Divergence of Tissue-Memory T Cells: Distribution and Function-Based Classification

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Tissue-resident memory T cells (Trm) comprise the majority of memory cells in nonlymphoid tissues and play a predominant role in immunity at barrier surfaces. A better understanding of Trm cell maintenance and function is essential for the development of vaccines that confer frontline protection. However, it is currently challenging to precisely distinguish Trm cells from other T cells, and this has led to confusion in the literature. Here we highlight gaps in our understanding of tissue memory and discuss recent advances in the classification of Trm cell subsets based on their distribution and functional characteristics.

Memory T cells are established after an infection or vaccination and have the ability to mediate faster and stronger responses to subsequent antigen challenge. Until recently, memory T cells were broadly divided into two main subsets, effector memory T (Tem) and central memory T cells (Tcm). Tem cells lack the expression of a lymph node (LN) homing receptor CCR7 and can exert immediate effector functions upon restimulation, whereas Tcm cells express CCR7 and generally do not express immediate effector functions (Sallusto et al. 1999). Tem and Tcm cells also differ in their tissue distribution: Tem cells are abundant in nonlymphoid tissues (NLTs) (Masopust et al. 2001; Reinhardt et al. 2001), whereas Tcm cells predominate in the secondary lymphoid organs (SLOs) such as spleen and LN. Recently, it has been discovered that most memory cells in the NLTs are not actually Tem cells, but rather a distinct third population of memory cells. Cells in this third population reside permanently within tissues and have therefore been termed tissue-resident memory T cells (Trm) (Gebhardt et al. 2009; Masopust et al. 2010; Wakim et al. 2010; Teijaro et al. 2011). This led to the current paradigm of three memory subpopulations defined by their differential migratory properties: two circulatory populations (Tcm cells through the SLOs and Tem cells through the NLTs) and a resident population (Trm cells in NLTs and SLOs) (Takamura 2018). A recent study has proposed a further subdivision of Tem cells based on their expression of CX3CR1: $CX3CR1^{hi}$ cells exhibit a Tem cell phenotype but are present only in the blood (i.e., absent in SLOs and NLTs), whereas $CX3CR1^{int}$ cells, termed as peripheral memory (Tpm), behave like classical Tem cells (i.e., circulate between tissues and blood). Because of the overlapping features of classical Tem and Tpm cells, we have used the classical Tem-cell

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designation for tissue-circulatory memory T cells in this review.

Trm cells play a central role in controlling infections at barrier surfaces. They occupy tissue-specific niches without recirculating and can be divided into subsets that are related to their location and function. However, a precise understanding of the biology of Trm cell subsets has been hampered by the limited fidelity of surface markers and methodologies that validate residency, and the complexity of different models of infection and immunization. For example, although intravascular (i.v.) staining labels blood cell contaminants in the tissues (Anderson et al. 2012), it cannot distinguish Trm from Tem cells. Moreover, well-established markers of Trm cells (CD69 and/or CD103) are not present on all Trm cell populations (Steinert et al. 2015; Kumar et al. 2017), potentially resulting in Trm cell subpopulations being missed in previous studies. Parabiosis studies in which surgery is used to establish a shared anatomic circulation between host and partner is a reliable method in excluding partner-derived circulatory populations, but is incapable of discriminating host-derived Tem cells from nonmigrating host Trm cells (Takamura and Kohlmeier 2019; Takamura et al. 2019). Furthermore, the functions and features of Trm cells differ depending on their localization within the same tissue (epithelium vs. stroma), and this localization is influenced by the route of infection/vaccination (systemic vs. local), the nature of the pathogens used (acute vs. chronic), and the experimental conditions (such as conventional specific pathogen-free vs. germ-free vs. animals with diverse microbial experience). Therefore, careful consideration of the pros and cons of each experimental technique and model system is required to fully understand tissue memory diversity. Herein we will summarize the current knowledge of tissue memory diversity, given these technological limitations.

EPITHELIAL Trm CELLS

Epithelial tissues, comprised of sheets of epithelial cells, cover the surfaces of barrier tissues including the skin, gastrointestinal, respiratory, and urogenital tracts, as well as hollow parts of exocrine and endocrine glands. Basement membrane underlies the bottom layers of epithelial cells, thereby providing physiological and environmental separation of the epithelium from the stromal tissues (dermis, lamina propria, lung interstitium, etc.). Because epithelial tissues are avascular and essentially lack lymphatic drainage, memory T cells maintained in these tissues do not return to the circulation under steady-state conditions and are classified as Trm cells (note that a low level of traffic between the epithelium and stroma has been observed [Dijkgraaf et al. 2019; Thompson et al. 2019]). Epithelial Trm cells include cells in the skin epidermis (Gebhardt et al. 2009; Jiang et al. 2012), the intestinal intraepithelial lymphocyte (IEL) compartments (Sheridan et al. 2014; Bergsbaken and Bevan 2015), the lung airways (Hogan et al. 2001), the epithelium of the female reproductive tract (FRT) (Shin and Iwasaki 2012), and the salivary glands (Smith et al. 2015; Thom et al. 2015). An overwhelming majority of adoptive immune cells in the epithelium are $CD8^+$ Trm cells, although some $CD4^+$ Trm cells are also present (Gebhardt et al. 2011; Kumar et al. 2017).

Intraepithelial Migration

After being primed in the draining LNs, antigen-specific T cells home to the site of infection/immunization. Upon entry into the stroma, a fraction of effector T cells acquire tissue-derived instructions that enable them to traffic through the basement membrane (Fig. 1A). An actin-driven morphological change is required for traversing the basement membrane, as T cells lacking myosin IXb (Myo9b), an F-actin-based cytoskeletal motor protein, fail to enter the epidermal compartment (Moalli et al. 2018). In the case of a localized infection, inflammatory chemokines such as CXCL9 and CXCL10 (ligands for CXCR3) secreted at the site of infection play a key role in inducing cytoskeletal remodeling of effector T cells, thereby promoting intraepithelial migration and subsequent formation of $CD8^+$ Trm cells in the epithelium (Nakanishi et al. 2009; Mackay et al. 2013; Abboud et al. 2016; Gilchuk et al. 2016; Pizzolla et al. 2017; Caldeira-Dantas et al. 2018). This step may be

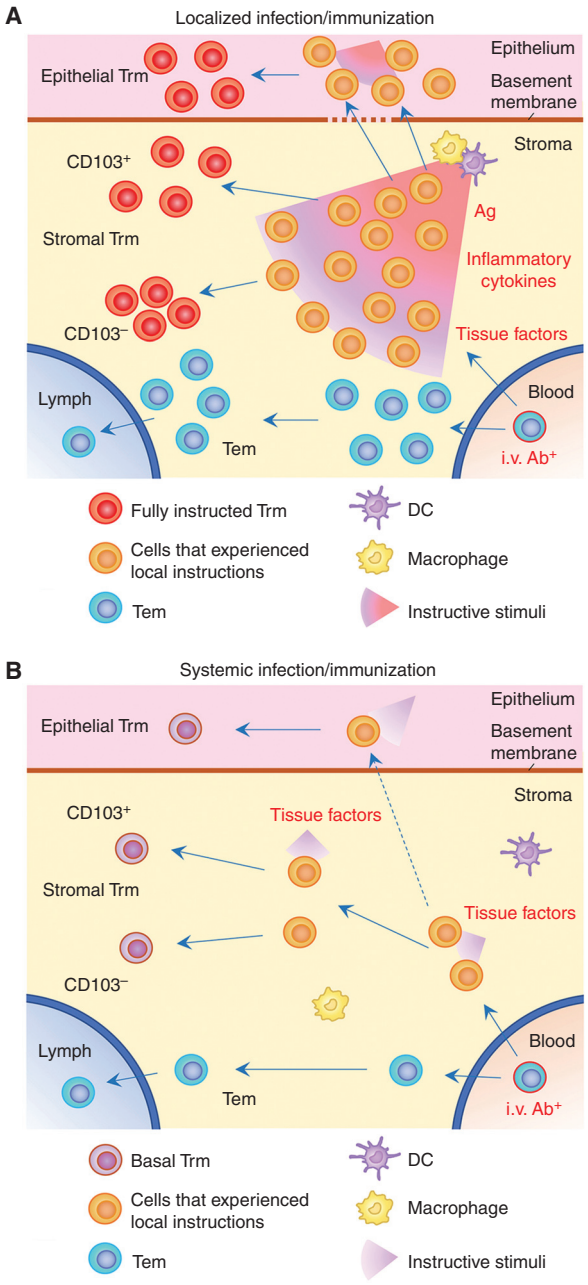

Figure 1. Models of tissue memory diversity. (*A*) Establishment of tissue-resident memory T cells (Trm) at the site of infection/immunization. Trm precursor T cells ($KLRG1^{-}CX_3CR1^{-}$) recruited to the stroma receive tissue-derived instructive signals, including strong antigenic and inflammatory stimuli. Cells receiving appropriate instruction traffic through the basement membrane and differentiate into a unique population of epithelial Trm cells after receiving additional instructive cues. In the stroma, cells receive differential instructive stimuli and mature into diverse populations of Trm cells, such as the $CD103^{+}$ and $CD103^{-}$ subpopulations. Cells that did not receive any instructions do not up-regulate master transcription factors and leave the tissues as effector memory T cells (Tem). (*B*) Establishment of Trm cells at sites distal to infection/immunization sites. Basal levels of tissue instructive cues (e.g., TGF-β, IL-15, and aryl hydrocarbon receptor [AhR]) promote the establishment of quantitatively and qualitatively distinct populations of Trm cells as compared to their counterparts at the site of infection/immunization. In both cases, only cells in the blood are labeled by intravascular (i.v.) staining. (Ag) antigen, (DC) dendritic cell.

facilitated through the interaction of CD49a (integrin α1β1) with collagen IV, a major component of basement membrane (Topham and Reilly 2018), leading to the preferential accumulation of CD49a$^+$ Trm cells in some epithelial tissues, such as skin and lung (Ray et al. 2004; Gebhardt et al. 2009; Cheuk et al. 2017). T cells recruited to the stroma of an infection site encounter antigen-presenting cells (APCs), which induce terminal effector differentiation and additional rounds of expansion (McGill et al. 2008, 2010; McGill and Legge 2009; McKinstry et al. 2014). Reactivation with cognate antigen in the stroma also serves as a primary tissue-derived instruction required for Trm cell differentiation and intraepithelial migration (Khan et al. 2016; Takamura et al. 2016; McMaster et al. 2018). This "second hit" up-regulates the expression of the activation marker CD69, which stabilizes the residency of CD8$^+$ Trm cells by inhibiting sphingosine-1-phosphate receptor 1 (S1P1)-mediated tissue egress (Shiow et al. 2006; Mackay et al. 2015a). A second antigen hit also induces the activation and conformational change of various integrins, such as CD103 and CD49a, which mediate firm interactions with their respective ligands, E-cadherin and collagen, in the epithelium. Because regional reactivation of CD8$^+$ T cells occurs even when MHC class I molecules are down-regulated on virus-infected cells (Lauron et al. 2019), professional APCs, such as CD103$^+$ dendritic cells (DCs), and monocyte-derived macrophages that acquire and cross-present viral antigens at the site of infection, also contribute to this process (Wakim et al. 2015; Desai et al. 2018). Importantly, the interaction of effector CD8$^+$ T cells with APCs at the site of infection is highly competitive (Muschaweckh et al. 2016) and selects for CD8$^+$ Trm cells expressing high-affinity T-cell receptors (TCRs) (Frost et al. 2015). Thus, local antigen encounter is vital for shaping the local repertoire of CD8$^+$ Trm cells in the epithelium.

Although circulating T cells have extremely limited access to uninflamed epithelial tissues under steady-state conditions (Klonowski et al. 2004), there is a basal level of recruitment of tissue-imprinted T cells that is mediated by constitutively expressed chemokines in the epithelium. These include cutaneous T-cell-attracting chemokine (CTACK) expressed by epidermal keratinocytes (Morales et al. 1999), and CCL25 expressed by intestinal epithelial cells (Kunkel et al. 2000). We, and others, have demonstrated that basal levels of inflammatory chemokines, such as CXCR3 ligands, are also expressed in the lung airways presumably because of continuous exposure to airborne contaminants, which facilitates the basal recruitment of tissue-circulating CD8$^+$ Tem cells into the epithelium (Slütter et al. 2013; Takamura et al. 2019). Such tissue-specific basal pathways potentially explain a broad distribution of Trm cells at the remote epithelial sites following systemic infection (Fig. 1B; Steinert et al. 2015; Milner et al. 2017). It should be emphasized, however, that epithelial Trm cells established through basal recruitment mechanisms are far less robust than, and phenotypically distinct from, Trm cells generated by local infection (Sheridan et al. 2014; Takamura et al. 2016). Thus, it is reasonable to speculate that Trm cells established in the same location, but in the presence or absence of local infection, will have distinct functional capacities (Fig. 1; Takamura and Kohlmeier 2019).

It is now appreciated that the topical administration of chemokines, or the induction of antigen-independent inflammation, is sufficient to recruit circulating (memory-precursor) effector CD8$^+$ T cells to the epithelium and establish epithelial Trm cells, even in the absence of cognate antigen, a strategy referred to as "prime-and-pull" (Mackay et al. 2012; Shin and Iwasaki 2012). This strategy is extremely efficient in certain epithelial tissues, such as the skin and vagina, where preexisting niches are available for CD8$^+$ Trm cells to establish residency (Takamura 2018). For example, skin epidermal CD8$^+$ Trm cells become established in niches previously occupied by dendritic epidermal T cells (DETCs) (Zaid et al. 2014). In contrast, we and others have demonstrated that lung is a unique tissue where simple prime-and-pull strategies fail to establish CD8$^+$ Trm cells because of a lack of appropriate niches (Takamura et al. 2016; McMaster et al. 2018). Instead, a combination of local inflammation and cognate

antigen in the presence of antigen-specific $CD8^+$ T cells in the circulation (prime-and-pull plus cognate antigen) leads to immune-mediated tissue damage, which creates de novo Trm cell niches associated with tissue damage and repair (repair-associated memory depots [RAMDs]). These niches subsequently promote lung $CD8^+$ Trm cell residency.

Similarly, targeting antigen presentation to hepatocytes effectively traps circulating antigen-specific $CD8^+$ T cells within the liver sinusoid and promotes Trm cell formation, a strategy termed as "prime-and-trap" (Fernandez-Ruiz et al. 2016). In this case, activation but not local antigen presentation is essential for the cells to differentiate into Trm cells (Holz et al. 2018). Given the differences in microenvironmental structures and instructive signals necessary for Trm cell formation in each tissue, development of tissue-specific vaccination strategies is likely required.

Adaptation of Epithelial Trm Cells

Following intraepithelial migration, T cells receive additional tissue-specific instructive cues that promote Trm cell maturation (adaptation) (Fig. 1A). These include activation signals via cognate antigen and/or inflammatory cytokines, and other factors such as TGF-β, IL-15, and AhR ligands. Although activation signals sustain the expression of CD69, which helps retain the cells in the epithelium through the inhibition of S1P1, CD69 expression is not essential for retention as epithelial tissues lack lymphatic drainage. Consistent with this, there is only a partial reduction in the formation of epithelial Trm cells in the absence of CD69 (Mackay et al. 2015a; Takamura et al. 2016; Walsh et al. 2019). However, activation-induced events do play an as-yet-undefined cell-intrinsic role in maintaining cells in the tissues, as nearly all $CD69^-$ cells (presumably nonactivated) in this tissue exhibit short-lived effector phenotypes ($KLRG1^+$ $CD127^-$) and are committed to die after antigen clearance (Sheridan et al. 2014). In some tissues, basal levels of inflammatory cytokines produced in the epithelium or cross-reactive antigens seem to be sufficient to induce maturation in some cells as epithelial Trm cells can be formed even in the absence of local infection (Masopust et al. 2010; Casey et al. 2012). These (antigen-nonspecific) activation signals are more prominent under conditions where there is a diverse infection history and can result in substantial numbers of epithelial Trm cells (Beura et al. 2016).

The latent (inactivated) form of TGF-β is constitutively produced at basal levels in most epithelial/stromal tissues. This latent form of TGF-β can be activated through the actions of the integrins αvβ6 and αvβ8 expressed on various cell types in the mucosa, such as keratinocytes, DCs, macrophages, and regulatory T (Treg) cells (Wakim et al. 2015; Worthington et al. 2015; Mohammed et al. 2016; Kelly et al. 2018; Hirai et al. 2019). The active form of TGF-β is a critical factor for the up-regulation of CD103 (integrin αE7), which facilitates retention of Trm cells within the epithelium through the binding to E-cadherin, a component of epithelial tight junctions (Pauls et al. 2001). Consequently, epithelial Trm cells are highly enriched for expression of CD103 as compared to memory T cells in the stroma and circulation. CD103 could be considered a reliable marker for Trm cells; however, small numbers of $CD103^-$ $CD8^+$ Trm cells are also present in the epithelium, and a CD103 deficiency does not result in the global absence of epithelial Trm cells (Lee et al. 2011; Mackay et al. 2013; Sheridan et al. 2014). These data suggest that the tethering role of CD103 could be compensated for, in part, by other adhesive molecules, such as CCR8 (McCully et al. 2018). Importantly, studies relying exclusively on CD103 to identify Trm cells will underestimate the overall populations of Trm cells in tissues. Interestingly, while a majority of epithelial $CD8^+$ Trm cells express CD103, most $CD4^+$ Trm cells in these tissues largely lack the expression of this molecule (Watanabe et al. 2015; Kumar et al. 2017; Romagnoli et al. 2017). Because reactivation of $CD4^+$ Trm cells requires interaction with MHC class II^+ APCs, it is tempting to speculate that the lack of CD103 may be important in retaining the migratory (motional) flexibility of $CD4^+$ Trm cells to access to the proximal lymphoid struc-

tures where efficient APC T-cell interactions occur during secondary infections. In contrast to the conventional epithelial tissues, $CD8^+$ Trm cells in the liver sinusoid entirely lack the expression of CD103, presumably reflecting the lack of tight junctions in the sinusoidal epithelium (Fernandez-Ruiz et al. 2016).

IL-15 is also known to be important for the maturation and maintenance of epithelial Trm cells in some tissues, such as the skin, salivary gland, and kidney (Schenkel et al. 2016). Upon arrival in the epithelium, memory precursor $CD8^+$ T cells receive IL-15 signals that prevent TGF-β-mediated down-regulation of T-bet, thereby promoting increased survival (Mackay et al. 2015b). In the skin, signaling through IL-15 and the AhR is essential for the long-term maintenance of both epidermal $CD8^+$ Trm cells and DETCs, thereby resulting in competition for the same survival niche (Kadow et al. 2011; Zaid et al. 2014). However, in several other epithelial tissues, such as the lung, gut, and FRT, $CD8^+$ Trm cells can be generated and maintained in the absence of IL-15, highlighting the heterogeneity of Trm cell development in different tissues (Verbist et al. 2011; Schenkel et al. 2016).

Unique Features of Epithelial Trm Cells

It is well established that epithelial Trm cells differ significantly in morphology, phenotype, function, and maintenance, compared to their stromal counterparts. The best example is in the skin. Epidermal $CD8^+$ Trm cells in the skin display a highly dynamic dendritic morphology, whereas dermal Trm cells display a more amoeboid shape. The dendritic morphology of epidermal $CD8^+$ Trm cells is consistent with their need to actively crawl between keratinocytes to sense rare virally infected cells and trigger an innate interferon (IFN) response in response to cognate antigen (Ariotti et al. 2012, 2014; Schenkel et al. 2013, 2014; Dijkgraaf et al. 2019). Epidermal $CD8^+$ Trm cells are further divided into two distinct subpopulations based on CD49a expression: $CD49^+CD103^+CD8^+$ Trm cells are poised for the production of IFN-γ and cytolytic molecules and tend to accumulate in lesional vitiligo, whereas $CD49^-CD103^+CD8^+$ Trm cells preferentially produce IL-17 and potentially contribute to the development of psoriasis (Cheuk et al. 2017). In both cases, epidermal Trm cells excel in cytokine production relative to their dermal counterparts. Higher cytotoxic T-cell (CTL) activity is also characteristic of intestinal epithelial Trm cells (Booth et al. 2019), although this may not be the case in a model of systemic infection where cognate antigens are absent in the intestinal epithelium (Beura et al. 2015). $CD8^+$ Trm cells in the IEL compartment are also unique. These cells maintain effector-like semi-activated status enabling them to rapidly regain function. This semi-activated state is tightly regulated by a reduced metabolic capacity mediated by alterations in mitochondrial membrane composition. The regulation of metabolic activity in this case is thought to be a mechanism to prevent immunopathology, a feature that may be unique to IEL Trm cells (Konjar et al. 2018). Trm cells in the epithelial tissues are also known to metabolically adapt to their environment. As the skin and intestinal epithelia are rich in fatty acid but limited in other nutrients, epithelial Trm cells in these tissues appear to utilize exogenous fatty acid to support their differentiation, longevity, and protective function (Fahrer et al. 2001; Pan et al. 2017; Bachem et al. 2019).

The function and maintenance of lung airway $CD8^+$ Trm cells is also unique. These cells progressively lose the expression of CD11a (LFA-1) upon migration into this tissue, thereby losing cell contact-mediated cytolytic activity (Hogan et al. 2001; Ely et al. 2006; Kohlmeier et al. 2007). Yet, airway $CD8^+$ Trm cells are sufficient to confer heterosubtypic protection against influenza challenge through the rapid and robust production of IFN-γ upon recall (McMaster et al. 2015). Recently, we have demonstrated that environmental cues in the lung airways drive huge transcriptional and epigenetic changes in airway $CD8^+$ Trm cells, including the induction of genes associated with the integrated stress response (ISR), which shortens the life span of the cells (Hayward et al. 2020). Together with the cell-extrinsic factors (e.g., bio-

physical removal by barrier function of airway mucosa), $CD8^+$ Trm cells in the lung airways have a relatively short half-life (~2 weeks), necessitating the continual recruitment of $CD8^+$ T-cell memory to sustain their numbers (Ely et al. 2006; Zammit et al. 2006). This is consistent, at least in part, with previous data suggesting that populations of memory $CD8^+$ T cells in the lung (including Tem and Trm cells in the interstitium and airways) are continuously replenished by Tem cells from the circulation (implying Tem to Trm cell conversion) in an antigen-independent manner (Slütter et al. 2017). However, we have undertaken a precise characterization of lung memory subsets and demonstrated that a majority of airway $CD8^+$ Trm cells are seeded by the Trm cell pool maintained in RAMD niches in the lung interstitium, with only a minimal contribution by Tem cells (Takamura et al. 2019). This study also demonstrated that $CD8^+$ Trm cells in the lung interstitium are maintained independently from Tem cells (minimum, if any, Tem to Trm cell conversion). This highlights the importance of the precise classification and separation of tissue memory subtypes to better understand their biology (Takamura and Kohlmeier 2019).

In other tissues, Tem cells may be essential for Trm cell maintenance. In the mouse model of murine cytomegalovirus (MCMV) infection, antigen-specific memory $CD8^+$ T cells that undergo memory inflation (antigen-driven expansion of the circulatory memory during the late stages of infection) are stably maintained in the epithelium of the salivary gland as Trm cells, while the number of noninflating Trm cells significantly decline over time along with a decline in the Tem cell population in the circulation, suggesting the inflationary Tem cell–dependent maintenance of epithelial Trm cells in the salivary gland (Smith et al. 2015; Thom et al. 2015). Furthermore, Tem cell–dependent and TGF-β-independent maintenance of $CD8^+$ Trm cell IELs is also evident in animals chronically infected with lymphocytic choriomeningitis virus (LCMV) (Zhang and Bevan 2013), suggesting the role of repeated antigen encounter (presumably in the circulation) in promoting Tem to Trm cell conversion.

STROMAL MEMORY T CELLS (INCLUDING BOTH Trm AND Tem CELLS)

Stromal tissues (e.g., dermis, intestinal lamina propria, and lung interstitium) that underlie the basement membrane are mainly composed of fibroblasts and extracellular matrix (a network of elastin and collagen fibers), and harbor a variety of immune cell populations, including Trm and Tem cells. Many of these cells are distributed in organized lymphoid structures but are also found diffused throughout the stroma. Both $CD4^+$ and $CD8^+$ Trm cells are found in these tissues, although $CD4^+$ Trm cells generally dominate. Because blood and lymphatic vessels are rich in the stroma, Trm cells in the stroma need to continuously silence tissue egression programs for their long-term maintenance. It is important to note here that both tissue-circulating Tem and bona fide Trm cells are not labeled with i.v.-injected antibodies (Fig. 1). This highlights the need for combining additional strategies to distinguish these populations. Furthermore, there is strict anatomical compartmentalization between Tem and Trm cells in the stroma, as $CD8^+$ Trm cells are predominantly deposited in their specific niches at the site of previous infection while $CD8^+$ Tem cells are widely diffused throughout the tissue (Takamura et al. 2016). Hence, it is likely that, under steady-state condition, Tem cells traffic through the stromal tissues where local instructive signals are rarely accessible (Fig. 1).

Developmental Bifurcation of Tem and Trm Cells

Upon entry into the stroma, memory precursor T cells are subjected to migratory (developmental) signals directing them to either remain in the stroma (including subsequent intraepithelial migration) or leave the tissues as Tem cells (Fig. 1A). These decisions are driven by the acquisition of tissue-derived instructions, including signals through the TCRs, costimulatory molecules, cytokines, and other unknown factors, that trigger the up-regulation of "master" transcription factors, such as Runx3, Hobit, and Blimp-1 (Mackay et al. 2016; Milner et al.

2017). Although the critical stimuli that regulate these transcription factors are not fully understood, each of these transcription factors universally instruct retention primarily (but not exclusively) through the repression of KLF2, thereby suppressing the expression of downstream tissue egress molecules, S1P1, CCR7, and CD62L (Skon et al. 2013). The expression of master transcription factors also promotes the up-regulation of CD103 and CD69, which accelerates tissue retention through ligand binding and antagonistic down-regulation of S1P1, respectively (Behr et al. 2018; Milner and Goldrath 2018). Whereas most resident cell populations share a common transcriptional program, biased usage of particular transcription factors is also evident. For example, the formation of $CD103^+CD8^+$ Trm cells in the lung critically depends on Blimp-1 but not Hobit (Behr et al. 2019). Because Blimp-1 expression is linked to terminal effector differentiation (Kallies et al. 2009; Rutishauser et al. 2009), and antigen recognition potentially down-regulates Hobit expression (van Gisbergen et al. 2012), Blimp-1-dependent and Hobit-independent formation of $CD103^+CD8^+$ Trm cells might be unique in tissues where the establishment of Trm cells largely relies on a second hit with cognate antigen (Takamura et al. 2016; McMaster et al. 2018). Thus, defining the overall picture of instructive signals and their downstream transcription factors in each tissue will have significant implications for the development of vaccines designed to establish Trm cells in different mucosal sites.

Stromal $CD8^+$ Trm Cell Subpopulations

Accumulating evidence indicates that stromal $CD8^+$ Trm cells are heterologous in terms of their phenotype, localization, and function. In fact, using a parabiosis approach, we have demonstrated that host-derived (noncirculating) $CD8^+$ Trm cells in the lung stroma include a canonical $CD69^+/CD103^+$ population and a similarly sized $CD69^+/CD103^-$ population (Tem cells are excluded from these populations as these are mostly $CD69^-$) (Takamura et al. 2016; Takamura and Kohlmeier 2019). The formation of $CD103^+CD8^+$ Trm cells strictly depends on TGF-β, as lack of TGF-β signaling results in the complete loss of $CD103^+$ Trm cells (Hu et al. 2015). However, as most of the previous studies have not considered $CD103^-CD8^+$ T cells as Trm cells, the biology of these relatively large $CD103^-CD8^+$ Trm cells is largely unknown. Comparison of Trm cell phenotypes between different epitope-specific $CD8^+$ T cells showed that elevated expression of CD103 on $CD8^+$ Trm cells correlated with weaker activation status, as biased expression of CD103 on influenza virus polymerase (PA)-specific but not nucleoprotein (NP)-specific $CD8^+$ T cells is inversely correlated with their expression of PD-1 (low on PA-specific T cells but high on NP-specific T cells) (Suarez-Ramirez et al. 2019). Enriched proinflammatory gene expression status on NP-specific cells and higher expression of Hobit on PA-specific cells also support this idea (Yoshizawa et al. 2018). Thus, the quality and quantity of activation signaling (in combination with TGF-β) may direct developmental bifurcation between $CD103^+$ and $CD103^-CD8^+$ Trm cells. Such activation events likely take place at the site of infection rather than the initial priming site in the draining LN, as up-regulation of CD103 only occurs upon arrival in the stroma. Given that CD103 expression contributes to synapse formation between $CD8^+$ Trm and target cells (Franciszkiewicz et al. 2013), and accelerates cytotoxic effector functions via a direct outside-in signaling pathway (Le Floc'h et al. 2007, 2011), $CD103^+CD8^+$ Trm cells may have superior functionalities compared to their $CD103^-$ counterparts. This raises interesting questions regarding the significance of $CD103^-CD8^+$ Trm cells in the stroma.

A recent study reveals that $CD103^+$, but not $CD103^-$, $CD8^+$ Trm cells have a significantly greater reliance on extracellular ATP (eATP)-driven signals via its receptor P2RX7, which promotes mitochondrial activity and fusion (Borges da Silva et al. 2018). P2RX7 is selectively expressed on Trm cells (presumably primarily on $CD103^+$ cells) (Stark et al. 2018; Yoshizawa et al. 2018; Borges da Silva et al. 2019), suggesting a regulatory overlap between CD103 and P2RX7 expression. In contrast to its supportive role in Trm cell formation and maintenance,

excessive P2RX7 signaling in high eATP environments (e.g., damaged tissues) induces selective deletion of Trm cells (Stark et al. 2018; Borges da Silva et al. 2019). Importantly, TCR triggering down-regulates P2RX7 expression, thereby rescuing Trm cells from eATP-induced cell death (Stark et al. 2018), suggesting a requirement for continuous antigen-driven signaling for the long-term maintenance of Trm cells, particularly those maintained in the damaged tissues such as $CD8^+$ Trm cells in the lung interstitium (Takamura et al. 2016). This supports our speculation that lower CD103 expression on Trm cells (relative resistance to high eATP-induced cell death) may be attributed to persistent antigen signaling (theoretically low P2RX7 expression).

$CD69^+CD103^-CD8^+$ Trm cells are also present in the stroma of various tissues, such as the skin, gut, FRT, salivary gland, and brain (Wakim et al. 2010; Bergsbaken and Bevan 2015; Smith et al. 2015; Thom et al. 2015; Watanabe et al. 2015; Pattacini et al. 2019). A $CD103^-CD8^+$ Trm cell population has also been described in the brain (Wakim et al. 2010). Presumably, the lack of lymphatic drainage in the parenchyma in the brain allows for the establishment of $CD103^-$ cells with reduced tissue-retention capacity. $CD103^+$ and $CD103^-CD8^+$ Trm cells in the brain also display distinct gene expression profiles (Wakim et al. 2012; Landrith et al. 2017). $CD103^+$ Trm cells have a highly enriched tissue-retention signature, accelerated expression of activation-related molecules such as PD-1, and superior effector functions as compared to $CD103^-$ Trm cells (Shwetank et al. 2017), reflecting the impact of TGF-β and local antigen encounters in the development of $CD103^+$ Trm cells.

In the case of the small intestine, TGF-β is required for the development of $CD103^+$ Trm cells, while the inflammatory cytokines IFN-α and IL-12 facilitate the formation of the $CD103^-$ Trm cell subset (Bergsbaken and Bevan 2015; Bergsbaken et al. 2017). Localization of these Trm cell subsets also differs. Whereas $CD103^+CD8^+$ Trm cells are evenly distributed throughout the stroma, $CD103^-CD8^+$ Trm cells are maintained in clusters along with $CD4^+$ T cells and CX_3CR1^+ APCs (Bergsbaken and Bevan 2015). The proximal positioning with other immune cell populations might compensate for the cells' weakened retention due to the absence of CD103. Taken together, it is clear that distinct environmental cues generate distinct subsets of Trm cells in the stroma. Given the diversity of Trm cell populations in the stroma, it is of interest to investigate the actual contribution and potential division of labor of each Trm cell subset in the recall response.

Stromal $CD4^+$ Trm Cell Subpopulations

Memory $CD4^+$ T cells outnumber memory $CD8^+$ T cells in the stroma of most mucosal and barrier tissues (Sathaliyawala et al. 2013). They include Tem circulating between NLTs and SLOs that rapidly traffic through the stroma (Gebhardt et al. 2011) and Trm cells that are established and maintained at the site of infection (Teijaro et al. 2011; Iijima and Iwasaki 2014; Stary et al. 2015; Romagnoli et al. 2017). As with $CD8^+$ T cells, tissue-specific instructions, including cognate antigen-driven second hits early after initial priming, govern $CD4^+$ Trm cell fate decisions (Fig. 1A). In the mouse models of influenza virus infection and asthma, second hit–driven autocrine IL-2 signaling in combination with IL-15 signaling favors memory commitment in the lung interstitium by inducing prolonged survival (McKinstry et al. 2014; Hondowicz et al. 2016; Strutt et al. 2018). Down-regulation of T-bet is also an essential cell-intrinsic event necessary for the establishment of Trm cells (Dhume et al. 2019). Additional master cytokine signaling probably plays a role in dictating the heterogeneity of well-known $CD4^+$ T-cell subsets.

Emerging data suggests that $CD4^+$ Trm cells can also be divided into two subpopulations based on their expression of CD103 (Turner et al. 2014; Collins et al. 2016; Romagnoli et al. 2017; Wilk et al. 2017). Although the actual role of CD103 in their localization within the stroma is largely unknown, canonical Trm cell transcriptional signatures and superior polyfunctionality (Th1 cytokines) has been reported for $CD103^+CD4^+$ Trm cells (Watanabe et al. 2015;

Oja et al. 2018). In contrast, in a mouse model of chronic antigen exposure, antigen-specific $CD103^{-}CD4^{+}$ Trm cells generated in the lung display a greater ability to secrete proinflammatory cytokines than their $CD103^{+}$ counterparts, and cause fibrotic responses through elevated production of Th2 cytokines, including IL-4, IL-5, and IL-13 (Ichikawa et al. 2019). IL-33 signaling accelerates the generation of the pathogenic subpopulation of resident $CD103^{-}CD4^{+}$ T cells, while TGF-β potentially promotes the establishment of $CD103^{+}FoxP3^{+}CD4^{+}$ T cells with regulatory capacities (Morimoto et al. 2018; Ichikawa et al. 2019). A better understanding of the biology of these Trm cell subpopulations may lead to the development of new immunomodulatory therapeutics.

Unlike $CD8^{+}$ Trm cells, which are usually distributed throughout the stroma and without forming lymphoid structures, $CD4^{+}$ Trm cells in the stromal tissues preferentially localize in lymphoid aggregates, including ectopic lymphoid structures such as inducible bronchus-associated lymphoid tissue (iBALT) (Clark et al. 2006; Iijima and Iwasaki 2014; Turner et al. 2014; Collins et al. 2016). This distribution reflects their tropism for sites that promote interactions with APCs. Interestingly, stromal $CD4^{+}$ Trm cells established at sites distal to the infection site mostly lack the expression of CD103 and fail to form clusters (Beura et al. 2019), suggesting a primary role for a second hit with cognate antigen. One exception is the dermis in the skin, where $CD69^{+}CD103^{+}CD4^{+}$ T cells could be established and form clusters in the perifollicular area even in the absence of infection (Collins et al. 2016). This suggests a role for local tissue-resident macrophages in attracting $CD4^{+}$ T cells under steady-state conditions. Of note, long-period parabiosis experiments (12–16 weeks) using naive animals has revealed the slow emergence of partner (circulation)-derived $CD69^{+}CD103^{+}CD4^{+}$ T cells, which coincides with the loss of host $CD69^{+}CD103^{+}CD4^{+}$ T cells in the dermis (Collins et al. 2016). This suggests that dermal $CD4^{+}$ Trm cells leave tissues in the same manner as Tem cells (theoretically after down-regulation of CD69). In fact, a recent study identified the presence of skin-tropic $CD69^{-}/CD103^{+}$ memory $CD4^{+}$ T cells having a Trm cell gene signature in the circulation and proposed a model of skin $CD4^{+}$ Trm cell recirculation (ex-Trm cell model). Because ectopic lymphoid structures usually consist of high endothelial venules (HEVs) and efferent lymph vessels (Randall and Mebius 2014), this slow rate of recirculation may be a feature of $CD4^{+}$ Trm cells. This ex-Trm cell model does not contradict a previously proposed model of $CD4^{+}$ Trm cell tissue residency (Glennie et al. 2015; Snyder et al. 2019), because the stable expression of CD69, especially at the site of infection/immunization, induces prolonged retention (Turner et al. 2014; Shinoda et al. 2016). Taken together, the data suggest that activation signals likely dictate the durability of $CD4^{+}$ Trm cells, and, thus, the route of infection/immunization is a critical factor (Fig. 1).

CONCLUDING REMARKS

The discovery of Trm cells has substantially advanced our understanding of regional protective immunity. However, further progress has been complicated by the lack of precise definitions of Trm cell subsets. For example, categorizing Trm cells exclusively by surface markers potentially fails to identify noncanonical Trm cell subpopulations (e.g., the $CD103^{-}$ Trm cell subpopulations). Furthermore, inattention to a subpopulation's antigenic experience and specific anatomical location or distribution in a tissue might reduce our ability to distinguish distinct Trm cell subpopulations (e.g., lung $CD103^{+}$ Trm cells generated by pulmonary or systemic infections). Hence, it is important to remember that Trm cells are defined fundamentally by their tissue residency, and the role of local instructive stimuli have to be considered in the differential fate commitment of Trm cells.

In addition to the role of Trm cells as a first-line defense against infection, Trm cells also drive autoimmunity, allergy, and inflammatory disease (Masopust and Soerens 2019). Furthermore, $CD8^{+}$ T cells with Trm cell signatures are being identified among tumor-infiltrating lymphocytes (TILs), and their presence is often associated with a favorable prognosis (Amsen et al.

2018). On the other hand, because immune checkpoint molecules, such as PD-1, are known to be frequently expressed on Trm cells, their participation in the development of immune-related adverse events is suspected during immune checkpoint blockade therapy. Thus, identification of the specific Trm cell subsets responsible for protective immunity as well as progressive pathogenesis has significant implications for therapeutic intervention. In light of this, a unifying classification of tissue memory is urgently needed. As technologies advance for the study of these cells, the establishment of fundamental Trm cell subset definitions will be essential for understanding the complexities of Trm cell biology and for the development of treatments to improve human health.

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