IMMUNOLOGY

The evolving role of tissue-resident memory T cells in infections and cancer

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Resident memory T cells (T_{RM}) form a distinct type of T memory cells that stably resides in tissues. T_{RM} form an integral part of the immune sensing network and have the ability to control local immune homeostasis and participate in immune responses mediated by pathogens, cancer, and possibly autoantigens during autoimmunity. T_{RM} express residence gene signatures, functional properties of both memory and effector cells, and remarkable plasticity. T_{RM} have a well-established role in pathogen immunity, whereas their role in antitumor immune responses and immunotherapy is currently evolving. As T_{RM} form the most abundant T memory cell population in nonlymphoid tissues, they are attractive targets for therapeutic exploitation. Here, we provide a concise review of the development and physiological role of $CD8^+$ T_{RM}, their involvement in diseases, and their potential therapeutic exploitation.

INTRODUCTION

Memory responses enable humans and animals to rapidly mount an effective response to previously encountered pathogens. Memory T cells (T_{MEM}) constitute an essential component of secondary defense to viruses and other threats to health. T_{MEM} are heterogeneous with unique transcriptional programs and protein expression that correspond to functionality, frequency, and localization. Reflecting growing appreciation for more complex T cell heterogeneity (*1*), T_{MEM} can be broken up into three main subsets: central memory (T_{CM}), effector memory (T_{EM}), and tissue-resident memory T cells (T_{RM}) (*1*–*3*). T_{CM} and T_{EM} collectively comprise a pool of $CD8^+$ circulating memory cells (T_{CIRCM}) that move through the bloodstream and lymph as a means of providing secondary defense. T_{RM} have been the subject of intense investigation because of their abundance, heterogeneity in tissues, and residence in nearly all tissues examined in mice and humans including secondary lymphoid organs (SLOs), and nonlymphoid tissues (NLTs) including barrier tissues (skin, gut, etc.) and nonbarrier tissues (brain, liver, etc.) (*2*, *4*–*6*). Elegant experiments have identified T_{RM} as nonmigratory (*7*, *8*) and with a unique capacity of coordinating rapid immune responses (*9*–*11*). Developmentally, T_{RM} are thought to arise early on during the peak effector T cell expansion phase because, within tissues, these cells exhibit 90% of signature transcripts that identify and differentiate T_{RM} from T_{CIRCM} (*6*, *12*). Despite this central transcriptional understanding, the exact mechanisms that underpin T_{RM} ontogeny remain poorly understood. Two models have been proposed for the T_{RM} lineage divergence: one supporting tissue-specific differentiation and local divergence and a second supporting systemic residence memory differentiation and systemic divergence (*6*). The local divergence model proposes that factors within a specific tissue microenvironment drive the memory cell population toward a T_{RM} fate. Experimental evidence supporting this model hinges on the entry of memory cells to NLTs expressing factors, such as transforming growth factor–β (TGF-β) and interleukin-15 (IL-15), which can promote differentiation and survival of T_{RM} (*13*). In contrast, the systemic residence memory differentiation and systemic divergence model posits that T cells are transcriptionally marked and skewed toward a specific subset fate before tissue entry. Studies have generated direct experimental evidence that naïve T cells with variable or identical T cell receptors (TCRs) can skew progeny toward either a T_{RM} or T_{CIRCM} lineage based on exposure to different encounters during priming. For example, interactions of $CD1c^+CD163^+$ dendritic cells (DCs) with naïve T cells can drive a T_{RM}-specific phenotype (*14*); monocytes have the ability to drive T_{RM} differentiation by IL-10–mediated TGF-β release (*15*), whereas migratory DC (*16*) and keratinocytes promote T_{RM} differentiation by activating TGF-β (*17*). In addition to providing insight into the developmental process, both these models also highlight the uniquely plastic potential of T_{RM} that can not only be transcriptionally influenced before entry to a tissue but also adapt to unique tissue microenvironments to enable distinct functionality.

T_{RM} ESTABLISHMENT

Given their unique role as mediators of localized responses within NLTs, the transcriptional changes that T_{RM} undergo during differentiation have been extensively studied (Fig. 1). Up-regulation of four transcription factors have been identified as important for T_{RM} development: *Runx3*, *Notch*, *Hobit*, and *Blimp1 (12*, *18*–*20)*. Computational analysis of an in vivo RNA interference screen identified *Runx3* as a critical regulator of T_{RM} differentiation, homeostasis, and expression of tissue-resident genes (*12*). Use of an adoptive transfer mouse model of melanoma provided evidence that *Runx3*-deficient T cells failed to accumulate within tumors, resulting in greater growth and mortality, whereas T cells overexpressing *Runx3* had greater abundance and resulted in prolonged survival, and greater functionality compared to controls (*12*). *Hobit*, a homolog of *Blimp1*, has been shown to be important for the development of T_{RM} in mice

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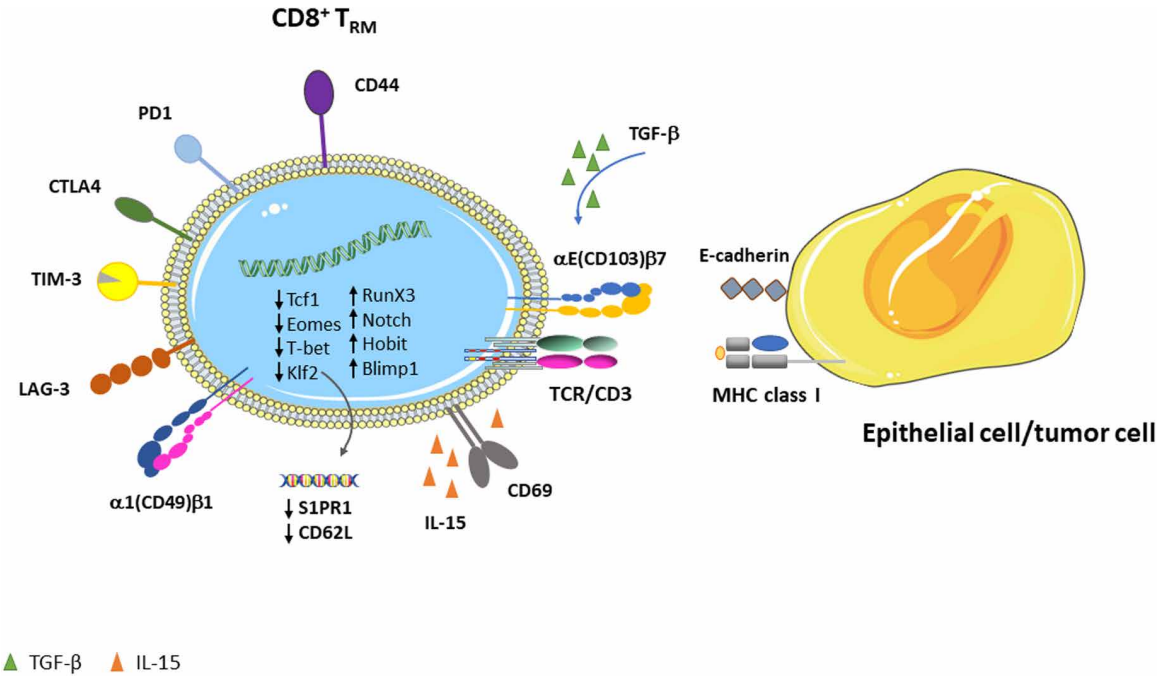

Fig. 1. Characteristics of T_{RM}. T_{RM} are identified by CD103 and CD69 expression. CD103 interacts with E-cadherin and promotes T_{RM} effector function and retention at mucosal tissues. TGF-β and IL-15 promote differentiation and survival of T_{RM}. T_{RM} can express several immune checkpoint receptors including PD-1, TIM-3, CTLA-4, and LAG-3, depending on the tissue/context. General transcriptional profile includes expression of Runx3, Hobit, Blimp1, and Notch and down-regulation of T-bet, Eomes, and Klf2. T_{RM} also display decreased expression of the egress receptors CD62L and S1pr1.

(*21*). Using a *Hobit* reporter/deleter system, it was found that virus-specific T_{RM} development required *Hobit*, a transcription factor exclusively expressed in T_{RM} precursors and absent from T_{CIRCM}. It was also found that Hobit and Eomes expression displayed an inverse correlation and that expression of Hobit in $CD8^+$ T effector cells was regulated by T-bet and Eomes, which induced or suppressed Hobit expression, respectively (*21*). In addition, T_{RM} display decreased expression of Klf2, which regulates expression of CD62L and sphingosine-1-phosphatase receptor 1 (S1pr1) (*22*). *Runx3*, *Hobit*, *and Blimp1* are all up-regulated within precursor T_{RM} but down-regulated within T_{CIRCM}, highlighting that unique developmental lineages are present during memory differentiation (*20*). More recently, single-cell RNA-sequencing (RNA-seq) analysis identified other essential transcription factors for T_{RM} generation such as *Nr4a2*, *Junb*, and *Fosl2*. *Junb* and *Fosl2* are both essential to down-regulate T-bet expression, whereas *Fosl2* is also a positive regulator of Smad3, a key transcription factor of TGF-β signaling, which is an indispensable cytokine for T_{RM} development (*23*). A distinct set of transcription factors has been identified in $CD103^+$ lung-resident T_{RM}, among which Notch has a mandatory role for their maintenance and persistence (*20*). In the lung, *Blimp1* works in conjunction with *Hobit*, or instead of it, to suppress the expression of genes involved in tissue egress including *CCR7* and *S1pr1* (*19*, *24*).

Within NLT, either barrier or nonbarrier, along with transcriptional changes, T_{RM} down-regulate expression of receptors that promote T cell recirculation including S1pr1, CD62L (L-selectin) (*25*, *26*), and CCR7 (*22*, *27*), thereby reducing their mobility and enabling localization within tissues. In contrast, T_{RM} up-regulate expression of integrins such as CD103 and CD49a (*28*, *29*). CD103 (integrin αE; encoded by Itgae) pairs with integrin β7 to form a complete heterodimeric integrin molecule aEβ7 at epithelial barriers and enables binding to the epithelial marker E-cadherin, providing insight into the surveillance functions of T_{RM} in mucosal tissues.

PHYSIOLOGICAL ROLES OF T_{RM}

T_{RM} provide a unique role in orchestrating local secondary defense responses. There are three main traits by which T_{RM} aid in secondary defense: longevity and residence in NLT, immediate cytotoxic response, and recruitment and activation of other defense responders. The high expression of CD49a or CD103 T_{RM} within NLTs, such as the epidermis, is induced in response to local antigen challenge (*29*). In addition, some T_{RM} have increased expression of CXCR3 and medium to low expression of CX3CR1 (*20*, *29*, *30*). The increased expression of CXCR3 might provide a mechanistic understanding of the role T_{RM} play in type 1 responses in certain tissues such as the lungs, as CXCL9, CXCL10, and CXCL11 are ligands for CXCR3 and are commonly released at local inflammatory sites during type 1 responses (*31*). T_{RM} express basal levels of cytotoxic molecules such as granzyme B, which are up-regulated upon reactivation, enabling a rapid cytotoxic function. T_{RM} can also heterogeneously express inhibitory receptors including PD-1, TIM-3, CTLA-4, BTLA, LAG-3, SPRY1, adenosine receptor A2AR, CD39, CD101, and 2B4, although it is currently unclear whether this expression is independent of antigen persistence or is induced upon antigen reexposure (*32*, *33*). The precise role of these inhibitory receptors in T_{RM} is currently unclear. However, T_{RM} can be reactivated and mediate effector functions despite the presence of these inhibitors (*34*, *35*).

T_{RM} have unique roles within the tissues that they reside as first responders and local regulators of defense during pathogen reencounter,

which is anatomically and functionally distinct from a primary T cell response. During a primary immune response, naïve T cells are primed in SLOs, such as lymph nodes (LNs) and other internal sites, which drain infected barrier tissues. Once primed, T cells proliferate and enter tissues to initiate effector responses. This can be likened to an "inside-out" response originating in SLO (inside) and migrating out to peripheral tissues where they can mediate effector responses. In contrast, during a recall response, T_{MEM} residing in peripheral tissues after resolution of infection respond rapidly upon rechallenge activating local immunity and, recently demonstrated in viral infections, can rejoin the circulation and repopulate lymphoid structures. This can be likened to an "outside-in" response originating in tissues (outside) and migrating in to SLO/blood. During this recall response, T_{RM} produce inflammatory cytokines and develop a broad spectrum of defensive responses by altering the properties of neighboring cells, thereby promoting DC maturation, activation of natural killer (NK) and T cells, and recruiting circulating innate and adaptive cells to tissues. T_{RM} can also participate in viral clearance by directly killing infected cells due to their cytolytic capacity (*36*). During recall, T_{RM} can up-regulate cellular egress receptors but do not undergo terminal differentiation, allowing interconversion between T_{RM} and T_{CIRCM} (*37*). Thus, due to developmental plasticity, T_{RM} may be able to replenish T_{CIRCM} populations after reexposure to pathogens or maintain their T_{RM} fate depending on the tissue microenvironment (*10*, *37*).

T_{RM} IN VIRAL IMMUNITY

Function, classification, and origin of T_{RM} in viral immunity

T_{RM} are positioned in tissues to rapidly mount a defensive response upon a secondary encounter with a pathogen and restrict infection within local tissues (Fig. 2 and Table 1). Although T_{RM} were initially identified in pathogen entry sites such the mucosae, they are now known to have an emerging role in internal organs including the liver and brain (*38*–*40*). In these tissues, it is thought that their protective responses strike a balance between infection control and immunotoxicity. For instance, brain T_{RM} are sufficient to protect against intracranial lymphocytic choriomeningitis virus (LCMV) infection with minimal immunotoxicity; however, this is exacerbated by T_{CM}, which produce immunopathological damage in the brain (*41*).

Successful retention of pathogen-specific T_{RM} relies on unique tissue properties such as structure and nutrient availability (*3*). T_{RM} adapt themselves in the distinct features of different tissues, thereby resulting in distinct phenotypes. This has hindered a clear classification of T_{RM} based on expression markers and raised a debate about their activation status. Currently, CD103 and CD69 are no longer considered exclusive identification markers for T_{RM}. For instance, following herpes simplex virus 1 (HSV1) infection in the skin, $CD8^+$ T_{RM} found in the epidermis were mainly $CD103^+$ and showed a high effector function, whereas dermal T_{RM} were $CD103^-$ but presented higher proliferative capacity (Fig. 2) (*42*, *43*). It was reported that $CD8^+$ T cells specific for nonhepatotropic viruses such as cytomegalovirus (CMV), HSV, and Epstein-Barr virus (EBV) were present in the $CD103^-$ subpopulation but not in the $CD103^+$ subpopulation (*44*). Similarly, $CD103^+$ T_{RM} exhibited a higher production of interferon-γ (IFN-γ) than their $CD103^-$ counterparts after murine polyomavirus (MuPyV) infection in the brain (Fig. 2) (*45*). Furthermore, these $CD103^+$ T_{RM} specific for chronic polyomavirus infection and an acute vesicular stomatitis virus infection expressed the inhibitory marker PD-1, while $CD103^+$ cells from the spleen did not (*34*, *35*). Notably, despite PD-1 expression, brain T_{RM} has the ability to respond effectively to antigen reexposure. For this reason, it has been proposed that PD-1 expression in brain T_{RM} might have a beneficial role by curbing T_{RM} overactivation that might lead to detrimental immunopathology, without preventing immune activation sufficient to mediate viral clearance (*38*).

T cells generated during antigen encounter at effector and memory phases of infection have distinct expression profile of immune markers. In the intestinal tissue, two discrete lineages of antigen-specific $CD8^+$ T cells have been identified (Fig. 2) (*46*, *47*). The first is constituted of $Blimp^{hi}Id3^{lo}KLRG1^{hi/int}CD127^{lo}$ cells, representing tissue-resident T effector cells and is mainly abundant during the early phase of infection. The second is characterized by a $Blimp1^{lo}Id3^{hi}KLRG1^{lo}CD127^{hi}$ signature, which identifies T_{RM} and predominates during later infection incidents (Fig. 2).

Mechanisms of T_{RM} action in viral immunity

In the skin and female reproductive tract, it has been shown that even in the absence of antigen, T_{RM} patrol tissues extending dendrite-like arms in search of antigens during their inactivated state (*48*). Upon reencounter with cognate antigen, T_{RM} limit their motility, boost their proliferative capacity, and alert the tissue to a reinfection (*42*, *49*). T_{RM} secrete cytokines that trigger rapid adaptive and innate immune responses, including local humoral responses, maturation of local DCs, activation of NK cells, and recruitment of T_{CIRC} cells (*10*, *11*). These combined actions of T_{RM} on innate immune activation profoundly alter the local tissue environment, creating a "pathogen alert" state that is sufficient to provide immediate protection from infection, even after challenge with an antigenically unrelated virus (*9*–*11*). Moreover, IFN-γ release by activated T_{RM} up-regulates adhesion molecules such as VCAM-1 and chemokines such as CXCL9 and CXCL10, facilitating the entry of circulating $CD8^+$ T cells to the tissues (*10*, *50*). By using a mathematical predictive model, it was proposed that the rapid elimination of HSV-2 latent virus reactivation in genital tissues, despite the low abundance of T_{RM}, might rely practically on the potent antiviral response mediated by bystander cells (*51*). An intriguing study using intracranial LCMV infection in mice suggested that T_{RM} may also be capable of an autonomous cytotoxic response within the brain to mediate viral clearance. In this work, it was found that in mice depleted of circulating CD8 T cells, T_{RM} adopted effector cell functions upon viral rechallenge and killed infected cells through the release of granzyme B and perforin, achieving pathogen control independently of T_{CIRC} cells and NK cells (*41*). However, the extent to which this autonomous cytotoxic T_{RM} response occurs in other tissues/infections is unclear, and several of the studies outlined above suggest that although the recognition of infected cells by antigen-specific T_{RM} is necessary for mounting an active response, other cell populations also contribute to tissue-wide protection.

Maintenance of pathogen-specific T_{RM} in tissues

Despite extensive studies, it is still unclear when, where, and how T cells are committed to transformation into T_{RM} after pathogen encounter. Two main models have been proposed to explain T_{RM} origin in the context of viral infections. The first, "one cell, one fate," model supports that each naïve T cell can only generate one type of memory cell, i.e., T_{EM}, T_{CM}, or T_{RM}. This fate determination might be based on TCR–major histocompatibility complex (MHC) interaction strength, although there is contradictory evidence for what

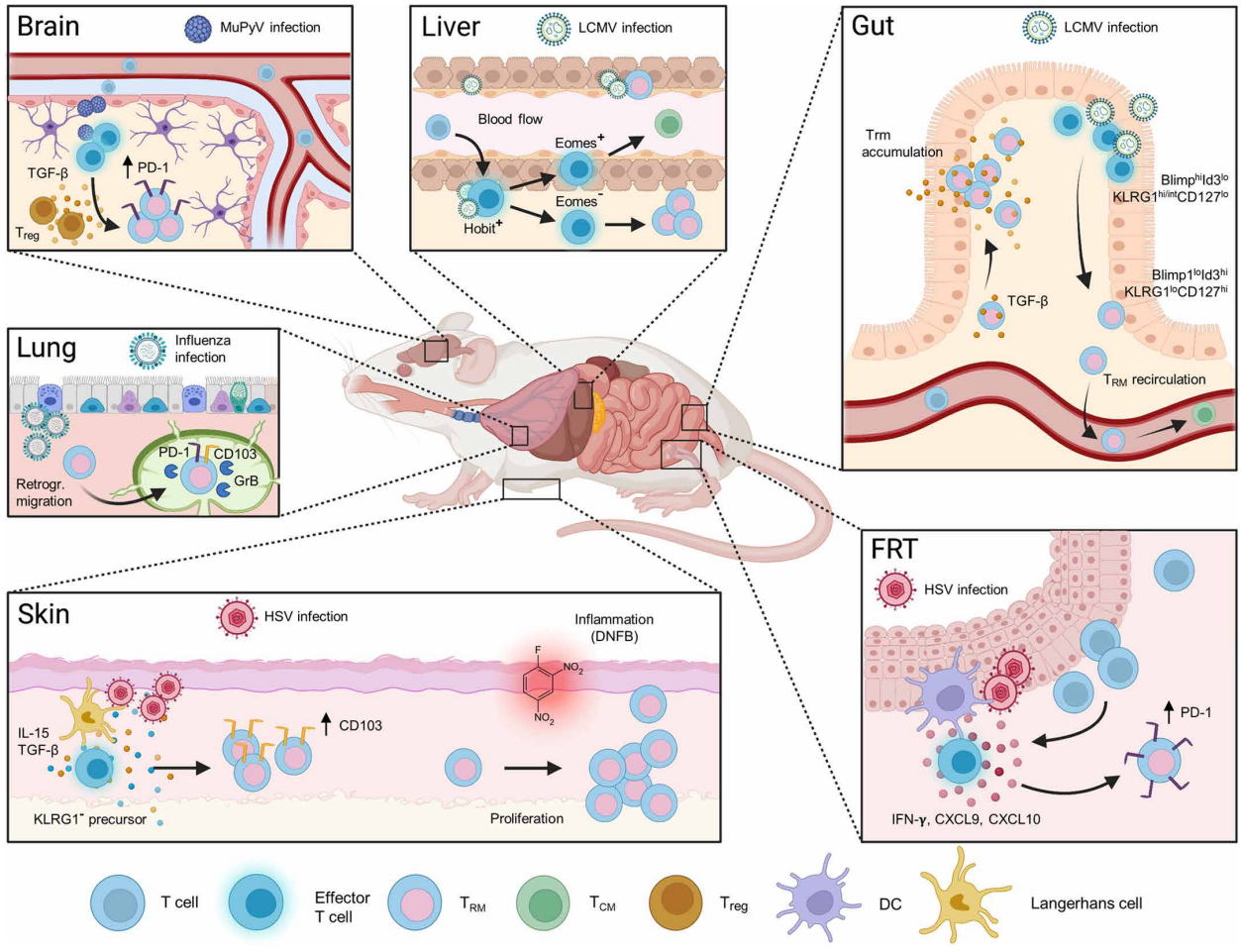

Fig. 2. Examples of T_{RM} in viral infections. T_{RM} develop in NLTs after viral infections. Brain T_{RM} express PD-1, and in MuPyV infection models, their recruitment is facilitated by TGF-β release by T_{regs} (*35*, *137*). In the liver, Hobit$^+$ effector T cells were identified as precursors of T_{MEM}, giving rise to T_{CM} or T_{RM}, characterized by up-regulation or down-regulation of Eomes, respectively (*21*). In the gut, during LCMV infection, T_{EF} cells are characterized by a Blimp1^{hi}Id3^{lo}KLRG1$^{hi/int}$CD127^{lo} phenotype, which switch to Blimp1^{lo}Id3^{hi}KLRG1^{lo}CD127^{hi} in the newly generated T_{RM}, in response to TGF-β (*46*, *47*). Gut T_{RM} may also exit tissue and convert to other types of T_{MEM} (*37*). Influenza-specific T_{RM}, expressing PD-1, CD103, and granzyme B (GrB), can repopulate lung-draining LNs (*66*). In the skin, after HSV infection, T_{RM} are generated from KLRG$^-$ T_{RM} precursors, which up-regulate CD103 expression under the control of local IL-15 and TGF-β production (*60*). Skin T_{RM} expansion can be boosted by inflammatory stimuli, such as DNFB (*67*). IFN-γ, CXCL9, and CXCL10 recruit T cells to HSV-infected female reproductive tract (FRT) and up-regulate PD-1 expression in T_{RM} (*10*, *50*).

magnitude of signal strength promotes T_{RM} establishment. For example, following persistent MuPyV intracerebral inoculation in mice, brain T_{RM} presented a 20-fold higher mean affinity than splenic CD8$^+$ T_{MEM} for the immunodominant epitope of MuPyV (*52*). This is supported by a study finding that higher-affinity CD8$^+$ T cells specific for chronic *Toxoplasma gondii* were preferentially retained in the brain (*53*). In contrast, during a systemic MuPyV infection, TCRs with weak affinity preferentially formed more functional brain T_{RM} (*54*). This is consistent with a recent study that found that low-affinity TCRs favored the formation of lung T_{RM} (*55*).

The second, "one cell, multiple fates," model advocates that a single naïve T cell can differentiate into any T cell precursor, and its fate might depend on three determinants: asymmetric cell division (ACD), inflammatory/costimulatory signal strength, and antigenic decreasing potential (*56*). ACD implies unequal inheritance of intracellular components, which will produce two different daughter cells. A correlation between cell stemness and ability of CD8$^+$ T cells to undergo ACD has been proposed (*57*). Using CD8$^+$ T cells isolated from spleens of LCMV-infected mice and evaluating ACD based on CD8 cell surface distribution after stimulation, it was observed that both naïve and memory CD8$^+$ T cells, but not short-lived effector cells (SLECs) or exhausted cells, maintained the ability to generate asymmetry during mitosis. Transient inhibition of the mammalian target of rapamycin (mTOR) pathway, which is thought to promote memory generation (*58*), increased ACD rates in CD8$^+$ T cells. A higher ACD leads to improved memory potential and viral clearance and increased memory and homing signatures, including up-regulated expression of *Il7r*, Ccr7, and *Cxcr3* (*57*).

In addition to the antigen-mediated signal strength that governs the level of activation, costimulatory signals and cytokines also determine T cell fate. In this regard, a study evaluated the effects of IFN-α/β and IL-12 signaling on the differentiation of SLEC and memory precursor effector cells (MPECs). In Indiana vesiculovirus (VSV)–ovalbumin–infected mice, adoptively transferred IFNAR$^{-/-}$ and IL-12rβ$^{-/-}$IFNAR$^{-/-}$ OT-I cells not only failed to generate SLEC but also displayed increased MPEC, suggesting that inflammatory

Table 1. Role of T_{RM} in viral immunity. CMV, cytomegalovirus; MCMV, murine cytomegalovirus; HSV, herpesvirus; EBV, Epstein-Barr virus; MuPyV, murine polyomavirus; LCMV, lymphocytic choriomeningitis virus; VacV, vaccinia virus; VSV, Indiana vesiculovirus; HBV, hepatitis B virus; HPV, human papillomavirus; SIV, simian immunodeficiency virus; T_{RM}, tissue-resident memory T cells; T_{CM}, central memory T cells; T_{EM}, effector memory T cells; NLT, nonlymphoid tissue; SLO, secondary lymphoid organ; LN, lymph node; HIF-2α, hypoxia-inducible factor–2α; PD-1, programmed cell death–1; Blimp1, B lymphocyte–induced maturation protein 1; KLRG1, killer cell lectin-like receptor subfamily G member 1; Id3, inhibitor of DNA binding 3; Nr4a2, nuclear receptor subfamily 4 group A member 2; Fosl2, FOS like 2; TGF-β, transforming growth factor–β; T-bet, T-box expressed in T cells; FRT, female reproductive tract; IFN-γ, interferon-γ; CXCL9 and CXCL9/10, C-X-C motif chemokine ligand 9/10; VCAM-1, vascular cell adhesion molecule–1; GrB, granzyme B; Hobit; homologous of Blimp1 in T cells; Runx3, runt-related transcription factor 3; S1PR1/5, sphingosine-1-phosphate receptor 1/5; CD62L, selectin L; FA, fatty acid; FABP4/5, fatty acid binding protein 4/5; mTOR, mammalian target of rapamycin; Klf2, Krüppel-like factor 2; TIM-3, T cell immunoglobulin mucin 3; CTLA-4, cytotoxic T lymphocyte antigen 4.

Virus	Host	Tissue	Phenotype	Findings	References
CMV, HSV, EBV	Human	Liver	$CD8^+CD69^+CD103^-$	$CD8^+CD69^+CD103^-$ T_{RM} development depended on HIF-2α up-regulation	(*44*)
HSV1	Mouse	Epidermis	$CD103^+$	Predominantly effector function	(*42*, *43*)
		Dermis	$CD103^-$	Showed higher proliferation	
MuPyV	Mouse	Brain, spleen	PD-1	T_{RM} in brain were PD-1^+ but PD-1^- in the spleen	(*35*)
LCMV Armstrong	Mouse	Intestine	Blimp1, KLRG1, CD127, Id3, *Nr4a2*, *Junb*, *Fosl2*, TGF-β	Effector phase cells were $Blimp^{hi}Id3^{lo}KLRG1^{hi/int}CD127^{lo}$ and memory cells $Blimp1^{lo}$ $Id3^{hi}KLRG1^{lo}CD127^{hi}$; Junb and Fosl2 repress T-bet; Fosl2 up-regulates TGF-β	(*23*, *46*)
MCMV	Mouse	Brain	TGF-β	T_{regs} recruit T cells by producing TGF-β	(*137*)
HSV-2, LCMV	Mouse	FRT	IFN-γ, CXCL9, CXCL10, VCAM-1	These molecules recruit T cells to infected zone and up-regulate PD-1	(*9*–*11*, *50*)
HSV-2	Human	Genital tract, in silico	IFN-γ, GrB		(*51*)
HSV	Mouse	Skin	KLRG1, IL-15, TGF-β	$CD8^+CD103^+$ T_{RM} are generated from KLRG1$^-$ T_{RM} precursors after infection and entrance in tissue, through IL-15 and TGF-β, which up-regulates CD103	(*60*)
LCMV	Mouse	Intestine, lung, skin, brain, kidney, salivary glands, brain	Blimp1, Hobit, Runx3, S1PR1, CD62L	T_{RM} development requires up-regulation of Blimp1, Hobit, and Runx3 and down-regulation of S1PR1 and CD62L	(*12*, *18*, *22*)
VacV	Mouse	Skin	FABP4, FABP5	FABP4 and FABP5 permit FA uptake for T_{RM} metabolism switch to lipid β-oxidation	(*77*)
LCMV, VacV	Mouse	Liver, lung	PD-1, mTOR	PD-1 regulates mTOR ensuring T cell metabolism switches to FA β-oxidation	(*138*)

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Virus	Host	Tissue	Phenotype	Findings	References
LCMV, VSV	Mouse	Skin, FRT, spleen	*Klf2*, *s1pr1*, *s1pr5*, CD62L	Antigenic stimulation in NLT enhanced T_{RM} accumulation in SLOs, with a similar signature to T_{CM} and FRT T_{RM} (low *Klf2*, *s1pr1*, or *s1pr5* but $CD62L^+$).	(*78*)
Influenza	Mouse	Lung, LNs	CD103, CD69, GrB	$CD103^+CD69^+GrB^+$ lung T_{RM} populate lung-draining LNs after retrograde migration	(*66*)
LCMV, VSV	Mouse	Intestine, blood	N/A	T_{RM} can recirculate and differentiate into T_{EM}, T_{CM}, or T_{RM}	(*37*)
Influenza, LCMV	Mouse	Lung, brain, intestine	TGF-β	T_{RM} accumulate due to TGF-β during lifetime and may cause chronic inflammation	(*47*, *65*, *83*, *84*)
HBV	Human	Liver	CD103, IL-2, PD-1	Chronic HBV T_{RM} had increased CD103, PD-1, and IL-2. They showed expanded TCR clonotypes and expressed low PD-1. Peptides and IL-2 reactivated dysfunctional hepatocyte-primed T_{RM}	(*86*, *98*, *99*)
HBV, HCV	Human	Liver	PD-1, TIM-3, CTLA-4	T_{RM} PD-1, TIM-3, and CTLA-4 up-regulated in chronic infections.	(*87*, *88*)
HPV	Mouse	FRT	N/A	Intramuscular immunization followed by intravaginal boost with specific antigens enhanced T_{RM} recruitment	(*96*)
EBV	Humanized mouse	Kidney, liver, spleen	N/A	Adoptive transfer of EBV-specific cells control EBV later infections	(*139*)
SIV	Macaque	Intestine, lung, LNs	N/A	Adoptive transfer of SIV-specific cells reduce SIV chronic phase viral loads	(*140*)

signals, such as IL-12, favor development of SLECs over MPECs (*59*). Although this study did not investigate the role of IL-12 and type I IFN in T_{RM} differentiation, it provided evidence about the importance of these factors in T cell fate commitment. Last, the decreasing-potential model proposes that cumulative exposure to antigen during infections and inflammatory signals gradually guides T cell differentiation toward a terminally differentiated state with progressive restriction for T_{CM}-associated features such as longevity and proliferation but retains features of effector cells such as cytolytic capacity. This model explains the observation that T_{RM} develop by persistent local antigen exposure in the NLT microenvironment and the fact that T_{RM} development is supported specifically in tissues that favor T_{RM} retention and local antigen exposure (*60*, *61*). Using skin infections with vaccinia virus (VacV)–expressing model antigens, it was found that activated $CD8^+$ T cells trafficked to VacV-infected skin in an inflammation-dependent but antigen-independent manner (*62*). In contrast, after viral clearance, there was a 50-fold increase in T_{RM} formation when antigen remained present in the NLT. During a second skin infection with VacV, T cells developing potent localized inflammatory responses were $CD8^+$ T_{RM} generated by local exposure to antigen and not recruited from other T cell memory pools. Although all the proposed factors might be contributing, several studies have suggested that the context of priming in SLOs might be an important determinant driving T cell commitment to T_{EM}, T_{CM}, or T_{RM} (*56*, *63*, *64*). For example, T cells primed in SLOs by type I classical DCs (cDC1) are characterized by

a $CD127^{hi}KLRG1^{lo}$ phenotype and form precursors that can generate T_{RM}, although their differentiation program will start only after they reach tissues (*60*, *63*, *65*, *66*).

While it is clear that local antigen within tissues strongly promotes T_{RM} establishment, several studies have demonstrated antigen-independent inflammation as a driver of T_{RM} formation. For example, effector T cells primed with an HSV vaccine were pulled into the female reproductive tract with vaginal application of chemokine, promoting T_{RM} establishment (*50*). Consistent with this, in vitro activated T cells transferred intravenously into a naïve mouse were pulled into the skin with topical application of the inflammatory agent 1-fluoro-2,4-dinitrobenzene (DNFB), where they formed T_{RM} in the absence of antigen (*67*). Moreover, a recent study demonstrated that brain T_{RM} were established in mice following peripheral vaccination. While the group did not rule out the possibility that small amounts of antigen were present in the brain, this suggests that a local central nervous system (CNS) infection is not needed for T_{RM} seeding (*68*). Last, local inflammation may not even be necessary for T_{RM} establishment; in a lymphopenic setting, transferred naïve $CD8^+$ T cells seeded several NLTs and acquired phenotypic markers of T_{RM} (*69*).

Once in tissues after an infection, different cues promote T cell conversion to T_{RM}. An important question is whether antigen-dependent inflammation is required to initiate such process. It has been observed that the presence of antigen is required for T_{RM} generation in tissues such as brain or lung but not in other tissues such as skin, gut, and mucosae (*38*, *39*, *66*, *67*, *69*–*71*). In these latter tissues, inflammatory signals mediated by cytokines seem sufficient to boost T_{RM} recruitment. In the skin or the gut, two of the most studied tissues where T_{RM} reside, the release of TGF-β by epithelial cells up-regulates the expression of CD103, which serves as an anchor for retaining T cells in the tissue by binding with E-cadherin (*47*, *60*). The presence of other cytokines, including IL-15 or IL-7, also has a decisive role in T_{RM} long-term survival in the context of pathogens (*72*), although it has been reported that T_{RM} might also be maintained by IL-15–independent mechanisms (*73*) . Furthermore, the lack of oxygen in hypoxia conditions is considered a pivotal cue for T_{RM} generation (*74*). Under these conditions, T cells undergo a large number of changes, acquiring increased expression of CD69, Hobit, Blimp1, or Runx3, and down-regulating of CD62L, S1PR1, Tcf1, T-bet, or Eomes, acquiring properties of T_{RM} (*12*, *18*, *19*, *22*, *75*). This modulation is accompanied by enhancement of signaling pathways including Notch, Janus kinase (JAK)/signal transducer and activator of transcription 5 (STAT5), phosphatidylinositol 3-kinase (PI3K)/Akt, and Wnt, which promote T_{RM} survival (*76*). In addition, a study focused on skin T_{RM} reported that metabolism switches preferentially to fatty acid uptake and β-oxidation, as demonstrated by the essential role of fatty acid binding proteins 4 and 5 (FABP4 and FABP5) for the maintenance of skin T_{RM} (*77*).

T_{RM} were historically thought to have limited migratory capacity (*3*). However, this paradigm has recently been challenged by studies that observed T_{RM} presence in SLOs. Although the precise mechanisms remain elusive, T_{RM} can exit tissues and colonize draining LNs in a process named retrograde migration (*37*, *66*, *78*, *79*). By this process, it is thought that T_{RM} can protect SLOs upon reinfection, by coordinating recall responses with other immune cells and being ready to repopulate NLTs when needed (*37*, *66*, *78*, *79*). Moreover, $CD4^+CD103^+$ T_{RM} with transcriptional and clonal profiles of cutaneous T_{RM} have been found in the circulation and LNs of healthy humans (*80*). In the lung, where memory cells undergo a rapid contraction after infection, it has been observed that T_{RM} are relocated to mediastinal LNs (medLNs) via lymphatic vessels to preserve regional immunity. Although T_{RM} appeared much later in medLNs than in the lung, they represented a more durable memory pool (*66*). In this context, pulmonary antigen encounter was required for recruitment of pathogen-specific T effector cells and T_{RM} establishment in the lung (*81*). The ability of T_{RM} to rejoin the circulation and differentiate into T_{EM}, $T_{CM,}$ or T_{RM}, while preserving the preference to return to their tissue of origin, was also documented by a different study (*37*). It should be noted that additional mechanisms might control local T_{RM} maintenance because it has been found that specific niches for lung-resident T_{RM} at sites of tissue injury provide a source of T_{RM} maintenance in a manner independent from CD69 (*82*). Together, these findings outdate the notion that T_{RM} are permanently parked within tissues, opening new directions in the studies of T_{RM} migration and plasticity.

T_{RM} in chronic inflammation

T_{RM} cannot be fully understood without considering their accumulation in tissues throughout lifetime. Notably, considerable differences have been observed in the function of T_{RM} among children, adults, and elderly individuals. For example, expansion of influenza-specific CD8 T_{RM} is very poor during infancy, which some investigators attribute to the higher expression of T-bet of T_{RM} in children than in adults, potentially explaining why children experience more frequent respiratory infections (*83*). In aged individuals, in contrast, excessive accumulation of malfunctioning T_{RM} is associated with chronic lung inflammation and fibrotic sequelae following influenza infection (*84*). It was found that the higher T_{RM} presence in aged tissues depends on the increase of TGF-β over time and that these T_{RM} have impaired TCR signaling and effector function.

In the brain, the enhanced production of IFN-γ by T_{RM} accumulating during persistent neurotropic infections can activate microglia and promote cognitive impairment (*38*). In that sense, T_{RM} play a decisive role in chronic inflammation, where antigen is repeatedly or continuously present. Cells such as keratinocytes, DCs, and fibroblasts are constantly sampling antigens and releasing polarizing cytokines like IL-7, IL-15, IL-17, or TGF-β, which are considered responsible for an aberrant accumulation of virus-specific T cells over time (*76*). In the context of chronic LCMV infection, however, de novo generation of T_{RM} is impaired by the down-regulation of TGF-β caused by the antiviral environment, which is balanced by the recruitment of other $CD8^+$ T cells (*47*, *65*). This suggests that the proportion of $CD8^+$ T_{RM} versus recruited $CD8^+$ T cells may be orchestrated by cytokine levels (*47*, *65*). In support of this concept, acute damage in chronic hepatitis A virus (HAV) infection in the liver correlates with overactivation of bystander CD8 T cells (*85*).

Not all the T_{RM} subpopulations show the same behavior during persistent antigen exposure. A $CD103^+$ subpopulation is increased in patients with hepatitis B virus (HBV) chronic infection. These cells not only produced higher amounts of IL-2 when stimulated with HBV peptides but also expressed increased levels of the inhibitory receptor PD-1 than their $CD103^-$ counterparts (*86*). Furthermore, PD-1 up-regulation was also reported to be accompanied by higher expression of CTLA-4 and TIM-3 in HBV and hepatitis C virus (HCV) chronic infections, respectively (*87*, *88*). In contrast to $CD8^+$ T cells, $CD103^{hi}$ $CD4^+$ T cells can curb lung fibrosis induced by $CD103^{lo}$ $CD4^+$ T_{RM}, in the context of *Aspergillus fumigatus* chronic

exposure (*89*). Nonetheless, little is known about how to prevent T_{RM} inflammatory exacerbation in chronic disease. To date, attempts to treat chronic inflammatory diseases, particularly psoriasis and multiple sclerosis, using drugs that inhibited T cell recruitment were unsuccessful (*90*, *91*), whereas targeting TGF-β down-regulation by exposing skin to ultraviolet irradiation effectively reduced T_{RM} abundance and ameliorated chronic skin inflammation (*92*).

Induction of T_{RM} for viral vaccines and treatment of infections

Because of their ability to provide rapid and robust protection in tissues, T_{RM} have been considered an attractive target for vaccine development and treatment of various diseases. Several experimental approaches have been developed to generate site-specific T_{RM} and to elicit T_{RM} after vaccination, among which the most attractive are represented by the "prime and pull" and "prime and trap" strategies (*50*, *93*–*97*). In the prime and pull strategy, a first vaccination step ("priming") is followed by local application of chemokines or local inflammation that enhance T_{RM} development in the tissue ("pull"). This approach was first applied successfully in mouse models to protect from genital HSV by intravaginal topical application of the chemokine ligands CXCL9 and CXCL10 (*50*). Generation of focal skin inflammation or scarification, two other prime and pull strategies, was also found to boost responses against HSV and poxvirus, respectively (*67*, *93*, *94*). The prime and trap strategy aims in "trapping" or recruiting new T cells to become T_{RM} by administration of antigen to the tissue of interest that will be, eventually, presented by DCs or other antigen-presenting cells (*41*, *95*). By using this approach, it was found that immunization followed by intravaginal boost using adenoviral vectors expressing modified E6 and E7 human papillomavirus (HPV) proteins induced generation and recruitment of IFN-γ– and tumor necrosis factor–α (TNF-α)–producing HPV-specific $CD8^+$ T cells to the cervicovaginal tract (*96*).

The concept of T_{RM} enhancement may be extended to SLOs. Studies in the context of HIV vaccination showed that local restimulation within specific NLTs increased the abundance of T_{RM} in the draining LNs, which are a reservoir of the virus and thus considered a potential target to increase $CD8^+$ T_{RM} immunosurveillance (*78*, *97*). It would be valuable to identify which T_{RM} clonotypes populate each tissue to develop more specific strategies to enhance their effector function. Cheng *et al.* (*98*) found that HBV-specific $CD8^+$ T_{RM} populations in the liver were formed by clonally expanded cells, and some of the clonotypically conserved αβ TCRs were present in both healthy liver margin and hepatocellular carcinoma (HCC) tissues. This finding points to the use of peptides together with IL-2 as a strategy to reactivate HCC-specific T_{RM} as previously done for HBV-specific T_{RM} in the liver (*99*).

Last but not least, adoptive T_{RM} transfer might constitute a promising therapeutic approach against viral infections. These strategies will be particularly valuable for the control of viral infections in immunocompromised hosts after allogeneic hematopoietic stem cell transplantation, where ongoing attempts using ex vivo generated virus-specific T cells have provided promising results (*100*).

THE ROLE OF T_{RM} IN CANCER

Evidence of T_{RM} involvement in cancer

The role of T cells in antitumor immunity is well established, and the important contributions of T effector cells (T_{EF}) and T_{MEM} in the therapeutic responses to cancer immunotherapy have been extensively studied. Because of their unique functions including retention in tissues and rapid response to rechallenge, T_{RM} can be actively involved in cancer immunosurveillance and antitumor immunity. Increasing evidence from experimental work in mouse tumor models and patients' samples supports an important role of T_{RM} in cancer immunology and a potential therapeutic utility of T_{RM} in tumor immunotherapy.

Similarly to pathogen-related T_{RM}, cancer-related T_{RM} are defined by the expression of CD103, CD69, and/or CD49 (Fig. 3A) (*101*). The discovery that Runx3 is an indispensable transcription factor for T_{RM} differentiation was made in a tumor model and suggested the potential involvement of T_{RM} in antitumor immunity (*12*). Using single-cell RNA-seq, subsequent studies determined that, similarly to infections, T_{RM} detected in the context of cancer display high heterogeneity and identified effector-like $Id3^{lo}Blimp1^{hi}$ and memory-like $Id2^{hi}Blimp1^{lo}$ T_{RM} subsets with distinct transcription programs and capacities for effector function and memory potential (*46*). The biological relevance of these findings is supported by multiple observations that have identified T_{RM} in various types of human cancer including melanoma, non–small cell lung cancer (NSCLC), urothelial cancer, squamous cell carcinoma of head and neck, ovarian cancer, and breast cancer (*102*–*106*).

Elegant studies provided evidence for the causative role of $CD103^+CD69^+$ T_{RM} in antitumor immunity (Fig. 3B) (*107*). Malik *et al.* used a mouse model of melanoma-associated vitiligo (MAV) induced by depletion of regulatory T cells (T_{regs}) and surgical excision of primary dermal B16 melanoma, in which they infused congenic pmel T cells, which carry a TCR that recognizes the melanoma antigen gp100, to study the function and phenotype of antigen-specific responses in the skin. In this model, skin T_{RM} were generated naturally, expressed $CD44^{hi}$ $CD62L^{lo}$ $CD103^+$ $CD69^+$, and lacked PD-1 and LAG-3, but half of them also expressed cutaneous lymphocyte antigen. T_{RM} were highly enriched at the skin compared with spleen and LNs. Ex vivo stimulation of pmel cells from the skin produced higher levels of IFN-γ than LN pmel cells. Notably, although $CD103^+$ and $CD103^-$ T_{RM}-like cells could induce vitiligo, only $CD103^+$ T_{RM} could protect from rechallenge with implanted melanoma (*107*), providing the first experimental evidence for the indispensable role of CD103 in mediating the antitumor function of T_{RM}.

A different study used an epicutaneous melanoma mouse model to investigate the function of T_{RM} in cancer-immune equilibrium (Fig. 3B) (*108*). In this study, 40% of mice did not develop melanoma in the skin and were defined as nondevelopers. Comparison among tumor area, peritumoral area, and nondeveloper skin revealed that $CD69^+CD103^+$ T_{RM} were highest in nondeveloper skin, peritumoral area, and tumor, respectively. The investigators suggested that controlling B16 melanoma growth required dynamic interaction between T_{RM} and cancer cells. Moreover, by using CD69 knockout (KO) and CD103 KO mice, this study provided evidence for the causative role of these molecules in the generation of T_{RM} that regulate cancer-immune equilibrium, because CD69 KO and CD103 KO were more susceptible to melanoma formation (*108*).

Using mice with von Hippel–Lindau (VHL) deficiency, it was shown that up-regulation of hypoxia-inducible factor–1α (HIF-1α) induced constitutive elevation of CD103 expression and promoted cytokine production and cytotoxic function of T_{RM}-like $CD8^+$ tumor-infiltrating lymphocyte (TIL) in tumor (Fig. 3B) (*109*). VHL-deficient TILs expressed core T_{RM} transcription factors including Egr2, Runx3, and Prdm1 and down-regulated expression of T-bet and Eomes,

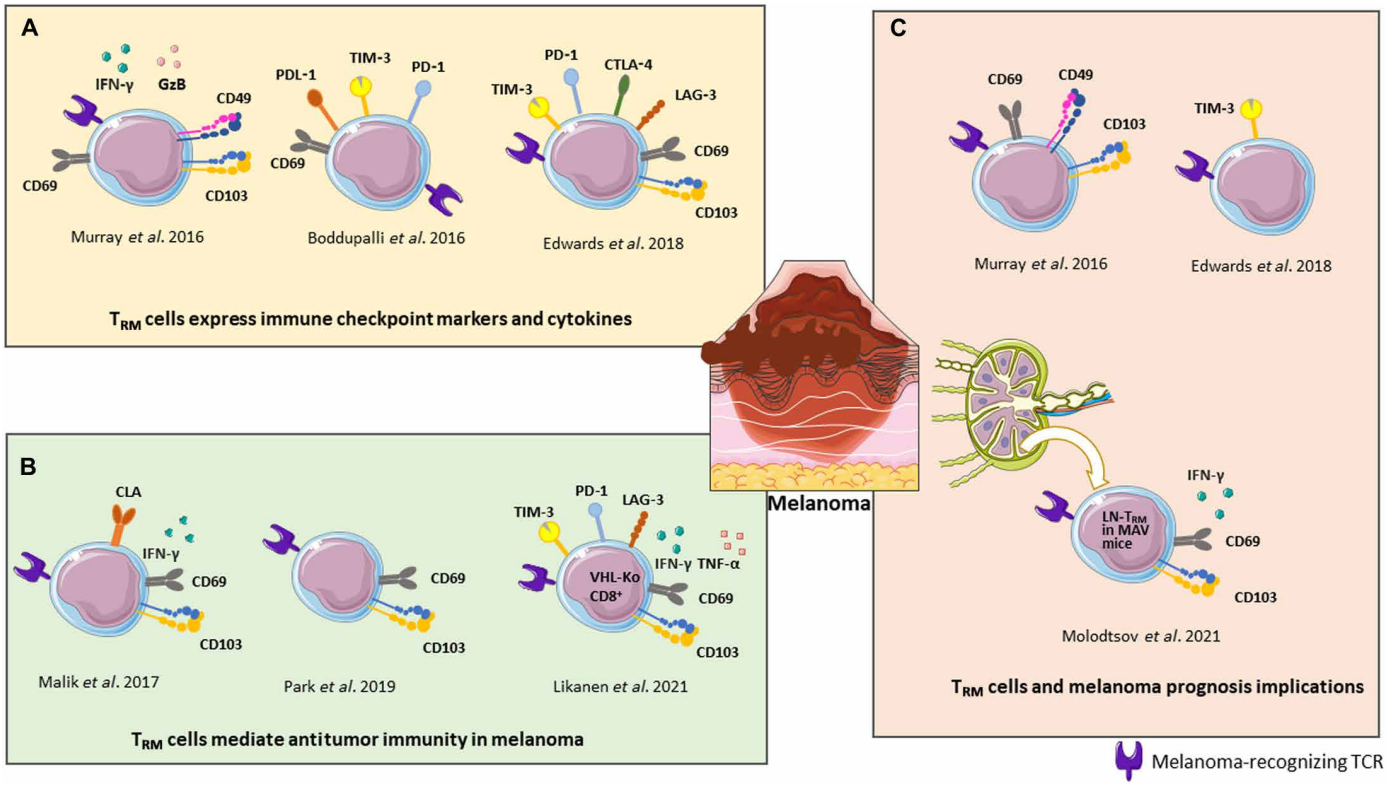

Fig. 3. T_{RM} in cancer illustrated by melanoma models. (**A**) T_{RM} express immune checkpoint markers and cytokines. Tumor-infiltrating T cells expressing CD49a or coexpressing CD49a and CD103 secrete IFN-γ and granzyme B (*134*). T_{RM} in melanoma patients express immune checkpoint receptors such as PD-1, PD-L1, TIM-3, LAG-3, and CTLA-4 (*33*, *102*). (**B**) T_{RM} mediate antitumor immunity in melanoma. $CD103^+$ CD8 T_{RM} produce IFN-γ and play a key role against melanoma rechallenge (*107*). T_{RM} promote melanoma immune equilibrium (*108*). T_{RM}-like VHL KO $CD8^+$ TILs up-regulate CD103 and promote antitumor activity (*109*). (**C**) T_{RM} correlate with prognosis in melanoma. The abundance of $CD103^+$ T_{RM} correlates with improved 5-year survival rate (*102*). In advanced-stage melanoma, T_{RM} expressing high levels of the retention integrin, CD49a, or high P selectin imply better median overall survival rate (*134*). Patients whose metastatic LNs are composed of LN-T_{RM} have longer overall survival (*123*).

whereas the $CD103^+$ subset displayed decreased Klf2 expression preventing T_{RM} egress. Treatment of VHL-deficient mice with an anti-CD103 antibody resulted in inability to suppress tumor growth. These findings suggest that HIF-1α functions in a manner dependent on CD103 integrin, which enhances retention of T_{RM} in tissues, and provide evidence for the beneficial role of T_{RM} in cancer (*109*).

Phenotype and function of T_{RM} in cancer

As mentioned above, T_{RM} have transcriptional and immunophenotypic features that distinguish them from circulatory memory T cells and other TILs. Studies in tumor-reactive $CD8^+$ memory T cells demonstrated the effector function of T_{RM} in cancer (*12*, *108*, *110*). In the context of cancer, TGF-β can induce CD103 expression through binding of Smad2/3 and NFAT-1 transcription factors to promote and enhance elements of the ITGAE gene and ITGB7 gene that encode CD103 (αE) and β7 subunits of the aEβ7 integrin, respectively (*103*, *106*, *111*–*114*). Furthermore, TGF-β can activate and strengthen CD103–E-cadherin adhesion (*115*). CD103 may be an important integrin that mediates T_{RM} residence and potential effector functions in TGF-β–rich tumor microenvironments (*101*). Interaction between CD103 and E-cadherin promotes phosphorylation and triggers activation of extracellular signal–regulated kinases 1 and 2 (ERK1/2), lytic granule polarization, and T cell effector function (*116*, *117*).

Similarly to their profile in other locations, T_{RM} residing in tumors express several immune checkpoint receptors such as PD-1, TIM-3, CTLA-4, and LAG-3, and transcription factors such as Blimp1, Hobit, and Runx3 that are indispensable in T_{RM} differentiation and function (*12*, *18*, *117*–*119*). In some contexts, these cells retain polyfunctionality and cytolytic capacity despite expressing high level of immune checkpoint markers and respond to PD-1–blocking immunotherapy (*119*). In addition, it was reported that the expression of PD-1 and TIM-3 is correlated with IFN-γ levels and cytotoxicity, as cancer-infiltrating $PD\text{-}1^+CD103^+$ T_{RM} were capable of inducing robust cytokine production after pharmacologic stimulation (*120*). Consistent with these observations, T_{RM} in breast cancer patients express high levels of PD-1, although in this context TIM-3 and LAG-3 were not detected (*121*). Furthermore, T_{RM} in lung cancer express cytolytic proteins granzyme A and granzyme B (*122*), providing additional evidence that T_{RM} in cancer patients have effector functions.

To investigate in-depth the role of T_{RM} in antitumor immunity at metastatic locations, Molodtsov *et al.* (*123*) generated a MAV mouse model in which $CD8^+$ T cells were accumulated in vitiligo skin region. In MAV mice, melanoma protection is sustained in the dermis and against intravenous rechallenge in the lungs (*124*). After adoptive transfer of congenic pmel T cells, which recognize the melanocyte/melanoma antigen gp100, and eradicating T_{reg} using anti-CD4 antibody treatment, pmel cells strongly expressing the $CD103^+$ $CD69^+CD62L^{lo}$ T_{RM} signature accumulated in the skin and tumor-draining LNs. Pmel cells expressing $CD103^+CD69^+CD62L^-$ cells also accumulated in lung and liver, albeit in the small numbers. This

Table 2. Role of T_{RM} in tumor immunity.

Cancer	Host	Tissue	Phenotype	Findings	References
Melanoma	Human	Tumor	PD-1, TIM-3, PD-L1	T_{RM} express PD-1, TIM3, and PD-L1 in the tumor.	(*33*)
Melanoma	Human	Tumor	PD-1, LAG-3, 2B4, CD137, granzyme B, CD137, HLA-DR	$CD69^+CD103^+CD8^+$ T_{RM} express high PD-1, LAG-3, 2B4, and TIM-3 and moderate expression of granzyme B.	(*102*)
		Anti–PD-1–treated tumor	IL-15	IL15 levels may influence $CD103^+$ tumor-resident $CD8^+$ T cells. The number of $CD103^+$ T_{RM} tends toward response of PD-1 inhibitor on melanoma patients.	
Melanoma	Mouse	Tumor, peritumoral skin, non- developer mice skin after epicutaneous injection	$CD103^+$ $CD69^+$	Nondevelopers' skin and peritumoral skin have higher number of $CD103^+CD69^+$ T_{RM} than in tumor area. T_{RM} control melanoma growth.	(*108*)
Melanoma	Melanoma- associated vitiligo mouse (MAV) Human	Skin, Lung, lymph node, liver, spleen	ITGAE (CD103), CD69, CXCR6, CXCR3, IFN-γ, IL-7, Klf2, S1p1	Parabiosis shows skin T_{RM} and lymph node T_{RM} share high ITGAE and CXCR6 and low expression of Klf2 and S1p1. T_{RM} profiles differ between tissues Lymph node T_{RM} highly express IL7R(CD127), CXCR6, CXCR3, and IFN-γ. Regional lymph node T_{RM} strongly correlate with prognosis benefit in metastasis melanoma patients.	(*123*)
Melanoma	Human	Tumor, skin, and blood of long-term survival metastatic melanoma patients	CD69, RGS1, NR4A1, and CXCR6a	Subpopulation of T_{RM} from skin and tumor highly expresses cytotoxic transcripts (IFN-γ, TNF, CCL3, and CCL4) and immune checkpoint transcripts (TOX, LAG-3, PDCD1, and CTLA-4). T_{RM} clonotypes, which express IFN-γ/TNF, have strong prognostic value for patients.	(*141*)
Melanoma	VHL deficiency Mouse	Tumor	Granzyme A, granzyme B, Blimp1, Egr2, and Runx3	Increased expression of granzyme A and granzyme B in VHL-KO $CD69^+CD103^+$ TILs. VHL-KO T_{RM} express Prdm1, Egr2, and Runx3 and down-regulation of Bcl6, Tcf7, and Eomes.	(*109*)

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Cancer	Host	Tissue	Phenotype	Findings	References
Breast cancer (TNBC)	Human	Tumor	TIM-3, PD-1, CTLA-4, LAG-3, granzyme B, and perforin	$CD103^+CD8^+$ T_{RM} express higher TIM3, PD1, CTLA-4, TIGIT, and LAG-3 and increased expression of granzyme B and perforin as compared with $CD103^-CD8^+$ T cells.	(*110*)
Lung cancer (NSCLC)	Human	Tumor	PD-1, TIM-3	$CD8^+CD103^+$ TILs display characteristics of tissue-resident memory T cells and express PD-1 and TIM-3.	(*103*)
Lung cancer	Human	Tumor	Granzyme B, perforin, CD107a, and IFN-γ	$CD103^+$ T_{RM} express 4-1BB, PD-1, TIM-3, and link to cytotoxicity function such as granzyme B, granzyme A, perforin, and CD107a, and produced IFN-γ.	(*112*)
Lung cancer (NSCLC)	Human	Anti–PD-1– treated tumor	HOBIT, BLIMP1, PD-1, CTLA-4, TIM-3, TIGIT, CD39, and $IL\text{-}7^{lo}$	Transcriptional programming of mutation-associated neoantigen (MANA)–specific TIL after immune checkpoint therapy expresses T_{RM} transcription program. They highly express HOBIT and BLIMP1 and up-regulate PD-1, CTLA-4, TIM-3, TIGIT, and CD39.	(*119*)
Cholangiocarcinoma (ICC)	Human	Blood and tumor	PD-L1, Wnt/β-catenin, TGF-β	Tumor margin and core density have a higher density of $CD103^+$ $CD8^+$ TILs. ICCs with high proportions of $CD69^+CD103^+$ cells display higher levels of PD-L1. ICCs with lower proportions of $CD69^+CD103^+$ $CD8^+$ TILs are enriched for genes related to Wnt/β-catenin and TGF-β pathways.	(*136*)
Ovarian cancer	Human	Tumor	PD-1, TIM-3, CTLA-4, LAG-3	PD-1 and CD103 coexpress within $CD8^+$ TIL compartment. Ex vivo $PD\text{-}1^+CD103^+$ CD8 TILs produce cytokine after pharmacologic stimulation and express TIM-3, CTLA-4, and LAG-3.	(*135*)

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Cancer	Host	Tissue	Phenotype	Findings	References
Cervical cancer	Human/mouse	Tumor	ITGAE (CD103) CD137, CTLA-4, PD1, and PD-L1	Low number of T_{RM} is associated with poor prognosis, and $CD103^+CD8^+$ T cells express CD137, CTLA-4, PD-1, and PD-L1.	(*142*)
Head neck cancer (HNSCC)	Human	Tumor	$CD39^+$, $CD103^+$, PD-1, PD-L1, CTLA-4, TIM-3, CD127, KLF2, CD62L, S1PR1	T_{RM} are characterized as $CD39^+$, $CD103^+$ T cells. T_{RM} express PD-1, CTLA-4, TIM-3 Higher frequencies of T_{RM} in patients are associated with better overall survival.	(*106*)

study provided evidence that in the context of cancer, tumor-specific T_{RM} can populate not only nonlymphoid but also lymphoid organs and localize throughout multiple tissues. Single-cell RNA-seq of pmel-T_{RM} showed distinct phenotypic markers and transcription factors depending on their localization. T_{RM} from skin expressed CD103, CD69, Cxcr6, and Nr4a1 and lacked T_{CIRCM} markers. A subpopulation of LN T_{RM} expressed high levels of CD103, Cxcr6, and low Klf2 and S1pr1 T_{CIRCM} markers, similarly to skin T_{RM}. In contrast, T_{RM}-like pmel cells isolated from lungs expressed Gzma, Itgax (CD11c), and Fabp3. In immunofluorescence microscopy, many $CD103^+$ LN T_{RM} were located in the T cell zone and subcapsular region that is characterized by cells producing IFN-γ. Phenotypic analysis of these cells depicted the high expression of IL7r(CD127), Cxcr6, and Cxcr3, which can distinguish $CD103^+$ from $CD103^-$ T cell subsets. The study further illustrated the antitumor specificity of T_{RM} using single-cell RNA-seq and single-cell TCR-seq, which identified clonotype signatures of endogenous tumor-specific $CD8^+$ T cells in T_{RM} populations located in tumor-draining LNs. These LN cancer-specific T_{RM} provided protection against melanoma metastasis in regional LNs in the MAV model and were correlated with improved survival in patients with melanoma. While T_{RM} have been demonstrated to reside in SLO in the context of viral infections (*78*, *125*), these studies are the first to demonstrate that this occurs in the context of antitumor immunity. Together, these results challenge the dogma established in systems of viral infections that T_{RM} reside only in primary NLTs and provide evidence that in the context of cancer T_{RM} can be found not only in regional LNs but also in several distal organs such as liver and lung.

However, not all tumor T_{RM} are specific for tumor antigens. Virus-specific T_{MEM} expressing phenotypic markers of T_{RM} have been found in at least 14 different human tumor types, including brain, endometrial, lung, colorectal, and breast cancer (*106*, *126*–*128*). Harnessing the potent immune activating functions of T_{RM}, preclinical studies have identified these intratumoral virus-specific T cells as promising therapeutic targets to trigger antitumor immune responses (*128*–*131*). A recent study in patients with HCC demonstrated a link between activated HBV-specific T_{RM} and infiltration of bystander $CD8^+$ T cells into the tumor, providing evidence that therapeutically activating virus-specific T_{RM} may promote immune recruitment (*98*).

Transcriptional program of T_{RM} in response to anti–PD-1 blockade in cancer

A correlation between responses to checkpoint immunotherapy and T_{RM} expression in tumors is currently emerging (*119*). This observation raises the tentative clinical utility of T_{RM} detection as a biomarker of favorable therapeutic response to PD-1–blocking immunotherapy. In immunotherapy-naïve melanoma patients, $CD103^+$ T_{RM} showed early expansion during anti–PD-1 treatment in the responder group (*102*). In patients with NSCLC treated with neoadjuvant anti–PD-1 immunotherapy, mutation-associated neoantigen-specific TIL expressed hallmark T_{RM} transcriptional factors and coordinately up-regulated checkpoint inhibitory receptors and T cell activation markers (*119*). In a VHL-deficient mouse model, T_{RM} produced high IFN-γ levels in response to anti–PD-1 therapy and resulted in complete regression of B16 melanoma tumors (*109*). Ex vivo experiments showed that TILs in lung carcinoma are T_{RM} and can mediate cytolytic activity after PD-1 blockade (*103*). Together, these findings in experimental tumor models and patients' samples emphasize the important role of T_{RM} in enhancing efficacy of PD-1–blocking cancer immunotherapy.

T_{RM} in cancer prognosis

$CD8^+$ T_{RM} have been reported to correlate with tumor size, tumor grade, and overall survival in melanoma and solid cancers (Fig. 3C and Table 2) (*108*, *110*, *112*, *122*, *132*, *133*). In melanoma patients, the abundance of $CD103^+T_{RM}$ provides the strongest association with 5-year survival with 50% survival in the T_{RM} high group compared with 20% in the group with lower T_{RM} number (*102*). In advanced-stage melanoma, patients with T_{RM} expressing high levels of the retention integrin VLA-1 (CD49) or high P selectin display better median overall survival rate (*134*). Moreover, patients whose metastatic LNs are composed of LN-T_{RM} have overall survival at least 670 days longer than other patient groups (*123*). In primary triple-negative breast cancer (TNBC) patients, $CD8^+CD103^+$ T_{RM} were significantly correlated with improved relapse-free and overall survival rates after standard chemotherapy (*108*, *110*). T_{RM} numbers also correlate with prognosis for relapse-free and overall survival rate in basal-like subtype of breast cancer (*104*). In lung cancer (*103*), ovarian cancer (*135*), and other solid tumors (*106*), $CD103^+$ TIL correlates with improved patient survival rate. In patients with

cholangiocarcinoma, high proportion of $CD69^+CD103^+$ cells expressing coinhibitory receptors in intrahepatic cholangiocarcinoma tissues displayed a significant correlation with response to immune checkpoint inhibitors (*136*). In addition, analysis of samples from melanoma patients from The Cancer Genome Atlas by multiparameter flow cytometry and multiplex immunofluorescence staining provided evidence that T_{RM} abundance is a strong predictor of survival (*102*). These extensive studies provide compelling evidence that T_{RM} are important prognostic biomarker in cancer patients and provide evidence for the important role of T_{RM} in antitumor immunity.

CONCLUDING REMARKS

$CD8^+$ T_{RM} under steady-state conditions are excluded from the circulation and reside in tissues. T_{RM} reside preferentially in mucosal tissue, such as the lung, gut, and skin, and are typically identified by $CD103^+CD69^+CD62L^{lo}$ phenotype. T_{RM} differentiation is driven by the expression of the transcription factors Runx3, Hobit, and Blimp1 and simultaneous down-regulation of Klf2, which drives expression of S1pr1 and Ccr7 that promote T cell egress from NLTs. T_{RM} have an essential role in immune defense against pathogens and cancer and are currently emerging as key mediators of responses to checkpoint immunotherapy and as biomarkers with strong correlation with favorable prognosis in cancer. Therapeutic exploitation of T_{RM} might improve the efficacy of cancer immunotherapy.

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