The skin is a large and complex organ that acts as a critical barrier protecting the body from pathogens in the environment. Numerous heterogeneous populations of immune cells are found within skin, including some that remain resident and others that can enter and exit the skin as part of their migration program. Pathogen-specific CD8$^+$ T cells that persist in the epidermis following infection are a unique population of memory cells with important roles in immune surveillance and protective responses to reinfection. How these tissue-resident memory T cells form in the skin, the signals controlling their persistence and behavior, and the mechanisms by which they mediate local recall responses are just beginning to be elucidated. Here, we discuss recent progress in understanding the roles of these skin-resident T cells and also highlight some of the key unanswered questions that need addressing.

Keywords: skin immunity, tissue-resident memory T cell, intravital imaging, two-photon microscopy, DETC, cell migration
These cells can be identified by high expression of the CD8+ T cells.

CD8+ T cells may also reside in LN and spleen for extended periods and provide a unique pool of cells that could guard against systemic pathogen entry (37).

Tissue-resident memory T cells that form in the skin, intestine, and lungs were recently shown to express a core set of genes that may facilitate accurate dissection of this memory T cell subset at a molecular level (38). This transcriptional signature suggests TRM undergo a similar developmental program in different tissues. Elucidating the molecular pathways critical for TRM development from tissue-derived signals will be important for future therapeutic approaches.

In addition to CD8+ T cells, some CD4+ T cells may also form a TRM population in the lungs after respiratory viral infection (39). Although a portion of the memory CD4+ T cells found within the dermis appear to be capable of entering the circulation (18), it is not yet clear whether the remaining cells permanently or semi-permanently reside in this site (i.e., could be designated TRM) and might thus be distinguished from circulating T effector memory cells (TEM).

During infection or inflammation of the skin, effector CD8+ T cells enter the dermis from the blood, and can then be recruited into the epidermis. This process is dependent on chemokine receptor signals, including CXCR3 (38). Whether other chemokine receptors are also required for CD8+ T cell entry into the epidermis is unclear, though this is likely since TRM formation was only partially blocked when effector CD8+ T cells lacked CXCR3 expression. In contrast, in order to exit the skin via lymphatics, T cells need to upregulate expression of CCR7, and blocking this receptor signals, including CXCR3 (38). Whether other chemokine receptors are also required for CD8+ T cell entry into the epidermis is unclear, though this is likely since TRM formation was only partially blocked when effector CD8+ T cells lacked CXCR3 expression. In contrast, in order to exit the skin via lymphatics, T cells need to upregulate expression of CCR7, and blocking this receptor.

SKIN TISSUE-RESIDENT MEMORY T CELLS

CD8+ TRM cells that reside within the epidermis are retained in this compartment for very long periods without reentering the circulation (19, 28). Populations of TRM have also been described in other tissues including the small intestine (29, 30), vaginal mucosa (18, 31), brain (32, 33), lung (34), salivary glands (35), and thymus (36). These cells can be identified by high expression of the αβ TCR genotype (CD103) and the marker CD69 (19). T cells expressing this canonical TRM phenotype have also been observed in other tissues such as the kidney, pancreas, and heart (32), while CD69+ T cells may also reside in LN and spleen for extended periods and provide a unique pool of cells that could guard against systemic pathogen entry (37).

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CD8$^+$ T cells (red) localize to the dermis, while CD8$^+$ T$_{RM}$ persist in the epidermis. Nuclei are stained blue with DAPI. (B) Skin T$_{RM}$ localize to the basal epidermis in contact with the basement membrane that separates dermis from epidermis. CD8$^+$ T$_{RM}$, red; laminin-$\gamma$2, green; DAPI, blue. (C) The morphology of epidermis-resident T$_{RM}$, LC and DETC is distinct. Scale bars: A, B: 20 $\mu$m; C: 5 $\mu$m.

including CXCL10. Signals found within the epidermis instruct CD8$^+$ T cells to develop into T$_{RM}$ via upregulation of molecules involved in the persistence of these cells (CD103 and CD69), and downregulation of S1PR1 that is required for tissue egress (38, 40). Our recent data also revealed that T$_{RM}$ express high levels of regulator of G protein signaling-1 (RGS1) and RGS2 (38). RGS1 expression has been shown to reduce T cell migration in response to CXCL12 and CCL19 (41), suggesting that these molecules may also contribute to the migration and persistence of T$_{RM}$ within the skin as well as other tissues.

**MIGRATION BY SKIN T$_{RM}$**

CD8$^+$ T$_{RM}$ localize to the basal layers of the epidermis in mice and appear to be in regular contact with the basement membrane that separates the epidermis from the dermis (42) (Figure 2B). Whether T$_{RM}$ use this as a substrate for migration and adhesion is not known. Although the epidermal layer is considerably thinner in mice than in humans, CD8$^+$ T cells also appear to localize to the border between the epidermis and the dermis in humans following HSV-2 infection (43) and in healthy or psoriatic skin (44). A unique feature of skin T$_{RM}$ is their highly dynamic dendritic morphology (18, 42, 45) (Figure 2C). In contrast, T cells in the dermis consistently display a more amoeboid shape that is typical of T cells observed in all other tissues thus far. Whether T$_{RM}$ in other tissues display a similar morphology and slow mode of migration is yet to be determined.

The immediate tissue environment appears to dictate the morphology and locomotion of T cells. This is supported by our observations in mice that both CD4$^+$ and CD8$^+$ T cells displayed a pronounced dendritic morphology when present within the epidermis, irrespective of whether the T cells were activated effector cells or memory cells (42). In addition, epidermal LC and DETC both adopt dendritic shapes. Notably, each of these cells (T$_{RM}$, DETC, and LC) can be distinguished from each other by key differences in cell shape (Figure 2C). Whereas T$_{RM}$ form many amorphous shapes marked by short dendrites and many small projections similar to filopodia, DETC produce a relatively consistent number of long dendrites and are mostly immotile because they are anchored in the upper epidermis. LC are immotile and produce multiple long, branched dendrites. While both DETC and LC project their dendrites upwards toward the stratum corneum, T$_{RM}$ were only observed to extend projections laterally (42).

T cells migrating within the epidermis reduce their speed upon resolution of inflammation (42), suggesting that tight connections between keratinocytes present a difficult environment for T cells to navigate. It will be important to determine whether T$_{RM}$ regulate unique molecules that facilitate digestion of the surrounding matrix and cell–cell adhesions to allow them to move relatively freely. The mechanisms used by T$_{RM}$ to navigate the epidermis, including the molecules and pathways regulating the actin cytoskeleton to induce the unique cell shape are unclear. Since T cells migrating within tissues do not typically generate substantial protrusions such as lamellipodia or blebs (46), the way in which the actomyosin network generates force to propel T cells in the epidermis may differ from that in the dermis and other tissues. Moreover, the roles of adhesion molecules such as integrins and chemotactic factors including chemokines in controlling T cell migration in the epidermis is not known. The integrin CD103 is involved in the
attachment of DETC dendrites to the keratinocytes (23). We found that CD103 expression by TRM is important for their long-term retention in skin (38). This is unlikely to involve stable dendrite attachment due to the motile nature of TRM, though persistent adhesion to the keratinocytes via E-cadherin may facilitate the retention of TRM in this site. TRM also show increased expression of E-cadherin, the ligand for integrin α1β1, as well as the integrin α1β1 that binds collagen and laminin, both major components of the basement membrane separating epidermis from dermis. TRM in skin have increased expression of the chemokine receptor CCR8 compared with memory T cells in other tissues (38). Expression of CCR8 is programmed by the epidermis (47) suggesting that expression of this receptor is important for αβ T cell residence in this site. Together, these receptors potentially contribute to adhesion, morphology, and survival of T cells in the epidermis.

IMMUNOSURVEILLANCE AND LOCAL PERSISTENCE OF SKIN TRM
Although TRM localization in the skin can be relatively dispersed (28), they predominate at sites of infection or inflammation (19). This concentration of memory cells in mouse skin remains remarkably constant for >1 year after infection, despite their sustained motility (42). In silico simulation of the migration of TRM in the skin over long periods revealed that TRM move by random brownian motion and persist within the region of the epidermis in which they form simply as a result of this slow migration. These experiments suggest that TRM induced by infection or vaccination should persist for very long periods in the immediate environment where they were formed and provide robust site-specific immunity. While such site-specific immunity may be of little use against subsequent infections at remote sites, repeated infections can induce TRM in non-involved regions of skin (28), potentially providing more widespread protection at least in this tissue. Whether this is the case with many infections or tissues and the protective efficacy of these more dispersed TRM needs to be investigated further.

Skin TRM display a persistent mode of random migration that can facilitate surveillance of skin against reinfection or the recrudescence of latent viruses such as HSV (42, 45). Although TRM migrate considerably slower in the epidermis of mice than T cells in the dermis or in lymphoid tissues, the cells are trapped within the constrained epidermal environment and move largely two-dimensionally. How TRM survey the epidermis in humans remains to be visualized, although the location of these cells in the basal epidermis in human skin samples suggests that the mechanism and efficiency of immunosurveillance may be very similar to that observed in mice. Importantly, in addition to the shape and motility of TRM, the density of cells present in the epidermis will likely influence the efficiency of their surveillance, as suggested in experiments modeling TRM migration (45). Therefore, novel vaccine strategies designed to induce TRM in the skin or other sites in the body may need to reach a certain threshold of TRM density in the tissues for effective protection against disease.

EPIDERMAL NICHE
As mentioned above, large numbers of γδ T cells (DETC) exist in the epidermis in mice, where they contribute to homeostasis, would repair and inflammation. In humans, γδ T cells are present in the epidermis, though in lower numbers than αβ T cells. The reason for this difference is unclear, though both T cell subtypes present in human epidermis can contribute to wound repair (21), suggesting that this may reflect a functional specialization of all T cells that persist in this tissue, as opposed to only γδ T cells. DETC are the first T cells that form in mice very early in life. After migrating to the skin, they persist for life and are maintained by homeostatic turnover. Examination of DETC in mouse skin after the clearance of HSV infection revealed a substantial and sustained decrease in DETC numbers around the site of infection, and a corresponding increase in numbers of virus-specific TRM (42). This inverse relationship between DETC and TRM was maintained for months, suggesting that DETC were unable to repopulate regions of skin containing considerable numbers of TRM. These findings indicate the existence of a T cell-specific niche within the epidermis that regulates the total number of T cells in this site, irrespective of TCR usage or specificity. Both DETC and TRM rely upon the cytokine IL-15 and signals via the aryl hydrocarbon receptor (AhR) for persistence in the skin (38, 42, 48, 49). AhR is a transcription factor that can regulate a large number of genes, including c-kit and various cell cycle genes, suggesting that this pathway may influence T cell proliferation and homeostasis in the epidermis (50). Ligands for AhR are produced in the epidermis via metabolism of tryptophan or from microbiota such as yeast. Nevertheless, AhR ligands are abundant in the skin, suggesting that other mechanisms likely also contribute to the regulation of T cell numbers in the epidermis.

If the epidermis constitutes a privileged niche with limited space for populations of T cells, this may have implications for TRM persistence following subsequent infection or inflammation where new populations of effector CD8+ T cells are recruited to the skin. Therefore, whether there is a maximum number of T cells capable of persisting in the epidermal niche remains a key unanswered question. If so, we would expect that competition for space in this niche would restrict numbers of TRM that can persist in regions of skin prone to multiple infections. Moreover, if effective protection from infection requires a certain density of TRM in skin to rapidly respond, then competition for niche may influence such immunity. This also raises the intriguing question of whether low numbers of γδ T cells in the epidermis of adult humans, and correspondingly higher numbers of αβ T cells is, at least in part, the result of replacement of DETC via competition for space by TRM that are generated by infections and environmental antigens. Developing a better understanding of the mechanisms of T cell homeostasis within the epidermis is critical for the design of strategies to boost immunity to infections as well as potentially reducing unwanted T cell responses.

PROTECTION BY SKIN TRM
Reinfection with a previously encountered pathogen results in recruitment of circulating memory T cells to the inflamed tissues where they function to eradicate the infection. CD8+ T cells recruited to tissues then clear the pathogen by killing infected cells and releasing cytokines. This process is still relatively slow, yet appears to be significantly enhanced by the presence of TRM within the infected tissues. Notably, TRM present within mucosal tissue...
epithelia were found to rapidly produce interferon-γ upon peptide stimulation, resulting in the non-specific recruitment of circulating memory T cells into the tissue within hours (51). Thus, it has been suggested that T<sub>RM</sub> function as an antigen-specific sensor and rapidly respond by producing signals that induce local inflammation and recruit memory T cells from the blood. Though it is not yet clear whether T<sub>RM</sub> in different tissues behave the same way, it will be important to determine what signals are released by T<sub>RM</sub> in response to stimulation and the effects that these have on the subsequent response. For example, we found that T<sub>RM</sub> express high levels of the chemokine XCL1, which may allow them to recruit XCR1<sup>+</sup> cells such as dermal CD103<sup>+</sup> DC (52) and facilitate local recall responses.

In addition to an alarm function, T<sub>RM</sub> presumably also contribute directly to the clearance of pathogens in tissues. Whether they do this via the killing of target cells or production or cytokines, or both, has not yet been determined. Moreover, the relative contribution of T<sub>RM</sub> versus memory T cells recruited from the circulation is not known. Thus, examination of whether skin T<sub>RM</sub> have the capacity to eradicate a local infection without the assistance of circulating memory CD8<sup>+</sup> T cells will provide insight into the role of resident memory in protective immunity. The relative roles of T<sub>RM</sub> in raising the alarm versus directly clearing an infection may be influenced by their density with the tissue. We would predict that a high local density of T<sub>RM</sub> could protect against viral infection and possibly provide sterile immunity. There is some evidence to suggest that T<sub>RM</sub> also proliferate locally in response to challenge (53, 54), although the extent and widespread nature of this proliferation remains far from clear. Finally, given the restricted localization of T<sub>RM</sub> to epithelial layers such as the skin epidermis, we might predict that these memory cells are terminally differentiated and highly dependent on their environment to survive. Experiments suggest this is the case, since isolation of T<sub>RM</sub> from the brain followed by adoptive transfer into mice demonstrated poor survival and responses to challenge (33). Nevertheless, it remains unclear whether T<sub>RM</sub> can exit the epithelial layers upon recall and migrate through tissues or enter the circulation, and if they do whether they can survive. Finally, experiments are needed to determine if T<sub>RM</sub> form secondary memory in the tissues following restimulation, or are replaced by memory cells recruited from the circulation.

**PERPECTIVES**

There is considerable complexity in the immune cell content of the skin. While this content includes populations such as T cells and DCs, it is now clear that these are heterogeneous, comprised of a number of phenotypically and functionally distinct subsets. In the case of T cells in particular, their action is predominantly local, affording regional protection against skin-invading pathogens or promoting tissue repair after injury. Given the need for such restricted action, it is not surprising that the skin contains skin-resident populations. Despite this, the relative contribution of resident versus migrating cells still remains unclear in many instances. The existence of such uncertainty highlights the need for clear demarcation between resident and migrating populations in future studies of the skin immune system.

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