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Tissue-specific Control of Tissue Resident Memory T Cells

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Abstract

Tissue-resident memory T (T_{RM}) cells have emerged to be a major component of T cell biology. Recent investigations have greatly advanced our understanding of T_{RM}s. Common features have been discovered to distinguish memory T cells residing in various mucosal and non-mucosal tissues from their circulating counterparts. Given that most organs and tissues contain unique microenvironment, local signal-induced tissue-specific features are tightly associated with the differentiation, homeostasis and protective functions of T_{RM}s. We will discuss the recent advances in T_{RM} field with a special emphasis on the interaction between local signals and T_{RM} cells in the context of individual tissue environment.

Keywords

CD4; CD8; Infection; IL-15; Memory; TGF-β

Introduction

T lymphocytes or T cells are the central component of adaptive immunity. To prepare for the vast majority of potential antigenic encounter, T cells harbor a large repertoire of different T Cell Receptors (TCRs) with diverse reactivity. For each given TCR specificity, only a small number of T cells are present in human and un-manipulated mice due to the limit of total T cells that an individual can host.[1] Therefore, to effectively patrol the most parts of a body for potential pathogen invasion or other antigenic challenge, circulation and migration is an essential feature tightly associated with T cell function.

Under steady state, naïve T cells circulate through secondary lymphoid organs, blood and lymphatic vessels.[2] Upon antigen stimulation, naïve T cells differentiate into effector T cells with newly equipped effector functions that actively eliminate antigenic sources.[3] At later

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stages of an immune response, most effector T cells die via apoptosis and a small number of survived cells further differentiate into memory T cells, which carry the unique feature of adaptive immunity—immunological memory.[4] Although long-lasting debates have been focused on the identity of memory precursors and the differentiation path of memory T cells,[5] recent works have provided solid epigenetic evidence that virus-specific memory T cells transit through an effector stage, not directly derive from naïve cells in both mouse and human.[6,7]

Early studies in human peripheral blood have identified two distinct memory T cell populations based on their unique migratory patterns, namely central memory T cells (T_{CM}) and effector memory T cells (T_{EM}).[8] T_{CM}s carry lymph node homing receptors CCR7 and CD62L, and share a similar circulation path as naïve T cells. In contrast, T_{EM}s lack CCR7 and CD62L, and prefer non-lymphoid peripheral tissues during circulation. In addition to divergent migration patterns, different proliferative potential and effector functions have been attributed to T_{CM} and T_{EM}. Similar circulating memory T cell subsets have been confirmed in mouse and other animal models.[9]

Partition of memory T cells into T_{CM} and T_{EM} provides a convenient model to investigate the migration and function of memory T cells. However, in contrast to the generally accepted notion that T_{EM} cells patrol non-lymphoid tissues under steady state, recent studies have discovered that during local inflammation, T_{CM}s, but not T_{EM}s or long-lived effector T cells, migrate into inflamed tissues due to their superior capacity to induce O-glycosylation and generate P/E-selectin ligands, which facilitate the trans-endothelial extravasation of T cells.[10,11] Comparing with T_{EM}, T_{CM} cells generally express higher level of chemokine receptor CXCR3, which also enhances the migration of T_{CM} into inflamed peripheral tissues.[12] Thus, the migration pattern of memory T cells is dynamically controlled by inflammatory signals independent of antigenic stimulation.

A population of non-circulating tissue-resident memory T cells (T_{RM}) has been identified in almost all non-lymphoid tissues in both human and mouse.[13–19] It has been estimated that the number of T_{RM} cells exceeds the number of T cells in all lymphoid tissues and entire blood volume combined in both adult human and immunized mice. Therefore, as a newly discovered major T cell population, T_{RM} is a focus of extensive and active investigations.

Based on the results from decades of research on mucosal T cells, it is quickly realized that mucosal lymphocyte surface marker integrin αEβ7 (CD103) marks mucosa-associated T_{RM} cells.[20,21] Although with various specificity and accuracy, CD103, together with CD69 has been widely accepted as the common markers to identify T_{RM} cells in mucosal and some non-mucosal tissues in both mouse and human. Transforming growth factor-β (TGF-β) is a pleiotropic cytokines that control various aspects of T cell biology including thymocyte development, naïve T cell homeostasis and effector/memory T cell differentiation.[22,23] For more than two decades, it has been known that TGF-β enhances the expression of CD103 on activated T cells during in vitro culture.[24] Later, it has been validated in different in vivo models that TGF-β signaling is tightly linked with T_{RM} biology, which will be discussed in details in the following sections.

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In current review, we will focus on the recent advances in T_{RM} biology and will specifically address the following topics: I) Tissue-specific features of T_{RM} cells; II) Transcriptional control of T_{RM} cells and III) $CD4^+$ T_{RM} cells. As a rapidly expanding field, exciting overlap between T_{RM} cells and tumor infiltrating T cells has been observed. Due to the scope of current review, infection-induced T_{RM} cells will be the major topic with a special emphasis on the relationship between TGF-β signaling and T_{RM} biology. As $CD4^+$ T_{RM} cells will be discussed in the last section, $CD8^+$ T_{RM} cells will be the main focus in the first two sections.

I. Tissue specific features of T_{RM} cells

T_{RM} cells are broadly distributed in both mucosal and non-mucosal tissues outside lymphoid compartment. In addition, a small number of $CD8^+$ T_{RM} cells reside in secondary lymphoid organs isolated from infected mice and Peyer's patches from naïve mice.[25,26] Interestingly, a substantially increased population of memory T cells bearing T_{RM} markers is present in the secondary lymphoid organs isolated from adult human[27,28] presumably due to prolonged history of antigen exposure.[29] A recent report has demonstrated a direct link between non-lymphoid tissue resident $CD8^+$ T cells and T_{RM} cells in the draining LNs.[30] Secondary lymphoid organ T_{RM}s are largely differentiated from non-lymphoid tissue T_{RM}s during re-infection. However, the biological importance of secondary lymphoid organ-resident $CD8^+$ T_{RM} is not entirely clear. In this section, we will focus our discussion on the recent discoveries of T_{RM} cells in a collection of non-lymphoid organs.

A. Skin

Skin harbors a large number of antigen-specific $CD8^+$ T_{RM} cells following various infections in both mouse and human.[31,32] As one of the pioneer focuses of T_{RM} research, skin T_{RM} population is relatively well characterized. During the early phase of skin infection, effector $CD8^+$ T cells with a Killer Cell Lectin Like Recrptor $G1^-$ ($KLRG1^-$) phenotype (i.e., the common precursors for memory T cells) migrate to the skin via a P/E-selectin ligand- and CXCR6-dependent manner.[33–35] Skin T_{RM}s isolated from both mouse and human share common TCR sequences with circulating memory T cells in the lymph nodes from the same individual, suggesting that common precursor effector T cells give rise to both skin-resident and circulating memory T cells.[36]

Using skin Vaccinia virus (VACV) infection model, it has been demonstrated that DNGR-1^+ dendritic cell (DC)-mediated cross-Priming is specifically required for the formation of skin T_{RM}, but not for that of circulating memory T cells.[37] $CD8\alpha^+$ DCs in mouse lymphoid organs and $CD103^+$ DCs in non-lymphoid organs express chemokine receptor Xcr1 and C-type lectin DNGR-1 (encoded by *Clec9a*). This subset of DCs develop in a transcription factor Batf3-dependent manner and exhibit superior capacity to cross-Present exogenous antigen to $CD8^+$ T cells.[38,39] Interestingly, it is in the draining lymph node (LN) during the very early phase of naïve $CD8^+$ T cell priming that $DNGR1^+$ DCs deliver critical signals to instruct $CD8^+$ T cells to differentiate into skin T_{RM} at later stages.[37] Cross-Priming DCs extend the retention of activated $CD8^+$ T cells in draining LNs via repressing transcription factor Kruppel Like Factor 2 (K1f2) and its target Sphingosine-1-Phosphate Receptor 1 (S1pr1). Defects in cross-Priming DCs result in early egress of $CD8^+$ effector T cells from

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the draining LNs and enhanced accumulation of KLRG1$^+$ effector CD8$^+$ T cells in the skin at early stages following infection. Further, DNGR-1$^+$ DCs provide IL-12, IL-15 and CD24 signals, all of which are required for optimal formation of skin T_{RM} cells.[37] A separated line of research has established Xcr1$^+$ cross-Priming DCs as an essential player to convey CD4-help signals during CD8$^+$ T cell priming in the LNs.[40,41] Even though CD4-help is not required for the initial recruitment of CD8$^+$ effector T cell to the skin,[33] the role of CD4-help in the formation and long-term maintenance of skin T_{RM} population remains to be determined. Indeed, CD4$^+$ T cell depletion leads to enhanced CD8$^+$ T cell recruitment to the skin,[33] phenocopying the accelerated lymph node egress and increased skin CD8$^+$ T cell accumulation in cross-Priming DC deficient animals at the early phases of an infection.[37] Together, it is likely that through cross-Priming DCs, early CD4-help is required for the formation of skin T_{RM} cells.[42] However, the molecular programs linking CD4 helped effector CD8$^+$ T cells in the LNs with later formed skin T_{RM}s remain to be elucidated, although a recent work started to dissect the connections.[43]

After arrival at the skin, CD8$^+$ T cells up-regulate CD69 and CD103 in a progressive order.[34] CD69 promotes the early retention of CD8$^+$ T cells in the skin before the expression of *Klf2* and *S1pr1* are efficiently suppressed.[44] Mechanistically, CD69 inhibits the function of S1pr1 and blocks the egress of T cells.[45] Even though the down-regulation of *Klf2* and *S1pr1* is a common signature of T_{RM},[46] the rapid induction of CD69 helps to retain T_{RM} precursors when there is residual activity of S1pr1 at early stages of T_{RM} differentiation. In the absence of CD69, skin T_{RM} population is greatly reduced. However, CD69 deficient T cells can differentiate into CD103$^+$ T_{RM}s in the skin, similar as the situation in lung T_{RM} cells.[47] These results demonstrate that CD69 per se is not required for the subsequent differentiation of T_{RM} cells. The induction of CD69 in skin T_{RM} cells is independent of TGF-β and type I interferon (IFN). Local antigen is not required for skin T_{RM} formation.[48] However, local antigen greatly promotes CD69 induction and skin T_{RM} differentiation.[49–51] Using VACV skin infection model, it has been demonstrated that the early recruitment of activated CD8$^+$ T cells to the skin is cognate antigen-independent. After arrival, skin T cells compete for antigen-Presenting cells for cognate antigen recognition, which leads to the induction of CD69. Notably, local TCR signal only provides differentiation, but not proliferation signals to T_{RM} precursors.[50,51]

TGF-β is required for the induction of CD103 and long-term maintenance of skin T_{RM} cells.[34] The expression of CD103 reduces the mobility of skin T_{RM} cells as demonstrated by multi-photon microscopy.[35] Integrin αvβ6 and αvβ8 expressed by keratinocytes cooperate to activate latent TGF-β and are essential for the maintenance of skin T_{RM} population.[52] Interestingly, the activity of αvβ6 and αvβ8 is continuous required even after the establishment of skin T_{RM} population. This observation suggests that the unique T_{RM} transcription program is not permanently fixed. Instead, constant environmental cues (e.g., TGF-β) are essential to maintain the identity of skin T_{RM} cells at least under the circumstance of systemic viral infection. Most CD8$^+$ skin T_{RM} cells reside in the epidermis layer. Hair follicle derived IL-7 and IL-15 and a special metabolic program involving exogenous lipid uptake are required for the long-term survival of skin T_{RM} cells.[53,54] Further, as a skin homing chemokine receptor, CCR10 is required for the long-term

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homeostasis of both circulating and skin-resident memory $CD8^+$ T cells during skin infection.[35]

A small number of $CD8^+$ T cells can seed distal non-infected regions of the skin and provide critical local protection, suggesting that a low number of skin T_{RM}s are sufficient to provide effective protection.[33,49] Re-encounter of cognate antigen induces rapid activation of skin T_{RM} cells. Activated T_{RM}s stimulate both innate and adaptive immune components of the skin and recruit circulating memory T cells in an IFN-γ-dependent manner.[55] Skin T_{RM}s provide sufficient protection in adult human as demonstrated by the lack of infections in alemtuzumab-treated cutaneous T cell lymphoma patients whose circulating T cells are depleted while skin T_{RM} cells are spared.[56] During the recall response, skin T_{RM} cells undergo in situ expansion and contraction, and do not rejoin circulating effector/memory T cell pool. Thus, skin T_{RM} population is a relatively stable local immune component during the subsequent challenges.[57]

Most previously mentioned skin T_{RM} cells are generated in response to a specific pathogen introduced by intradermal injection or scarification, which causes both local infection and skin damage. Without causing skin injury, topical application of certain strains of skin commensal bacteria leads to a typical antigen-specific $CD8^+$ T cell response including expansion, contraction and long-term maintenance of a memory T cell population in the skin carrying a common T_{RM} phenotype (i.e., $CD69^+CD103^+$).[58] In addition to IFN-γ producing cells, this commensal bacteria-induced skin T_{RM} population contains a significant subset of IL-17 producing cells. Cross-priming DCs are required for the formation of these IL-17^+ $CD8^+$ T_{RM} cells. In addition to the divergent effector cytokines, regular pathogen-induced T_{RM}s are different from commensal-specific T_{RM}s in three major aspects: 1) Pathogen infection-induced skin T_{RM} cells are largely restricted to the injured site while commensal-specific T_{RM}s are scattered; 2) Pathogen infection-induced T_{RM}s directly respond to infected epidermal cells to produce IFN-γ while IL-17 production from commensal-specific T_{RM} cells requires $CD11b^+$ local DCs;58–60 and 3) the unique population of IL-17 producing $CD8^+$ skin T_{RM} cells differentiate from non-classical MHC-Ib-restricted $CD8^+$ T cells and promote tissue repair.[59]

As a common T_{RM} signature, skin T_{RM} cells exhibit a T-$bet^{lo}Eomes^{neg}$ phenotype.[60] In T-bet deficient cells and therefore complete lack of T-box transcription factors, skin T_{RM} cells up-regulate transcription factor RORγt and become IL-17 producing cells.[60] Similar IL-17-Producing $CD8^+$ T cells have been observed in T-bet/Eomes double deficient T cells in lymphoid organs after systemic viral infection.[61] Commensal bacteria-induced IL-17^+ skin T_{RM} cells carry minimal amount of T-bet while maintain a high level of RORγt, suggesting that upon the suppression of T-box transcription factors, RORγt-mediated type 17 effector program may be an important default path of $CD8^+$ T cell differentiation. Importantly, IL-17 producing $CD8^+$ T cells are present in both human and non-human primates.[59] In human skin, the presence or absence of CD49a expression can divide T_{RM}s into IFN-γ or IL-17-Producing cells and associated with type 1 or type 17 effector T cell-related disease settings.[62] However, the molecular and cellular control of the type 17 effector program in $CD8^+$ T cells or T_{RM} cells remains unclear.

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Together, skin T_{RM} cells are differentiated from common memory T cell precursors in the circulation. Local antigen is not required, but significantly promotes the induction of CD69 and differentiation of skin T_{RM}s. Local signals including TGF-β, IL-7 and IL-15 controls the formation and homeostasis of skin T_{RM}s. Pathogen-induced and commensal-specific T_{RM}s exhibit distinct features.

B. Lung

Lung T_{RM} cells exhibit both common T_{RM} features and lung-specific properties. Most lung parenchyma and interstitium-resident $CD8^+$ memory T cells carry either $CD69^+CD103^+$ or $CD69^+CD103^-$ phenotype, similar as T_{RM}s isolated from most other mucosal sites. Lung $CD8^+$ T_{RM} cells are essential for the local protection against influenza viral infection in mouse.[63–66] Further, it has been recently confirmed that influenza-specific T_{RM} cells isolated from human lungs mount a robust proliferative response with superior effector functions.[67]

The differentiation of $CD103^+$ lung T_{RM} cells is TGF-β-dependent[64,68] and requires CD4-help and cross-Priming signals from DNGR-1^+ DCs during the initial priming phase.[37,42] 4–1BB signal to T cells is critical for the formation of lung T_{RM} cells in a competitive setting.[69] In addition, Notch signaling and Notch inducing transcription factor EGR2 are up-regulated in $CD103^+$ lung T_{RM} cells and essential for the formation and maintenance of lung T_{RM} cells.[70,71] The survival of $CD103^+$, but not $CD103^-$ lung T_{RM} requires IL-15 signaling.[60] Interestingly, Notch may promote the maintenance of lung T_{RM} cells via an IL-15-independent and metabolism-related mechanism.[70]

In contrast to antigen-independent and local inflammation-driven T_{RM} differentiation in the vagina and salivary gland, local cognate antigen is essential for lung T_{RM} differentiation,[47,64] consistent with the findings that T cells with different TCR specificity elicit distinct T_{RM} forming potential during polyclonal response against influenza virus infection in mice.[67,72,73] Further, TCR signal can induce the expression of anti-viral protein IFITM3 (Interferon Induced Transmembrane Protein 3) in lung T_{RM} cells. IFITM3 protects lung T_{RM} cells from direct viral infection-induced cell death.[74]

Distinct from long lasting protection provided by T_{RM} cells residing in other mucosal sites, lung T_{RM} cells wane over time due to enhanced apoptosis of $CD103^+$ T_{RM} in lung microenvironment.[63,75] The maintenance of $CD8^+$ memory compartment in the lung requires continuous recruitment of circulating memory T cells.[76,77] In contrast to lung T_{RM} differentiation during the acute phase of influenza virus infection, at the memory phase, previously infected lung is permissive to de novo T_{RM} differentiation from circulating T_{EM} cells in a cognate antigen-independent, but IL-33 and TNF-dependent manner.[75] The waning of lung T_{RM} cells is caused by the increase of circulating T_{CM} and decrease of T_{EM}, and therefore the decline of continuous T_{RM} induction.

Not completely exclusive from the above explanation, recent publications have identified a specific niche in injured lungs that supports T_{RM} differentiation and maintenance. These lung T_{RM} niches are the tissue repair-associated regions and co-localize with the production of T_{RM} promoting factors TGF-β and IL-15.[47,72] Notably, the regeneration of damaged

airway epithelium is also TGF-β-dependent,[78] providing an example of complex functions of TGF-β signaling in both local immunity and tissue homeostasis. The gradual decline of lung T_{RM} cells is caused by the completion of injured lung regeneration and the shrinking of lung T_{RM} niches. These observations are also consistent with the lack of lung T_{RM} formation in most systemic infection models that do not induce significant lung injury.

Thus, gradual changes of both circulating memory T cells and lung microenvironment may be together responsible for the decline of lung T_{RM} cells over time. However, there is one piece of observation needed to be reconciled. Considering that T_{EM} cells continuously migrate and differentiate into lung T_{RM} cell after influenza viral infection,[75] it seems counterintuitive that seven weeks of parabiosis does not lead to significant de novo lung T_{RM} formation in a similar animal model.[47] One possible explanation may be that parabiosis surgery itself causes unexpected inflammation and tissue damage. Systemic and local inflammatory signals introduced by surgical procedures may alter the migration of circulating memory T cells as TCM cells are sensitive to inflammation-induced O-glycosylation and migration.[11] It is well documented that surgery has immediate impacts on the immune system of human patients.[79] Therefore, even as the golden standard in T_{RM} research, the results from parabiosis experiments should be carefully interpreted along with the experiments involving less invasive procedures.

CD69 promotes the early migration and retention, but not the differentiation or long-term maintenance of lung T_{RM} cells.[47] Similar as skin T_{RM}s, early expression of CD69 inhibits the residual activity of K1f2/S1pr1 pathway. In addition, CD69 may directly facilitate effector $CD8^+$ T cell migration into inflamed lung via interacting with its ligands myosin light chain 9, 12a and 12b.[80]

Using VACV immunization and infection models, it has been demonstrated that intranasal, but not systemic intra-Peritoneal infection induces the differentiation of two populations of lung $CD8^+$ T_{RM} cells, i.e., a major population of $CXCR3^{lo}$ interstitium T_{RM} and a minor population of $CXCR3^{hi}$ airway T_{RM}. $CXCR3^{lo}$ T_{RM} cells provide critical protection.[81] An independent investigation also confirms that $CXCR3^{hi}$ and $CXCR3^{lo}$ lung $CD8^+$ T cells represent different differentiation stages in response to local inflammation (e.g., IL-12 and IL-15) and occupy distinct niches in the lung. Further, cooperative action from both $CXCR3^{hi}$ and $CXCR3^{lo}$ lung T_{RM}s is required for the protection against lethal respiratory VACV challenge.12 Considering that $CXCR3^{hi}$ airway-resident $CD8^+$ T cells are established protectors against respiratory infections,[82,83] lung T_{RM} cells may not represent a homogenous population of cells. Instead, different subsets or differentiation stages of T_{RM} cells may occupy different niches and cooperate to achieve maximal protection.

In terms of effector functions for lung T_{RM}, in addition to IFN-γ production, which is a common effector cytokine produced by T_{RM}s isolated from various tissues, tissue-specific production of IL-22 is labeled as a unique feature for lung T_{RM} cells upon cognate antigen re-stimulation.[84]

Together, during the effector phase of a respiratory infection, lung T_{RM} cells are formed in a cognate antigen-dependent and CD69-dependent manner. During the memory phase, de

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novo T_{RM} formation and maintenance may be mediated by an antigen- and CD69-independent mechanism. Local signals, such as TGF-β, IL-15, IL-33 and TNF promote lung T_{RM} differentiation and homeostasis. Different microenvironment inside the lung supports various subsets of lung T_{RM} cells.

In addition to lung T_{RM}, a series of elegant investigations have established upper respiratory tract as a key site to support local T_{RM} against respiratory viral infection.[73,85,86] Virus-specific $CD69^+$ and $CD69^+CD103^+$ $CD8^+$ T cells carrying common T_{RM} signature genes can be readily isolated from upper respiratory tract including nasal tissue and nasal-associated lymphoid tissues in mouse and tonsils in human. Distinct from TGF-β- and cognate antigen-dependent induction of lung T_{RM} cells, both TGF-β and cognate antigen recognition are dispensable for upper respiratory tract T_{RM} cells. Further, in contrast to the gradual decline of lung T_{RM} cells over time, upper respiratory tract T_{RM} cells persist at a steady level and are sufficient to provide protective immunity.[73] Thus, upper and lower respiratory tract associated T_{RM} cells provide us a perfect example that different local environment supports T_{RM} differentiation and maintenance through distinct mechanisms.

C. Intestine

Intestine contains one of the largest mucosal surfaces in the body. The complete overview of intestinal T cell components is beyond the scope of current review. In this section, we will limit our discussion to $CD8\alpha\beta^+TCR\alpha\beta^+$ memory T cells residing in the intraepithelial lymphocyte (IEL) and lamina propria (LP) compartments of the intestines.

Both local and systemic infection leads to the generation of gut $CD8^+$ T_{RM} cells. Local infection is often more effective in inducing gut T_{RM}s. Generally, most T_{RM} cells carry a $CD69^+CD103^+$ surface phenotype in the IEL compartment while LP T_{RM} cells contain both $CD69^+CD103^+$ and $CD69^+CD103^-$ subsets. $CD103^+$ T_{RM} cells are evenly distributed. $CD103^-$ T_{RM} cells are clustered around infected loci in the LP of both small and large intestines via a CXCR3-dependent mechanism and critical for local immunity.[87] In contrast to most other mucosal and non-mucosal tissues, local antigen is not required for the differentiation of gut T_{RM} cells. Indeed, persistent local antigen may inhibit gut T_{RM} cell formation revealed by delayed induction of CD103.[88]

During the early phase of oral infection, intestinal $CD8^+$ T cells congregate around infected cells and receive inflammatory signals (e.g., IL-12). IL-12 prevents the induction of CD103. However, in the absence of IL-12 signaling, although the initial induction of CD103 is accelerated, the long-term survival of both $CD103^-$ and $CD103^+$ gut T_{RM} cells is significantly impaired.[89] These results provide an elegant example of the complicated impacts of local inflammation on the differentiation and maintenance of T_{RM} cells.

During chronic viral infection, TGF-β inhibits the expression of gut-homing receptor integrin α4β7 on effector $CD8^+$ T cells isolated from secondary lymphoid organs and therefore dampens the migration of effector $CD8^+$ T cells to the intestine.[90] Interestingly, low dose rapamycin treatment during the effector phase of an immune response inhibits the expression of gut homing receptors and greatly reduces the formation of gut T_{RM} population.[91] Considering that TGF-β inhibits the serine and threonine kinase mammalian

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target of rapamycin (mTOR) in NK cells,[92] the possible crosstalk between TGF-β signaling and mTOR pathway in gut T_{RM} cell biology warrants future investigation.

In the intestinal tissues, TGF-β signaling is required for the induction of CD103, but dispensable for CD69 expression.[87] TGF-β is essential for the differentiation of gut T_{RM} cells during both local and systemic infections as TGF-β unresponsive T_{RM}s (both $CD103^+$ and $CD103^−$) are dramatically reduced in both IEL and LP compartments of the intestines at the memory phase of an immune response.[90,93] However, in contrast to the generally accepted notion that CD103 helps gut T_{RM} cell retention by interacting with epithelial derived E-cadherin, CD103 deficient T cells only exhibit a two-fold reduction in the initial establishment, but not in the long-term maintenance of gut T_{RM} cells in the IEL compartment.[93] CD103 is not involved in the homeostasis of gut T_{RM}s in the LP compartment.[88,93] These results demonstrate that TGF-β mediates essential functions via CD103-independent mechanisms in gut T_{RM} cells.

Through abrogating the function of latent TGF-β activating integrin αvβ6 in the gut, it has been recorded that continuous TGF-β signaling is required for the maintenance of gut T_{RM} cells in the IEL, but not LP compartment.[52] However, underlying mechanisms explaining the difference between IEL and LP compartments are not addressed. Different TGF-β dependency of T_{RM} subsets or additional molecules mediating the activation of local TGF-β in the LP may be the possible explanations. The factors that mediate the long-term survival of gut T_{RM} cells are not clear. In contrast to lung and skin T_{RM} cells, IEL and LP gut T_{RM} cells are maintained in an IL-15-independent manner.[94]

In addition to the common effector molecules associated with memory $CD8^+$ T cells, gut T_{RM} cells have been demonstrated to produce both type I and type III IFNs to activate the innate antiviral status of gut epithelium.[95] However, whether these properties are gut-specific or generally associated with T_{RM}s isolated from other tissues awaits future clarification.

Together, intestinal T_{RM} is formed during both local and systemic infection in a cognate antigen-independent manner. $CD103^+$ and $CD103^−$ T_{RM} cells exhibit different location and function. TGF-β, but not IL-15 is required for the initial differentiation and long-term maintenance of gut T_{RM} cells. The capacity to respond to (e.g., IL-12R) or being recruited to (e.g., CXCR3) local inflammatory loci controls the formation and homeostasis of gut T_{RM} cells.

D. Female reproductive tract

Female reproductive tract (FRT) represents another well-studied mucosal tissue in T_{RM} field. Similar to skin, $CD8^+$ T_{RM}s are highly enriched in the epithelial layer of FRT.[32] Remarkably, different segments of FRT exhibit distinct immunological properties that impact $CD8^+$ T cell priming and T_{RM} formation. The unique local environment of lower FRT restricts the immediate production of type I and type III IFN following vaginal viral infection, which in turn results in defective DC maturation and delayed $CD8^+$ T cell priming.[96] Interestingly, the dampened innate immune response is restricted to lower FRT while upper FRT mounts a relatively normal response. The mechanisms underlying this

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striking difference between lower and upper FRT remain unknown. In addition to variable immune components, different epithelial structure and the restricted association of microbiome with lower FRT may be the potential contributing factors.[97]

After priming, the migration of activated $CD8^+$ T cells to vaginal mucosa is tightly regulated by local immune environment. Following vaginal infection, $CD4^+$ T cell-derived IFN-γ activates FRT epithelium to produce CXCL9/10 and enhance the migration of antigen-specific effector $CD8^+$ T cells in a CXCR3-dependent fashion.[98] Dysbiosis-induced IL-33 production leads to greatly enhanced ILC2 (type 2 innate lymphoid cell) mediated accumulation of eosinophils and defective recruitment of both $CD4^+$ and $CD8^+$ T cells after vaginal herpes virus infection,[99] suggesting a potential crosstalk between lower FRT associated microbiome and T_{RM} formation. Different from current paradigm that DCs carry local antigens to the draining LNs to prime antigen-specific naïve T cells, lower FRT mucosa is able to support naïve $CD8^+$ T cell priming and proliferation in situ without the involvement of secondary lymphoid organs.[100] The significance of mucosa initiated naïve T cell priming remains to be validated in different infection settings. Further, whether different priming sites (i.e., vaginal mucosa versus draining LNs) impact the formation of T_{RM} cells is left to be demonstrated.

Local antigen recognition is not required for FRT T_{RM} differentiation.[88] Non-specific local inflammation or exogenous chemokines are sufficient to attract circulating $CD8^+$ T cells and allow newly recruited cells to further differentiate into long-lasting $CD69^+CD103^+$ FRT-resident memory T cells.[48,101] IL-15 is not required for the homeostasis of FRT T_{RM} population.[94] Upon antigenic recall, T_{RM}s quickly produce IFN-γ and function as an alarming system to activate both local innate and adaptive immune components and recruit circulating memory T cells.[102,103] $CD301b^+$ LP DCs are required to activate vaginal T_{RM}s upon vaginal herpes virus re-challenge.[104] In contrast, dorsal root ganglia resident T_{RM}s are re-activated by recruited monocyte-derived DCs[105] and skin $CD8^+$ T_{RM}s are reactivated by almost any directly infected epidermal cells carrying cognate antigens.[106] Recent results have demonstrated that FRT T_{RM} cells undergo expansion and differentiation in situ during re-challenge. This T_{RM}-autonomous response dominants the local CD8 recall response. Thus, in addition to a sentinel system, mucosal T_{RM} function as a robust self-sufficient defense system and can function independent of circulating T cells.[104,107]

Together, the formation and maintenance of FRT T_{RM} are independent of local antigen and IL-15. Different regions of FRT harbor distinct immune environment that impacts $CD8^+$ T cell response. Local DCs are required for the recall response of FRT T_{RM}s. The involvement of TGF-β signaling in FRT T_{RM}s remains to be determined.

E. Non-mucosal tissues

Following systemic infection, kidney supports the differentiation and maintenance of a significant population of both $CD69^+$ and $CD69^-$ T_{RM} cells.[108] Similar as other non-mucosal T_{RM} cells, most kidney T_{RM} cells do not express CD103. TGF-β is required for the optimal differentiation of kidney T_{RM}s via facilitating effector $CD8^+$ T cell extravasation. Mechanistically, TGF-β signaling promotes the expression of CXCR3 and E/P-selectin ligands on effector $CD8^+$ T cells. Both CXCR3 and E/P-selectin ligands participate in the

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transendothelium migration of $CD8^+$ effector T cells in the kidney.[109] The potential functions of local antigens in kidney T_{RM}s have not been determined. One study has found that kidney T_{RM}s are enriched for T cells with high-affinity TCRs during chronic viral infection,[110] suggesting that local antigen may facilitate kidney T_{RM} induction. Common T_{RM} transcriptional program is active in kidney T_{RM} cells as deficiency in transcription factors Blimp-1, Hobit or Runx3 leads to impaired maintenance of kidney T_{RM} cells.[111,112] Similar to skin, lung and salivary gland T_{RM} cells, the long-term maintenance of kidney T_{RM} cells is IL-15-dependent.[60,94] However, the protective function of kidney T_{RM} cells remains to be demonstrated. During polyomavirus BK reactivation following kidney transplant in human patients, the presence of $CD69^+$ kidney T_{RM} cells is associated with diminished effector functions and poor virus control while $CD69^-$ kidney $CD8^+$ T cells are associated with better clinical outcomes.[113] Together, TGF-β promotes the formation of kidney T_{RM}s. IL-15 is required for the long-term survival of kidney T_{RM}s while the protective function of kidney T_{RM}s remains to be determined.

Even though considered as a non-mucosal tissue, salivary gland supports the differentiation and maintenance of a significant population of $CD69^+CD103^+$ intraepithelial $CD8^+$ T_{RM} cells. Similar as intestinal mucosal, but distinct from most other tissues which have been examined, the differentiation of salivary gland T_{RM} does not require cognate antigen recognition.[114–116] Local inflammation does not affect T_{RM} differentiation in salivary gland as least during murine cytomegalovirus infection. Integrin α4β1 is required for the accumulation of $CD8^+$ T cells in the salivary gland mediated via the interaction with endothelial VCAM-1 (Vascular Cell Adhesion Molecule-1).[115,117] Often used as an epithelium marker, E-cadherin is highly expressed by salivary gland T_{RM} and promotes $CD8^+$ T cell accumulation presumably via homotypic interactions between E-cadherin.[116] TGF-β signaling is required for the induction of CD103 and long-term maintenance of salivary gland T_{RM}s. Similar as the situation for intestinal T_{RM} cells, CD103 itself is only involved in the initial establishment, but not long-term maintenance of salivary gland T_{RM}s. Thus, CD103-independent but TGF-β-dependent mechanisms may be essential for the maintenance of T_{RM} cells. The initial induction of CD69 is TGF-β- and type I IFN-independent and may involve the signals from IL-33 and TNF.114,118 IL-15 is not required for the initial differentiation,[114] but essential for the long-term survival of salivary gland T_{RM}s.[94] In summary, initial CD69 induction on salivary gland T_{RM}s is independent of local antigen and TGF-β. The long-term maintenance of T_{RM}s requires both TGF-β and IL-15. Adhesion molecules including integrin α4β1, CD103 and E-cadherin promote the accumulation of salivary gland T_{RM}s.

Home to a large collection of diverse immune cell types, liver has been proposed as a lymphoid organ and functions as an essential battle field against various liver-targeting pathogens, such as malaria, hepatitis B and hepatitis C virus.[119] Murine liver T_{RM} cells are identified as $CD69^+CXCR6^+CXCR3^+CD11a^+CD103^-$.[120,121] In contrast to most T_{RM} cells that are located outside the vasculature, the vast majority of liver T_{RM} cells reside inside the blood vessels and display active crawling behavior to patrol hepatic sinusoids.[108,120–122] This unique feature excludes the usage of intravascular labeling technique in liver T_{RM} research. Even constantly exposed to blood circulation, liver T_{RM} are not travelling along the bloodstream and considered as bona fide liver-resident cells as demonstrated by

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parabiosis experiments. Their liver residency is dependent on integrin LFA-1 (Lymphocyte Function-associated Antigen-1) and chemokine receptor CXCR3.[120,121] Local antigen is required for liver T_{RM} formation. At the transcription level, both Blimp-1 and Hobit are required for the maintenance of liver T_{RM} in mouse.[111] However, liver T_{RM} isolated from human hepatitis B virus infected patients display a Blimp-1^{hi}Hobit^{lo} phenotype.[123] In contrast to the situation that most mouse liver T_{RM}s are $CD103^{-}$, a distinct $CD69^{+}CD103^{+}$ T_{RM} population is present in human liver. TGF-β together with IL-15 may mediate liver T_{RM} formation in human. However, the function of TGF-β in mouse liver T_{RM} has not been determined. Regarding the effector functions, both human and mouse liver T_{RM}s are associated with enhanced local protection. Interestingly, in response to TLR4 or TLR9 signals, inflammatory monocytes forms cocoon-like cell aggregates in mouse liver to support local proliferation of $CD8^{+}$ T cells. These cellular structures may represent a key site for liver T_{RM} function.[124] Human liver T_{RM}s display an IFN-γ^{hi} IL-2^{hi} GranzymeB^{lo} phenotype[123] while mouse liver T_{RM}s are GranzymeB^{hi} IFN-γ^{hi} [120] and produce colony-stimulating factor-2.[84] In addition to the species difference, various infection settings may also contribute to the phenotypic and functional distinctions in liver T_{RM} populations. Together, liver T_{RM}s are closely associated with blood vasculature. Local antigen recognition is required for the induction of liver T_{RM}s. LFA-1 and CXCR3 promote liver T_{RM} formation. The requirement of TGF-β signaling remains to be determined. Prominent distinctions have been identified between mouse and human T_{RM}s in the liver.

Following local infection, $CD8^{+}$ effector T cells migrate to the brain and differentiate into both $CD69^{+}CD103^{-}$ and $CD69^{+}CD103^{+}$ T_{RM} cells.[125,126] Local antigen presentation is required for the differentiation of brain T_{RM} cells, consistent with the findings that during persistent brain infection, the TCR affinity of brain T_{RM} cells gradually increases.[110] TGF-β signaling likely promotes the induction of $CD103^{+}$ brain T_{RM} cells as depletion of $Foxp3^{+}$ regulatory T cells (Tregs) and Treg-derived TGF-β impairs the formation of brain T_{RM} population.[127] Further, similar as kidney T_{RM} cells, TGF-β promotes the trans-endothelial migration of $CD8^{+}$ effector T cells into the brain.[109] Locally produced survival cytokines IL-7 and/or IL-15 may promote brain T_{RM} homeostasis as a sizable population of brain T_{RM}s contains phosphorylated STAT5 and undergoes homeostasis proliferation in vivo.[128] Interestingly, $pSTAT5^{+}$ and proliferating brain T_{RM} cells are enriched around the brain surface comparing with brain parenchyma. However, the cellular source and location of IL-7 and IL-15 have not been determined. Brain T_{RM} cells up-regulate the expression of inhibitory receptors PD-1 and CTLA-4.[126] PD-1/PD-L1 interaction is required to limit the accumulation of PD-$1^{hi}$$CD103^{-}$ $CD8^{+}$ T cells and promote brain T_{RM} population.[129] In contrast to lung and FRT T_{RM}s, the differentiation and maintenance of brain T_{RM} cells are independent of CD4-help.[126,128] Cognate antigen re-challenge activates brain T_{RM}s to recruit circulating memory T cells. However, in the absence of circulating memory T cells, activated brain T_{RM} cells proliferate in situ and provide sufficient immune protection.[128] Thus, in addition to functioning as a component of local alarming system, brain T_{RM}s can function as an organ-autonomous defense system. Together, brain T_{RM} induction depends on local antigen encounter and is independent of CD4-help. TGF-β promotes T_{RM} formation and IL7/15 may provide the survival signals for T_{RM}s in the brain.

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In response to oral infections, mesenteric white adipose tissue supports efficient $CD69^+CD103^-$ T_{RM} differentiation. Surprisingly, white adipose tissue contains more T_{RM} cells and provides better protection than intestinal LP against intestinal infections.[130] White adipose tissue T_{RM} cells carry the receptors for survival cytokines IL-15 and IL-7. However, the local signals which drive the differentiation and maintenance of while adipose tissue T_{RM} remains unknown. Considering the unique metabolic requirement of T_{RM} cells, i.e., the uptake of exogenous lipid,[54] white adipose tissue may provide an ideal environmental niche for T_{RM}s.

With proper infection settings, almost all non-lymphoid organs support the differentiation of T_{RM} cells. Different microenvironment and local signals dictate the phenotype and behavior of T_{RM} cells isolated from various tissues. The tissue specific features of $CD8^+$ T_{RM} isolated from various non-lymphoid organs are summarized in Table 1. Be aware that when T_{RM} is studied in different tissues, it is often involved distinct infection models. Therefore, in addition to tissue-specific local environment, infection-specific properties may also impact T_{RM} cells.

II. Transcriptional regulation of T_{RM} cells

Transcription factors (TFs) control the development of multiple immune cell types through activating and/or repressing genes that are critical to cell identity.[131] Comparing with effector and memory T cells in lymphoid tissues and circulation, T_{RM} cells in non-lymphoid tissues are a unique and distinct memory T cell population that displays a specific TF expression pattern. T_{RM} cell fate is determined by the integrated activity of multiple TFs, which contributes to optimal survival and function within their local environment.[132] Functional illumination of TFs-modulated T_{RM} formation will facilitate future manipulation of these TFs to foster T_{RM} accumulation, which ultimately yield desirable and effective protective memory T cells in tissues. In this section, TFs with a well-established role in T_{RM} formation are discussed in details below.

A. Krüppel-Like Factor 2 (KLF2)

Krüppel-like factors (KLFs) are a family of zinc-finger TFs including 15 mammalian family members, in which Klf2 is one of the core transcriptional regulators that affect T cell trafficking.[133,134] The reduction of *Klf2* is required to establish tissue-residency of various immune cells, including mouse and human $CD8^+$ T_{RM},[46,86,111] $CD4^+$ T_{RM},135 NK and NKT cells,[111,136] and $CD8\alpha\alpha^+$ $TCR\alpha\beta$ T cells and $TCR\gamma\delta$ T cell in the IEL compartment of the gut.[137] As a possible exception to the universal down-regulation of *Klf2* in tissue-resident lymphocytes, a significant population of conventional $TCR\alpha\beta$ T cells (both $CD4^+$ and $CD8\beta^+$) in the IEL compartment of the large intestine, but not in that of the small intestine maintain a high level of *Klf2* expression.[137] The biological significance of this unique expression pattern of *Klf2* in large intestine IEL remains unclear. Klf2 controls the expression of receptors required for emigration and peripheral trafficking, including S1pr1, CD62L, CCR7 and β7 integrin.[133] Once entry into peripheral non-lymphoid tissues, local cytokines such as TGF-β, IL-33 and TNF cooperate to extinguish the expression of both *Klf2* and its target *S1pr1*, which potentiates the retention of T_{RM} cells in the tissue.[46,75,88]

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Mechanistically, PI3K/Akt pathway is activated by cytokine signals to inhibit the expression of transcription factor Foxo1 and therefore enforce the down-regulation of *K1f2* 46 Various combinations of pro-inflammatory cytokines can suppress the expression of *Klf2* in activated $CD8^+$ T cells in vitro, including type I IFN, IL-12 and IL-18.[46,88] However, type I IFN does not significantly alter T_{RM} differentiation[44] and IL-12 inhibits early differentiation and promotes long-term maintenance of gut T_{RM}.[89] Thus, the function of different cytokines in T_{RM} cells will require further clarification in different tissues under various inflammatory conditions in vivo. TCR signal is not involved in the down-regulation of *Klf2* during acute viral infections. In summary, as a key regulator of T cell trafficking, local cytokine-mediated repression of *Klf2* is essential to establish tissue residency of most T_{RM}s.

B. T-bet and Eomes

T-bet (encoded by *Tbx21)* and Eomesodermin (encoded by *Eomes*), as two members of T-box binding TFs, are essential regulators for the differentiation and function in distinct immune cells including $CD4^+$ T, $CD8^+$ T, NKT, NK, innate lymphocytes and B cells.[138] In $CD8^+$ T cells, *Tbx21* expression is highest in short-lived effector cells, whereas *Eomes* expression is increased in long-lived memory cells.[139] Temporal and spatial down-regulation of both *Tbx21* and *Eomes* represents a pivotal step in the lodging and maturation of skin T_{RM} cells, in which *Eomes* is virtually extinguished, either before or after $CD8^+$ T cells enter the epithelium and prior to the acquisition of CD103.[60] However, *Tbx21* deficient $CD103^+CD8^+$ T_{RM} cells ultimately vanish over time, because complete loss of *Eomes* during the final maturation of $CD103^+CD8^+$ T_{RM} cells renders them dependent on low level of T-bet for persistent survival. This phenomenon is supported by the notion that at least one T-box TF, in particular T-bet, is necessary to maintain the expression of cytokine receptor subunit CD122 (IL-2/IL-15R β chain), which delivers a survival signal to certain memory T cell populations.[60,140,141] However, the requirement of IL-15 in the long-term survival of T_{RM}s is tissue type-dependent.[94] Whether IL-15-independent T_{RM}s requires residual expression of CD122 and T-bet remains to be clarified. In addition, complete lack of T-box TFs in $CD8^+$ T cells may lead to the activation of RORγt-mediated type 17 effector program. The transcriptional regulation of type 17 $CD8^+$ effectors is not entirely understood.

Smad3 is required for TGF-β mediated CD103 (encoded by *Itgae)* expression. Both Smad3 and T-bet directly bind to the first intron of *Itgae* locus, suggesting the potential mechanisms by which T-bet might repress *Itgae* transcription. T-bet may directly compete with Smad3 for DNA binding, interact with Smad3 to prevent its transcription, or recruit other transcriptional repressors to the *Itgae* locus.[42] Further, the well-orchestrated down-regulation of both T-bet and Eomes strengthens TGF-β signaling pathway that reciprocally inhibits the expression of T-bet and Eomes, indicating a feed-forward loop forms to optimize $CD103^+CD8^+$ T_{RM} cell formation.[60] Interestingly, previous reports have documented that enhanced T-bet expression and defective T_{RM} formation are often associated in various scenarios. $CD8^+$ T cell priming in the absence of CD4 help,[42] deficiency in cross-Priming DCs[37] or in infant animals and human[142] all lead to increased T-bet expression and defective T_{RM} formation. The common factors controlling T-bet expression in above-mentioned settings remain unknown. In addition to TGF-β and IL-15, other signals that control the expression of T-bet and Eomes during T_{RM} differentiation remain to be discovered.

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TGF-β signaling pathway is composed of a complicated network of molecular interactions.[143] Briefly, upon ligand binding, TGF-β receptor complex phosphorylates Smad2 and Smad3. Phosphorylated Smad2/3 associate with Smad4 and translocate to the nucleus. In addition to TGF-β, other members of TGF-β superfamily can also activate Smad (e.g., Activins and Bone Morphogenetic Proteins). For instance, Smad4-mediated Myc expression is essential for T cell homeostasis and function via a TGF-β-independent and presumably other TGF-β superfamily member(s)-dependent fashion.[144] Except for Smad4, other factors, such as Tripartite Motif Containing 33 (encoded by *Trim33)* can cooperate with phosphorylated Smad2/3 to initiate transcription.145 Further, TGF-β also activates non-Smad pathways including MAP kinase pathways, Rho-like GTPase and PI3K/Akt pathways.[146] Accumulating evidence suggest that TGF-β does not control T_{RM} differentiation via the canonical Smad4-dependent pathway. Indeed, Smad4 deficient and TGF-β unresponsive $CD8^+$ T cells exhibit opposite phenotypes during T_{RM} differentiation. Smad4 deficient $CD8^+$ T cells exhibit dramatically enhanced differentiation of $CD103^+T_{RM}$ cells comparing with TGF-β unresponsive $CD8^+$ T cells that fail to up-regulate CD103 under similar settings.68 Similarly, TGF-β and Smad4 antagonize each other during Th17 differentiation in $CD4^+$ T cells. TGF-β signaling reverses Smad4-mediated suppression of RORγt via a SKI-dependent mechanism.[147] Whether similar mechanisms are underlying TGF-β-induced T_{RM} differentiation remains to be demonstrated. In addition, TGF-β regulates several T cell-related target genes (e.g., Eomes and RORγt) in a Smad2/3-independent manner.[148,149] TGF-β represses the expression of *Klf2* via the non-Smad PI3K/Akt pathway.46 However, direct genetic evidence to support a TGF-β-dependent and Smad-independent mechanism in T_{RM} differentiation remains to be established. Considering the importance of TGF-β in Th17 $CD4^+$ T cell differentiation, it is interesting to determine the role of TGF-β in type 17 $CD8^+$ T_{RM} cells and the interconnected regulation between TGF-β, T-bet, Eomes and RORγt. Together, considering the facts that Smad3 directly binds to *Itgae* locus, TGF-β may control the differentiation and homeostasis of T_{RM}s via both Smad2/3-dependent and Smad-independent pathways.

C. Blimp1 and Hobit

Homolog of B lymphocyte-induced maturation protein (Blimp1) in T cells (Hobit, encoded by *Zfp683* or *Znf683)* and Blimp1 (encoded by *Prdm 1)* play a universal role in tissue residency of distinct immune cells.[111] In $CD8^+$ T cells, Blimp1 is increased in effector cells and important for efficient effector function and terminal differentiation, whereas Hobit shows relatively low expression in effector and circulating memory $CD8^+$ T cells.[150] In contrast, Hobit expression is specifically up-regulated in T_{RM} cells including $CD8^+$, ILC1 and NKT cells from different anatomical sites. Transcriptional analysis indicates that both Blimp1 and Hobit deletion in $CD8^+$ T cells re-activates genes associated with tissue egress including *Ccr7, S1pr1* and *Klf2*, which in turn enhances the ability of T cells to exit from peripheral tissues and abolishes tissue residency. Deficiency in either Blimp1 or Hobit leads to partial reduction of $CD8^+$ T_{RM} cells, while simultaneously abolishing both Blimp1 and Hobit near-completely inhibits the formation of $CD8^+$ T_{RM} cells in diverse organs including the skin, liver, gut and kidney, suggesting the synergistic function of both TFs is required to establish tissue residency.[111]

In contrast to the situation in mouse T_{RM}, the function of Hobit in human is less clear. The unique induction of Hobit in T_{RM} cells is only observed in mouse. Human T_{EM} cells express a significant level of Hobit. Therefore, even though most other T_{RM} core signature genes are highly conserved between mouse and human, the function of Hobit in human T_{RM}s may require additional evidence.[70,123,151–153]

D. Runx3

Runx protein family (Runx1, 2 or 3) has a unique DNA-binding α subunit, which forms a complex with cofactor CBFβ (Core-binding factor subunit β) that stabilizes the Runx-DNA interaction.[154] As DNA-binding TFs, Runx proteins control thymocyte differentiation and determine the fate of $CD4^+$ and $CD8^+$ T cell lineages. Specifically, Runx3 represses TF Th-Pok (encoded by *Zbtb7b*), therefore inhibits CD4 lineage potential and contributes to the development of $CD8^+$ single-Positive thymocytes.[155,156] Further, Runx3 induces the expression of CD103 in $CD8^+$ single-Positive thymocytes. Synergizing with T-bet and Eomes, Runx3 is required to maintain the cytotoxicity program of activated $CD8^+$ T cells via transcriptional regulation of key effectors including IFN-γ, perforin and granzyme B.[157,158] In addition, Runx3 deploys epigenetic marks (i.e., H3K27me3) to guard the fate of effector $CD8^+$ T cells and prevent the expression of follicular helper T cell-related genes.[159] As to be discussed in the next section, a small population of $CD4^+$ T cells acquire the expression of Runx3 and differentiate into $CD8\alpha\alpha^+$ $CD4^+$ T_{RM} cells in the gut IEL compartment.[160,161] More recently, using computational and pooled *in vivo* RNAi screens, Runx3 is reported to be a critical regulator in the establishment of T_{RM} cell populations in both non-barrier tissues (salivary gland and kidney) and barrier tissues (IEL, skin and lung parenchyma) even though the expression of Runx3 is not specifically induced in T_{RM} cells. Runx3 supports the expression of tissue-residency genes and represses genes associated with egress and recirculation. In addition, Runx3 is also a driver for both human and mouse $CD8^+$ tumor-infiltrating lymphocytes (TILs) that exhibit characteristics of T_{RM} cells.[112]

E. Other TFs and Perspectives

Nur77 (encoded by *Nr4a1*), together with Nurr1 (encoded by *Nr4a2)* and NOR-1 (encoded by *Nr4a3*), constitute the NR4A subfamily of orphan nuclear receptors in the steroid thyroid receptor family.[162] In the thymus, Nur77 controls $CD8^+$ T cell development by suppressing the expression of *Runx3*.[163] In the periphery, as an immediate early response gene downstream of TCR signaling, Nur77 regulates $CD8^+$ T cell expansion and effector function through transcriptional repression of *Irf4*. Lack of Nur77 leads to enhanced $CD8^+$ T cell expansion, especially in $KLRG\text{-}1^+$ terminally differentiated effector cells.[164] T cells from $Nr4a1^{-/-}$ mice display reduced capacity to generate T_{RM} cells, suggesting the potential role of Nur77 in the generation and/or tissue residency of T_{RM} cells. Interestingly, at memory phase of influenza infection, lung and liver T_{RM} cells exhibit a 2 to 4 fold reduction while gut IEL T_{RM}s display a 90 fold decrease in the absence of Nur77 expression. The mechanisms leading to this dramatic tissue-specific requirement of Nur77 remain unclear.[165] Notably, under different infection settings, both lung and liver T_{RM}s, but not gut T_{RM}s require local antigen recognition. The connection between local TCR signal and the requirement of Nur77 in T_{RM}s remains to be visited in the future.

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The expression of Notch and its down-streaming TF recombination signal binding protein for immunoglobulin kappa J (encoded by *Rbpj)* is enriched in human and mouse lung CD103$^+$ T_{RM} cells. Simultaneous disruption of both Notch1 and Notch2 in T cells results in a two-fold reduction in CD103$^+$ T_{RM} cells in the lung after influenza virus infection. Activation of Notch signaling pathway promotes the persistence of CD103$^+$ T_{RM} cells via controlling metabolic programs.70 The involvement of Notch signals in T_{RM} cells isolated from other tissues is largely unknown.

Further, the targeting genes of hypoxia-inducible factor-1α (HIF-1α) are significantly enriched in human lung T_{RM} cells.70 Interestingly, oxygen-sensing prolyl-hydroxylase (PHD) proteins degrade HIF-1α via their enzymatic activity. Disruption of PHD proteins in T cells results in elevated HIF-1α expression and enhanced both CD4$^+$ and CD8$^+$ T cell response specifically in the lung, but not other tissues.[166]

In addition, arylhydrocarbon receptor (AhR) is required for the maintenance of skin T_{RM}167 and γδ T cells in the epithelial surface and CD8αα$^+$ αβ T cells in the IEL compartments of the gut.[168,169]

TFs act as a link between signals from extrinsic microenvironment and intrinsic regulation of cellular response. Fluctuations of environmental cues, including cytokines, chemokines, pathogen insult and the persistence of microbiome can modulate the expression of disparate TFs. The cooperation among these TFs in turn instructs T cell differentiation and/or homeostasis. Considering the dramatically variable microenvironment inside different tissues, the knowledge of tissue-specific control of TFs will be essential to understand T_{RM} biology. After leaving the circulation, tissue-specific transcriptional reprogram represents a key step for T_{RM}s to adapt to the new environment and remains largely ill defined. Further, studies of TF cofactors or epigenetic regulators in T_{RM} formation are just in their infancy. These studies will facilitate our understanding of how TFs from the same family, such as T-bet and Eomes, Blimp1 and Hobit, perfo$_{RM}$ both segregated and cooperative functions at the molecular level. In addition, these investigations will help to address the question that how numerous TFs function in a temporal-and spatial-dependent manner.

III. CD4$^+$ T_{RM} cells

The vast majority of recent T_{RM} studies have been focused on CD8$^+$ T cells. CD4$^+$ T_{RM} cells represent a critical adaptive component of local immunity.[170] We will use the last section to summarize the recent findings about CD4$^+$ T_{RM} cells in various tissues. We will not include Foxp3$^+$ regulatory T cells in our discussion as recent reviews have covered the related findings.[171,172]

A. Skin

Early research in mouse has demonstrated that after skin herpes viral infection, CD8$^+$ T cells fo$_{RM}$ a distinct population of T_{RM} cells in the epidermis while memory CD4$^+$ T cells are largely located in the dermis and continue to recirculate.[32] As unique structure components of the skin, hair follicles produce survival cytokines IL-7 and IL-15, which are essential for the maintenance of skin T cells.[53] As a consequence, skin CD4$^+$ T cells are often clustered

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around hair follicles. Widely used T_{RM} markers CD69 and CD103 are generally believed to contribute to T_{RM} cell retention. Interestingly, even though a significant population of skin $CD4^+$ T cells carry both CD69 and CD103, they reach equilibration with the circulation at steady state, which further questions the function of CD103 in T_{RM} cell biology. Local inflammation promotes $CD8^+$ T cell-and $CD11b^+$ myeloid cell-mediated recruitment and retention of skin $CD4^+$ T cells.[173] Therefore, in the absence of local inflammation, skin $CD4^+$ T cells are a component of circulating memory cells even with typical T_{RM} markers.

Different infection models can induce the formation of bona fide skin-resident $CD4^+$ memory T cells. Skin infection of *Candida albicans* in C57BL/6 mice results in acute infection cleared in less than two weeks. Interestingly, *C. albicans* infection induces a distinct population of IL-17 producing and largely sessile $CD69^+CD4^+$ T_{RM} cells in the superficial layer of the dermis providing *C. albicans-specific* protection.[174] These IL-17^+CD4^+ T_{RM} cells are often co-localized with $CD11c^+$ dendritic cells months after the clearance of the infection, suggesting a role for residual antigen or inflammatory cues for the retention of skin $CD4^+$ T_{RM} population. Consistent with previous findings that many dermis $CD4^+$ T cells are rapidly exchanging with the blood, a substantial subset of circulating $CD4^+$ T cells is present in the deeper layer of the dermis. These mobile skin $CD4^+$ T cells express low levels of CD69 and do not produce IL-17. These results suggest that different local environment within the dermis can support different subsets of memory $CD4^+$ T cells, including both circulating and tissue-resident cells with distinct effector functions.

Another recent example of skin $CD4^+$ T_{RM} comes from *Leishmania major* (*L. major*) infection model in C57BL/6 mice, which leads to prolonged skin lesion that lasts for 12 weeks. After the clearance of the infection, skin $CD4^+$ T_{RM} cells can be identified at both infected and non-infected skin,[175] similar as $CD8^+$ T_{RM} cell spreading to non-infected skin after repeated skin infections.[33] In contrast to skin $CD4^+$ T cells residing in naïve mice,[173] *L. major-specific* $CD4^+$ T_{RM} cells are not exchanging with circulating cells as demonstrated by grafting infected skin into naïve animals. Consistent with the dermal location of skin $CD4^+$ T cells,[32] *L. major-specific* $CD4^+$ T_{RM} cells are sensitive to antibody-mediated depletion. Functionally, during high dose re-challenge, $CD4^+$ T_{RM} -mediated and IFN-γ-dependent recruitment of circulating memory T cells are required for long-term protection.[175] However, during low dose re-challenge, $CD4^+$ T_{RM} and T_{RM}-recruited inflammatory monocytes are sufficient to provide immediate protection without the contribution from circulating T cells.[176]

Human skin harbors a large number of $CD69^+CD4^+$ T cells in the dermis, which is identified as the major T_{RM} population resistant to antibody-mediated depletion. Further, both $CD103^+CD4^+$ and $CD103^+CD8^+$ T cells are enriched in the epidermis of human skin.[31] Keratinocyte derived TGF-β is likely involved in the induction of $CD103^+CD4^+$ T_{RM} cells in human. However, genetic evidence to support a role of TGF-β in skin $CD4^+$ T_{RM}s in mouse is missing.

Strictly speaking, bona fide skin $CD4^+$ T_{RM} cells are only formed under certain infection circumstances in mouse. Local inflammatory signals and cognate antigens may regulate the dynamic behavior of skin $CD4^+$ T cells. CD103 is not a reliable marker for skin $CD4^+$ T_{RM}

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in mouse and the definitive evidence supporting a role of TGF-β in skin $CD4^+$ T_{RM} cell differentiation is lacking.

B. Lung

In both mouse and human lungs, distinct populations of $CD4^+$ T cells carrying typical T_{RM} markers can be identified.[27,28,67,152,177,178] Comparing with $CD8^+$ lung T_{RM}, $CD4^+$ T_{RM} cells usually carry less CD103 or express CD11a instead of CD103.[170,178,179] Genome wide transcriptional analysis reveals that $CD4^+$ lung T_{RM} cells resemble $CD8^+$ lung T_{RM} cells.[151,152,179] Similar transcription programs including the down-regulation of T-bet and Eomes, and the up-regulation of Blimp-1 and Notch signaling, direct the local differentiation of lung $CD4^+$ T_{RM} cells.[152] Interestingly, human and mouse infant T cells (including both $CD4^+$ and $CD8^+$ T cells) express enhanced levels of T-bet and exhibit defective lung T_{RM} cell formation, further suggesting that down-regulation of T-bet is a conserved common mechanism underlying both $CD4^+$ and $CD8^+$ T_{RM} differentiation.[142]

Local signals that induce lung $CD4^+$ T_{RM} cells are not entirely known. Similar as $CD4^+$ T_{RM} clusters in the skin and vagina, clusters of lung $CD4^+$ T_{RM} have been identified after influenza virus infection,[170] suggesting a common mechanism underlying $CD4^+$ T_{RM} differentiation and/or maintenance. In contrast to lung $CD8^+$ T_{RM} cells, one report has suggested that mouse lung $CD4^+$ T_{RM} is TGF-β-independent, consistent with a $CD103^-$ phenotype. Distinct from $CD103^+CD8^+$ T_{RM}, IL-15 is required during the early differentiation, but not the long-term maintenance of $CD4^+$ lung T_{RM} cells in mouse.[179] Following both acute viral infection (a Th1 response) and brief allergy exposure-induced lung inflammation (a Th2 response), a clear population of lung-resident antigen-specific $CD4^+$ T cells that is separated from bloodstream forms in an IL-2-dependent manner and play essential functions in local immunity.[180,181] In response to prolonged allergen exposure, a similar $CD69^+$ and Th2-biased $CD4^+$ T_{RM} population persists in the lung parenchyma.[182] Even in the absence of circulating T cells, these $CD4^+$ T_{RM}s are sufficient to mount a robust recall response. Similar autologous recall response has also been observed for helminth-induced lung $CD4^+$ T_{RM}s after T cell migration has been blocked.[183] Together, similar as lung $CD8^+$ T_{RM} cells, lung $CD4^+$ T_{RM} cells are formed under various infectious and inflammatory settings. However, the cellular and molecular mechanisms underlying their differentiation and long-term maintenance remain to be demonstrated.

C. Other Non-lymphoid Tissues

Murine cytomegalovirus infection induces a distinct population of $CD69^+CD4^+$ T_{RM} cells in the salivary gland. In contrast to antigen-independent differentiation of $CD8^+$ T_{RM} cells in the same tissue and same infection model, $CD4^+$ T_{RM} formation requires local antigen in the salivary gland.[114] The role of TGF-β in salivary gland $CD4^+$ T_{RM} remains undetermined.

In both naïve and mucosal infected mice, $CD69^+CD103^-CD4^+$ T_{RM} cells are identified in the white adipose tissue and provide potent protective response.[130] White adipose tissue $CD4^+$ T_{RM} cells are isolated from circulation as demonstrated by parabiosis experiments. Further, they carry mucosal homing integrin α4β7.[130] Considering that TGF-β inhibits

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integrin α4β7 expression on effector $CD8^+$ T cells,[90] it will be interesting to test the involvement of TGF-β signaling in white adipose tissue $CD4^+$ T_{RM}.

Further, genital mucosa supports $CD4^+$ T_{RM} cell differentiation after herpes simplex virus infection. Similar as skin and lung $CD4^+$ T_{RM} cells, genital CD4 T_{RM} cells fo_{RM} clusters.[135] In contrast to the more mobile behavior of skin $CD4^+$ T_{RM} cells isolated from mouse dermis, vaginal $CD4^+$ T_{RM} cells are locally restricted and isolated from the circulation. Remarkably, even mucosal vaccination at a remote site (i.e., intra nasal priming) induces protective $CD4^+$ T_{RM} formation at vaginal mucosa in a Chlamydia infection model. Similar as $CD8^+$ T_{RM} cells, vaginal $CD4^+$ T_{RM} differentiation is limited to the early stage of effector phase when a large number of activated T cells exit secondary lymphoid organs and migrate to peripheral mucosal sites.[184] The relationship between TGF-β and the differentiation of $CD4^+$ T_{RM} in FRT remains unknown.

Comparing with $CD8^+$ T_{RM}s, $CD4^+$ T_{RM}s are a minor cell population within the IEL compartment of the small intestines in naïve specific pathogen free mice.[21] Most of these unique $CD4^+$ T_{RM} cells carry surface expression of CD 8αα. Both conventional effector and regulatory $CD4^+$ T cells can differentiate into IEL CD8αα+ $CD4^+$ T_{RM} cells in response to specific microbiota stimulation.[185] In addition, gut enriched local signals, such as TGF-β and retinoic acid are essential for the differentiation of $CD8\alpha\alpha^+CD4^+$ T_{RM} cells in the IEL compartment. The down-regulation of lineage specific TF Th-POK (conventional $CD4^+$) or Foxp3 (Treg) and the up-regulation of T_{RM} and $CD8^+$ related TF Runx3 are crucial for their differentiation.[160,161,186]

Distinct from microbiota-induced $CD8\alpha\alpha^+CD4^+$ T_{RM} cells, listeria oral infection leads to the differentiation of $CD4^+$ gut T_{RM} cells without the surface expression of CD 8aa. These $CD4^+$ T_{RM} cells carry CD69 and reside in both IEL and LP compartments.[187] A small percentage of IEL $CD4^+$ T_{RM} cells also express CD103. These gut $CD4^+$ T_{RM}s provide essential Th1 response-mediated protection against re-infection and maintained in an IL-15-independent manner, similar as gut $CD8^+$ T_{RM} cells. Intestine-restricted helminth infection induces a large population of Th2 $CD4^+$ memory T cells in both gut LP compartment and peritoneal cavity. However, whether these protective Th2 memory $CD4^+$ T cells are bona fide T_{RM}s remains elusive.[188]

Together, consistent with the complexity and plasticity of effector $CD4^+$ T cell differentiation programs, different local signals drive the differentiation of distinct $CD4^+$ T_{RM} cells at the intestinal mucosal surface.

D. Secondary Lymphoid Tissues

A series of recent discoveries have demonstrated that a significant population (up to 50%) of $CD44^{hi}$ effector/memory $CD4^+$ T cells reside in secondary lymphoid organs (i.e., spleen, LNs and Peyer's patches) without continuous recirculation for a prolonged period of time.[26,189–191] Similar as T_{RM} isolated from non-lymphoid organs, these secondary lymphoid organ $CD4^+$ T_{RM} express higher levels of CD69 and lower levels of S1pr1 than their circulating counterparts. In contrast to the widely accepted notion that secondary lymphoid organs are mainly occupied by circulating T cells, antigen-specific $CD4^+$ memory T cells

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residing in the draining lymph nodes are largely sessile after immunization.[191] Further, similar CD4$^+$ T$_{RM}$ cells are present in the secondary lymphoid organs of naïve specific pathogen free mice presumably due to prolonged TCR stimulation by self-antigens and microbiome-derived antigens. The population of secondary lymphoid organ CD4$^+$ T$_{RM}$ expands with age.[26] Interestingly, a significant population of secondary lymphoid organ CD4$^+$ T cells express T$_{RM}$ marker CD69 in adult human.[151] These secondary lymphoid organ T$_{RM}$s may represent a conserved phenomenon in CD4$^+$ T cell biology although the functional importance and molecular control of these CD4$^+$ T$_{RM}$s remain to be determined.

In summary, with unique tissue-specific features, CD4$^+$ T$_{RM}$ cells are present in a variety of lymphoid and non-lymphoid tissues, and play a non-redundant function in local immunity. Considering the complexity of effector CD4$^+$ T cell lineages, the differentiation and maintenance of CD4$^+$ T$_{RM}$ cells may be controlled in a tissue-specific and inflammation-specific manner while preserve a common gene signature that restricting the recirculation. TGF-β controls the differentiation of almost every individual lineage of effector CD4$^+$ T cells under certain conditions. However, the contribution of TGF-β signal to CD4$^+$ T$_{RM}$ cells remains largely unknown presumably due to the difficulties to dissect the roles of TGF-β in tissue residency from those in effector CD4$^+$ lineage specification.

Conclusions

T$_{RM}$ cells represent a major memory T cell population without continuous recirculation. Recent advances have established that common transcriptional and metabolic programs distinguish T$_{RM}$ cells from circulating T cells and are closely associated with the behavior and function of T$_{RM}$ cells. In various infection settings, it has been demonstrated that T$_{RM}$ cells can function both as an alarming system and a self-sufficient defense system without significant contribution from circulating T cells, which further emphasize the importance of inducing desired T$_{RM}$ populations in future vaccine design.

In addition to the common differentiation programs, to establish residency in different tissues, T$_{RM}$ cells are required to adapt tissue-specific programs to accommodate unique local environmental cues. Recent investigations have accumulated evidence to support the paradigm that local signals, including cognate antigens, TGF-β, survival and inflammatory cytokines may impact T$_{RM}$ cells in a tissue-specific and infection-specific manner. The mechanisms underlying tissue-specific T$_{RM}$ regulation remain largely unknown. Even within a given tissue, the microenvironment is not homogenous. Thus, it is conceivable that the heterogeneity of T$_{RM}$ population in a given tissue may be tightly linked with their functions. Together, studies on the intercellular and intracellular programs that are induced by local environmental signals may provide important information to deepen our understanding of T$_{RM}$ biology and guide the development of TRM-focused future vaccine strategies.

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Glossary

T_{CM}	Central memory T cell
DC	Dendritic cell
T_{EM}	Effector memory T cell
FRT	Female reproductive tract
IEL	Intraepithelial lymphocyte
LP	Lamina propria
LN	Lymph node
TCR	T cell receptor
T_{RM}	Tissue-resident memory T cell
TF	Transcription factor
TGF-β	Transforming growth factor-β
VACV	Vaccinia virus

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Table 1.

Tissue-specific features of $CD8^+$ T_{RM}s.

	Local Ag	**TGF-β**	**IL-15**	**Xcr-1$^+$DC**	**CD4-help**	**Unique Effector**
Skin	N.R., but promote	Required *	Required	Required	N.R. ?	IL-17 from a subset
Lung	Required	Required *	Required	Required	Required	IL-22
URT	N.R.	N.R.	Unknown	Unknown	Unknown	Unknown
SI	N.R./Suppress	Required *	N.R.	Unknown	Unknown	Type I/III IFN
FRT	N.R.	Unknown	N.R.	Unknown	Required	Unknown
Kidney	Unknown	Promote	Required	Unknown	Unknown	Unknown
SG	N.R.	Required *	Required	Unknown	Unknown	Unknown
Liver	Required	Maybe	Maybe	Unknown	Unknown	CSF-2
Brain	Required	Maybe	Maybe	Unknown	N.R.	Unknown
WAT	Unknown	Unknown	Maybe	Unknown	Unknown	Unknown

URT, Upper respiratory tract; SI, Small intestine; FRT, Female reproductive tract; SG, Salivary gland; WAT, White adipose tissue.

Ag, Antigen; N.R., not required.

*, TGF-β is required for $CD103^+$ TRM, but not for $CD69^+CD103^-$ TRM.

?, The involvement of CD4-help in skin T_{RM} formation may require future investigation.