residence [9–11]. Additionally, IL-15 expression can regulate T_{RM} survival in certain tissues, but not all, highlighting that the regulation of T_{RM} may differ depending on the anatomic compartment [10,55].

Antigen-independent inflammation can also promote T_{RM} establishment within tissues. For example, HSV gB-specific T cells primed by flu-gB (which does not infect the skin) home to the skin and become T_{RM} when a non-antigen specific inflammatory agent (DNFB) was topically applied [19]. Consistent with this, vaginal application of chemokine alone during the effector phase of a primary immune response can promote T_{RM} seeding in the FRT [56]. Inflammation, however, is not absolutely necessary for T_{RM} establishment, as naïve CD8+ T cells transferred into a lymphopenic host resulted in seeding of CD8+ T cells into many NLTs which subsequently adopted phenotypic markers of residence [52].

Antigen is not required for T_{RM} establishment in many contexts. However, some studies reveal a striking reliance on local antigen for optimal T_{RM} development. This was demonstrated in a study that utilized two recombinant vaccinia viruses expressing distinct antigens. After transferring naïve cells specific for either antigen, researchers infected the skin of both ears with either virus and demonstrated that T_{RM} preferentially developed within skin where cognate antigen was expressed [57]. Defining the local and systemic parameters that regulate T_{RM} development and distribution remain a priority for the field and it is apparent that the rules will not be the same for all tissues and infectious contexts.

Implications for vaccines

It is clear that T_{RM} are capable of providing robust and rapid immune protection at critical barrier sites frequently exposed to pathogens. A critical question is whether the establishment of T_{RM} through vaccination can increase protective efficacy against certain pathogens. Addressing this issue poses logistical hurdles, extending even to mere immunogenicity measurements, as T_{RM} cannot be evaluated in blood (ergo tissues must be biopsied). Moreover, T_{RM} must be extracted from tissues before assessment with conventional techniques for assessing antigen specificity (e.g. ELISPOT and flow cytometric assays), and the isolation efficiency of this T cell subset may be very poor [12]. However,

these barriers are not impossible to overcome. A recent study explored the mechanism of action of a newly developed malaria vaccine, PfSPZ, which has exhibited very promising efficacy in human clinical trials. Perplexingly, patients that were protected exhibited low levels of T cells (and vaccine-specific antibody) within blood. Closer examination (aided by nonhuman primate studies) revealed that the frequency of T_{RM} within the liver (the relevant site for T cell-mediated protection) was 100-fold higher [58]. This study may provide valuable lessons for vaccine development as well as a cautionary tale against limiting immunogenicity studies to blood.

In summary, T_{RM} are positioned at frontline tissues and are poised for rapid detection of reinfection events and mobilization of antiviral mechanisms of host protection. T_{RM} defense strategies likely extend beyond canonical cytolytic function and include cytokine-mediated activation of other components of innate and adaptive immunity. Importantly T_{RM} remain hidden from view when analyses are limited to peripheral blood, which creates logistical challenges. However, protection studies, both in animal models and limited human studies, suggest that advancement of T_{RM} inducing vaccine modalities holds promise for the future.

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References

1. Sallusto F, Lenig D, Förster R, Lipp M, Lanzavecchia A. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. *Nature*. 1999; 401:708–712. [PubMed: 10537110]
2. Masopust D, Schenkel JM. The integration of T cell migration, differentiation and function. *Nat Rev Immunol*. 2013; 13:309–320. [PubMed: 23598650]
3. Weninger W, Manjunath N, Von Andrian UH. Migration and differentiation of CD8+ T cells. *Immunol Rev*. 2002; 186:221–233. [PubMed: 12234374]
4. Mackay CR, Marston WL, Dudley L. Naive and memory T cells show distinct pathways of lymphocyte recirculation. *J Exp Med*. 1990; 171:801–817. [PubMed: 2307933]
5. Mueller SN, Mackay LK. Tissue-resident memory T cells: local specialists in immune defence. *Nat Rev Immunol*. 2016; 16:79–89. [PubMed: 26688350]
6. Schenkel JM, Masopust D. Tissue-resident memory T cells. *Immunity*. 2014; 41:886–897. [PubMed: 25526304]
7. Sancho D, Gómez M, Sánchez-Madrid F. CD69 is an immunoregulatory molecule induced following activation. *Trends Immunol*. 2005; 26:136–140. [PubMed: 15745855]
8. Lehmann J, Huehn J, de la Rosa M, Maszyra F, Kretschmer U, Krenn V, Brunner M, Scheffold A, Hamann A. Expression of the integrin alpha Ebeta 7 identifies unique subsets of CD25+ as well as CD25– regulatory T cells. *Proc Natl Acad Sci U S A*. 2002; 99:13031–13036. [PubMed: 12242333]
9. Mackay LK, Minnich M, Kragten NAM, Liao Y, Nota B, Seillet C, Zaid A, Man K, Preston S, Freestone D, et al. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science*. 2016; 352:459–463. [PubMed: 27102484]
10. Mackay LK, Rahimpour A, Ma JZ, Collins N, Stock AT, Hafon M-L, Vega-Ramos J, Lauzurica P, Mueller SN, Stefanovic T, et al. The developmental pathway for CD103+CD8+ tissue-resident memory T cells of skin. *Nat Immunol*. 2013; 14:1294–1301. [PubMed: 24162776]
11. Skon CN, Lee J-Y, Anderson KG, Masopust D, Hogquist KA, Jameson SC. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory CD8+ T cells. *Nat Immunol*. 2013; 14:1285–1293. [PubMed: 24162775]

12. Steinert EM, Schenkel JM, Fraser KA, Beura LK, Manlove LS, Igyártó BZ, Southern PJ, Masopust D. Quantifying Memory CD8 T Cells Reveals Regionalization of Immunosurveillance. *Cell*. 2015; 161:737–749. [PubMed: 25957682]
13. Beura LK, Hamilton SE, Bi K, Schenkel JM, Odumade OA, Casey KA, Thompson EA, Fraser KA, Rosato PC, Filali-Mouhim A, et al. Normalizing the environment recapitulates adult human immune traits in laboratory mice. *Nature*. 2016; 532:512–516. [PubMed: 27096360]
14. Sathaliyawala T, Kubota M, Yudanin N, Turner D, Camp P, Thome JJC, Bickham KL, Lerner H, Goldstein M, Sykes M, et al. Distribution and Compartmentalization of Human Circulating and Tissue-Resident Memory T Cell Subsets. *Immunity*. 2013; 38:187–197. [PubMed: 23260195]
15. Thome JJC, Yudanin N, Ohmura Y, Kubota M, Grinshpun B, Sathaliyawala T, Kato T, Lerner H, Shen Y, Farber DL. Spatial map of human T cell compartmentalization and maintenance over decades of life. *Cell*. 2014; 159:814–828. [PubMed: 25417158]
16. Clark RA, Watanabe R, Teague JE, Schlapbach C, Tawa MC, Adams N, Dorosario AA, Chaney KS, Cutler CS, LeBoeuf NR, et al. Skin Effector Memory T Cells Do Not Recirculate and Provide Immune Protection in Alemtuzumab-Treated CTCL Patients. *Sci Transl Med*. 2012; 4:117ra7–117ra7.
17. Iijima N, Iwasaki A. T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. *Science*. 2014; 346:93–98. [PubMed: 25170048]
18. Gebhardt T, Wakim LM, Eidsmo L, Reading PC, Heath WR, Carbone FR. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat Immunol*. 2009; 10:524–530. [PubMed: 19305395]
19. Mackay LK, Stock AT, Ma JZ, Jones CM, Kent SJ, Mueller SN, Heath WR, Carbone FR, Gebhardt T. Long-lived epithelial immunity by tissue-resident memory T (TRM) cells in the absence of persisting local antigen presentation. *Proc Natl Acad Sci U S A*. 2012; 109:7037–7042. [PubMed: 22509047]
20. Jiang X, Clark RA, Liu L, Wagers AJ, Fuhlbrigge RC, Kupper TS. Skin infection generates non-migratory memory CD8+ TRM cells providing global skin immunity. *Nature*. 2012; 483:227–231. [PubMed: 22388819]
21. Bevan MJ. Memory T cells as an occupying force. *Eur J Immunol*. 2011; 41:1192–1195. [PubMed: 21469134]
22. Thom JT, Weber TC, Walton SM, Torti N, Oxenius A. The Salivary Gland Acts as a Sink for Tissue-Resident Memory CD8(+) T Cells, Facilitating Protection from Local Cytomegalovirus Infection. *Cell Rep*. 2015; 13:1125–1136. [PubMed: 26526997]
23. Verjans GMGM, Hintzen RQ, van Dun JM, Poot A, Milikan JC, Laman JD, Langerak AW, Kinchington PR, Osterhaus ADME. Selective retention of herpes simplex virus-specific T cells in latently infected human trigeminal ganglia. *Proc Natl Acad Sci U S A*. 2007; 104:3496–3501. [PubMed: 17360672]
24. Khanna KM, Bonneau RH, Kinchington PR, Hendricks RL. Herpes Simplex Virus-Specific Memory CD8+ T Cells Are Selectively Activated and Retained in Latently Infected Sensory Ganglia. *Immunity*. 2003; 18:593–603. [PubMed: 12753737]
25. Wakim LM, Waithman J, Rooijen N, van Heath WR, Carbone FR. Dendritic Cell-Induced Memory T Cell Activation in Nonlymphoid Tissues. *Science*. 2008; 319:198–202. [PubMed: 18187654]
26. Knickelbein JE, Khanna KM, Yee MB, Baty CJ, Kinchington PR, Hendricks RL. Noncytotoxic Lytic Granule-Mediated CD8+ T Cell Inhibition of HSV-1 Reactivation from Neuronal Latency. *Science*. 2008; 322:268–271. [PubMed: 18845757]
27. Liu T, Khanna KM, Chen X, Fink DJ, Hendricks RL. CD8(+) T cells can block herpes simplex virus type 1 (HSV-1) reactivation from latency in sensory neurons. *J Exp Med*. 2000; 191:1459–1466. [PubMed: 10790421]
28. Zhu J, Peng T, Johnston C, Phasouk K, Kask AS, Klock A, Jin L, Diem K, Koelle DM, Wald A, et al. Immune surveillance by CD8αα+ skin-resident T cells in human herpes virus infection. *Nature*. 2013; 497:494–497. [PubMed: 23657257]
29. Schiffer JT, Corey L. Rapid host immune response and viral dynamics in herpes simplex virus-2 infection. *Nat Med*. 2013; 19:280–290. [PubMed: 23467247]

30. Frost EL, Kersh AE, Evavold BD, Lukacher AE. Cutting Edge: Resident Memory CD8 T Cells Express High-Affinity TCRs. *J Immunol Baltim Md 1950*. 2015; 195:3520–3524.
31. Wakim LM, Woodward-Davis A, Bevan MJ. Memory T cells persisting within the brain after local infection show functional adaptations to their tissue of residence. *Proc Natl Acad Sci*. 2010; 107:17872–17879. [PubMed: 20923878]
32. Steinbach K, Vincenti I, Kreutzfeldt M, Page N, Muschaweckh A, Wagner I, Drexler I, Pinschewer D, Korn T, Merkler D. Brain-resident memory T cells represent an autonomous cytotoxic barrier to viral infection. *J Exp Med*. 2016; doi: 10.1084/jem.20151916
33. Zhou X, Ramachandran S, Mann M, Popkin DL. Role of lymphocytic choriomeningitis virus (LCMV) in understanding viral immunology: past, present and future. *Viruses*. 2012; 4:2650–2669. [PubMed: 23202498]
34. Baenziger J, Hengartner H, Zinkernagel RM, Cole GA. Induction or prevention of immunopathological disease by cloned cytotoxic T cell lines specific for lymphocytic choriomeningitis virus. *Eur J Immunol*. 1986; 16:387–393. [PubMed: 3084281]
35. Wu T, Hu Y, Lee Y-T, Bouchard KR, Benechet A, Khanna K, Cauley LS. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. *J Leukoc Biol*. 2014; 95:215–224. [PubMed: 24006506]
36. Gilchuk P, Hill TM, Guy C, McMaster SR, Boyd KL, Rabacal WA, Lu P, Shyr Y, Kohlmeier JE, Sebзда E, et al. A Distinct Lung-Interstitial-Resident Memory CD8+ T Cell Subset Confers Enhanced Protection to Lower Respiratory Tract Infection [Internet]. *Cell Rep*. 2016
37. Zens KD, Chen JK, Farber DL. Vaccine-generated lung tissue-resident memory provides heterosubtypic protection to influenza infection. *J Immunol*. 2016; 196:145.9–145.9.
38. McMaster SR, Wilson JJ, Wang H, Kohlmeier JE. Airway-Resident Memory CD8 T Cells Provide Antigen-Specific Protection against Respiratory Virus Challenge through Rapid IFN- γ Production. *J Immunol Baltim Md 1950*. 2015; 195:203–209.
39. Hogan RJ, Usherwood EJ, Zhong W, Roberts AA, Dutton RW, Harmsen AG, Woodland DL. Activated antigen-specific CD8+ T cells persist in the lungs following recovery from respiratory virus infections. *J Immunol Baltim Md 1950*. 2001; 166:1813–1822.
40. Laidlaw BJ, Zhang N, Marshall HD, Staron MM, Guan T, Hu Y, Cauley LS, Craft J, Kaech SM. CD4+ T Cell Help Guides Formation of CD103+ Lung-Resident Memory CD8+ T Cells during Influenza Viral Infection. *Immunity*. 2014; 41:633–645. [PubMed: 25308332]
41. Teijaro JR, Turner D, Pham Q, Wherry EJ, Lefrançois L, Farber DL. Cutting Edge: Tissue-Retentive Lung Memory CD4 T Cells Mediate Optimal Protection to Respiratory Virus Infection. *J Immunol*. 2011; 187:5510–5514. [PubMed: 22058417]
42. Purwar R, Campbell J, Murphy G, Richards WG, Clark RA, Kupper TS. Resident memory T cells (T(RM)) are abundant in human lung: diversity, function, and antigen specificity. *PloS One*. 2011; 6:e16245. [PubMed: 21298112]
43. Jozwik A, Habibi MS, Paras A, Zhu J, Guvenel A, Dhariwal J, Almond M, Wong EHC, Sykes A, Maybeno M, et al. RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. *Nat Commun*. 2015; 6:10224. [PubMed: 26687547]
44. Masopust D, Vezys V, Marzo AL, Lefrançois L. Preferential Localization of Effector Memory Cells in Nonlymphoid Tissue. *Science*. 2001; 291:2413–2417. [PubMed: 11264538]
45. Ariotti S, Beltman JB, Chodaczek G, Hoekstra ME, van Beek AE, Gomez-Eerland R, Ritsma L, van Rheenen J, Marée AFM, Zal T, et al. Tissue-resident memory CD8+ T cells continuously patrol skin epithelia to quickly recognize local antigen. *Proc Natl Acad Sci*. 2012; 109:19739–19744. [PubMed: 23150545]
46. Gebhardt T, Whitney PG, Zaid A, Mackay LK, Brooks AG, Heath WR, Carbone FR, Mueller SN. Different patterns of peripheral migration by memory CD4+ and CD8+ T cells. *Nature*. 2011; 477:216–219. [PubMed: 21841802]
47. Hickman HD, Reynoso GV, Ngudankama BF, Cush SS, Gibbs J, Bennink JR, Yewdell JW. CXCR3 chemokine receptor enables local CD8(+) T cell migration for the destruction of virus-infected cells. *Immunity*. 2015; 42:524–537. [PubMed: 25769612]

48. Ariotti S, Beltman JB, Borsje R, Hoekstra ME, Halford WP, Haanen JBAG, de Boer RJ, Schumacher TNM. Subtle CXCR3-Dependent Chemotaxis of CTLs within Infected Tissue Allows Efficient Target Localization. *J Immunol*. 2015; 195:5285–5295. [PubMed: 26525288]
49. Ariotti S, Hogenbirk MA, Dijkgraaf FE, Visser LL, Hoekstra ME, Song J-Y, Jacobs H, Haanen JB, Schumacher TN. Skin-resident memory CD8⁺ T cells trigger a state of tissue-wide pathogen alert. *Science*. 2014; 346:101–105. [PubMed: 25278612]
50. Schenkel JM, Fraser KA, Beura LK, Pauken KE, Vezys V, Masopust D. Resident memory CD8 T cells trigger protective innate and adaptive immune responses. *Science*. 2014; 346:98–101. [PubMed: 25170049]
51. Schenkel JM, Fraser KA, Vezys V, Masopust D. Sensing and alarm function of resident memory CD8⁺ T cells. *Nat Immunol*. 2013; 14:509–513. [PubMed: 23542740]
52. Casey KA, Fraser KA, Schenkel JM, Moran A, Abt MC, Beura LK, Lucas PJ, Artis D, Wherry EJ, Hogquist K, et al. Antigen-independent differentiation and maintenance of effector-like resident memory T cells in tissues. *J Immunol Baltim Md 1950*. 2012; 188:4866–4875.
53. Lee Y-T, Suarez-Ramirez JE, Wu T, Redman JM, Bouchard K, Hadley GA, Cauley LS. Environmental and antigen receptor-derived signals support sustained surveillance of the lungs by pathogen-specific cytotoxic T lymphocytes. *J Virol*. 2011; 85:4085–4094. [PubMed: 21345961]
54. Zhang N, Bevan MJ. Transforming growth factor- β signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. *Immunity*. 2013; 39:687–696. [PubMed: 24076049]
55. Schenkel JM, Fraser KA, Casey KA, Beura LK, Pauken KE, Vezys V, Masopust D. IL-15-Independent Maintenance of Tissue-Resident and Boosted Effector Memory CD8 T Cells. *J Immunol Baltim Md 1950*. 2016; 196:3920–3926.
56. Shin H, Iwasaki A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. *Nature*. 2012; 491:463–467. [PubMed: 23075848]
57. Khan TN, Mooster JL, Kilgore AM, Osborn JF, Nolz JC. Local antigen in nonlymphoid tissue promotes resident memory CD8⁺ T cell formation during viral infection. *J Exp Med*. 2016; 213:951–966. [PubMed: 27217536]
58. Ishizuka AS, Lyke KE, DeZure A, Berry AA, Richie TL, Mendoza FH, Enama ME, Gordon IJ, Chang L-J, Sarwar UN, et al. Protection against malaria at 1 year and immune correlates following PfSPZ vaccination. *Nat Med*. 2016; 22:614–623. [PubMed: 27158907]

Highlights

- Tissue resident memory T cells (T_{RM}) are the main surveyors of non-lymphoid tissues.
- T_{RM} activate innate and adaptive immunity and establish an antiviral state within tissues.
- T_{RM} provide protection against numerous viral pathogens in multiple tissues.
- Vaccines aimed at promoting T_{RM} hold promise for the future.

Figure 1. Patterns of memory T cell migration

Memory T cells are parsed into subsets that have different migration patterns. The prevailing model is described here. Central memory T cell (T_{CM}) migration is similar to that of naïve T cells and emphasizes immunosurveillance of secondary lymphoid organs (SLOs, such as lymph nodes, intestinal Peyer's patches, and the white pulp of spleen). Specifically, T_{CM} migrate from blood into SLOs, exit via lymphatic vessels, then rejoin the blood supply to begin this recirculation pattern anew. Effector memory T cells (T_{EM}) recirculate through blood, nonlymphoid tissue (NLT), then back into the blood via the lymph (while transiently passing through SLOs). Tissue resident memory cells (T_{RM}) are parked within tissues and do not recirculate. Studies indicating that T_{RM} may dominate immunosurveillance of NLTs have exposed gaps in our understanding of bona fide T cell recirculation through these compartments.

Figure 2. Broad evidence that T_{RM} accelerate viral control upon rechallenge

This figure summarizes several mouse studies demonstrating that T_{RM} can protect a wide array of tissues against many viral challenges.

Figure 3. CD8+ T_{RM} functions

Some CD8+ T_{RM} express high basal levels of granzyme B suggesting reactivated T_{RM} may be constitutively poised to kill infected cells, although this has not been formally tested in vivo. Upon recognition of cognate antigen, T_{RM} also secrete pro-inflammatory cytokines, namely IFN γ , IL-2 and TNF α , which act to upregulate chemokines such as CXCL9 and CXCL10, as well the adhesion molecule VCAM-1 on endothelial cells. This facilitates recruitment of recirculating subsets of memory CD8+ T cells and B cells into the tissue. Interferon stimulated genes (ISGs) are also upregulated in cells surrounding reactivated T_{RM} which may increase their resistance to viral infection. Furthermore, recognition of viral antigen by T_{RM} also precipitates upregulation of granzyme B by natural killer cells (NK) and bystander memory CD8+ T cells and maturation of local dendritic cells (DCs). In summary, T_{RM} trigger a cascade of immunostimulatory and antiviral responses at sites of viral re-exposure.