REVIEW

T-cell memory in tissues

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Immunological memory equips our immune system to respond faster and more effectively against reinfections. This acquired immunity was originally attributed to long-lived, memory T and B cells with body wide access to peripheral and secondary lymphoid tissues. In recent years, it has been realized that both innate and adaptive immunity to a large degree depends on resident immune cells that act locally in barrier tissues including tissue-resident memory T cells (Trm). Here, we will discuss the phenotype of these Trm in mice and humans, the tissues and niches that support them, and their function, plasticity, and transcriptional control. Their unique properties enable Trm to achieve long-lived immunological memory that can be deposited in nearly every organ in response to acute and persistent infection, and in response to cancer. However, Trm may also induce substantial immunopathology in allergic and autoimmune disease if their actions remain unchecked. Therefore, inhibitory and activating stimuli appear to balance the actions of Trm to ensure rapid proinflammatory responses upon infection and to prevent damage to host tissues under steady state conditions.

Keywords: Exhaustion · Hobit · Memory · Persistent infection · Tissue-resident memory T cells

Introduction to T-cell memory and duration of tissue-resident memory T cells

Immunological memory equips our immune system to respond faster and more effectively against reinfections. This memory was originally attributed to long-lived, memory T and B cells that are maintained in the blood and circulate through peripheral and secondary lymphoid tissues [1, 2]. In addition, the BM was identified early on as a niche for long-lived antibody-producing plasma cells and memory T cells [3]. In recent years, however, it has also become apparent that peripheral tissues themselves, including barrier sites like skin and intestinal mucosa, retain memory of immune responses. This memory seems to consist of at least two components, namely trained innate immunity and tissue resident adaptive immunity [4–8].

Trained immunity in tissues seems to be induced by microbe- or danger-associated molecular patterns (MAMPs or DAMPs) that are recognized by pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), but also altered-self recognition by innate lymphocytes [9–11]. These receptors induce altered epigenetic programming of innate myeloid and lymphoid cells as well as progenitor populations of somatic cells, like epithelial cells [4]. This epigenetic programming allows the respective innate leucocytes to respond more rapidly to reencounters of the same or closely related immunogenic stimuli including reinfection. Such innate protection often lasts for months and is mediated by...
were demonstrated to provide regional protection [25]. Both T- or B-cell receptors, have adaptive tissue-resident memory populations that are equipped with somatically recombined organisms [15]. In addition, vertebrates, with their lymphocyte populations, that are already in the tissue, or innate leucocytes, such as NK cells and monocytes, that acquire tissue residency during the primary immune response [12–14] (Fig. 1). This trained immunity seems to be also present in invertebrates and is possibly sufficient for the life-span of most of these organisms [15]. In addition, vertebrates, with their lymphocyte populations that are equipped with somatically recombined T- or B-cell receptors, have adaptive tissue-resident memory (Trm) cell populations that are maintained for years [16–21] (Fig. 1).

Mouse Trm CD8$^+$ T cells were initially described in the skin after HSV and in the small intestine after lymphocytic choriomeningitis virus (LCMV) infection [22–24]. In addition, tissue-resident CD4$^+$ T cells in lungs of influenza virus-infected mice were demonstrated to provide regional protection [25]. Both CD4$^+$ and CD8$^+$ Trm have been subsequently characterized in most mucosal tissues, including skin, salivary gland, lungs, gut and female reproductive tract, as well as in several nonbarrier tissues including brain, liver, pancreas, heart, and kidneys [6, 26].

Trm have further been described in lymphoid tissues, including thymus, spleen, LNs [27–30], and BM [31, 32], of both mice and men.

The defining feature of Trm is their commitment to a particular tissue and lack of circulation under "steady state" conditions. This has been elegantly assessed in animal studies in several ways including transplantation [22, 24, 33], parabiosis [25, 34, 35], T-cell depletion [36, 37], use of lymphocyte trafficking inhibitors (FTY720, pertussis toxin, and anti-CXCR3 antibodies) [33, 35, 38], and intravascular labeling [38–40]. In humans, persistence of donor Trm after transplantation [41–43] strongly suggests a similar propensity for these cells to remain within their tissue environments. In this review, we will discuss the phenotype of these Trm, the tissues and their niches that support them, their function, plasticity, and transcriptional control. These factors determine the T-cell mediated long-lived immunological memory that can be deposited in nearly every organ in response to infection, cancer, allergy, and autoimmunity.

Trm phenotype and heterogeneity

Mouse Trm have been described as having a phenotype, similar to effector memory T cells (Tem) (CD62L$^-$/CCR7$^-$ and CD44$^+$ in mice [22, 25, 38] or CD45RO$^+$/CD45RA$^-$ in humans [44–46]). They are distinct, however, in their continued expression of the early-activation marker CD69, even at prolonged periods postinfection [35, 47]. Animal studies utilizing parabiosis and intravascular labeling techniques demonstrated that the vast majority, but not all memory T cells, retained in tissues expressed CD69 [34, 38, 39]. In humans, CD69$^+$ memory T cells from various tissues demonstrated a conserved transcriptional profile similar to that observed in Trm from mice and distinct from that observed in memory T-cell subsets in peripheral blood [45, 47]. A key function of CD69 is its ability to mediate T-cell tissue retention; this occurs both in the LNs during initial T-cell activation, and, it is thought, later in the tissue of residence [48–50]. Additional studies in mice identified CD103 as a phenotypic marker of CD8$^+$ and some CD4$^+$ Trm [22, 51–53], which was also observed in studies of human tissues [45, 47, 54, 55]. CD103 (a subunit of the $\alpha_5\beta_7$ integrin) binds to E-Cadherin, which is commonly expressed by epithelial cells, and is thus, thought to play a role in retaining Trm within the epithelium. It has also become clear that Trm express elevated levels of inhibitory receptors, such as CD101, PD-1, CTLA-4, LAG-3, and TIM-3, which may modulate their function in the absence of inflammation or in sensitive tissues [45, 47, 54, 55].

Identification of Trm, however, is complicated by the fact that no single phenotypic marker, or even set of markers, appears to be exclusive to this subset. While CD69 and CD103 continue to be the most commonly used markers to identify both mouse and human CD4$^+$ and CD8$^+$ Trm, several studies have demonstrated that exceptions to this "rule" exist. CD69 expression is dispensable for Trm generation and long-term maintenance in some tissues [56–59]. Similarly, CD103 is not always present or required for Trm generation – particularly for CD4$^+$ Trm and for CD8$^+$ Trm in nonmucosal tissues [16, 60, 61], though it does seem to be necessary for long-term maintenance in the nonmucosal tissues [16–21].

Work in mouse models, corroborated by studies of human tissues, suggests that Trm from different organs generally express adhesion and cell-trafficking molecules in a tissue-specific manner. Indeed, CD103 mediates epithelial localization and retention in the majority of Trm in the skin, salivary glands, lungs, and gut [21, 46, 47, 62], but not necessarily on all Trm in nonbarrier tissues such as the BM [31, 32], LN [28, 45], liver [54, 63], and kidney [64]. In other tissues, including the skin, lungs, and...
As mentioned, Trm are defined by their maintenance in tissues with minimal “steady state” recirculation in blood and lymph vessels. These migratory properties have primarily been investigated in mouse models. Trm accumulation in the skin seems to be dependent on the chemokine receptors CXCR3, CXCR6, and CCR10 [84]. These chemokine receptors allow Tcm to migrate to inflamed tissues. In contrast, Trm in secondary lymphoid organs carry CXCR5 and CXCR4 [29] that are associated with GC homing. Once localized in tissues, residency by T cells seems to require anchoring, downregulation of receptors that would allow them to leave, and cytokine support and metabolic adaptation for long-term persistence. TGF-β has an essential role in long-term residency in skin and intestine [56, 85, 86]. TGF-β is activated by the αvβ6 integrin after secretion [87]. Deficiency of αvβ6 and αvβ8 integrins on keratinocytes compromised this activation in the skin and decreased tissue residence of Trm and recirculating memory T cells [88, 89]. Activated TGF-β upregulates CD103, which binds to E-cadherin, anchoring Trm in epithelia. In the lungs CD103+ DCs are the source of TGF-β for Trm induction [90]. The other characteristic T-cell residency marker CD69 targets sphingosine-1-phosphate receptor (SIPPR) for degradation, preventing Trm from sensing sphingosine-1-phosphate and egressing from tissues to the blood stream. In order to be maintained in the tissue Trm rely on the survival cytokines IL-7 and IL-15 [61, 91, 92]. These cytokines are produced by hair follicles in the skin, triggering clusters of Trm cells around them [91]. IL-15 is also transpresented by myeloid cells [93] and macrophages to support Trm motility and maintenance in salivary glands [94]. Furthermore, migratory DCs also activate TGF-β to predispose CD8+ T cells in LNs for skin retention [95]. In addition to DC and macrophage-mediated support for Trm cells, helper CD4+ T cells can essentially contribute to the maintenance of CD8+ Trm cells. Tissue-resident follicular helper T cell-like CD4+ T cells have been reported to support CD8+ Trm and B cells in lungs via IL-21 [96, 97]. Thus, APCs and Trm seem to cooperate in clusters to maintain regional immune memory. Trm have also shown metabolic adaptations dependent upon the tissue microenvironment. In the skin, Trm highly utilize oxidative phosphorylation, taking up fatty acids from their local environment to fuel this metabolic pathway and express fatty acid binding proteins in a tissue-specific manner [98, 99]. The magnitude of tissue-resident memory in nonlymphoid tissues and secondary lymphoid tissue might be determined by a limited number of viable niches, sites of tissue regeneration, or expanding secondary and tertiary lymphoid structures to accommodate Trm expansion. Along these lines, it has been shown that multiple waves of migratory Trm can be accommodated in the skin and BM [31, 55], even so they compete with recirculating T cells for activated TGF-β in the skin [86]. Furthermore, Trm also accumulate in secondary lymphoid organs of mice and humans over their lifetime [21, 100]. Additionally, Trm cells can replace innate lymphocytes from their niches in epithelia of the skin and mucosa [101, 102] or utilize sites of lung tissue regeneration [57]. Thus, as a whole the T-cell memory pool is most likely an expanding cellular compartment that accumulates over an individual’s lifetime for rapid defense against antigen re-encounters such as reinfection.
Trm function and plasticity

A key aspect of Trm function is their localization to sites of previous infection, where they are poised to rapidly respond to pathogen reencounter. Much work has demonstrated that both mouse and human Trm proliferate upon reactivation [55, 103] and release effector cytokines and cytotoxic mediators including IFN-γ, TNF-α, perforin, and granzyme B [25, 66, 104, 105]. Mouse models have demonstrated that these effectors have direct cytotoxic functions, and further serve to recruit additional immune cells (including DCs, macrophages, NK cells, and circulating T cells) and broadly enhance tissue-wide immunity [106, 107]. Interestingly, it has recently been observed in a mouse model that lung Trm can be reactivated by numerous antigen-presenting partners, and that the quality of functional responses depends on the identity of the APCs, with hematopoietic APCs inducing more limited inflammatory responses compared to non-hematopoietic counterparts [108]. While it was initially thought that Trm exerted their effector roles entirely “in situ,” more recent work in mice suggests that a proportion of Trm, upon restimulation, may reenter the circulation and migrate to the draining LNs, where they resettle as a LN-resident Trm population [109–112].

In fact, it has come to be appreciated that reactivated Trm retain a considerable degree of developmental plasticity. Trm not only have the ability to form secondary Trm in their local environment and in the draining LNs, they also retain the potential to form a secondary wave of circulating memory T cells [30, 109]. In particular, Tem and, to a lesser extent, central memory T cells develop downstream of reactivated Trm [30, 109]. Although the potential of Trm to generate secondary immune responses does not match that of central memory T cells (Tcm), Trm substantially contribute to the next generation of memory T cells [30]. The Trm-driven reformation of Trm appears highly relevant, given that Tcm cells appear to have limited capacity to form Trm at mucosal sites such as the skin and the small intestine [30, 95, 113, 114]. In particular, Tcm appear to be compromised in their ability to form CD103+ Trm [30, 115] suggesting that the reformation of CD103+ Trm requires a substantial contribution from Trm themselves. In this manner, Trm may imprint tissue-specific properties in secondary memory T cells in the circulation such as the ability to relocate to their tissue of origin. However, it is important to note that the protective role of Trm in these situations has not yet been completely elucidated.

Trm in persistent antigen environments

Much of our understanding of the phenotype, function, and plasticity of Trm has been elucidated predominantly in the context of infectious disease, and even more narrowly, for acute viral infections. Roles for Trm in cases where infection (antigen) and inflammatory signaling do not resolve, such as persistent infection, autoimmunity, transplantation, and cancer, are less clear.

Persistent infections with latency

Persistent infections are defined by prolonged presence (even lifelong) of a pathogen within the body. In infections, such as caused by HSV-1 and -2, CMV, and EBV, causative pathogens may enter periods of semiquiescence referred to as latency. While latency makes it nearly impossible for the immune system to detect and eliminate infected cells (thus preventing the infection from being resolved), cell-mediated immune responses are thought to be necessary to control episodes of viral reactivation. Studies have suggested that Trm are particularly important in this process. Mouse and human studies have revealed that virus-specific Trm can be found in affected tissues (i.e. the skin, female reproductive tract, and sensory ganglia in HSV-1 and -2 [17, 18, 22, 55, 116–118], the salivary glands in CMV [76, 119], and the tonsils in EBV [120–122]. Importantly, these Trm are highly functional, and, it has been suggested in HSV and CMV infection, that they play critical roles in controlling episodes of viral reactivation and limiting disease severity. Significantly, these findings suggest that, in the context of latent infections, Trm may have both therapeutic and preventive potential, not only controlling viral reactivation, but perhaps also preventing or substantially limiting initial infection [18]. This has the potential to be especially valuable in the context of EBV, which is an oncogenic virus and can drive the formation of B cell-derived lymphomas, T-cell lymphomas, and nasopharyngeal cancer (reviewed in [123]). Whether virus-specific Trm can limit tumorigenesis in the context of infection, however, is not yet clear.

Persistent infections without latency

Another important distinction can be made for persistent infections which do not enter latency and where antigen continues to be present. CD69-expressing T cells have been described in the context of chronic infections, including hepatitis B and C virus (HBV, HCV) and HIV in human patients. A recent study of chronic versus acute LCMV infection utilizing parabiotic mice further established that CD69 expressing cells in chronic infection do not migrate substantially, whereas memory T cells generated in acute infection equilibrate between mice, suggesting that the CD69+ cells in chronic infection establish residency [124].

The immune response to such chronic infections, however, is a continuous effort. A substantial body of work has shown that repeated antigenic stimulation of T cells leads to induced hyporesponsiveness known as T-cell exhaustion, with exhausted T cells expressing increased levels of coinhibitory markers, such as PD-1, CTLA-4, TIM-3, and LAG-3, among others. Whether CD69-expressing cells generated in the context of continued antigen exposure are truly “Trm” and how such continued antigen exposure impacts the function of these “Trm” in this context is not yet clear. Interestingly, Trm in both acute infections, as well as those described in latent and chronic persistent infections, have been shown to express canonical exhaustion markers in the steady state, and during infection. While expression of these
inhibitory receptors likely serves to modulate activation and functional capacities or to prevent immunopathology, it does not, however, seem to interfere with their function. Trm described in HBV, HCV, and varicella zoster virus infections express high levels of the exhaustion markers PD-1 and/or CD39, but remain capable of producing IFN-γ, TNF-α, and granzyme B [54, 125, 126] (Fig. 2). Similarly, a recent study comparing HBV-associated and non-viral hepatocellular carcinomas revealed that a Trm signature correlated with improved prognosis [127]. Similarly, in HIV patients, increased functional and polyfunctional Trm (including those producing IFN-γ, TNF-α, and CD107a) correlate with better control of infection [28, 128, 129].

These findings suggest a protective role for Trm, also in the context of chronic infection. However, a key point is that the immune system, even with such Trm, ultimately remains unable to clear infection. Furthermore, whether continued, high functionality among Trm in this context might eventually contribute to immunopathology, such as cirrhosis and hepatocellular carcinoma during HBV and HCV infections, remains unclear. Recent work in a mouse model of influenza (although not a persistent infection), demonstrated enhanced accumulation of lung Trm with age [130], which, in turn, drove persisting immunopathology and fibrosis, likely through continued recruitment of monocytes and neutrophils. Importantly, such findings suggest an underappreciated potentially pathological role for this subset in such contexts.

Allergy and autoimmunity

It is further understood that Trm have an overt pathological role in some cases. Indeed, CD4+ Th2-type lung Trm that trigger significant immunopathology have been described in mouse studies of allergic asthma [36, 131]. The acute hypersensitivity reaction of contact dermatitis has also been shown to be mediated by CD4+ (Th-2 and Th17 cytokine-producing) and CD8+ Trm [132–135]. Interestingly, these Trm express the inhibitory receptors PD-1 and TIM-3, as described in acute and persistent infection. However, inhibitory receptor blockade in this setting actually exacerbated disease severity [132, 133], indicating a role in preventing excessive activation by Trm. In addition to roles in allergy, Trm have been described in the pathology of multiple autoimmune diseases (Fig. 2). Both psoriasis and vitiligo have been shown to be mediated by IL-17 and IL-23 (psoriasis) and perforin and Granzyme B-producing Trm (vitiligo) in the skin [66, 136–140]. Trm in additional tissues, including the intestinal tract, pancreas, joints, and brain, have been further implicated in the pathogenesis of inflammatory bowel disease [141–145], type 1 diabetes [146], rheumatoid disease [147–151], and MS [152–154], respectively. Significantly, in situations where Trm play a pathogenic role, their localization and long-lived nature are deleterious. Although not fully elucidated, Trm rely on multiple cytokines and chemokines for their development, survival, and activation and appear to have unique metabolic requirements. Therapeutic strategies for Trm-mediated diseases could potentially specifically target such pathways.

Transplantation

In solid organ transplantation, studies have demonstrated that donor-derived tissue lymphocytes are transferred within the graft and that these cells can remain within their tissue of origin for prolonged periods [41, 42, 155]. In the absence of rejection, donor-derived Trm persisted and even expanded within the graft. The persistence of donor-derived Trm in lung transplants has been associated with reduced incidence of rejection [42, 156]. However, whether Trm always play a protective role is unclear (Fig. 2). Donor-derived Trm have been associated with both protective effects and graft-versus-host disease (GvHD) in intestinal transplants [43, 157] and studies of facial, skin, and renal transplantation have suggested that they may contribute to pathology [158–162]. Following hematopoietic cell transplantation in macaques, donor CD8+ T cells trafficking to the gastrointestinal tract were able to establish a Trm phenotype and acted as drivers of acute GvHD [163]. Additional work will be necessary to clarify the role of Trm in this context, in particular, it will be essential to define which donor cells are protective (pathogen-specific, for example) versus pathogenic (alloreactive). Such work could potentially have important implications in improving transplantation outcomes.

Cancer

Due to their functionality, Trm are considered as promising targets in fighting cancer. The capacity of Trm to protect against tumor growth has now been shown in numerous settings. Multiple patient studies have demonstrated that increased numbers of Trm-like tumor-infiltrating lymphocytes (TILs) correlate with improved survival in several different cancers and Trm-like TILs expressing higher levels of effector molecules were associated with better disease prognosis [164–170]. Similar to Trm in persistent infections, Trm-like TILs have repeatedly been observed to express high levels of immune checkpoint molecules while maintaining high-level production of cytotoxic molecules and effector cytokines [80, 166, 168, 171–173]. Interestingly, in a study of melanoma patients undergoing anti-PD-1 therapy, Trm-like TILs were expanded and Trm number correlated with improved survival [174]. Therefore, Trm may be one of the major targets for immune checkpoint inhibitors during cancer therapy (Fig. 2). A better understanding of how the protective capacities and functional roles for Trm differ in these various settings is essential for our ability to harness the therapeutic capacities of this subset.

Transcriptional control of Trm cells

The differentiation, commitment, maintenance, tissue retention, and effector functions of Trm are under the control of a network of transcription factors that, through the regulation of gene expression, organize all of these aspects of Trm. In this section, we will discuss how transcription factors induce gene programs resulting in the unique characteristics of Trm.
Figure 2. Trm function in different disease settings. Differences in Trm function during acute and persistent infections, cancer, organ transplantation, and allergy/autoimmunity. During acute infection, established Trm are thought to proliferate robustly following restimulation, as well as to produce effector cytokines such as IFN-γ and TNF-α. Increased Trm numbers are associated with reduced disease upon subsequent pathogen reencounter. Their function is balanced by appropriate levels of inhibitory receptor expression. In persistent infections (latent/chronic), Trm are thought to proliferate and produce cytokines similar to acute infection. They are also thought to play critical roles in controlling viral reactivation. However, whether repeated stimulation can eventually contribute to immunopathology, and the role of checkpoint inhibitor expression in controlling this, remains unclear. In cancer, Trm have been shown to produce effector cytokines as in acute infection. Increased numbers of Trm (or TILs) are associated with improved survival/outcomes in patients. Such Trm express high levels of inhibitory receptors and function is possibly improved by checkpoint inhibitor blockade. Roles for Trm in transplantation are less clear. Donor Trm have been shown to persist long term within grafts. However, they have been both positively and negatively associated with rejection, possibly suggesting site-specific roles for Trm in this setting. Levels of cytokine expression and how this is balanced by inhibitory molecules is not yet clear. In the context of allergy/autoimmunity, Trm are overtly pathogenic. Increased numbers are associated with exacerbated disease, suggesting that the expressed inhibitory receptors are insufficient to appropriately control function and immune checkpoint blockade may further enhance disease.
Trm differentiation

Similar to circulating memory T cells, Trm develop from naïve T cells after triggering by pathogen-derived antigens in the LNs. The transition of naïve T cells into Trm is accompanied by the downregulation of essential features of naïve T cells such as their stemness, their expansion, and multipotent potential, and their LN homing capacity. Transcription factors that support these processes, such as TCF-1 and KLF-2, are strongly downregulated in Trm, but not in Tcm that retain many of the properties of naïve T cells [50, 175]. In mice, TCF-1 has been shown to maintain expression of stem cell genes and to induce expression of the LN homing molecules CD62L and CCR7 in naïve CD8+ T cells and Tcm [176]. KLF-2 drives expression of the tissue-exit receptor S1PR1 that enables naïve CD8+ T cells and Tcm to recirculate by facilitating their exit from the LNs [50]. The shutdown of the expression of these transcription factors is essential for the formation of Trm [50, 175]. In comparison to naïve CD8+ T cells and Tcm, Trm have improved capacity to directly counter pathogens through the rapid upregulation of effector molecules including cytotoxic molecules and proinflammatory cytokines. The maintenance of expansion and multipotent potential appears to form a trade off with the acquisition of immediate effector functions during the differentiation of naïve CD8+ T cells into Trm [177]. The transcriptional regulation of Trm differentiation appears to reflect this transition of potential into direct antiviral or antibacterial activity. Trm upregulate the activity of the CD8+ T-cell lineage determining factor Runx3, which is crucial for the development of Trm [178]. Runx3 induces direct effector functions, including cytotoxic molecules such as granzyme B and perforin and proinflammatory cytokines such as IFN-γ [179]. Runx3 is also upstream of the Zinc Finger containing transcription factor Blimp-1 [179]. Together with the related transcription factor Hobit, Blimp-1 has been shown in mice to drive Trm differentiation across peripheral tissues [78, 180]. An important action of these transcription factors is the direct repression of TCF-1 and KLF-2 that maintain essential properties of naïve CD8+ T cells [78, 180]. Moreover, Hobit and Blimp-1 ensure that Trm maintain granzyme B expression at the protein level [181], thereby enabling Trm to directly engage in cytotoxic responses for the elimination of infected cells. Other transcription factors that are active in Trm, including Notch and Id2, are also involved in the regulation of effector functions of Trm [47, 82, 182, 183]. Thus, the differentiation of Trm is under the control of a transcriptional program that appears to establish immediate effector functions at the expense of self-renewal and expansion potential (Fig. 3).

Trm commitment

Naïve T cells have multipotent potential to develop into terminal effector cells and into memory precursors that eventually give rise to different subsets of memory T cells such as Tcm and Tem [184, 185]. The multipotent potential of individual naïve T cells includes their ability to form Trm, which have been shown to share clonal origin with circulating memory T cells [186]. It has not been completely resolved how transcription factors drive lineage choices resulting in the separation of the Tcm, Tem, and Trm subsets. It is clear that these memory subsets, including Trm, only develop downstream from memory precursors rather than terminal effectors. Transcriptional regulators, including Runx3, Tbet, Notch, Id2, and Blimp-1 have been shown in mice to preferentially drive the formation of terminal effectors, indicating that these factors control the branching point between terminal effectors and memory precursors (Fig. 3A) [182, 183, 187–192]. However, transcriptional regulators that act at branching points between memory precursors with exclusive potential for development into either Tcm, Tem, or Trm have remained largely unresolved. Several studies have indicated that commitment of memory precursors to the Trm lineage occurs at an early time-point after infection in spleen or LNs and before release into the bloodstream [191–193]. These findings suggest the involvement of transcriptional regulators that establish early separation of Trm precursors from other lineages. The transcription factors Runx3 and Blimp-1 have been shown to act during the acute phase of infection to establish the formation of Trm [78, 178].
Given that these transcription factors also drive terminal effector differentiation, they cannot fully account for the separation of Trm precursors from terminal effectors. The regulation of Trm commitment likely requires a transcription factor that is uniquely expressed in the Trm lineage. Only very few transcription factors appear to display Trm-restricted expression. The Blimp-1 homologue Hobit is exclusively expressed in the Trm lineage and essential contributes to Trm differentiation in collaboration with Blimp-1 [78], but it remains unclear whether this transcription factor is involved in early events of Trm commitment.

Trm maintenance

Trm form long-lived populations, which are maintained independently from other memory lineages. Their permanent residence in the peripheral tissues requires persistent downregulation of their migratory abilities to prevent access to draining LNs. The transcription factors Hobit and Blimp-1 directly suppress the expression of tissue exit receptors, including CCR7 and S1PR1, and also indirectly impair expression of these tissue exit receptors through suppression of TCF-1 and KLF2 [78]. These actions permanently lock Trm into the peripheral tissues. Similar to other memory CD8+ T cells, many but not all Trm populations require access to homeostatic cytokines, such as IL-7 and IL-15, for their survival under steady state conditions. Expression of the IL-15Rβ subunit, which is essential to access IL-15, crucially depends on the transcription factors Tbet and Eomes in circulating memory CD8+ T cells [194]. Despite near complete downregulation of Eomes, Trm maintain minimal expression of Tbet to sustain their IL-15 responsiveness [92]. Mucosal Trm also crucially depend on TGF-β-dependent signaling for their maintenance in the epithelial tissues and for expression of the CD103 subunit of the αEβ7 integrin that facilitates binding to E-cadherin on epithelial cells [85]. In fact, the downregulation of Tbet and Eomes in Trm compared to circulating memory T cells prevents transcriptional blockade of the expression of the TGF-β receptor [92, 195]. However, positive transcriptional regulators that induce and maintain TGF-β signaling have remained unclear. It appears that the transcription factor Notch maintains Trm in a deployment ready mode through constitutive upregulation of transcripts of proinflammatory cytokines [47]. Thus, transcriptional regulation ensures permanent residence of Trm in the peripheral tissues, the maintenance of Trm on homeostatic cytokines, and their immediate ability to upregulate effector functions, which is essential for Trm to act as sentinels of pathogen entry (Fig. 3B).

Tissue adaptation of Trm

Trm take residence in diverse tissues, including skin, lungs, liver, and intestine, with unique local environments that may require tissue-specific adaptations of Trm to generate tissue-tailored immune responses. However, the emerging role of transcription factors in the regulation of Trm throughout different tissues remains incomplete. Runx3 is ubiquitously expressed in Trm and has been found essential in mice for Trm differentiation in skin, lungs, kidneys, and salivary glands [178]. Similarly, Blimp-1 and Hobit mediate Trm differentiation in skin, liver, small intestine, lungs, and kidneys, although their relative impact varies per tissue [78, 180]. These findings suggest that these transcription factors drive universal aspects of Trm differentiation in line with their role in the regulation of tissue retention, cytotoxicity, and the release of proinflammatory cytokines, which are likely relevant for Trm populations throughout tissues. Nevertheless, this view has been challenged in recent single-cell transcriptional profiling studies showing that intratissue heterogeneity exists in the expression of transcription factors in Trm of the small intestine [81, 82]. Distinct subsets of Trm were identified that expressed either the transcription factor Id3 or Blimp-1. Id3+ Trm appeared to form long-lived populations in contrast to more terminally differentiated populations of Blimp-1+ Trm [82]. Access to local cytokines may trigger expression or activity of transcription factors in Trm in a tissue-specific or site-specific manner. TGF-β suppresses Blimp-1 expression resulting in downregulation in the epithelial layer of the small intestine [196]. In contrast, Id3, similar to Runx3 and Notch, is upregulated by TGF-β signaling, suggesting that they are more relevant at mucosal sites, which contain the active form of TGF-β [47, 178, 196]. Although these external signals may strengthen the activity of these transcriptional regulators between different tissues or sites, the regulation of Trm populations at different sites through tissue-specific transcription factors remains largely unexplored.

Trm in chronic immune responses

The more recent realization that Trm also develop in settings of chronic infection, autoimmunity, and cancer suggests that the transcriptional network underlying their differentiation may also be active under these conditions. A major difference between acute infection and chronic disease is the persistence of antigen in the chronic setting, which may have impact on the transcriptional regulation of Trm differentiation. For example, Hobit is rapidly and strongly downregulated in Trm after antigen encounter [198], suggesting that this transcription factor does not have a major role in Trm differentiation in chronic disease. The antigen-driven downregulation of Hobit may be an adaptation of Trm to retain plasticity, given that it may enable Trm to leave the tissues and provide immune protection at distant sites [198]. In contrast to Hobit, Runx3 has been described to regulate Trm differentiation in a murine tumor model [178]. In addition, the inflammation-driven transcription factor Blimp-1 appears to be more dominant in a chronic setting than Hobit [199]. It remains unclear whether these transcription factors similarly impact the transcriptional network of Trm in chronic disease. Persistent downregulation of TCF-1 also drives terminal differentiation of exhausted CD8+ T cells in cancer and in chronic infection [200–202]. These findings suggest that transcription factors, such as Runx3 and Blimp-1, may similarly counteract TCF-1 to induce Trm differentiation.
in a chronic setting. However, the position of Trm in the differentiation pathway of exhausted CD8+ T cells has not yet been elucidated. Therefore, currently, much remains unclear regarding the transcriptional framework underlying Trm in a chronic setting. Improved definitions of Trm under chronic conditions appear to be required for the further unraveling of the relevant transcription factors driving Trm formation in chronic disease. It is also important to note that the differentiation pathways of Trm developing in latent infection, persistent chronic infection, cancer, and autoimmune disease may be distinct to enable adaptation of Trm to local circumstances.

Conclusions and outlook

The groundbreaking findings about a decade ago that memory T cells locked inside mucosal and epithelial tissues were of utmost importance in providing protection against secondary infections has sparked the current great interest in the differentiation pathway of Trm. In light of the current SARS-CoV-2 pandemic, further research into the potential of Trm in the lungs to provide protection upon secondary encounter with this airway virus or after vaccination appear highly relevant. Moreover, the recent realization that the presence of Trm associates with improved prognosis in cancer and with immunopathology and, therefore, poor prognosis in autoimmune or inflammatory disease has already led to extensive research on Trm. It has become clear that Trm are ubiquitously present throughout tissues and localize not only to barrier tissues, but also to internal organs and even secondary lymphoid tissues. The prevalence of Trm appears to increase with pathogen reencounter suggesting increased relevance of these memory T cells in “dirty” settings of laboratory animals and in the nonsterile conditions of our daily lives. Trm appear to form a more versatile and heterogenic population of memory T cells that retains plasticity to generate not only immediate cytokine responses, but also more durable secondary responses that extend beyond their tissue of origin. Therefore, it remains a formidable task for immunologists to unravel all of the facets of Trm biology in the years to come.

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References

1. Sallusto, F., Lenig, D., Forster, R., Lipp, M. and Lanzavecchia, A., Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature 1999. 401: 708–712.
2. Cancro, M. P., Age-associated B cells. Annu. Rev. Immunol. 2020. 38: 315–340.
3. Tokoyoda, K., Hauser, A. E., Nakayama, T. and Radbruch, A., Organization of immunological memory by bone marrow stroma. Nat. Rev. Immunol. 2010. 10: 193–200.
4. Netea, M. G., Dominguez-Andres, J., Barreiro, L. B., Chavakis, T., Divangahi, M., Fuchs, E., Joosten, L. A. B. et al., Defining trained immunity and its role in health and disease. Nat. Rev. Immunol. 2020. 20: 375–388.
5. Netea, M. G., Joosten, L. A., Latz, E., Mils, K. H., Natoli, G., Stunnenberg, H. G., O’Neill, L. A. et al., Trained immunity: a program of innate immune memory in health and disease. Science 2016. 352: aaf1098.
6. Mueller, S. N. and Mackay, L. K., Tissue-resident memory T cells: local specialists in immune defence. Nat. Rev. Immunol. 2016. 16: 79–89.
7. Masopust, D. and Soerens, A. G., Tissue-resident T cells and other resident leukocytes. Annu. Rev. Immunol. 2019. 37: 521–546.
8. Ordoñez-Montanes, J., Beyza, S., Rakoff-Nahoum, S. and Shalek, A. K., Distribution and storage of inflammatory memory in barrier tissues. Nat. Rev. Immunol. 2020. 20: 308–320.
9. Quintin, J., Saeed, S., Martens, J. H. A., Giamaretos-Bourboulis, E. J., Ifrim, D. C., Logie, C., Jacobs, L. et al., Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes. Cell Host Microbe 2012. 12: 223–232.
10. Sun, J. C., Beilke, J. N. and Lanier, L. L., Adaptive immune features of natural killer cells. Nature 2009. 457: 557–561.
11. O’Leary, J. G., Goodarzi, M., Drayton, D. L. and von Andrian, U. H., T cell- and B cell-independent adaptive immunity mediated by natural killer cells. Nat. Immunol. 2006. 7: 507–516.
12. Nemeth, J., Olson, G. S., Rothchild, A. C., Jahn, A. N., Mai, D., Dufy, F. J., Delahaye, J. L. et al., Contained Mycobacterium tuberculosis infection induces concomitant and heterologous protection. PLoS Pathog. 2020. 16: e100855.
13. Dogra, P., Rancan, C., Ma, W., Toth, M., Senda, T., Carpenter, D. J., Kubota, M. et al., Tissue determinants of human NK cell development, function, and residence. Cell 2020. 180: 749–763 e713.
14. Kaufmann, E., Sanz, J., Dunn, J. L., Khan, N., Mendoza, L. E., Pacis, A., Tszelepis, F. et al., BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 2018. 172: 176–190.
15. Gourbal, B., Pinaud, S., Beckers, G. J. M., Van Der Meer, J. W. M., Conrath, U. and Netea, M. G., Invasive immune memory: an evolutionary perspective. Immunol. Rev. 2018. 283: 21–40.
16. Casey, K. A., Fraser, K. A., Schenkel, J. M., Moran, A., Abt, M. C., Beura, L. K., Lucas, P. J. et al., Antigen-independent differentiation and maintenance of effector-like resident memory T cells in tissues. J. Immunol. 2012. 188: 4866–4875.
17. Mackay, L. K., Stock, A. T., Ma, J. Z., Jones, C. M., Kent, S. J., Mueller, S. N., Heath, W. R. et al., Long-lived epithelial immunity by tissue-resident memory T (TRM) cells in the absence of persisting local antigen presentation. Proc. Natl. Acad. Sci. U.S.A. 2012. 109: 7037–7042.
18. Shin, H. and Iwasaki, A., A vaccine strategy that protects against genital herpes by establishing local memory T cells. Nature 2012. 491: 463–467.
19. Onodera, T., Takahashi, Y., Yokoi, Y., Ato, M., Kodama, Y., Hashimura, S., Kurosski, T. et al., Memory B cells in the lung participate in protective
humoral immune responses to pulmonary influenza virus reinfection. 

**Proc. Natl. Acad. Sci. U.S.A.** 2012. 109: 2485–2490.

20. Landsverk, O. J., Snir, O., Casado, R. B., Richter, L., Mold, J. E., Reu, P., Horneland, R. et al., Antibody-secreting plasma cells persist for decades in human intestine. *J. Exp. Med.* 2017. 214: 309–317.

21. Thome, J. J., Yudanin, N., Ohmura, Y., Kubota, M., Grinshpun, B., Sathaliyawala, T., Kato, T. et al., Spatial map of human T cell compartmentalization and maintenance over decades of life. *Cell* 2014. 159: 814–828.

22. Gebhardt, T., Wakim, L. M., Eidsmo, L., Reading, P. C., Heath, W. R. and Carbone, F. R., Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat. Immunol.* 2009. 10: 524–530.

23. Wakim, L. M., Waithman, J., van Rooijen, N., Heath, W. R. and Carbone, F. R., Dendritic cell-induced memory T cell activation in nonlymphoid tissues. *Science* 2008. 319: 198–202.

24. Masopust, D., Choo, D., Veys, V., Wherry, E. J., Duraiaisamy, J., Akody, R., Wang, J. et al., Dynamic T cell migration program provides resident memory within intestinal epithelium. *J. Exp. Med.* 2010. 207: 553–564.

25. Teijaro, J. R., Turner, D., Pham, Q., Wherry, E. J., Lefrancois, L. and Farber, D. L., Cutting edge: tissue-protective lung memory CD8 T cells mediate optimal protection to respiratory virus infection. *J. Immunol.* 2011. 187: 5510–5514.

26. Szabo, P. A., Miron, M. and Farber, D. L., Location, location, location: tissue resident memory T cells in mice and humans. *Sci. Immunol.* 2019. 4: eaaw9673.

27. Beura, L. K., Wijeyesinge, S., Thompson, E. A., Macchiottio, M. G., Rosato, P. C., Pierson, M. J., Schenkel, J. M. et al., T cells in nonlymphoid tissues give rise to lymph-node-resident memory T cells. *Immunity* 2018. 48: 327–338.

28. Buggert, M., Nguyen, S., Salgado-Montes de Oca, G., Bengsch, B., Darko, S., Ransier, A., Roberts, E. R. et al., Identification and characterization of HIV-specific resident memory CD8 T cells in human lymphoid tissue. *Sci Immunol.* 2018. 3: eaaw452.

29. Miron, M., Kumar, B. V., Meng, W., Granot, T., Carpenter, D. J., Senda, T., Chen, D. et al., Human lymph node maintain TCF-1 memory T cells with high functional potential and clonal diversity throughout life. *J. Immunol.* 2018. 201: 2123–2140.

30. Behr, F. M., Beumer-Chuwonpad, A., Kratgen, N. A. M., Wesselink, T. H., Stark, R. and van Gisbergen, K., Circulating memory CD8 T cells are limited in forming CD103+ tissue-resident memory T cells at mucosal sites after reinfection. *Eur. J. Immunol.* 2020. 51:151-166.

31. Pascutti, M. F., Geerman, S., Collins, N., Brassier, G., Nota, B., Stark, R., Behr, F. et al., Peripheral and systemic antigens elicit an expandable pool of resident memory CD8+ T cells in the bone marrow. *Eur. J. Immunol.* 2019. 49: 853–872.

32. Skirecki, T., Swacha, P., Hoser, G., Golab, J., Nowis, D. and Kozłowska, E., Bone marrow is the preferred site of memory CD4+ T cell proliferation during recovery from sepsis. *JCI Insight* 2020. 5: e134475.

33. Glennie, N. D., Yermilov, Y. A., Beiting, D. P., Volk, S. W., Weaver, C. T. and Scott, P., Skin-resident memory CD4+ T cells enhance protection against Leishmania major infection. *J. Exp. Med.* 2015. 212: 1405–1414.

34. Jiang, X., Clark, R. A., Liu, L., Wagers, A. J., Fulbright, R. C. and Kupper, T. S., Skin infection generates non-migratory memory CD8+ TRM cells providing global skin immunity. *Nature* 2012. 483: 227–231.

35. Klonowski, K. D., Williams, K. J., Marzo, A. L., Blair, D. A., Lingenheld, E. G. and Lefrançois, L., Dynamics of blood-borne CD8 memory T cell migration in vivo. *Immunity* 2004. 20: 551–562.

36. Hondonwicz, Brian D., An, D., Schenkel, Jason M., Kim, Karen S., Steach, Holly R., Krishnamurty, Akshay T., Keitany, Gladys J. et al., Interleukin-2-dependent allergen-specific tissue-resident memory cells drive asthma. *Immunity* 2016. 44: 155–166.

37. Schenkel, J. M., Fraser, K. A., Veys, V. and Masopust, D., Sensing and alarm function of resident memory CD8+ T cells. *Nat. Immunol.* 2013. 14: 509–513.

38. Turner, D. L., Bickham, K. L., Thome, J. J., Kim, C. Y., D’Orodivi, F., Wherry, E. J. and Farber, D. L., Lung niches for the generation and maintenance of tissue-resident memory T cells. *Mucosal Immunol.* 2014. 7: 501–510.

39. Anderson, K. G., Sung, H., Skon, C. N., Lefrancois, L., Deisinger, A., Veys, V. and Masopust, D., Cutting edge: intravascular staining redefines lung CD8 T cell responses. *J. Immunol.* 2012. 189: 2702–2706.

40. Steiner, Elizabeth M., Schenkel, Jason M., Fraser, Kathryn A., Beura, Lalit K., Manlove, Luke S., Igysartó, Botond Z., Southern, Peter J. et al., Quantifying memory CD8 T cells reveals regionalization of immunosurveillance. *Cell* 2015. 161: 737–749.

41. Bartolomé-Casado, R., Landsverk, O. J. B., Chauhan, S. K., Richter, L., Phung, D., Greiff, V., Risnes, L. F. et al., Resident memory CD8 T cells persist for years in human small intestine. *J. Exp. Med.* 2019. 216: 2412–2426.

42. Snyder, M. E., Finlayson, M. O., Connors, T. J., Dogra, P., Senda, T., Bush, E., Carpenter, D. et al., Generation and persistence of human tissue-resident memory T cells in lung transplantation. *Sci. Immunol.* 2019. 4: eaav5581.

43. Zuber, J., Shonts, B., Lau, S.-P., Obrodavic, A., Fu, J., Yang, S., Lambert, M. et al., Bidirectional intragraft alloreactivity drives the repopulation of human intestinal allografts and correlates with clinical outcome. *Sci. Immunol.* 2016. 1: eaah3732.

44. Purwar, R., Campbell, J., Murphy, G., Richards, W. G., Clark, R. A. and Kupper, T. S., Resident memory T cells (TRM) are abundant in human lung: diversity, function, and antigen specificity. *PLoS One* 2011. 6: e16245.

45. Kumar, B. V. M., Wu, M., Miron, M., Granot, T., Guyer, R. S., Carpenter, D. J., Senda, T. et al., Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. *Cell Rep.* 2017. 20: 2921–2934.

46. Sathaliyawala, T., Kubota, M., Yudanin, N., Turner, D., Camp, P., Thome, Joseph J. C., Bickham, Kara L. et al., Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. *Immunity* 2013. 38: 187–197.

47. Hombrink, P., Helbig, C., Backer, R. A., Piet, B., Oja, A. E., Stark, R., Brasser, G. et al., Programs for the persistence, vigilance and control of human CD8+ lung-resident memory T cells. *Nat. Immunol.* 2016. 17: 1467–1478.

48. Bankovich, A. J., Shiov, L. R. and Cyster, J. G., CD69 suppresses sphingosine 1-phosphate receptor-1 (S1P1) function through interaction with membrane helix 4. *J. Biol. Chem.* 2010. 285: 22328–22337.

49. Mackay, L. K., Braun, A., Macleod, B. L., Collins, N., Tehartz, C., Bedouli, S., Carbone, F. R. et al., Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. *J. Immunol.* 2015. 194: 2059–2063.

50. Skon, C. N., Lee, J.-Y., Anderson, K. G., Masopust, D., Hoggquist, K. A. and Jameson, S. C., Transcriptional downregulation of S1P1 is required for the establishment of resident memory CD8+ T cells. *Nat. Immunol.* 2013. 14: 1285–1293.

51. Hofmann, M. and Pircher, H., E-cadherin promotes accumulation of a unique memory CD8 T-cell population in murine salivary glands. *Proc. Natl. Acad. Sci.* 2011. 108: 16741–16746.
tissue-specific epidermal localization of CD8+ T lymphocytes. J. Invest. Dermatol. 2001. 117: 569–575.

53 Wakim, L. M., Woodward-Davis, A. and Bevan, M. J., Memory T cells persisting within the brain after local infection show functional adaptations to their tissue of residence. Proc. Natl. Acad. Sci. 2010. 107: 17872–17879.

54 Pallett, L. J., Davies, J., Colbeck, E. J., Robertson, F., Hansi, N., Easom, N. J. W., Burton, A. R. et al., IL-2high tissue-resident T cells in the human liver: sentinels for hepatotropic infection. J. Exp. Med. 2017. 214: 1567–1580.

55 Park, S. L., Zaid, A., Hor, J. L., Christo, S. N., Prier, J. E., Davies, B., Alexandre, Y. O. et al., Local proliferation maintains a stable pool of tissue-resident memory T cells after antiviral recall responses. Nat. Immunol. 2018. 19: 183–191.

56 Mackay, L. K., Rahimpour, A., Ma, J. Z., Collins, N., Stock, A. T., Hafon, M. L., Vega-Ramos, J. et al., The developmental pathway for CD103+CD8+ tissue-resident memory T cells of skin. Nat. Immunol. 2013. 14: 1294–1301.

57 Takamura, S., Yagi, H., Hakata, Y., Motozono, C., McMaster, S. R., Masumoto, T. F., Misawa, M. et al., Specific niches for lung-resident memory CD8+ T cells at the site of tissue regeneration enable CD69-independent maintenance. J. Exp. Med. 2016. 213: 3057–3073.

58 Walsh, D. A., Borges da Silva, H., Beura, L. K., Peng, C., Hamilton, S. E., Masopust, D. and Jameson, S. C., The functional requirement for CD69 in establishment of resident memory CD8+ T cells varies with tissue location. J. Immunol. 2019. 203:946-955.

59 Ugur, M., Schulz, O., Menon, M. B., Krueger, A. and Pabst, O., Resident CD4+ T cells accumulate in lymphoid organs after prolonged antigen exposure. Nat. Commun. 2014. 5: 4821.

60 Iijima, N. and Iwasaki, A., A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. Science 2014. 346: 99–98.

61 Strutt, T. M., Dhume, K., Finn, C. M., Hwang, J. H., Castonguay, C., Swain, S. L. and McKinstry, K. K., II-15 supports the generation of protective lung-resident memory CD4+ T cells. Mucosal. Immunol. 2018. 11: 668–680.

62 Watanabe, R., Gehad, A., Yang, C., Scott, L. L., Teague, J. E., Schlapbach, C., Elco, P. et al., Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. Sci. Transl. Med. 2017. 9: 279ra239.

63 Fernandez-Ruiz, D., Ng, Wei Y., Holz, L. E., Ma, Joel Z., Zaid, A., Wong, Yik C., Lau, Lei S. et al., Liver-resident memory CD8+ T cells form a front-line defense against malaria liver-stage infection. Immunity 2016. 45: 889–902.

64 Ma, C., Mishra, S., Demel, E. L., Liu, Y. and Zhang, N., TGF-β controls the formation of kidney-resident T cells via promoting effector T cell extravasation. J. Immunol. 2017. 198: 749–756.

65 Ray, S. J., Franki, S. N., Pierce, R. H., Dimitrova, S., Kotelsiansky, V., Sprague, A. G., Doherty, P. C. et al., The collagen binding alphabeta1 integrin VLA-1 regulates CD8 T cell-mediated immune protection against heterologous influenza infection. Immunity 2004. 20: 167–179.

66 Cheuk, S., Schlums, H., Gallais Sérézal, I., Martini, E., Chiang, S. C., Marquardt, N., Gibbs, A. et al., CD49a expression defines tissue-resident CD8+ T cells poised for cytotoxic function in human skin. Immunity 2017. 46: 287–300.

67 Reilly, E. C., Lambert Emo, K., Buckley, P. M., Reilly, N. S., Smith, I., Chaves, F. A., Yang, H. et al., Tm integrins CD103 and CD49a differentially support adhesion and motility after resolution of influenza virus infection. Proc. Natl. Acad. Sci. 2020. 117: 12306–12314.

68 Bromley, S. K., Akbaba, H., Mani, V., Mora-Buch, R., Chasse, A. Y., Sama, A. and Luster, A. D., CD49a regulates cutaneous resident memory CD8+ T cell persistence and response. Cell Rep. 2020. 32: 108085.

69 Mehara, E. J., Schön, M., Hassett, D., Parker, C., Havran, W. and Gardner, H., Reduced gut intraepithelial lymphocytes in VLA1 null mice. Cell. Immunol. 2000. 201: 1–5.

70 Clark, R. A., Chong, B., Mirchandani, N., Brinster, N. K., Yamanaka, K.-I., Dowgiert, R. K. and Kupper, T. S., The vast majority of CLA+ T cells are resident in normal skin. J. Immunol. 2006. 176: 4431–4439.

71 McCully, M. L., Ladell, K., Andrews, R., Jones, R. E., Miners, K. L., Roger, L., Baird, D. M. et al., CCR9 expression defines tissue-resident memory T cells in human skin. J. Immunol. 2018. 200: 1639–1650.

72 McMamara, H. A., Cai, Y., Wagle, M. V., Sontani, Y., Roots, C. M., Miosge, L. A., O’Connor, J. H. et al., Up-regulation of LFA-1 allows liver-resident memory T cells to patrol and remain in the hepatic sinusoids. Sci. Immunol. 2017. 2: eaaj1996.

73 Wein, A. N., McMaster, S. R., Takamura, S., Dunbar, P. R., Cartwright, E. K., Hayward, S. L., McManus, D. T. et al., CXCR6 regulates localization of tissue-resident memory CD8 T cells to the airways. J. Exp. Med. 2019. 216: 2748–2762.

74 Swarnaalekha, N., Schreiner, D., Litzler, L. C., Iftikhar, S., Kirchmeier, D., Künzli, M. and King, C. G., Redefining CD4 T cell residency: helper T cells orchestrate protective humoral immunity in the lung. bioRxiv 2020. https://doi.org/10.1101/2020.02.28.963280.

75 Bergsbaken, T. and Bevan, M. J., Proinflammatory microenvironments within the intestine regulate the differentiation of tissue-resident CD8+ T cells responding to infection. Nat. Immunol. 2015. 16: 406–414.

76 Thom, J. T., Webster, T. C., Walton, S. M., Torti, N. and Oxenius, A., The salivary gland acts as a sink for tissue-resident memory CD8+ T cells, facilitating protection from local cytomegalovirus infection. Cell Rep. 2015. 13: 1125–1136.

77 Kumar, B. V., Kretchmarov, R., Miron, M., Carpenter, D. J., Senda, T., Lerner, H., Friedman, A. et al., Functional heterogeneity of human tissue-resident memory T cells based on dye efflux capacities. JCI Insight 2018. 3: e123568.

78 Mackay, L. K., Minnich, M., Kratgen, N. A., Liao, Y., Nota, B., Seillet, C., Zaid, A. et al., Hobiit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. Science 2016. 352: 455–463.

79 Wakim, L. M., Woodward-Davis, A., Liu, R., Hu, Y., Villadangos, J. M., G. and Bevan, M. J., The molecular signature of tissue resident memory CD8+ T cells isolated from the brain. J. Immunol. 2012. 189: 3462–3471.

80 Clarke, J., Panwar, B., Madrigal, A., Singh, D., Gujar, R., Wood, O., Chee, S. J. et al., Single-cell transcriptomic analysis of tissue-resident memory T cells in human lung cancer. J. Exp. Med. 2019. 216: 2128–2149.

81 Kurd, N. S., He, Z., Louis, T. L., Milner, J. J., Omlulisik, K. D., Jin, W., Tsai, M. S. et al., Early precursors and molecular determinants of tissue-resident memory CD8+ T lymphocytes revealed by single-cell RNA sequencing. Sci. Immunol. 2020. 5: eaaz6894.

82 Milner, J. J., Toma, C., He, Z., Kurd, N. S., Nguyen, Q. P., McDonald, B., Quezada, L. et al., Heterogenous populations of tissue-resident CD8+ T cells are generated in response to infection and malignancy. Immunity 2020. 52: 808–824.

83 Szabo, P. A., Levin, H. M., Miron, M., Snyder, M. E., Senda, T., Yuan, J., Cheng, Y. L. et al., Single-cell transcriptomics of human T cells reveals tissue and activation signatures in health and disease. Nat. Commun. 2019. 10: 4706.

84 Zaid, A., Hor, J. L., Christo, S. N., Groom, J. R., Heath, W. R., Mackay, L. K. and Mueller, S. N., Chemokine receptor-dependent control of skin tissue-resident memory T cell formation. J. Immunol. 2017. 199: 2451–2459.
Frizzell, H., Pan, Y., Swarnalekha, N., Zhang, N. and Bevan, M. J. 2021. TGF beta 1: a mechanism for regulating pulmonary inflammation and metabolism. Cell 1999. 96: 319–328.

Mohammed, J., Beura, L. K., Bobr, A., Astry, B., Chicoine, B., Kashem, S. W., Welby, N. E. et al. Stromal cells control the epithelial residence of DCs and memory T cells by regulated activation of TGF-beta. Nat. Immunol. 2016. 17: 414–421.

Hirai, T., Tenke, Y., Yang, Y., Bartholin, L., Beura, L. K., Masopust, D. and Kaplan, D. H. Keratinocyte-mediated activation of the cytokine TGF-beta maintains skin recirculating memory CD8+ T cells. Immunity 2019. 50: 1249–1261.

Wakim, L. M., Smith, J., Caminschi, I., Lahoud, M. H. and Villadangos, J. A., Antibody-targeted vaccination to lung dendritic cells generates tissue-resident memory CD8 T cells that are highly protective against influenza virus infection. Mucosal Immunol. 2015. 8: 1060–1071.

Adachi, T., Kobayashi, T., Sugihara, E., Yamada, T., Ikuta, K., Pittet, J. F. et al. Skin-resident memory CD8+ T cells trigger a state of tissue-wide pathogen alert. Science 2014. 346: 101–105.

Chen, Y. et al. Developmental plasticity allows outside-in immune responses by resident memory T cells. Nat. Immunol. 2020. 21: 412–421.

Klicznik, M. M., Morawski, P. A., Schenkel, J. M., Inavalli, V., Mielke, L. and Masopust, D., Resident memory CD8 T cells provide antigen-specific protection against respiratory virus challenge through rapid IFN-gamma production. J. Immunol. 2015. 195: 203–209.

Roychoudhury, P., Swan, D. A., Duke, E., Carey, L., Zhu, J., Varela, V., Spuhler, L. R. et al. Tissue-resident T cell-derived cytokines eliminate herpes simplex virus-2-infected cells. J. Clin. Invest. 2020. 130: 2903–2919.

Ariotti, S., Hogenbirk, M. A., Dijkgraaf, F. E., Visser, L. L., Hoekstra, M. E., Song, J.-Y., Jacobs, H. et al. Skin-resident memory CD8+ T cells trigger a state of tissue-wide pathogen alert. Science 2014. 346: 98–101.

Schenkel, J. M., Fraser, K. A., Beura, L. K., Pauken, K. E., Veysy, V. and Masopust, D., Homeostatic organ surveillance. Immunity 2012. 36: 825–836.

Low, J. S., Farsakoglu, Y., Amezcua Vesely, M. C., Sekif, E., Kelly, J. B., Harman, C. D. C., Jackson, R. et al. Tissue-resident memory T cell reactivation is governed by resident memory T cells. J. Exp. Med. 2020. 217: e20192291.

Fonseca, R., Beura, L. K., Quintero, C. F., Ghoneim, H. E., Fan, Y., Zebeley, C. C., Scott, M. C. et al. Developmental plasticity allows outside-in immune responses by resident memory T cells. Nat. Immunol. 2020. 21: 412–421.

Klich, M. M., Morawski, P. A., Holbbacher, B., Varkhande, S. R., Motley, S. J., Kuri-Cervantes, L., Goodwin, T. et al. Human CD4+CD103+ cutaneous resident memory T cells are found in the circulation of healthy individuals. Sci. Immunol. 2019. 4: eaav8995.

Stolley, J. M., Johnston, T. S., Soerens, A. G., Beura, L. K., Rosato, P. C., Joag, V., Wijeyesinghe, S. F. P. et al. Retrograde migration supplies resident memory T cells to lung-draining LN after influenza infection. J. Exp. Med. 2020. 217: e2019219.

Suarez-Ramirez, J. E., Chandran, K., Brocke, S. and Cauley, L. S., Immune surveillance during respiratory infection is reinforced through early proliferation of lymphoid TRM cells and prompt arrival of effector CD8 T cells in the lungs. Front. Immunol. 2019. 10: 1370.

Enamorado, M., Iborra, S., Priego, E., Cueto, F. J., Quintana, J. A., Martinez-Cano, S., Mejias-Perez, E. et al. Enhanced anti-tumour immunity requires the interplay between resident and circulating memory CD8+ T cells. Nat. Commun. 2017. 8: 16073.

Osborn, J. F., Hobbs, S. J., Monks, M. W., Barry, C. H., Harty, J. T., Hill, A. B. et al. Enzymatic synthesis of core 2 O-glycans governs the tissue-trafficking potential of memory CD8+ T cells. Sci. Immunol. 2017. 2: eaan6049.

Osborn, J. F., Hobbs, S. J., Mooster, J. L., Khan, T. N., Kilgore, A. M., Harbour, J. C. and Nola, J. C., Central memory CD8+ T cells become CD69+ tissue-residents during viral skin infection independent of CD62L-mediated lymph node surveillance. PLoS Pathog. 2015. 15: e1007633.
Stelma, F. and Hislop, A. D., Human immunodeficiency virus-infected women have high hepatitis B virus-related hepatocellular carcinoma. J. Viral. 2017. 91: e00278–00217.

Verjans, G. M. G. M., Hintzen, R. Q., van Dun, J. M., Poot, A., Milikan, J. C., Laman, J. D., Langerak, A. W. et al., Selective retention of herpes simplex virus-specific CD8+ T cells in latently infected human trigeminal ganglia. Proc. Natl. Acad. Sci. 2007. 104: 3496–3501.

Smith, C. J., Caldeira-Dantas, S., Turula, H. and Snyder, C. M., Marine CMV infection induces the continuous production of mucosal resident T cells. Cell Rep. 2015. 13: 1137–1148.

Hislop, A. D., Kuo, M., Drake-Lee, A. B., Akbar, A. N., Bergler, W., Hammerschmidt, N., Khan, N. et al., Tonsillar homing of Epstein-Barr virus-specific CD8+ T cells and the virus-host balance. J. Clin. Invest. 2005. 115: 2546–2555.

Woodberry, T., Suscovich, T. J., Henry, L. M., August, M., Waring, M. T., Kaur, A., Hess, C. et al., eIF7p (CD103) expression identifies a highly active, tonsil-resident effector-memory CTL population. J. Immunol. 2005. 175: 4355–4362.

Woon, H. G., Braun, A., Li, J., Smith, C., Edwards, J., Siero, F., Feng, C. G. et al., Compartmentalization of total and virus-specific tissue-resident memory CD8+ T cells in human lymphoid organs. PLoS Pathog. 2016. 12: e1005799.

Ruhl, J., Leung, C. S. and Müinz, C., Vaccination against the Epstein-Barr virus. Cell. Mol. Life Sci. 2020, 77: 4315–4324.

Im, S. J., Konieczny, B. T., Hudson, W. H., Masopust, D. and Ahmed, R., PD-1+ stemlike CD8 T cells are resident in lymphoid tissues during persistent LCMV infection. Proc. Natl. Acad. Sci. 2020. 117: 4292–4299.

Stelma, F., de Niet, A., Sinnige, M. J., van Dort, K. A., van Gisbergen, K. F. J. M., Verheij, J., van Leeuwen, E. M. M. et al., Human intrahepatic CD69+ CD8+ T cells have a tissue-resident memory T cell phenotype with reduced cytolytic capacity. Sci. Rep. 2017. 7: 6172.

Vukmanovic-Stjeic, M., Sandhu, D., Seidel, J. A., Patel, N., Sobande, T. O., Agius, E., Jackson, S. E. et al., The characterization of varicella zoster virus-specific T cells in skin and blood during aging. J. Immunol. 2015. 195: 1752–1762.

Lim, C. J., Lee, Y. H., Pan, L., Lai, L., Chua, C., Wasser, M., Lim, T. K. H. et al., Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. Gut 2019. 68: 916–927.

Gibbs, A., Buggert, M., Edfeldt, G., Ranefall, P., Introni, A., Cheuk, S., Martíni, E. et al., Human immunodeficiency virus-infected women have high numbers of CD103+ CD8+ T cells residing close to the basal membrane of the ectocervical epithelium. J. Infect. Dis. 2017. 218: 453–465.

Kiniry, B. E., Li, S., Ganesh, A., Hunt, P. W., Somsouk, M., Skinner, P. J., Deeks, S. G. et al., Detection of HIV-1-specific gastrointestinal tissue resident CD8+ T-cells in chronic infection. Mucosal Immunol. 2018. 11: 909–920.

Copley, N. P., Wu, Y., Son, Y. M., Li, C., Wang, Z., Cheon, I. S., Jiang, L. et al., Tissue-resident CD8+ T cells drive age-associated chronic lung sequelae after viral pneumonia. Sci. Immunol. 2020. 5: eabc4557.

Turner, D. L., Goldklang, M., Cvetković, F., Paik, D., Trischler, J., Barhona, J., Cao, M. et al., Biased generation and in situ activation of lung tissue-resident memory CD4 T cells in the pathogenesis of allergic asthma. J. Immunol. 2018. 200: 1561–1569.

Gadeh, A.-S. Ø., Lee, M. H., Panch, A. B., Albede, M., Mraz, V., Weber, J. F., Callender, L. A. et al., Pathogenic CD8+ epidermis-resident memory T cells displace dendritic epidermal T cells in allergic dermatitis. J. Invest. Dermatol. 2020. 140: 806–815.

Gamradt, P., Laoubi, L., Nosbaum, A., Mutez, V., Lenief, V., Grande, S., Redoules, D. et al., Inhibitory checkpoint receptors control CD8+ resident memory T cells to prevent skin allergy. J. Allergy Clin. Immunol. 2019. 143: 2147–2157.

Kim, S., Kim, J., Park, C., Kupper, T. and Lee, K., Distinct transcriptional signature of skin-resident memory T cells and migratory memory T cells in atopic dermatitis. J. Invest. Dermatol. 2018. 138: 54.

Kim, S., Park, C., Shin, J., Noh, J., Kim, J., Kim, J., Lee, H. et al., 049 Multicytokine-producing tissue resident memory (TRM) cells in atopic dermatitis patient. J. Invest. Dermatol. 2016. 136: 59.

Boniface, K., Jacquemin, C., Darrigade, A.-S., Dessartre, B., Martins, C., Boukhedouni, N., Vernisse, C. et al., Vitiligo skin is imprinted with resident memory CD8+ T cells expressing CXC8. J. Invest. Dermatol. 2018. 138: 355–364.

Boymar, O., Hefti, H. P., Conrad, C., Nickoloff, B. J., Suter, M. and Nestle, F. O., Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-a. J. Exp. Med. 2004. 199: 731–736.

Cheuk, S., Wikén, M., Blomqvist, L., Nylen, S., Talme, T., Stähle, M. and Ekdamo, L., Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. J. Immunol. 2014. 192: 3111–3120.

Matos, T. R., O’Malley, J. T., Lowry, E. L., Hamm, D., Kirsch, I. R., Robins, H. S., Kupper, T. S. et al., Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing αT cells clones. J. Clin. Invest. 2017. 127: 4031–4041.

Richmond, J. M., Strassner, J. P., Rashighi, M., Agarwal, P., Garg, M., Essien, K. I., Peil, L. S. et al., Resident memory and recirculating memory T cells cooperate to maintain disease in a mouse model of vitiligo. J. Invest. Dermatol. 2019. 139: 769–778.

Boland, B. S., He, Z., Tsai, M. S., Olera, J. G., Omulisik, K. D., Duong, H. G., Kim, J. S. E. et al., Heterogeneity and clonal relationships of adaptive immune cells in ulcerative colitis revealed by single-cell analyses. Sci Immunol 2020. 5: eabf4432.

Bottois, H., Ngollo, M., Hammoudi, N., Courau, T., Bonnerave, J., Chardiny, V., Grand, C. et al., KLRG1 and CD103 expressions define distinct intestinal tissue-resident memory CD8+ T cell subsets modulated in Crohn’s disease. Front. Immunol. 2020. 11: 896.

Corridoni, D., Antanaviciute, A., Gupta, T., Fawwnker-Corbett, D., Aulicino, A., Jagiełowicz, M., Parikh, K. et al., Single-cell atlas of colonic CD8+ T cells in ulcerative colitis. Nat. Med. 2020. 26: 1480–1490.

Noble, A., Durant, L., Hoyles, L., Mccartney, A. L., Man, R., Segal, J., Costello, S. P. et al., Deficient resident memory T cell and CD8 T cell response to commensals in inflammatory bowel disease. J. Crohn’s Col. 2019. 14: 525–537.

Zundler, S., Becker, E., Sopcinska, M., Slawik, M., Parga-Vidal, L., Stark, R., Wiendl, M. et al., H0bit- and Blimp-1-driven CD4+ tissue-resident memory T cells control chronic intestinal inflammation. Nat. Immunol. 2019. 20: 288–300.

Kuric, E., Seiron, P., Krogvold, L., Edwin, B., Buanes, T., Hanssen, K. F., Skog, O. et al., Demonstration of tissue resident memory CD8 T cells in insulinic lesions in adult patients with recent-onset type 1 diabetes. Am. J. Pathol. 2017. 187: 581–598.
Strobl, J. Mijnheer, G., van Konijnenburg, D. P. H., van der Wal, M. M., Giovannone, B., Mocholi, E., Vaziripanah, N. et al. PD-1+ CD8+ T cells are clonally expanding effectors in human chronic inflammation. J. Clin. Invest. 2018. 128: 4669–4681.

Qaiyum, Z., Gracey, E., Yao, Y. and Imman, R. D., Transcriptomic profiles identify a distinctive syngeneic CD8+ T cell subpopulation in spondyloarthritides. Ann. Rheum. Dis. 2019. 78: 1566–1575.

Sherlock, J. P., Joyce-Shaikh, B., Turner, S. P., Chao, C.-C., Sathe, M., Grein, J., Gorman, D. M. et al. IL-23 induces spondyloarthropathy by acting on ROR γt+ CD3+ CD4+ CD8+ enthesal resident T cells. Nat. Med. 2012. 18: 1069–1076.

Steel, K. A., Srenath, U., Ridley, M., Durham, L. E., Wu, S.-Y., Ryan, S. E., Hughes, C. D. et al. Polymicrobial, proinflammatory, tissue-resident memory phenotype and function of syngeneal interleukin-17A+ CD8+ T cells in psoriatic arthritis. Arthritis Rheumatol. 2020. 72: 455–467.

Fransen, N. L., Hisao, C.-C., van der Poel, M. E., Engelenburg, H. J., Verdaasdonk, K., Vincenten, M. C. J., Remmerswaal, E. B. M. et al. Tissue-resident memory T cells invade the brain parenchyma in multiple sclerosis white matter lesions. Brain 2020. 143: 1714–1730.

Hisao, C.-C., Fransen, N. L., van den Bosch, A. M. R., Brandwijk, K. I. M., Huitinga, I., Hamann, J. and Smolders, J., White matter lesions in multiple sclerosis are enriched for CD20dim CD8+ tissue-resident memory T cells. Eur. J. Immunol. 2021. 51: 483–486.

Machado-Santos, J., Saji, E., Tröcscher, A. R., Paunovic, M., Liblau, R., Gabry, G., Bień, C. G. et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. Brain 2018. 141: 2066–2082.

Pallett, L. J., Burton, A. R., Amin, O. E., Rodriguez-Tajes, S., Patel, A. A., Zakeri, N., Jeffery-Smith, A. et al. Longevity and replenishment of human liver-resident memory T cells and mononuclear phagocytes. J. Exp. Med. 2020. 217: e20200050.

Bellmás Sanz, R., Hitz, A., Wiegmann, B., Bläsing, K., Sommer, W., Ius, F., Kühne, J. et al. Donor T and NK cells with a special tissue-resident memory phenotype migrate into the periphery of lung transplant recipients—a potential feature for tolerance development. J. Heart Lung Transplant. 2020. 39: S198.

Weiner, J., Svetlicky, N., Kang, J., Sadat, M., Khan, K., Duttargi, A., Stovroff, M. et al. CD69+ resident memory T cells are associated with graft-versus-host disease in intestinal transplantation. Am. J. Transplant. https://doi.org/10.1111/ajt.16405

de Leur, K., Dieterich, M., Hesselink, D. A., Corneth, O. B. J., Dor, F. J. M. F., de Graaf, G. N., Peeters, A. M. A. et al. Characterization of donor and recipient CD8+ tissue-resident memory T cells in transplant nephrectomies. Sc. Rep. 2019. 9: 5984.

Lian, C. G., Bueno, E. M., Granter, S. R., Laga, A. C., Saavedra, A. F., Lin, W. M., Susa, J. S. et al. Biomarker evaluation of face transplant rejection: association of donor T cells with target cell injury. Mod. Pathol. 2014. 27: 788–799.

Strobl, J., Pandey, R. V., Krausgruber, T., Bayer, N., Kleinr, I., Reinerger, B., Vieyra-Garcia, R. et al. Long-term skin-resident memory T cells proliferate in situ and are involved in human graft-versus-host disease. Sci. Transl. Med. 2020. 12: eabb7028.

Wang, D., Yuan, R., Feng, Y., El-Asady, R., Farber, D. L., Gress, R. E., Lucas, P. J. et al. Regulation of CD103 expression by CD8+ T cells responding to renal allografts. J. Immunol. 2004. 172: 214–221.

Yuan, R., El-Asady, R., Liu, K., Wang, D., Drachenberg, C. B. and Hadley, G. A., Critical role for CD103+ CD8+ effectors in promoting tubular injury following allogeneic renal transplantation. J. Immunol. 2005. 175: 2868–2879.

Tkachev, V., Kaminski, J., Potter, E. L., Furlan, S. N., Yu, A., Hunt, D. J., McGuckin, C. et al. Spatiotemporal single-cell profiling reveals that invasive and tissue-resident memory donor CD8+ T cells drive gastrointestinal acute graft-versus-host disease. Sci. Transl. Med. 2021. 13: eabc0227.

Bösmüller, H. C., Wagner, P., Peper, J. K., Schuster, H., Pham, D. L., Greif, B., Beschorner, C. et al. Combined immunoscore of CD103 and CD3 identifies long-term survivors in high-grade serous ovarian cancer. Int. J. Gynecol. Cancer 2016. 26: 671–679.

Djenidi, F., Adam, J., Goubar, A., Durgeau, A., Meurice, G., de Montpréville, V., Validire, P. et al., CD8+ CD103+ tumor-infiltrating lymphocytes are tumor-specific tissue-resident memory T cells and a prognostic factor for survival in lung cancer patients. J. Immunol. 2015. 194: 3475–3486.

Ganesan, A.-P., Clarke, J., Wood, O., Garrido-Martín, E. M., Chee, S. J., Mellows, T., Samaniego-Castruita, D. et al., Tissue-resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. Nat. Immunol. 2017. 18: 940–950.

Komdeur, F. L., Prins, T. M., van de Wall, S., Plat, A., Wisman, G. B. A., Holma, H., Daemen, T. et al., CD103+ tumor-infiltrating lymphocytes are tumor-reactive intraepithelial CD8+ T cells associated with prognostic benefit and therapy response in cervical cancer. OncoImmunology 2017. 6: e138230.

Savas, P., Virassamy, B., Ye, C., Salim, A., Mintoff, C. P., Caramia, F., Salgado, R. et al., Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. Nat. Med. 2018. 24: 986–993.

Wang, B., Wu, S., Zeng, H., Liu, Z., Dong, W., He, W., Chen, X. et al., CD103+ tumor infiltrating lymphocytes predict a favorable prognosis in urothelial cell carcinoma of the bladder. J. Urol. 2015. 194: 556–562.

Workel, H. H., Komdeur, F. L., Wouters, M. C. A., Plat, A., Klip, H. G., Eggink, F. A., Wisman, G. B. A. et al., CD103 defines intraepithelial CD8+ PD1+ tumor-infiltrating lymphocytes of prognostic significance in endometrial adenocarcinoma. Eur. J. Cancer 2016. 60: 1–11.

Boddupalli, C. S., Bar, N., Kadaveru, K., Kruthhammer, M., Pornputpong, N., Mai, Z., Ariyan, S. et al., Interleisional diversity of T cell receptors in melanoma with immune checkpoints enriched in tissue-resident memory T cells. JCI Insight 2016. 1: e88955.

Hartana, C. A., Ahlén Bergman, E., Broomé, A., Berglund, J., Johansson, M., Almandari, F., Jakubczyk, T. et al., Tissue-resident memory T cells are epigenetically cytotoxic with signs of exhaustion in human urinary bladder cancer. Clin. Experimental. Immunol. 2018. 194: 39–53.

Park, S. L., Buzzai, A., Rautela, J., Hor, J. L., Hochheiser, K., Effern, M., McBain, N. et al., Tissue-resident memory CD8+ T cells promote melanoma-immune equilibrium in skin. Nature 2019. 565: 366–371.

Edwards, J., Wilmott, J. S., Madore, J., Gide, T. N., Quek, C., Tasker, A., Ferguson, A. et al., CD103+ tumor-resident CD8+ T cells are associated with improved survival in immunotherapy-naive melanoma patients and expand significantly during anti–PD-1 treatment. Clin. Cancer Res. 2018. 24: 3036–3045.

Wu, J., Madi, A., Mieg, A., Hotz-Wagenblatt, A., Weisshaar, N., Ma, S., Mohr, K. et al., T cell factor 1 suppresses CD103+ lung tissue-resident memory T cell development. Cell Rep. 2020. 31: 107484.

Zhou, X., Yu, S., Zhao, D. M., Harty, J. T., Badovinac, V. P. and Xue, H. H., Differentiation and persistence of memory CD8+ T cells depend on T cell factor 1. Immunity 2010. 33: 229–240.
Rosato, P. C., Wijeyesinghe, S., Stolley, J. M. and Masopust, D., Integrating resident memory into T cell differentiation models. *Curr. Opin. Immunol.* 2020. 63: 35–42.

Milner, J. J., Toma, C., Yu, B., Zhang, K., Omlulisik, K., Phan, A. T., Wang, D. et al., RunX3 programs CD8⁺ T cell residency in non-lymphoid tissues and tumours. *Nature* 2017. 552: 253–257.

Shan, Q., Zeng, Z., Xing, S., Li, F., Hartwig, S. M., Gullicksrud, J. A., Kurup, S. P. et al., The transcription factor Runx3 guards cytotoxic CD8⁺ effector T cells against deviation toward follicular helper T cell lineage. *Nat. Immunol.* 2017. 18: 931–939.

Behr, F. M., Kragent, N. A. M., Wesselink, T. H., Nota, B., van Lier, R. A. W., Amnsen, D., Stark, R. et al., Blimp-1 rather than Hobit drives the formation of tissue-resident memory CD8⁺ T cells in the lungs. *Front. Immunol.* 2019. 10: 400.

Kragten, N. A. M., Behr, F. M., Vieira Braga, F. A., Remmerswaal, E. B. M., Wesselink, T. H., Oja, A. E., Hombrink, P. et al., Blimp-1 induces and Hobit maintains the cytotoxic mediator granzyme B in CD8⁺ T cells. *Eur. J. Immunol.* 2018. 48: 1644–1662.

Backer, R. A., Helbig, C., Gentek, R., Kent, A., Laaidaw, B. J., Dominguez, C. X., de Souza, Y. S. et al., A central role for Notch in effector CD8⁺ T cell differentiation. *Nat. Immunol.* 2014. 15: 1143–1151.

Yang, C. Y., Best, J. A., Knell, J., Yang, E., Sheridan, A. D., Jesionek, A. K., Li, H. S. et al., The transcriptional regulators Id2 and Id3 control the formation of distinct memory CD8⁺ T cell subsets. *Nat. Immunol.* 2011. 12: 1221–1229.

Stemberger, C., Huster, K. M., Koffler, M., Anderl, F., Schiemann, M., Wagner, H. and Busch, D. H., A single naive CD8⁺ T cell precursor can develop into diverse effector and memory subsets. *Immunity* 2007. 27: 985–997.

Geiachs, C., van Heijst, J. W., Swart, E., Sie, D., Armstrong, N., Kerkhoven, R. M., Zehn, D. et al., One naive T cell, multiple fates in CD8⁺ T cell differentiation. *J. Exp. Med.* 2010. 207: 1235–1246.

Gaido, O., Emerson, R. O., Jiang, X., Gulati, N., Nizza, S., Desmarais, C., Robins, H. et al., Common clonal origin of central and resident memory T cells following skin immunization. *Nat. Med.* 2015. 21: 647–653.

Joshi, N. S., Cui, W., Chandele, A., Lee, H. K., Urso, D. R., Hagan, J., Gapin, L. et al., Inflammation directs memory precursor and short-lived effector CD8⁺ T cell fates via the graded expression of T-bet transcription factor. *Immunity* 2007. 27: 281–295.

Rutishauser, R. L., Martins, G. A., Kalachikov, S., Chandele, A., Parish, I. A., Meffe, E., Jacob, J. et al., Transcriptional repressor Blimp-1 promotes CD8⁺ T cell terminal differentiation and represses the acquisition of central memory T cell properties. *Immunology* 2009. 31: 296–308.

Kallies, A., Xin, A., Belz, G. T. and Nutt, S. L., Blimp-1 transcription factor is required for the differentiation of effector CD8⁺ T cells and memory responses. *Immunity* 2009. 31: 283–295.

Wang, D., Diao, H., Getzler, A. J., Rogal, W., Frederick, M. A., Milner, J. Y., Yu, B. et al., The transcription factor Runx3 establishes chromatin accessibility of cis-regulatory landscapes that drive memory cytotoxic T lymphocyte formation. *Immunity* 2018. 48: 659–674 e665.

Masopust, D., Vezys, V., Wherry, E. J., Barber, D. L. and Ahmed, R., Cutting edge: gut microbiome promotes differentiation of a unique memory CD8⁺ T cell population. *J. Immunol.* 2006. 176: 2079–2083.

Ibora, S., Martinez-Lopez, M., Khouri, S. C., Enamorado, M., Cueto, F. J., Conde-Garrosa, R., Del Fresno, C. and Sancho, D., Optimal generation of tissue-resident but not circulating memory T cells during viral infection requires crosspriming by DNGR-1⁺ dendritic cells. *Immunity* 2016. 45: 847–860.

Kok, L., Dijkgraaf, F. E., Urbanus, J., Bresser, K., Vredevoogd, D. W., Cardoso, R. F., Perie, L. et al., A committed tissue-resident memory T cell precursor within the circulating CD8⁺ effector T cell pool. *J. Exp. Med.* 2020. 217: e20191711.

Intlekofer, A. M., Takemoto, N., Wherry, E. J., Longworth, S. A., Northrup, J. T., Palanivel, V. R., Mullen, A. C. et al., Effector and memory CD8⁺ T cell fate coupled by T-bet and eomesodermin. *Nat. Immunol.* 2005. 6: 1236–1244.

Laidlaw, B. J., Zhang, N., Marshall, H. D., Staron, M. M., Guan, T., Hu, Y., Cauley, L. S. et al., CD4⁺ T cell help guides formation of CD103⁺ lung-resident memory CD8⁺ T cells during influenza viral infection. *Immunity* 2014. 41: 633–645.

Salehi, S., Bankoti, R., Benevides, L., Willen, J., Couse, M., Silva, J. S., Dhall, D. et al., B lymphocyte-induced maturation protein-1 contributes to intestinal mucosa homeostasis by limiting the number of IL-17-producing CD4⁺ T cells. *J. Immunol.* 2012. 185: 5682–5693.

Kee, B. L., Rivera, R. R. and Murre, C., Id3 inhibits B lymphocyte progenitor growth and survival in response to TGF-beta. *Nat. Immunol.* 2001. 2: 242–247.

Behr, F. M., Parga-Vidal, L., Kragent, N. A. M., van Dam, T. J. P., Wesselink, T. H., Sheridan, B. S., Arens, R. et al., Tissue-resident memory CD8⁺ T cells shape local and systemic secondary T cell responses. *Nat. Immunol.* 2020. 21: 1070–1081.

Shin, H., Blackburn, S. D., Intlekofer, A. M., Kao, C., Angelsanto, J. M., Reiner, S. L. and Wherry, E. J., A role for the transcriptional repressor Blimp-1 in CD8⁺ T cell exhaustion during chronic viral infection. *Immunity* 2009. 31: 309–320.

Utschneider, D. T., Charymon, M., Chennupati, V., Poussle, L., Ferreira, D. P., Calderon-Copete, S., Danilo, M. et al., T cell factor 1-expressing memory-like CD8⁺ T cells sustain the immune response to chronic viral infections. *Immunity* 2016. 45: 415–427.

Im, S. J., Hashimoto, M., Gerner, M. Y., Lee, J., Kissick, H. T., Burger, M. C., Shan, Q. et al., Defining CD8⁺ T cells that provide the proliferative burst after PD-1 therapy. *Nature* 2016. 537: 417–421.

He, R., Hou, S., Liu, C., Zhang, A., Bai, Q., Han, M., Yang, Y. et al., Follicular CXCR5- expressing CD8⁺ T cells curtail chronic viral infection. *Nature* 2016. 537: 412–423.

Abbreviations: CLA: cutaneous lymphocyte antigen  DAMPs: danger-associated molecular patterns  GvHD: graft-versus-host disease  HBV: hepatitis B virus  LCMV: lymphocytic choriomeningitis virus  MAMPS: microbe-associated molecular patterns  S1PR: sphingosine-1-phosphate receptor  scRNA-seq: single-cell RNA sequencing  Tcm: central memory T cells  TILs: tumor-infiltrating lymphocytes  Trm: tissue-resident memory  VLA-1: Very Late Antigen-1

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