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The emerging role of resident memory T cells in protective immunity and inflammatory disease

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Over the past decade, it has become clear that there is an important subset of memory T cells that resides in tissues—tissue-resident memory T (T_{RM}) cells. There is an emerging understanding that T_{RM} cells have a role in human tissue-specific immune and inflammatory diseases. Furthermore, the nature of the molecular signals that maintain T_{RM} cells in tissues is the subject of much investigation. In addition, whereas it is logical for T_{RM} cells to be located in barrier tissues at interfaces with the environment, these cells have also been found in brain, kidney, joint and other non-barrier tissues in humans and mice. Given the biology and behavior of these cells, it is likely that they have a role in chronic relapsing and remitting diseases of both barrier and non-barrier tissues. In this Review we discuss recent insights into the biology of T_{RM} cells with a particular focus on their roles in disease, both proven and putative.

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Memory T cells provide rapid and highly effective protective immunity against previously encountered pathogens and can recognize a wide variety of antigens, including those from malignant tumors and environmental substances. It was previously thought that memory T cells consisted of two major subsets: central memory T (T_{CM}) cells and effector memory T (T_{EM}) cells[1]. T_{CM} cells express the chemokine receptor CCR7 and the vascular addressin L selectin (CD62L), which enables them to access and enter lymph nodes from blood. T_{EM} cells express low levels of CCR7 and CD62L but have receptors that allow them to access peripheral tissues (for example, the E-selectin ligand Cutaneous Lymphocyte Antigen (CLA), which grants them access to the skin, and $\alpha_4\beta_7$, an integrin that allows them access to the gut[2,3]).

Over the past decade, it has become clear that there is another important subset of memory T cells: tissue-resident memory T cells, or T_{RM} cells. Under physiological conditions, T_{RM} cells reside in epithelial barrier tissues at the interface between the host and the environment, such as the gastrointestinal (GI) tract, respiratory tract, reproductive tract and skin. T_{RM} cells can respond rapidly to pathogen challenge at these sites independently of recruitment of T cells from the blood[4,5]. They thus mediate the rapid protective immunity that is the hallmark of adaptive immune memory[4]. T_{RM} cells in a barrier tissue are enriched for T cells specific for pathogens and other antigens that have been encountered previously through that barrier epithelium. Thus, the T cell receptor (TCR) repertoire of skin T_{RM} cells is largely different from that of lung T_{RM} cells, and both are different from that of gut T_{RM} cells[5]. However, T_{RM} cells are not simply memory T cells in an unexpected location; rather, they have a transcriptional program that distinguishes them from peripheral blood T_{EM} cells and T_{CM} cells[6].

The cell-signaling interactions that maintain T_{RM} cells in their resident tissues are the subject of much investigation. The role of T_{RM} cells in human tissue-specific immune and inflammatory diseases is just beginning to be appreciated[5]. In addition, although it is logical for T_{RM} cells to be stationed at interfaces with the environment, they have also been found in brain, kidney, joint and other non-barrier tissues. T_{RM} cells that appear in non-barrier tissues have similar transcriptional programs[7], and their location, biology and behavior make it likely that they have a role in chronic relapsing and remitting diseases of non-barrier tissues. Here we discuss how T_{RM} cells are generated after an immune response and review both common and distinctive features of T_{RM} cells in various barrier tissues, including skin, lung and GI tract. We also discuss how T_{RM} cells may be formed in sterile non-barrier tissues such as brain and kidney and speculate as to the role of T_{RM} cells in immune and inflammatory diseases involving tissues. Finally, we review the role of T_{RM} cells in cancer and the goal of generating T_{RM} cells through vaccination for both infectious diseases and cancer. The field is developing at a rapid rate, and new observations are being made on an ongoing basis.

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Generation of T_{RM} cells during an immune response

Naive T cells circulate between blood and lymph nodes, where they remain for 12–24 h before returning to the blood and then sampling another lymph node microenvironment[8]. Naive T cells are abundant but highly diverse with regard to TCR repertoire, and thus to pathogens

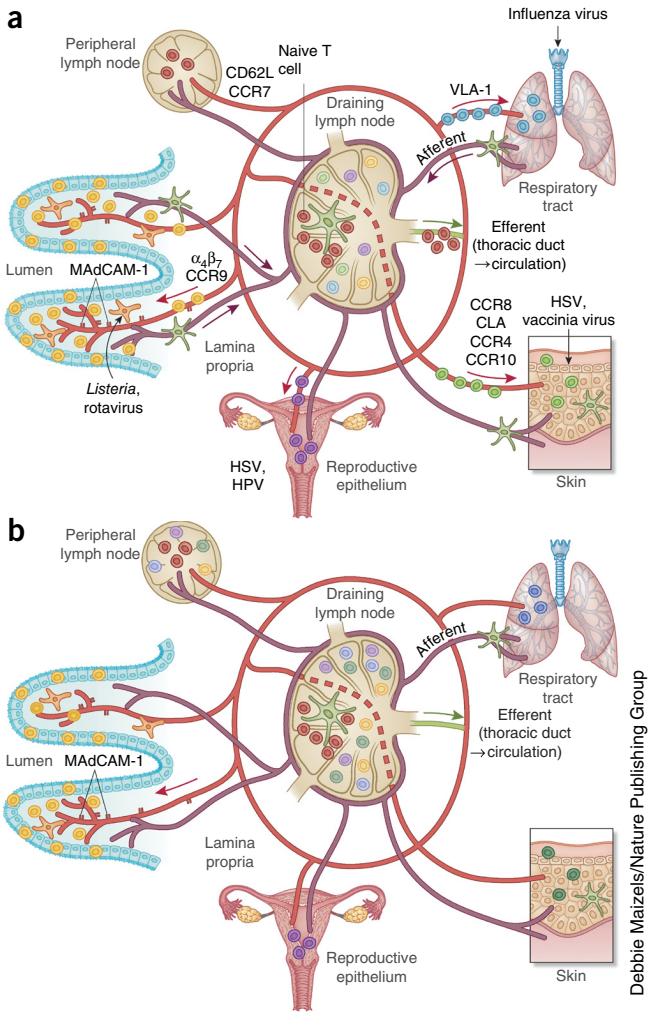

Figure 1 The generation of tissue T_{RM} cells after infection of barrier tissues. (**a**) Upon first encounter with a pathogen in a barrier tissue, dendritic cells carry antigen to draining lymph nodes and present it to naive T cells. Depending on the anatomic location of the lymph node, various trafficking molecules (indicated adjacent to vessels) are expressed on the expanding activated T cell population, and effector T cells with specific tissue-homing properties preferentially exit blood in peripheral tissues. Gut-draining lymph nodes induce the expression of gut-homing molecules on antigen-activated T cells, and skin-draining lymph nodes induce the expression of skin-homing molecules on antigen-activated T cells. Analogous processes, albeit less well characterized, occur in lymph nodes draining lung and reproductive mucosa. VLA-1, very late antigen 1 ($\alpha_1\beta_1$ integrin). (**b**) Long after the pathogen has been eliminated from the barrier tissue and inflammation has resolved, populations of T_{RM} cells remain behind in the tissue. These T_{RM} cells retain the tissue-homing molecules originally imprinted on them and acquire a molecular program that contributes to the maintenance of these cells in peripheral tissue. In parallel, circulating memory T cells are generated, and these have the capacity to enter lymph node and recirculate into blood and tissue. Recent evidence suggests that the same naive T cell may give rise to both T_{RM} cells and T_{CM} cells or circulating T cells[38]. Adapted with permission from ref. 113, Nature Publishing Group.

to which they may be targeted, such that naive T cells specific for any given antigen are rare[9]. Dendritic cells are the first to encounter infectious challenge in peripheral tissues, and they ferry pathogen fragments to draining lymph nodes, where they present processed peptides (antigens) to naive T cells. Those T cells that recognize the antigen become activated and clonally expand, such that one naive T cell gives rise to tens of thousands of progeny[9,10]. Although all these T cells derived from a single naive T cell have the same TCR, the expanded T cell population becomes heterogeneous with regard to the homing molecules that are expressed[11]. Some gain the ability to access peripheral tissues, and others retain the capacity to enter lymph nodes from blood (T_{CM} cells). Effector T cells also acquire new functions that are specific to the pathogen encountered; for example, type 1 helper T cells secrete interferon-γ (IFN-γ, a cytokine that induces a broad range of antiviral factors) in response to viral pathogens, and T_H17 cells produce interleukin-17 (IL-17), a potent inducer of neutrophil activation and recruitment, in response to bacterial and fungal pathogens[12].

The anatomic location of the draining lymph node has an important role in determining the expression of tissue-homing molecules on formerly naive T cells first activated in that microenvironment[11,13] (**Fig. 1a**). Naive T cells that are activated in skin-draining lymph nodes are induced to express CLA, a glycosylated variant of P-selectin glycoprotein ligand[12,14–16] and a ligand for E-selectin, as well as a subset of chemokine receptors that facilitate skin homing (for example, CCR4, CCR8 and CCR10)[17–19]. Alternatively, activation of naive T cells in gut-draining lymph nodes induces expression of $\alpha_4\beta_7$ integrin[20,21], the receptor of mucosal addressin cell-adhesion molecule (MAdCAM) expressed on post-capillary venules in intestinal lamina propria[22], as well as the expression of distinct chemokine receptors, including CCR9 (ref. 23), which binds to CCL25 produced by intestinal epithelium.

The clonally expanding T cell population includes cells that differentiate into tissue-homing effector cells, but also cells that retain CD62L and CCR7 and resemble T_{CM} cells. These latter cells leave the draining lymph node and travel to other lymph nodes, where a subset can differentiate to express different tissue-homing molecules[11]. After effector T cells exit a skin-draining lymph node and enter the blood, those with skin-homing markers are preferentially trapped by inflamed vessels in skin and are extravasated into dermis[24]. These T cells migrate along chemotactic gradients to the pathogen-infected tissue, where they become activated by antigen and produce cytokines and other effector molecules (for example, granzymes) that facilitate pathogen elimination[25–27]. It is now clear that some of these migrant T cells remain in place as T_{RM} cells long after the pathogen is eliminated. This sequence of events can play out again and again, in multiple barrier tissues, over the lifetime of an organism, and the result is the accumulation of diverse and largely (but not completely) non-overlapping populations of T_{RM} cells in each barrier tissue[4,5]. Thus, lung contains influenza-specific T_{RM} cells[28–30], gut contains rotavirus-specific T_{RM} cells[31], skin is enriched in *Candida*-specific T_{RM} cells[32,33] and reproductive mucosa contains herpes simplex virus (HSV)-specific T_{RM} cells[34–37] (**Fig. 1b**). Human peripheral blood T cells enriched in populations of skin (CLA), gut (α4β7) or lung (CLA and/or α4β7) tropic memory T cells are specific to previously encountered pathogens of those tissues[32]. It was recently shown that the same naive T cells that give rise to these T_{RM} cells also give rise to T_{CM} cells in parallel; thus the T_{RM} cell population in tissue is 'duplicated in antigen specificity' by a population of T_{CM} cells with an identical T cell repertoire[38].

The process of T_{RM} cell formation involves some additional nuances not mentioned above. For example, when mouse skin is infected with vaccinia virus by scarification, effector T cells accumulate not only at the vaccinated site but throughout the skin[4], and this was recently shown to be true for skin immunization with proteins and haptens[38].

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Non-inflamed skin contains post-capillary venules that express low levels of E-selectin, chemokines and intercellular adhesion molecule 1, all of the requisite molecules that allow skin-homing T cells[24] to be extravasated and home to uninfected skin sites. In the same fashion, endothelial molecules specific for gut-homing T cells are expressed on resting lamina propria endothelium[22], allowing gut-homing T cells to home to normal, non-inflamed gut. Additionally, multiple sequential encounters with a pathogen at distinct sites on skin lead to a further accumulation of pathogen-specific T_{RM} cells throughout the entire skin surface; thus there is a greater number of T_{RM} cells specific for pathogens encountered more frequently[4,38].

Furthermore, whereas each naive T cell (and its progeny) has a unique TCR, the expanded clone is otherwise heterogeneous. T_{CM} cells have limited effector function or protective capacity[4], but they have the potential to replenish the T_{RM} cell compartment upon activation[38]. The relationship between T_{RM} cells and T_{CM} cells is unclear, but both express low levels of KLRG-1 (ref. 6), a molecule strongly expressed by effector and T_{EM} cells. These data, in addition to a recent report demonstrating skin T_{RM} and lymph node T_{CM} cell clones sharing the same variable sequence (CDR3) of the TCR[38], indicate that many, if not all, T_{RM} cells and T_{CM} cells have a common precursor. With regard to the balance of T_{RM} cells and T_{CM} cells, a recent report suggests that the mTOR pathway may regulate this balance, as mTOR inhibitors such as rapamycin favor T_{CM} cell generation in mouse models[39]. Another recent study suggests that high expression of the transcription factor T-box specific protein 21, or T-bet, favors T_{EM} cell differentiation over T_{RM} cell differentiation, with lower expression of this protein found in T_{RM} cells[40].

Although T_{RM} cells are most likely to have evolved to protect humans against infection from dangerous environmental pathogens, it appears that normal flora of tissue microbiomes, as well as innocuous environmental proteins, can induce the production of T_{RM} cells as well. A recent study in mice and humans found that allergic contact dermatitis was mediated by T_{RM} cells that had been generated in response to topically applied allergens[38]. T_{RM} cells were described as early as 2001 (ref. 41), and the same group demonstrated that T_{RM} cells in gut do not recirculate between parabiotic mice, in contrast to T cells in lymph node and spleen[42].

Common features of T_{RM} cells in barrier tissues

Homing of T_{RM} cells. T_{RM} cells are characterized by their inability to recirculate from tissue to lymph node to blood[4,43–47], although the factors responsible for this are an area of active research. The glycoprotein CD69 is a marker of T_{RM} cells and is expressed on T_{RM} cells in skin, lung, GI tract and everywhere else T_{RM} cells have been identified[4–6,28,48–50]. CD69 was originally thought to be a marker of recent T cell activation in lymph node[51]; however, most T_{RM} cells in tissues have not recently been activated by antigen. CD69 seems to be involved in peripheral tissue retention of T_{RM} cells, which seems to involve downregulation of the G protein–coupled receptor for sphingosine 1 phosphate (S1P1)[52]. There is a gradient of levels of sphingosine 1 phosphate (S1P) in the body in humans and mice, with the lowest levels in peripheral tissue, intermediate levels in lymph node and the highest levels in blood[50,53,54]. These S1P gradients normally function to guide T cells out of tissues and into lymph nodes and out of lymph nodes into blood. Expression of CD69 by T_{RM} cells interferes with the cell-surface expression and function of S1P1, thereby blocking the capacity of these T cells to sense S1P gradients and supporting their stationary nature[50]. The transcription factor Kruppel-like factor 2, which normally enhances S1P1 expression, is downregulated in T_{RM} cells, which indirectly enables CD69 expression[53]. The mechanism by which CD69 and S1P1 compete with each other for cell-surface expression is not completely understood[54].

The chemokine receptor CCR7 is another G protein–coupled receptor that senses molecular gradients of its ligands CCL19 and CCL21 and directs T cells and dendritic cells from peripheral tissues to lymph node via afferent lymphatics[55]. T cells expressing CCR7 are able to migrate in response to gradients of its chemokine ligands, which are normally not abundant in tissue but are at their highest levels in lymph node and afferent lymphatics. It was recently shown in a mouse model that $CD4^+$ T cells in skin require CCR7 to migrate to afferent lymphatics and that blocking CCR7 expression prevents T cells from leaving skin[56]. In human skin, expression of CCR7 was seen on a population of T cells that migrated out of skin (so-called migratory memory T (T_{MM}) cells), whereas $CCR7^-$ T cells remained in skin as T_{RM} cells[57]. The respective contributions of S1P1-CD69 and CCR7 expression on T cells to the migration of these cells out of tissues have not been determined.

The integrin CD103 (also known as α_E, and which pairs with the β_7 integrin chain) is another marker of T_{RM} cells; however, its expression is more predominant on $CD8^+$ T_{RM} cells than on $CD4^+$ T_{RM} cells. It is a known ligand of E-cadherin, a homotypic adhesion molecule expressed by epithelial cells in barrier tissues[58]. In mouse models, $CD8^+$ T cells specific for HSV-1 do not express CD103 before they enter the skin, but they upregulate CD103 expression upon entering epidermis in response to transforming growth factor–β (TGF-β)[6]. CD103 is also expressed by T_{RM} cells in the lung and GI tract, and even in T_{RM} cells in the brain after CNS viral infection[7,40,48,59]. It is tempting to assume that $\alpha_E\beta_7$ on these cells binds to epithelial cells via interactions with E-cadherin. However, binding to E-cadherin is not required for tissue residence, as $CD103^+CD4^+$ and $CD8^+$ T_{RM} cells can be found in the dermis, and $CD103^+$ dendritic cells are plentiful in the dermis without ever entering the epidermis[60]. Although E-cadherin is expressed during brain development, it is absent in adult CNS tissue[61], despite abundant CD103 on brain $CD8^+$ T_{RM} cells in mice. Thus, although its role is incompletely understood, it does appear that CD103 expression is a marker of differentiation of T_{RM} cells[6] rather than a functional requirement for tissue residence. It is notable that $CD103^+$ T_{RM} cells have less proliferative potential and more significant effector cytokine–production capacity than do $CD103^-$ T cells in several human and mouse models[7,40,41,48,59,62,63]. Human skin T cells also are not strictly required to express CD103 in order to be T_{RM} cells[57]. A recent study of a mouse model suggests that $CD8^+CD103^-$ T_{RM} cells may have a unique role in gut, as they are generated in inflammatory microenvironments in the lamina propria and have a distinctive role in controlling infection compared to their $CD8^+CD103^+$ counterparts[64].

Less is known about $CD4^+$ T_{RM} cells than about $CD8^+$ T_{RM} cells, in part because these cells are less efficiently generated after viral infection in mouse models, in which T_{RM} cells have been most completely characterized. Studies of HSV infection of the female mouse reproductive tract suggest that local chemokine gradients from tissue mononuclear cells maintain $CD4^+$ T_{RM} cells in place[37]. In skin, evidence suggests that $CD4^+$ T_{RM} cells do not preferentially localize to the epidermis and express lower levels of CD103 than do $CD8^+$ T cells[4,63]. HSV-specific $CD4^+$ T cells in mouse skin may be more mobile than $CD8^+$ T_{RM} cells, and they may also be limited to the dermis[65]. $CD4^+$ T cells in skin may express CCR7 and/or CD69 (refs. 5,56). In a recent study, highly immunocompromised NOD SCID IL-2Rγ–deficient (NSG) mice bearing human skin xenografts were treated with alemtuzumab (an antibody that binds human

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CD52, a molecule present on all T cells). This humanized antibody has been shown to deplete human T cells in blood but not in tissue[57,66]. Two populations of $CD4^+$ T cells were depleted by alemtuzumab from the skin xenografts of these mice: those that expressed both CCR7 and CD62L (markers of T_{CM} cells), and those that expressed CCR7 but not CD62L (T_{MM} cells). These data demonstrate that these two populations normally migrate out of skin into blood, and thus although they transiently reside in skin, they are not authentic T_{RM} cells. The two populations of $CD4^+$ T cells that remained in the skin after alemtuzumab treatment both expressed CD69 and lacked CCR7 (and were thus unresponsive to S1P and CCL19/21 gradients) and included both $CD103^+$ and $CD103^-$ populations. Thus, four distinct populations of $CD4^+$ T cells could be identified in human skin, two of which were short-term residents and could exit skin and enter blood, and two of which were true T_{RM} cells[57].

Table 1 Heterogeneity of T_{RM} cells in mouse and human skin

Location	Mouse cell	Cell type	Human cell	Cell type	Reference(s)
Epidermis	γδ DETC	$Vγ3^+$	NA	NA	69,114
Epidermis	$CD8\text{-}αβ^+$ T	$CD103^+$	$CD8\text{-}αβ^+$ T	$CD103^+$ T_{RM}	4,6,63,73
Epidermis	NA	NA	$CD4\text{-}αβ^+$ T	$CD103^{+/-}$ T_{RM}	56,73
Dermis	γδ T	Non-$Vγ3/IL\text{-}17^+$	γδ T	Unknown	115–117
Dermis	$CD8\text{-}αβ^+$ T	$CD103^-$	$CD8\text{-}αβ^+$ T	$CD103^{+/-}$ T_{RM}	4,57,63,73
Dermis	$CD4\text{-}αβ^+$ T	$CCR7^+$	$CD4\text{-}αβ^+$ T	$CCR7^+$ T_{MM}	56,57,73
Dermis	$CD4\text{-}αβ^+$ T	$CCR7^-$	$CD4\text{-}αβ^+$ T	$CCR7^-$ T_{RM}	56,57,73
Dermis	NA	NA	$CD4\text{-}αβ^+$ T	$CCR7^+CD62L^+$ T_{CM}	57,66
Dermis	$CD4\text{-}αβ^+$ T_{reg}	$FoxP3^+$	$CD4\text{-}αβ^+$ T_{reg}	$FoxP3^+$ T_{MM}	57,73,79,118

A comparison of the T cells that inhabit mouse and human skin. Some but not all of these T cells in this barrier tissue are authentic T_{RM} cells. NA, not available or not evaluated yet.

Maintaining T_{RM} cells in tissues. The molecular factors that maintain T_{RM} cells in their resident tissue are not completely understood, but IL-15, TGF-β, tumor necrosis factor–α (TNF-α) and IL-33 have all been implicated[6,53]. TGF-β, TNF-α and IL-33 have all been shown to have a role in the induction of CD103 expression and acquisition of a T_{RM} cell phenotype. Factors that induce upregulation of CD69 expression include TNF-α and type I interferons[50,67]. The aryl hydrocarbon receptor is important for the maintenance of γδ T cells in mouse skin[68], and a recent report suggests that it is important for the generation of $αβ\text{-}TCR^+CD8^+$ T_{RM} cells[69]. A recently described additional common activity of $CD8^+$ T_{RM} cells is highlighted by several recent papers. One of the first cytokines made by virally induced $CD8^+$ T_{RM} cells upon antigen reactivation is IFN-γ. In both skin and reproductive mucosa, the IFN-γ released by activated T_{RM} cells creates a generalized antiviral microenvironment in tissue by upregulating a series of antiviral and antimicrobial genes in surrounding keratinocytes, enhancing the expression of vascular adhesion molecule in endothelium and activating other resident cells, including natural killer (NK) cells and dendritic cells[70,71]. In this fashion, activated T_{RM} cells can amplify and activate the innate immune system, creating an environment inhospitable to even completely unrelated viruses and other pathogens.

Properties of T_{RM} cells in distinct barrier tissues

Skin T_{RM} cells. In 2006, it was reported that normal resting human skin contains twice as many T cells as blood does[5,72,73], and it is now appreciated that most but not all of these cells are T_{RM} cells[57] (**Table 1**). Thus, memory T cells generated in response to previous pathogen exposure in the cutaneous environment are present in abundance in the skin, allowing for immediate response to pathogenic invasion[5]. These cells have a diverse TCR repertoire and can be activated by pathogens at a much lower threshold than circulating T cells via TCRs[72]. Moreover, they are heterogeneous: they include $CD4^+$ and $CD8^+$ T cells that produce IL-17, IFN-γ, TNF-α, IL-9, IL-13 and other cytokines, alone or in combination[5,32,72–76].

Mouse models have been instrumental in furthering our understanding of skin T_{RM} cells. Early studies showed that in mice transfused with HSV peptide–specific transgenic T cells and then infected with HSV, the transgenic $CD8^+$ T cells could be transferred from one mouse to another by a previously infected skin graft, and these transferred HSV-specific T_{RM} cells maintained their ability to clear virus upon challenge[63]. In another study it was shown that vaccinia virus (VACV) administration by skin scarification was far superior to other routes of immunization in generating skin-resident $CD8^+$ T_{RM} cells[77]. The same investigators showed that skin T_{RM} cells, in the absence of circulating T cells and antibody, can clear virus on re-challenge to skin. Furthermore, infection by skin scarification leads to the generation of lung T_{RM} cells that, in the complete absence of circulating antibodies and circulating T cells, can partially protect immunized mice from a lethal pulmonary challenge with VACV[77]. Thus, skin immunization can lead to widespread T_{RM} cells throughout the skin as well as in distant barrier tissues. This occurs not only at the site of infection but also at distant sites, and the number of accumulated $CD8^+$ T_{RM} cells throughout the skin increases after multiple infections at distinct sites[4]. However, $CD8^+$ T_{RM} cells do not recirculate, and mice that contain T_{CM} cells but lack T_{RM} cells cannot effectively clear VACV from skin, in contrast to mice that have immune skin T_{RM} cells[4]. Another study showed that after HSV challenge in mice, HSV-specific $CD8^+$ T_{RM} cells migrate to the epidermis and acquire a sessile phenotype, whereas HSV-specific $CD4^+$ T_{RM} cells localize to the dermis and show greater mobility[65].

Interestingly, the transcriptomes of T_{RM} cells from skin, lung and gut have common core features in mice[6]. A study showed that localization of $CD8^+$ T_{RM} cells in the epidermis and CD103 expression on T_{RM} cells were induced in the epidermis by TGF-β, and these $CD8^+$ T_{RM} cells homed to epidermis via a chemokine-mediated process[6]. Mouse $CD8^+$ T_{RM} cells were also shown to occupy epidermal niches formerly filled by a population of T cells that seed the epidermis before birth—γδ dendritic epidermal T cells (DETCs)—and when viewed by intravital microscopy these cells were found to move laterally between keratinocytes, unlike sessile γδ DETCs. These $CD8^+$ T_{RM} cells interacted transiently with Langerhans cells, suggesting that they were scanning the environment for antigen[69]. In humans, there are two isoforms of the dimeric CD8 molecule on T cells, composed of αβ and αα chains, respectively. After cutaneous HSV infection, $CD8\text{-}αα^+$ T_{RM} cells localize at the dermal epidermal junction. These cells, but not $CD8\text{-}αβ^+$ T cells, protect against the reactivation of HSV and lesion formation[78].

Somewhat less is known about $CD4^+$ skin T_{RM} cells in mice than about $CD8^+$ skin T_{RM} cells. It has been shown, however, that $CD4^+$ regulatory T (T_{reg}) cells are a major population of T cells emigrating from skin to lymph node after an immune response to contact hypersensitivity, as well as in the absence of stimulus[79]. Another group characterized $CD4^+$ T cells in mouse skin and demonstrated at least two populations, including one that did not leave skin (lacking CCR7 expression) and another that left skin by a CCR7-dependent mechanism, expressed low levels of CD62L and high levels of E-selectin

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ligand and was negative for CD69 expression[56]. This is consistent with a very recently published study of T cells in human skin[57].

T_{RM} cells in the GI tract. T_{RM} cells in gut are defined here as T cells that reside in the intestinal epithelium or in lamina propria[80]. It has been shown that a subset of $CD103^+$ dendritic cells in gut-draining lymph node can skew naive T cells toward differentiation into $\alpha_4\beta_7^+$ gut-homing memory T cells, primarily under the influence of retinoic acid secreted by these dendritic cells[81]. Gut-infiltrating T cells have been most exhaustively studied in mice during disease states, such as experimentally induced colitis, in which mice lacking CD103 have attenuated inflammation, suggesting a role for T_{RM} cells in inflammation. Until recently[48,70], less attention had been paid to T_{RM} cells that emerged after pathogen infection. Several pathogens, including lymphocytic choriomeningitis virus (LCMV), *Listeria* and others, have been shown to induce the generation of long-lived intraepithelial T cells with potent effector activities in mice[42]. Although many of these pathogens were delivered intravenously in past experiments, in a recent study mice were infected orally with *Listeria*, and the authors acquired information on gut T_{RM} cells[48]. The study showed that long-lived gut T_{RM} cells expressed KLRG-1 at low levels (similar to skin T_{RM} cells), whereas cells with high expression of KLRG-1 (as in T_{EM} cells) that entered gut underwent apoptosis. The oral immunization induced abundant long-lived gut T_{RM} cells, unlike nasal immunization, which induced gut entry by T cells with high KLRG-1 expression that did not persist long term. Gut $CD8^+$ T_{RM} cells express CD69 and CD103, as do mouse skin T_{RM} cells, and their maintenance in the gut is enhanced by TGF-β (ref. 80). When transcriptional profiles of skin T_{RM} cells generated in response to HSV infection were compared to those of gut T_{RM} cells induced by an LCMV infection[6], of 127 genes up- or downregulated in T_{RM} cells relative to expression in T_{CM} cells, 68 showed a pattern common to skin and gut, and the remainder were unique to gut (or possibly to the difference between LCMV and HSV infection)[6]. Thus, the T_{RM} cells that form in gut epithelium and lamina propria have many features in common with T_{RM} cells in other barrier tissues, although they also express gut-specific homing molecules.

Regarding what is known about gut T_{RM} cells in humans, a recent study that surveyed resident T cell populations in various human tissues demonstrated the presence of T_{RM} cells in both colon and small intestine[82]. We have further analyzed human GI tissue by deep sequencing of TCRB and identified a highly diverse T cell repertoire in normal non-inflamed tissue (R.A. Clark *et al.*, data not shown). Liver T_{RM} cells have been demonstrated after malaria infection[83], and the T cells that infiltrate the liver during viral hepatitis are likely to become tissue resident as well, causing significant and recurrent tissue injury in the absence of effective therapy[84].

T_{RM} cells in lung and respiratory tissue. The possibility that T_{RM} cells might exist in lung was first considered after the identification of $CD69^+CD8^+$ T_{RM} cells that remained in lung after influenza infection[28]. The original explanation for the expression of CD69 by these cells was that the cells were in an activated state, perhaps as a result of retained antigen; however, we now know that CD69 expression is a generic characteristic of resting T_{RM} cells[29]. There is good evidence that $CD8^+$ T_{RM} cells can be protective against subsequent infection with influenza. Intranasal but not intraperitoneal infection with influenza in mice results in the presence of lung T_{RM} cells, although both routes of infection efficiently produce influenza-specific splenic T_{EM} cells[30]. Furthermore, in the referenced study, the nasal influenza–immunized mice, but not the intraperitoneally immunized mice, were protected against a lethal intranasal challenge with influenza. This echoes work in skin showing that resident, but not circulating, memory T cells are most effective at limiting viral replication at the site of viral entry[4]. However, in this lung-infection study, the T_{RM} cells had essentially vanished from lung 90 d after a single influenza infection. Whether they could be made more abundant at this late stage via boosting strategies such as additional antigen challenge was not explored.

The anatomic location in lung where T_{RM} cells need to reside in order to be most protective against a flu challenge is also controversial; it is clear that lung T_{RM} cells express CD103, and its epithelial ligand, E-cadherin, is expressed most strongly on large and intermediate bronchial epithelial cells and less strongly on small or alveolar epithelia[85]. However, as discussed above, $CD103^+$ cells can persist at a distance from cells expressing E-cadherin. Regarding the levels of $CD4^+$ T cells versus those of $CD8^+$ T cells, TGF-β promotes the development of lung $CD103^+CD8^+$ T_{RM} cells, but in a fashion not dependent on Smad4 (ref. 86). $CD4^+$ T cells in lung aid in the development of $CD103^+CD8^+$ T_{RM} cells after influenza virus infection[40], but the respective roles of $CD4^+$ and $CD8^+$ T cells, and whether (as in skin) these two populations have different migratory capacities, have not been explored.

There is a growing body of evidence that points to the existence of T_{RM} cells in normal human lung. T cells have been observed in bronchoalveolar lavage samples, but these are typically acquired in the setting of diseased lung, and thus it is not known whether the cells noted are authentic T_{RM} cells. After pneumonectomy for isolated tumors, human lung tissue very distal to the tumors is histologically normal in appearance[87], and T cells isolated from such lung samples include $CD4^+$ and $CD8^+$ cells that produce TNF-α and IFN-γ (ref. 87), express CD69 and have a diverse TCR repertoire; from these data it was estimated that the number of T_{RM} cells in lung approximates the number of T cells in blood—on the order of 10 billion cells. Moreover, these populations of T cells are enriched in the cells that proliferate in response to inactivated influenza virus[87]. Lung T_{RM} cells express abundant $\alpha_1\beta_1$, although this is expressed in other tissues and is thus not lung specific[87]. $CD8^+CD103^+$ T cells in human lung are specific for influenza, as opposed to $CD8^+CD103^-$ T cells, which are also found in that tissue[59]. T_{RM} cells in human lung were also found in a large survey study that looked at multiple human tissues[82].

T_{RM} cells in the genitourinary tract. The mucosa of the female reproductive tract is an important barrier tissue. In mouse vaginal HSV infection, $CD4^+$ T cells must first enter the tissue and provide a recruiting cytokine and chemokine signal to facilitate the entry of $CD8^+$ T cells into infected vaginal mucosa[34]. This is different from the process in skin, in which CD4 help is not required to recruit antigen-specific $CD8^+$ T cells after VACV infection[4]. Protective immunity against HSV can also be generated by direct topical infection of the vaginal mucosa followed by the accumulation of T_{RM} cells[35], which suggests that the generation of T_{RM} cells should be a goal of vaccination[88]. Independently performed studies comparing HSV-infected skin and mucosa have yielded analogous results[36]. Approaches such as these are likely to be used in attempts to generate a protective vaccine against HSV-2. Very recently, it was shown that a local chemokine gradient maintained HSV-specific $CD4^+$ T_{RM} cells *in situ*, a previously unrecognized mechanism for the maintenance of T_{RM} cell residence[89]. Furthermore, it was recently shown that intravaginal administration of the human papillomavirus (HPV) vaccine in mice led to the generation of $CD8^+$ T_{RM} cells in vaginal mucosa[90,91]. This work is very promising, as not only HSV and HPV but also HIV can infect through this route, and the possibility of rapidly killing virally

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Box 1 T_{RM} cells and vaccination

The observation that pathogenic virus can be rapidly eliminated by T_{RM} cells in animal models, even in the absence of antibody, has led to a burgeoning interest in the induction of T_{RM} cells as a goal of vaccination[4,77]. Viruses show tissue tropism, with influenza specific for lung, rotavirus specific for gut and HSV specific for skin and other stratified squamous epithelia. T_{RM} cell–based vaccination would direct pathogen-specific T_{RM} cells to the relevant epithelial tissue[88]. Currently, the titer of neutralizing antibodies generated by a vaccine is considered a proxy for its efficacy. But for viruses invading barrier tissues, the process of infection of a resident cell and subsequent hijacking of the cell's program to make more virus is largely insensitive to extracellular antibody. In contrast, such infected cells express viral peptides on cell-surface class I molecules, making them ready targets for $CD8^+$ T_{RM} cells. Vaccination at epithelial surfaces, rather than intramuscularly, is thus a more effective way to generate robust T_{RM} cells[30,48,77,91]. Promising approaches in lung for influenza and in other mucosal tissues have been reported recently[39,40].

As proof of principle, in animal models, vaccinia virus (VACV) immunization of skin and lung, influenza infection of lung and *Listeria* immunization through oral administration have all led to the generation of highly effective tissue-resident T_{RM} cells. A recent HIV vaccine engineered to generate T_{EM} cells showed great promise, and although the investigators focused on blood, they did find memory T cells in mucosal tissue[119]. The wisdom of generating lung T_{RM} cells specific for conserved portions of the influenza virus or anogenital mucosal T_{RM} cells specific for conserved portions of HIV is clear. Virally infected cells could be targeted by T_{RM} cells for elimination shortly after exposure. The challenge with this approach to vaccination is at the level of practicality—how to immunize through an accessible tissue (such as skin) and generate T_{RM} cells in other distant barrier tissues that are specific to the infectious virus. One of several promising approaches involves using VACV vectors delivered via skin scarification; this has been shown to trigger the generation of protective lung T_{RM} cells in one model[77]. Also, because skin immunization in general generates both skin T_{RM} cells and a TCR-identical population of T_{CM} cells in lymph node[38], sequential skin and peripheral tissue immunization (to convert the T_{CM} cells into tissue-relevant T_{RM} cells) is a possible approach. Although most work on T_{RM} cells has been done in the setting of viral infection, this approach should be applicable to other tissue-selective pathogens. *Mycobacterium tuberculosis*, *Listeria*, *Vibrio cholerae* and *Mycobacterium leprae* are all candidate pathogens. What remains to be understood is what collection of factors in regional lymph nodes govern the acquisition of tissue-homing markers on effector T cells and how to ensure that these T cells that enter tissue remain as long-lived T_{RM} cells, poised to respond to pathogens through the appropriate environmental interface[88].

infected cells with T_{RM} cells *in situ*, however they are generated, is appealing (**Box 1**)[88]. More recently, work on cervical tissue—normal, dysplastic and malignant—has demonstrated that vaccination against oncogenic papillomavirus leads to the generation of T_{RM} cells in these tissues that are highly protective against reinfection[92].

The role of T_{RM} cells in human disease

Pathologic T_{RM} cells in barrier tissues. The best-characterized role for T_{RM} cells in disease is in mediating skin diseases (**Fig. 2**), with fixed drug eruption being the first and best described[93]. Recently, established psoriasis has been shown to be mediated largely by T_{RM} cells. Transcriptomic analysis of resolved lesional psoriatic skin in humans has revealed the presence of T cells and cytokines thought to be important in pathogenesis, suggesting the persistence of these T_{RM} cells[94,95]. More recently, analysis of cells extracted from resolved psoriatic lesions showed $CD8^+$ T cells that produce IL-17 and $CD4^+$ T cells that produce IL-22, providing additional support for the role of T_{RM} cells in psoriasis[96]. A recent report showed that allergic contact dermatitis in both human and murine settings is also mediated by T_{RM} cells[38]. In psoriasis, the putative antigen is considered to be an autoantigen, whereas in allergic contact dermatitis it is often an innocuous environmental molecule[97], and in fixed drug eruption it is typically an orally ingested chemical. Recurrence of treated and resolved psoriasis lesions in the same place suggests that although the activity of disease-causing T_{RM} cells was suppressed by therapy, their localization was unaffected. Vitiligo, as well as some forms of atopic and eczematous dermatitis, may also be mediated by T_{RM} cells[5]; here the antigen is a melanocyte-specific antigen. Interestingly, a variant of cutaneous T cell lymphoma was found to be a malignancy of T_{RM} cells[98], and another variant (leukemic cutaneous T cell lymphoma or Sezary syndrome) is a malignancy of skin-homing T_{CM} cells[66,98] (**Box 2**).

The GI tract is another site where certain diseases exhibit the behavior of T_{RM} cell–mediated diseases (**Fig. 2**). The discrete waxing and waning skip lesions—areas of disease separated by areas of normal mucosa—in Crohn's disease suggest a role for T_{RM} cells, whereas ulcerative colitis involves a more contiguous circumferential area of the

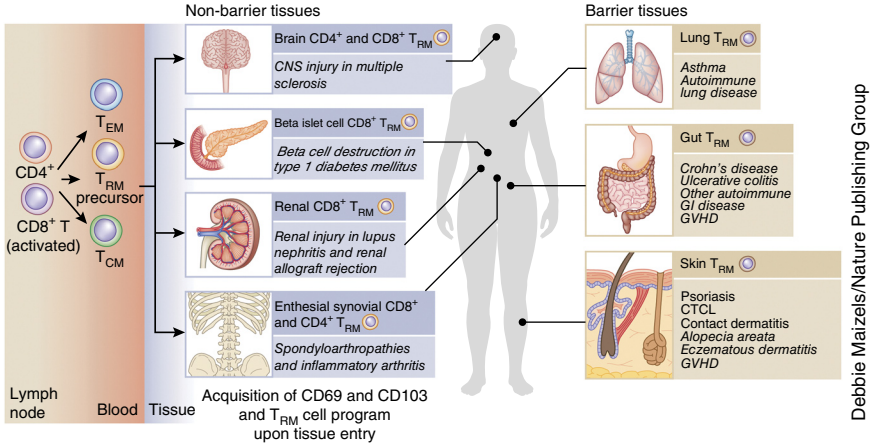

Figure 2 The role of T_{RM} cells in tissue-specific autoimmune and inflammatory disease. Right, diseases of lung, gut and skin clearly or potentially mediated by pathologically activated T_{RM} cells. Left, diseases of normally sterile non-barrier tissues mediated by infiltrating T cells that have acquired the properties of T_{RM} cells. Disease states in normal font indicate that there is experimental evidence supporting T_{RM} cell causation, whereas disease states in italic font are speculation on the part of the authors. GVHD, graft-versus-host disease.

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Box 2 Cancer and skin-resident T cells

Malignacies of T_{RM} cells. Cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of T cell malignancies[120]. Recent reports have supported the idea that one form of this disease, mycosis fungoides (MF), is a malignancy of $CD4^+$ T_{RM} cells from skin[66,98]. MF forms patches and plaques on the skin with well-demarcated borders and tends to recur in precisely the same locations after remission. It is responsive to skin-directed therapy in its early stages[120]. The malignant T cell does not express CD62L, is CLA^+CCR4^+ and often expresses CD69 (ref. 66). In advanced stages, T cells can travel to distant skin sites or to lymph node. It is not known whether this represents the acquisition of markers such as CCR7 (which facilitates exit from the skin) or a malignant dedifferentiation program that reduces skin tropism[121]. The other most common type of CTCL is leukemic CTCL, often called Sezary syndrome[98]. In patients with this disease, skin lesions are typically characterized by confluent erythema, also known as erythroderma, and lesions do not have well-defined borders. Malignant T cells are found in skin as well as blood, and sometimes lymph node. The malignant cells bear not only skin-homing markers (CLA, CCR4) but also T_{CM} cell markers (CD62L, CCR7) and have been shown to recirculate between skin and blood. The humanized antibody alemtuzumab depletes $CD52^+$ cells, including the malignant T cell clone, in blood, via a process largely mediated by neutrophil and NK antibody-dependent cell-mediated cytotoxicity[66]. However, even though alemtuzumab binds to T cells in skin, it does not deplete them, owing to an absence of antibody-dependent cell-mediated cytotoxicity effectors. Interestingly, alemtuzumab has absolutely no efficacy in MF, supporting the idea that MF T cells are T_{RM} cells and do not traffic into blood from skin[66]. The antibody has very high efficacy in leukemic CTCL, a malignancy of recently described skin-homing T_{CM} cells[57,121].

T_{RM} cells in solid tumors. We have proposed that T cells that enter any solid tissue acquire the T_{RM} cell phenotype, characterized by a unique transcriptional profile including expression of CD69 and CD103 (particularly on $CD8^+$ T cells) and downregulation of KLF-2 and S1P1. The infiltration of tumors, or peritumoral tissue, by T cells (so-called tumor-infiltrating lymphocytes, or TILs) is associated with a better long-term response[122]. One recent study suggested that such infiltration was predictive of the response to immunotherapy with antibodies to PD-1 (ref. 123). CD103 expression on T_{RM} cells in ovarian cancer is predictive of a more favorable prognosis[124], and analogous results were recently seen in lung cancer[125]. Thinking of T cells entering tumors or peritumoral tissue as having a T_{RM} cell phenotype may be a useful way of conceptualizing these cells. Expression of inhibitory molecules such as PD-L1 on tumor stroma or the production of other immunosuppressive factors will blunt the activity of these tumor-specific T_{RM} cells. However, work with antibodies to PD-1 and PD-L1 suggests that activating these T cells may be a highly effective means of activating immune-mediated tumor destruction[112,123]. Because tumors that contain TIL T_{RM} cells respond well to PD-1–blocking therapy, it is likely that it is important to generate *de novo* TILs in TIL-poor tumors. Even if these new TILs become suppressed in the tumor microenvironment, the patients may respond to PD-1–PD-L1 blockade.

large intestine[99]. It is unknown, however, whether immune-mediated diseases of the lung (e.g., asthma) involve T_{RM} cells (**Fig. 2**). There are no data that address this possibility, although the presence of T_{RM} cells in normal human lung makes the hypothesis a reasonable one. Certainly, the excessive inflammation in lung in the setting of fatal influenza infection may well involve hyperactive T_{RM} cells. Additionally, the fact that T cell–mediated diseases of the skin are mediated by T_{RM} cells, and the finding that these diseases can often be treated with skin-directed rather than systemic therapy, suggests that the approach of local rather than systemic treatment may apply to other tissues as well.

Pathologic T_{RM} cells in non-barrier tissues. It has been shown experimentally that T_{RM} cell accumulation can also occur in tissues generally considered sterile, such as the brain[7]. T_{RM} cells were identified in the brain after intranasal infection with vesicular stomatitis virus, and $CD103^+$ T_{RM} cells had a potent effector function after *in vitro* stimulation. The transcriptional profile of these brain $CD8^+$ T_{RM} cells resembled that of T_{RM} cells in skin, gut and lung[6,7]. Whether such T_{RM} cells can form in human brain after viral infection is unknown, and a putative role for these cells in diseases of the CNS requires additional evidence, although recent reports have linked putative pathogenic brain T_{RM} cells to multiple sclerosis (**Fig. 2**) and even schizophrenia[100,101]. Although T cell responses in non-barrier tissues may be necessary episodically to deal with a potentially lethal infection, the unintended consequence of such an event may be the generation of long-lived T_{RM} cells and the attendant predisposition to potential autoreactive and autoimmune diseases. One hypothesis is that the potential program for generating T_{RM} cells exists in all activated T cells, and a subset of those that gain entry into tissue (whether a barrier tissue or a normally sterile tissue) show activation of this T_{RM} cell program (**Fig. 2**).

Spondyloarthropathies such as human ankylosing spondylitis involve inflammation of entheseal tissues (sites of attachment of tendon to bone), and one recent study in mice demonstrated that entheseal resident T_H17 T_{RM} cells are essential for disease progression[102]. In human rheumatoid arthritis, the clinical recurrence of disease in individual joints bears the hallmarks of a T_{RM} cell–driven process, and a preliminary report describes the presence of T_{RM} cells in human joint synovium in rheumatoid arthritis[103]. It is thus likely that sterile chronic inflammation of peripheral tissues in human disease is mediated by these cells. For example, T cells from blood and kidney were examined in lupus nephritis, and a relatively limited set of T cell clones appeared to be responsible for progressive disease in individual patients, even over periods separated by months to years[104]. Although that study did not examine CD103 or CD69, it provides indirect proof of pathological renal T_{RM} cells (**Fig. 2**). In murine models of insulin-dependent diabetes mellitus and pancreatic islet beta cell rejection, infiltrating $CD8^+$ T cells acquire CD103 and remain in place during the immune response[105]. It is conceivable that in human type 1 diabetes mellitus, T cells that infiltrate pancreas and attack beta cells may take on the phenotype of T_{RM} cells (**Fig. 2**), favoring their long-term persistence *in situ*. In solid organ allograft rejection, infiltrating allogeneic T cells are able to acquire T_{RM} cell properties such as CD103 expression[106], and urinary CD103 is associated with acute graft rejection[107]. If these human diseases involve pathological T_{RM} cells, immunosuppressive regimens may suppress the activation of these cells but have no effect on their location and persistence, thereby setting the stage for recurrence and persistence of disease (**Fig. 2**).

Finally, there is evidence that some tissues of immune privilege, such as the eye, may have mechanisms to inactivate T_{RM} cells induced by inflammation[108] through expression of PD-L1 and promotion of T_{RM}

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cell PD-1 expression[109]. Through mechanisms that include PD-1–PD-LI interactions, cancer tissues can acquire similar immune privilege. Binding of T cell PD-1 to its natural ligand PD-L1 induces a state of T cell unresponsiveness. Tumor-infiltrating lymphocytes (TILs) by definition become 'resident' in neoplastic tissue. It is notable that TILs with surface markers of T_{RM} cells were found to be predictive of a more favorable prognosis in ovarian cancer[110]. The role of PD-1–PD-L1 interactions in suppressing the activity of TILs in malignant melanoma, and its reversal by therapeutic antibodies that block this interaction, is now well established[111,112].

Conclusions

In barrier tissues at interfaces with the environment, T_{RM} cells are an important part of adaptive immune memory, providing the capacity to rapidly address and clear tissue infections caused by previously encountered pathogens. When T_{RM} cells pathologically accumulate in barrier tissues in response to innocuous antigens, disease can result. The molecular program that facilitates the T_{RM} cell phenotype in barrier tissues can be activated in other tissues as well, where persistent immune-driven inflammation can cause chronic disease. Previously, when T cells were seen in pathologic infiltrates, it was assumed that this represented chronic and dynamic T cell infiltration, regardless of the tissue involved. It is more than a semantic difference to propose that these infiltrates in fact include resident populations of T cells in which a T_{RM} cell molecular program has been activated. If this is the case, therapies that suppress T cell function do not necessarily change T cell localization, and reactivated T_{RM} cells will mediate recurrent disease. Whether in CNS, joint, pancreas, kidney or heart, persistent and activated T_{RM} cells in sterile tissues (where they were not intended to be) may drive human autoimmune and inflammatory diseases. Therapies directed at selectively eliminating these T_{RM} cells, by depletion or through modification of the cells' ability to persistently reside in tissue, represent potential approaches to the treatment of such diseases.

It is worth noting that skin T_{RM} cells have been unknowingly targeted for decades, with relevant treatments far predating appreciation of these cells' existence. Skin-directed therapies, ranging from topical corticosteroids to UV-based phototherapy to low-dose radiation, have all led to the remission of what are now understood as T_{RM} cell–mediated diseases. Would gut mucosal–directed therapy via endoscope or synovial-directed therapy via arthroscope suppress T_{RM} cells in those tissues? The advantage of skin-targeted therapy is that repetitive therapy is straightforward and noninvasive, and the results can be assessed without sophisticated imaging techniques. Other approaches might be directed at features that maintain T_{RM} cells in tissue, namely, CD69 and CD103. Blocking or interfering with the function of these molecules might flush pathogenic T_{RM} cells out of tissues, although of course a balance would have to be struck in the depletion of pathogenic T_{RM} cells and physiologically protective normal T_{RM} cells. Finally, it was noted that T_{RM} cells in immune-privileged sites such as the eye express PD-1, and presumably remain quiescent in this fashion. We speculate that TILs are a form of T_{RM} cell and that the tumor may induce PD-1 expression on these tumor T_{RM} cells to suppress their activity. In tumor immunotherapy, the goal is to interfere with this immune suppression with antibodies that block PD-1–PD-L1 interactions. However, if this suppressive pathway exploited for immune privilege could be exploited in non-cancer diseases where unrestrained T_{RM} cell activity causes tissue inflammation and injury, yet another approach to suppressing disease-causing T_{RM} cells would exist. None of these approaches (save those long employed in skin) is more than hypothetical at present. However, what is clear is that although simply suppressing the activation of T_{RM} cells in psoriasis, inflammatory bowel disease or inflammatory arthritis may lead to transient clinical remission, disease recurrence is nearly inevitable if T_{RM} cells persist (as they are designed to do) in tissue. The next decade of T_{RM} cell biology will be devoted to modifying the cells' behavior and, perhaps, long-term residence and location.

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COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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