Tissue-resident memory T cells and their function in skin diseases

Xibei Chen, Yuxin Zheng, Xiaoyong Man, Wei Li

Department of Dermatology, Second Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang 310009, China.

Abstract

Tissue-resident memory T (TRM) cells are a recently defined subtype of non-recirculating memory T cells with longevity and protective functions in peripheral tissues. As an essential frontline defense against infections, TRM cells have been reported to robustly patrol the tissue microenvironment in malignancies. Accumulating evidence also implicates that TRM cells in the relapse of chronic inflammatory skin diseases such as psoriasis and vitiligo. In light of these developments, this review aims to synthesize these recent findings to enhance our understanding of TRM cell characteristics and actions. Therefore, after providing a brief overview of the general features of the TRM cells, including precursors, homing, retention, and maintenance, we discuss recent insights gained into their heterogeneous functions in skin diseases. Specifically, we explore their involvement in conditions such as psoriasis, vitiligo, fixed drug eruption – dermatological manifestations of drug reactions at the same spot, cutaneous T cell lymphoma, and melanoma. By integrating these diverse perspectives, this review develops a comprehensive model of TRM cell behavior in various skin-related pathologies. In conclusion, our review emphasizes that deciphering the characteristics and mechanisms of TRM cell actions holds potential not only for discovering methods to slow cancer growth but also for reducing the frequency of recurrent chronic inflammation in skin tissue.

Keywords: Tissue-resident memory T cells; Psoriasis; Vitiligo; Fixed drug eruption; Cutaneous T cell lymphoma; Melanoma

Introduction

The skin serves as the body's largest barrier organ, shielding it from the external environment. Continuous exposure to exogenous antigens and stimuli activates immune cells.[1] Upon antigen stimulation, naïve T cells undergo activation, expansion, and differentiation into effector T cells. Following the clearance of an infection, most effector cells undergo programmed death, while the remaining T cells transition into memory T cells that circulate between secondary lymphoid organs and the blood.[2,3] Circulating memory T lymphocytes are categorized into central memory T cells (TCM) and effector memory T cells (TEM).[4] Tissue-resident memory T (TRM) cells have recently been defined as a subset of non-recirculating memory T cells that reside in peripheral tissues, including the skin, gut, liver, kidneys, and brain.[5–8] Accumulating evidence highlights the indispensability of TRM cells against infection and cancer, both in mouse models and in human patients.[9–11] However, it appears that permanent TRM cells can also contribute to skin immune system disorders such as fixed drug eruptions (FDEs),[12] vitiligo,[13] and psoriasis.[14] In this context, we review recent advancements in understanding the characteristics of TRM cells and explore their involvement in the pathogenesis of skin diseases.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003499

Precursors of TRM Cells

During viral infection, naïve T cells in the lymph nodes recognize the antigen presented by basic leucine zipper ATF-like transcription factor 3 (Batf3)/dendritic cell natural killer group receptor-1 (DNGR-1)-dependent dendritic cells (DCs) and give rise to precursor TCM and TRM cells.[15] Certain effector T cells migrate into the circulatory system and respond to local microenvironmental factors (e.g., transforming growth factor β [TGF-β], interleukin [IL]-15, and IL-7) to establish residency.[16] Killer cell lectinlike receptor subfamily G member 1 $(KLRG1)^{low}$ combined with IL-7Rα (also known as $CD127)^{high}$ is identified as a memory precursor effector cell (MPEC) marker that generates memory T cells. However, $CD127^{low}KLRG1^{high}$ terminal effector cells cannot produce memory T cells.[17,18] Further, sphingosine-1-phosphorylated receptor 1 (S1PR1), which is regulated by the transcription factor Kruppel-like factor 2 (KLF2), is required by circulating memory T cells to exit peripheral tissue.[19] Consequently, downregulation of KLF2 expression results in the loss of S1PR1 expression, inducing the long-term residency of TRM cells. The CC-chemokine receptor 7 (CCR7) is another key receptor involved in adaptive immune cell migration that is activated by two different ligands, CC motif chemokine ligand 19 (CCL19) and CCL21.[20] Similar to S1PR1,

Correspondence to: Wei Li, Department of Dermatology, Second Affiliated Hospital, Zhejiang University, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China
E-Mail: Wei.Li@zju.edu.cn

Chinese Medical Journal 2025;138(10)
Received: 21-06-2024; **Online:** 11-03-2025 **Edited by:** Lishao Guo

suppression of CCR7 is necessary for the tissue residency of TRM cells.

Retention Mechanisms and Homing Molecules of TRM Cells

CD69 antagonizes S1PR1-mediated egress from tissues as an early activation marker of TRM cells.[21] Integrins regulate cellular growth, adhesion, and migration by binding to cell surface ligands to drive interactions between the extracellular matrix (ECM) and other cells.[22] For example, integrin αEβ7 (CD103) promotes the sustentation of $CD103^+$ TRM cells in the epithelium and is also used as a phenotypic marker of TRM cells.[23] Integrin α4/β7 mediates the migration of lymphocytes and facilitates their homing to gut-associated lymphoid tissue (GALT).[24] Human skin studies have reported the high expression of homing receptors, including cutaneous lymphocyte antigen (CLA), C-X-C chemokine receptor 3 (CXCR3), CCR4, CXCR6, CCR8, and CCR10.[25–28] Recent studies indicate that multiple human circulating T cell subsets are capable of differentiating into TRM in peripheral tissues, of which $CCR7^+$L-$selectin^+$ (CD62L) TCM cells are the most efficient precursors for human skin TRM cells.[29]

TGF-β plays a central role in promoting the differentiation of $CD8^+$ TRM cells.[30] Further, TGF-β induces CD103 through the Smad3 pathway, suppressing the level of T-bet and TCF-1.[31] CD103 expression is tissue-specific, with skin and salivary gland $CD8^+$ TRM cells, but not liver cells, expressing CD103.[32] Additionally, interleukin (IL)-7 and IL-15 that are produced by hair follicles facilitate the maintenance of TRM cells in a steady-state environment.[33,34] After cutaneous viral infection, $CD8^+$ TRM cells differentially express high levels of several molecules, including fatty acid-binding proteins 4 and 5 (FABP4 and FABP5).[35] Additionally, upregulation of exogenous free fatty acid (FFA) uptake and metabolism supports the long-term survival of TRM cells through utilizing mitochondrial fatty acid β-oxidation to generate ATP.[36] Conversely, treatment with fatty acid mitochondrial β-oxidation inhibitor (etomoxir) results in the inability to metabolize exogenous FFA of $CD8^+$ TRM in the skin. Moreover, several pathways participate in the regulation of TRM cells, including Janus kinase (JAK)/STAT and mTOR/PI3K/Akt pathway.[37,38]

The differentiation and maintenance of TRM cells are under the regulation of diverse transcription factors, including Hobit (also known as Zfp683), B lymphocyte-induced Runt-related transcription factor 2 (Runx2), B lymphocyte-induced Runt-related transcription factor 3 (Runx3), B lymphocyte-induced maturation protein 1 (Blimp-1),[39] Eomesodermin (EOMES), hypoxia-inducible factor 2α (HIF-2α), Notch, aryl hydrocarbon receptor (AhR),[40] and Bhlhe40.[41] Hobit is a specific regulator of TRM cells and is generally expressed in TRM cells in the skin, liver, kidneys, and lungs.[42] The activation of RunX2 and RUNX3 stimulates the development of cytotoxic $CD8^+CD103^+CD49a^+$ TRM cells, which provide immunosurveillance against malignant cells.[43,44] Eomes is required by effector T cells to prevent their development into TRM.[45] Interestingly, AhR is thought to promote $CD8^+$ TRM cell differentiation and balance the immune state in atopic dermatitis and psoriasis.[46] Bhlhe40, a stress-responsive transcription factor, maintains mitochondrial fitness in TRM cells. Bhlhe40 deficiency leads to reduced expression of several mitochondrial genes in TRM cells.[41] As a result, Bhlhe40-deficient TRM cells exhibit elevated levels of damaged mitochondria. Previous studies showed that the compromised mitochondrial fitness has been linked to reduced effector functions in exhausted $CD8^+$ T cells.[47] The interferon (IFN)-γ production by Bhlhe40-deficient $CD8^+$ T cells can be restored by providing extra tricarboxylic acid intermediates to enhance acetyl-CoA synthesis and promote histone acetylation.[41] The characteristics of TRM cells are summarized in Figure 1.

Phenotypes and Heterogeneous Functions of TRM Cells

Antigens in class I or II of major histocompatibility complexes (MHCs) determine the fate of $CD4^+$ and $CD8^+$ T cells during the positive selection phase. TRM cells include both $CD4^+$ and $CD8^+$ subsets, with a majority of studies focusing on $CD8^+$ TRM cells due to their robust defense against recurring infections. For example, Gebhardt *et al*[48] demonstrated that $CD8^+$ TRM cells reside at the sites where infections start limiting the extent of new herpes simplex virus (HSV) infections. Additionally, $CD8^+$ TRM cells are responsible for the swift and effective control of localized vaccinia virus (VACV) infection, not only at the local infection site but also on the overall skin surface.[49] In human skin epithelia, integrin α1β1 (CD49a), also called very late antigen 1 (VLA-1), distinguishes TRM cell subsets with $CD49a^+CD103^+CD8^+$ TRM cells specifically accumulating in the epidermis, while these cells are localized to both the epidermis and dermis.[50]

For effective pathogen clearance, TRM cells must remain at the site of pathogen invasion and launch a rapid immune response. In mice, pulmonary $CD8^+CD103^+$ TRM cells possibly expedite the recruitment of immune cells through IFN-γ-mediated induction of chemokine and cytokine production.[51] In response to a viral reinfection, brain $CD8^+$ TRM cells rapidly express the cytotoxic molecules granzyme B and IFN-γ eliminating the infected target cells.[52] Furthermore, activated $CD8^+$ TRM cells constitutively express transcripts of antiviral and antibacterial genes in mouse skin, reflecting a state of pre-inflammatory defense. This localized model allows $CD8^+$ TRM cells to respond directly *in situ*, with a few activated cells in an organ-extensive response.[53]

While studies have predominantly focused on $CD8^+$ TRM cells due to their strong defense against recurrent infections, the characteristics and functions of $CD4^+$ TRM cells remain poorly understood, potentially due to their dependence on antigen persistence. $CLA^+CD69^+CD103^+CD4^+$ TRM cells in human skin exhibit the ability to lose the expression of CD69, exit the tissue, migrate to a secondary skin site, and initiate regeneration of a TRM subset.[54] Moreover, $CD4^+$ TRM cells appear to express the epithelial adhesion molecule CD103 at a significantly lower level than that of $CD8^+$ TRM cells. Additionally, the permanent and irreversible depletion of proinflammatory $CXCR3^+CD4^+$ TRM cells

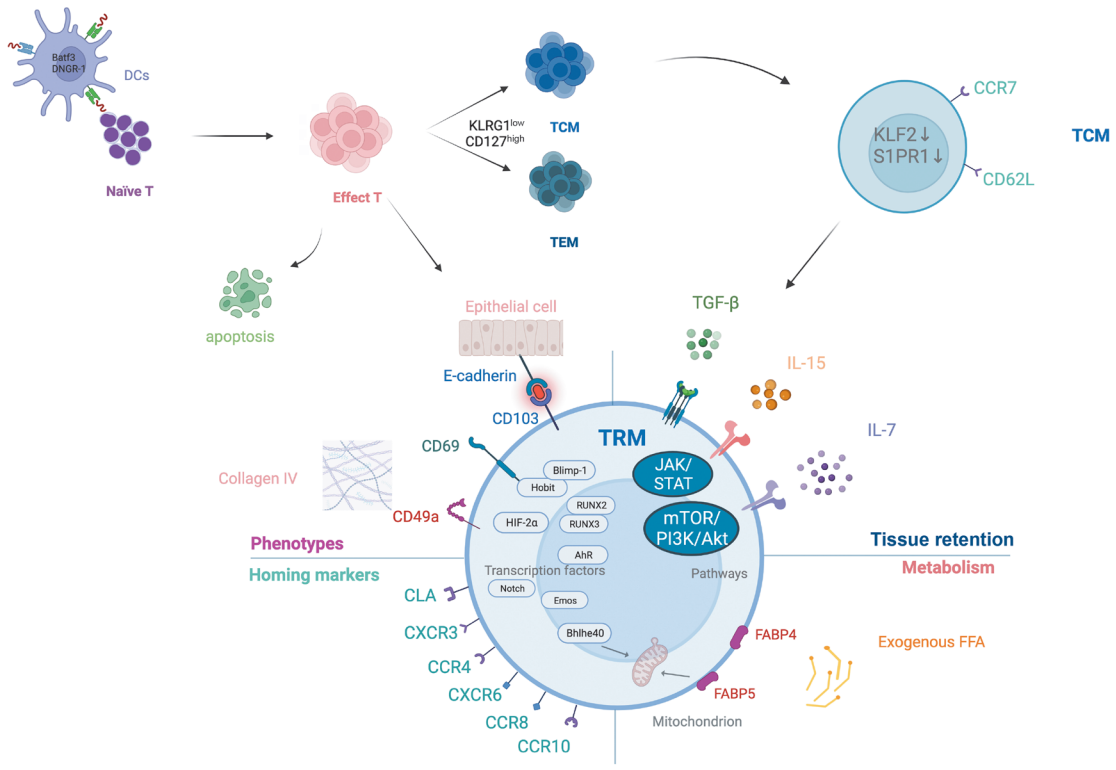

Figure 1: Characteristics of TRM cells. Naïve T cells accept antigens present by DCs and induce them to effect T cells. When the infection clears, the remaining T cells have formed the memory T and are divided into three clusters (TCM, TEM, TRM). $CCR7^{+}CD62L^{+}$ TCM cells are the major effective precursors for human skin TRM cells. Several transcription factors are involved in the regulation of TRM cells, including Hobit, Runx2, Runx3, Blimp-1, EOMES, HIF-2α, Notch, AhR, and Bhlhe40. Multiple upregulation expressions of homing markers are involved in TRM cells, including CLA, CXCR3, CCR4, CXCR6, CCR8, and CCR10. JAK/STAT and mTOR/PI3K/Akt pathways also participate in the regulation of TRM cells. The upregulation of exogenous FFA uptake and FABP4/FABP5 metabolism pathway support the long-term survival of TRM cells. AhR: Aryl hydrocarbon receptor; Blimp-1: B lymphocyte-induced maturation protein 1; CCR: C-C chemokine receptor; CLA: Cutaneous lymphocyte antigen; CXCR3: C-X-C chemokine receptor 3; DCs: Dendritic cells; EOMES: Eomesodermin; FABP4/FABP5: Fatty acid-binding proteins 4 and 5; FFA: Free fatty acid; HIF-2α: Hypoxia-inducible factor 2α; IL: Interleukin; JAK: Janus kinase; KLF2: Kruppel-like factor 2; mTOR: Mammalian target of rapamycin; Runx2: Runt-related transcription factor 2; S1PR1: sphingosine-1-phosphorylated receptor 1; STAT: Signal transducer and activator of transcription; TCM: Central memory T cells; TEM: Effector memory T cells; TGF: Transforming growth factor; TRM: Tissue-resident memory T.

in the skin and mucosa of HIV-infected patients shifts patients toward a Th2-like phenotype, increasing the risk of skin and mucosal cancers.[55] In the context of HSV-2 infection, $CD4^{+}$ TRM cells are maintained through a feedback loop in vaginal tissues. These cells rely on CCL5 released from resident macrophages, which, in turn, secrete local macrophages. After reinfection with HSV-2, $CD4^{+}$ TRM cells secrete high levels of IFN-γ, contributing significantly to viral clearance.[56]

Psoriasis

Psoriasis is a chronic papulosquamous skin disease with a worldwide prevalence of approximately 2%.[57] IL-23 and Th17 responses are recognized as major psoriasis drivers, along with TNFα, IFN-γ, IL-17, and IL-22, that fuel an ongoing cycle of inflammation. Memory T lymphocytes play a crucial role in the progression of psoriasis. Interestingly, biologics targeting CD11a or blocking E-selectin were ineffective against psoriasis, highlighting the complexity of its mechanisms.[58,59] However, non-psoriatic skin in a xenograft mouse model revealed the spontaneous development of psoriatic disease.[60] Moreover, the recurrence of lesions *in situ* and the occurrence of lesions at sites of trauma or pressure on the skin (Koebner phenomenon) indicate the involvement of TRM cells.[61]

In an imiquimod (IMQ)-induced psoriasiform mouse model, the number of $CD49a^{+}$ TRM cells showed a strong association with disease severity. Moreover, $CD49a^{+}$ TRM was found to accumulate in resolved prostatic lesions.[62] Cheuk *et al*[50] demonstrated that the $CD49a^{-}CD103^{+}CD8^{+}$ TRM cells subset predominantly produces IL-17, promoting local inflammation in psoriasis lesions. In addition, TRM maintenance in murine IMQ-induced psoriasiform lesions was linked to local IL-23 secretion by $CD301b^{+}$ myeloid cells.[63] However, epidermal $CD103^{+}CD8^{+}$ TRM cells were still enriched and retained in resolved psoriasis even after six years of TNF-α inhibition.[64] Further, during successful biologic therapies, such as adalimumab (TNFα inhibitor), ustekinumab (IL-12/IL-23 inhibitor), and secukinumab (IL-17a inhibitor), the fraction of CD103-TRM cells but not $CD103^{+}$ TRM cells markedly declined.[65] A small-sample study of mild plaque-type psoriasis suggested that $CD103^{+}CD8^{+}$ TRM cells can generate IL-17A in non-lesions, similar to the pre-inflammatory defense state.[66] Collectively, these results highlight the vital role of IL-17-producing $CD49^{-}CD103^{+}CD8^{+}$ TRM cells in psoriasis.

Several questions regarding TRM cells in psoriasis remain, particularly which antigens drive the TRM cells to the rapid secondary response. Initial autoantigens discovered,

include an antimicrobial peptide (LL37), ADAMTS-like protein 5 (ADAMTSL5), and phospholipase A2 group 4D (PLA2G4D).[67–69] LL37 binds self-DNA, which triggers the activation of plasmacytoid DCs, thus exacerbating the disease.[69] Furthermore, human primary neutrophils sense RNA-LL37 complexes, driving the release of various chemokines and cytokines, and amplifying the inflammatory loop.[70]

The morbidity rate of psoriatic arthritis (PsA) in patients with psoriasis is approximately 20%, and the correlation between the skin and joints remains unknown.[71] Leijten *et al*[14] revealed an increase in CCR10$^+$CD8$^+$ T cells in patients with PsA compared to that in patients with psoriasis. However, these T cells are TCM cells but exhibit characteristics similar to TRM cells, showing high expression of ITGAE, CD69, and CCR8 and downregulate the expression of KLRG1 and CX3CR1.[14] This result may partly explain the progression of arthritis in patients with PsA driven by the skin. Other recent studies on TRM cells in psoriasis have primarily focused on assessing inflammatory patterns through single-cell RNA sequencing (scRNA-seq) analysis. A comparison between psoriasis and transcriptional abnormalities in atopic dermatitis revealed that psoriasis-specific upregulated genes were predominantly concentrated in skin-resident memory T classes. These upregulated genes included *IL17F*, C-X-C motif chemokine ligand 13 (*CXCL13*), granulysin (*GNLY*), cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), killer cell lectin-like receptor B1 (*KLRB1*), monoacylglycerol O-acyltransferase 4 (*MGAT4*), and *PIK3R*, and recurrent excessive expression of signaling components such as mitogen-activated protein kinase kinase kinase 4 (MAP3K4) and protein tyrosine phosphatase non-receptor type 13 (PTPN13).[72] Therapeutic IL-23 treatment can reduce the number of Th17/Tc17 cells in psoriasis lesions but fails to normalize the inflammation pattern, indicating an inevitable recurrence of psoriasis even after receiving medication.[73]

These findings demonstrate that TRM cells play a vital role in disease relapse, suggesting that targeting TRM cells may be a potential therapeutic approach for reducing psoriasis recurrence. Further research is needed to assess the specific inflammatory programs and accurately identify TRM cell subsets in psoriasis.

Vitiligo

Vitiligo is a pigmentary disorder with an unknown origin, characterized by melanocyte dysfunction and a worldwide prevalence of 1%.[74] Previous studies suggest that autoreactive cytotoxic CD8$^+$ T cells secrete IFN-γ to promote the progression of the disease. However, similar to psoriasis, the interruption of IFN-γ signaling by the latest class of medications, the use of JAK inhibitors, which interrupt IFN-γ signaling, has not successfully prevented the recurrence of *in situ* vitiligo lesions,[75] indicating a potential role of antigen-specific TRM cells in vitiligo relapse.

CD49a expression has been identified as a marker outlining a subset of CD8$^+$ TRM cells in the human skin, which specifically accumulating in the epidermis. This CD8$^+$ TRM subpopulation displays preferential IFN-γ production and significant cytotoxic potential through cytotoxic granules.[50] Another study noticed a high frequency of CD69$^+$CD103$^+$CD8$^+$ TRM cells in vitiligo perilesional skin, with the majority expressing the homing marker CXCR3 and secreting IFN-γ and TNF-α.[76] Several groups have investigated the upregulation of CXCR3 ligands CXCL9 and CXCL10 in both vitiligo skin and serum.[77,78] These findings involvement of the CXCR3/IFN-γ axis in vitiligo.

Mackay *et al*[79] investigated the vital role of IL-15 in the formation of skin TRM cells from epithelium-infiltrating precursor cells. Similarly, IL-15-deficient mice show a significant reduction in memory CD8$^+$ T cells, highlighting the importance of IL-15 signaling in the generation and residency of these cells.[80] Moreover, CD122, expressed on TRM cells in both humans and mice, is integral to the receptor complex for both IL-2 and IL-15. Short exposure to an anti-CD122 antibody can inhibit TRM generation of IFN-γ and restore pigmentation in mice with established vitiligo.[81]

Further research is required to uncover the mechanisms of TRM cells, including their immediate functions. Multiple connected classical pathways, such as mTOR/PI3K/Akt, JAK/STAT, and Notch, contribute to the formation and retention of TRM cells in diverse immune microenvironments; however, their contribution to vitiligo still remains unclear. While CD4$^+$ TRM cells defend against viral infections but very few studies have assessed their role of these cells in vitiligo. Notably, a recent study suggested that TCM cells respond to restimulation, migrate, and differentiate into different T-cell subsets, including TRM cells. Furthermore, the reactivated TRM cells simultaneously rejoin the circulating lymph node pool,[82] indicating their participation in recurrent diseases alongside other T cell phenotypes. Future studies should focus on understanding the role and importance of the dynamic balance and intrinsic connections between different T cell subsets to develop novel intervention strategies.

FDE

FDE is a drug-related immunological reaction that primarily occurs at the same site every time the patient is exposed to the causative drug. The lesions caused by such adverse reactions are characterized by red-(erythematous) or violet-colored (violaceous) patches and plaques involving blisters which are called bullous lesions in medical terminology.[83]

Previous studies on resolved FDE lesions suggest that the majority of the epidermal T cells express TCR-αβ, CD8, CLA, and αEβ7, but not CD62L or CCR7, and most closely resemble CD8$^+$ TRM cells. Moreover, this subset of epidermal T cells is a constitutive component of CD69 in the steady state and can rapidly produce IFN-γ after the drug challenge. Notably, these cells have the ability to secrete IFN-γ more rapidly than dermal and peripheral tissues.[84,85] In addition, these epidermal T cells have a phenotype akin to that of natural killer cells and secrete

cytotoxic granules, causing keratinocytes to undergo apoptosis.[12] In the epidermis, regulatory CD4+ T cells abundantly surround FDE lesions, and are considered to suppress the damage of epidermal CD8+ T cells and limit further migration of circulating T cells.[86] Whether the suppressive function of Treg cells or the cytotoxic function of TRM cells are more important in resolving FDE lesions requires further investigation. Further, solving this query might lead to a breakthrough in treatment.

Notably, a specific type of FDE known as generalized bullous FDE (GBFDE) is characterized by extensive blisters and erosions and cutaneous or mucosal involvement, which are difficult to distinguish from Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[83] Iriki *et al*[87] demonstrated the presence of CD69+, CD4+, and CD8+ T cells using immunofluorescence microscopy in a patient with TEN. However, no other study has so far provided evidence that TRM cells play a critical role in the progression of GBFDE, SJS, or TEN.

Cutaneous T Cell Lymphoma (CTCL)

CTCL is a heterogeneous group of T cell lymphocyte malignancies involving the skin, of which mycosis fungoides (MF) is an ordinary primary CTCL.[88] Initially, MF is restricted to the skin and involves the formation of patches and plaques, but extracutaneous dissemination by malignant T cells can occur during the advanced stage.

A recent study using single cell RNA sequence analysis revealed that downregulation of the tissue residency-related markers CXCR4 and CD69 was unanimously associated with the progression of MF. However, malignant cells in non-lesioned skin displayed altered regulation of these markers.[89] For example, another study identified clonally expanded T cells in the skin expressing the characteristic features of CD69 and AhR as TRM cells. However, malignant clones in the blood and lymph nodes displayed a TCM-like phenotype and retained the tissue-homing receptors CLA and CCR10.[90] Importantly, the malignant clones displayed a transformed phenotype, and this phenomenon, which verified the hypothesis that CD8+ TRM cells from the skin re-enter the circulation after a secondary challenge.[82] These results partially explain the adaptive phenotypic and functional plasticity of TRM-like cells. Both these studies obtained data from advanced-stage MF patients; however, data from different subtypes of CTCL must be obtained for clarification.

Melanoma

Most cutaneous cancers originate from an epithelial layer. TRM cells, which play a critical role in local immune surveillance, may provide effective anticancer immunity against epithelial tumors such as melanoma. Park *et al*[91] reported that tumor-specific epidermal CD69+CD103+ TRM cells were associated with restricted tumor growth in a mouse model of transplantable cutaneous melanoma. Furthermore, another study that used a mouse model of melanoma indicated that VLA-1+CD8+ TRM cells differentiated inside tumors to exert immune effects.[92] However, co-localization with persistent melanoma cells revealed that TRM cells had a limited clearance capacity in the tumor. Further, biopsies obtained from melanoma patients who had undergone anti-PD-1/PD-L1 immune therapy compared to tumor specimens from naïve melanoma patients demonstrated that increased numbers of tumor-specific CD103+CD8+ TRM cells are not only associated with tumor control but may also be essential for responses to anti-PD-1 immunotherapy.[93] Further, several case reports have revealed immune-related adverse event responses (irAEs) in patients with melanoma that occur during immune checkpoint blockade therapy, such as vitiligo-like lesions.[94,95] Moreover, Nakashima *et al*[96] demonstrated that CD49a+CD103+CD8+ TRM cells accumulate in vitiligo-like lesions. These findings highlight the involvement of CD8+ TRM cells in tumor immune resistance. Thus, understanding the characteristics of TRM cells in melanomas is a necessary step in enhancing their ability to attack tumors.

The phenotypes of TRM cells in five different diseases are briefly summarized in Table 1. We also summarize the pattern of TRM cells in psoriasis and vitiligo [Figure 2].

Concluding Remarks

Over the past two decades, researchers have attempted to elucidate the common mechanisms by which TRM cells establish residence across multiple tissues. This effort has informed us that TGF-β, the TRM core activating factor is indispensable for skin TRM cells but deleterious for liver TRM cells.[32] Interestingly, in a similar microenvironment,

Table 1: TRM cell phenotypes in five different skin diseases.

Disease	Epidermis	Dermis	Correlation factors	References
Psoriasis	CD49−CD103+CD8+	CD103−CD8+	IL-17A, TNF-α, IL-22, IL-23	[49,63]
Vitiligo	CD49a+CD8+, CD69+CD103+CD8+	CD49a+CD8+	IL-15, perforin GzmB, IFN-γ, TNF-α, CXCL9, CXCL10	[49,74–76]
FDE	CD69+CD8+		IFN-γ	[82,83]
CTCL	CXCR4+CD69+	CXCR4+CD69+	CXCL9, CXCL10	[87]
Melanoma	VLA-1+CD8+ CD69+CD103+, CD103+CD8+	VLA-1+CD8+	IFN-γ, IL-15, TNF-α	[89–91]

CTCL: Cutaneous T cell lymphoma; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C chemokine receptor; FDE: Fixed drug eruption; Gzmb: Granzyme B; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor; TRM: Tissue-resident memory T; VLA-1: very late antigen 1.

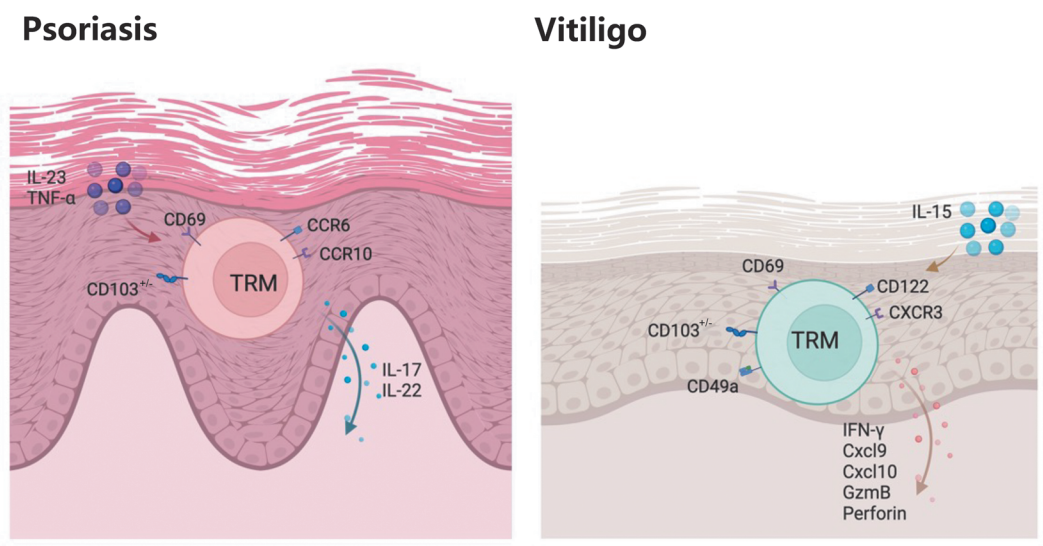

Figure 2: TRM cell phenotypes of psoriasis and vitiligo. CCR: CC-chemokine receptor; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C chemokine receptor; Gzmb: Granzyme B; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor; TRM: Tissue-resident memory T.

$CD103^+$ skin TRM cells appeared to be inherently constrained, whereas $CD103^+$ liver TRM cells easily differentiated upon relocation or re-stimulation. In addition, completely differentiated TRM cells derived from the epithelium of the small intestine undergo recall differentiation into TCM, TEM, and TRM cells.[82] This means TRM cells share key features of developmental and migration plasticity with TCM cells. Consequently, the phenotypic status of TRM cells complicates the efforts of the researchers to intervene in the rapid proliferation of TRM cells in recurrent skin inflammatory diseases or the enhanced synergistic effect of cytotoxicity in skin cancers and will likely impede the search for novel therapeutic strategies.

Unlike αβT cells, γδT cells participate in antigen presentation and are a component of innate immunity. Recent studies have reported that a few γδT cells display a tissue-resident phenotype, which more commonly exists in cancer tissues.[97–99] Here are a couple of questions that remain unanswered: (1) Are γδT cells present in skin tumors? (2) Do γδT cells synergize or interfere with the actions of traditional αβ cells? These questions highlight the importance of overall immunological balance and may lead researchers to use an alternative approach to design new therapeutics for skin cancers.

Until now, our knowledge about the metabolic mechanisms of TRM cells remains poor except through studies on exogenous lipid uptake and mitochondrial oxidative metabolism. Metabolic diseases (e.g., hyperlipidemia and diabetes mellitus) occur frequently in conjunction with chronic inflammatory skin diseases. During adaptive immunity, TRM cells require energy for rapid proliferation. If specific metabolic pathways of TRM cells are inhibited, the depletion of TRM cells can reduce the frequency of recurrence of inflammatory skin diseases.

$CD8^+$ TRM cells defend against infections and cancer. Contrastingly, a few studies have indicated that $CD4^+$ TRM cells contribute to recall responses; thereby protecting a host against chronic infection, facilitating repair during pathogen clearance, and mediating $CD8^+$ TRM generation.[56,100] Additionally, $CD4^+$ TRM cells expanded and strongly expressed TNFα, becoming a major source in Crohn's disease.[101] Thus, it appears that the function of $CD4^+$ TRM cells is a plausible explanation for chronic skin diseases. Future studies should examine distinct local skin immune responses to elucidate the function and crosstalk between these two clusters.

In conclusion, this review emphasizes the crucial role of TRM cells in skin diseases and highlights the enormous potential of TRM cells as a promising therapeutic target. Our current knowledge is based on the features of TRM cells under steady-state conditions or certain disease states. However, the data available currently is insufficient to determine the precise phenotype of TRM cells, and thus additional research is required to clarify the functional role of TRM cells across different skin diseases.

Funding

This work was supported by grants from the National Natural Science Foundation of China (NSFC) (Nos. 82230104 and 82073426).

Conflicts of interest

None.

References

1. Matejuk A. Skin immunity. Arch Immunol Ther Exp (Warsz) 2018;66:45–54. doi: 10.1007/s00005-017-0477-3.
2. Li L, Liu P, Chen C, Yan B, Chen X, Li J, *et al*. Advancements in the characterization of tissue resident memory T cells in skin disease. Clin Immunol 2022;245:109183. doi: 10.1016/j.clim.2022.109183.
3. Sabat R, Wolk K, Loyal L, Docke WD, Ghoreschi K. T cell pathology in skin inflammation. Semin Immunopathol 2019;41:359–377. doi: 10.1007/s00281-019-00742-7.

4. Mueller SN, Gebhardt T, Carbone FR, Heath WR. Memory T cell subsets, migration patterns, and tissue residence. Annu Rev Immunol 2013;31:137–161. doi: 10.1146/annurev-immunol-032712-095954.
5. Huang S, He Q, Zhou L. T cell responses in respiratory viral infections and chronic obstructive pulmonary disease. Chin Med J 2021;134:1522–1534. doi: 10.1097/CM9.0000000000001388.
6. Li Y, You Z, Tang R, Ma X. Tissue-resident memory T cells in chronic liver diseases: Phenotype, development and function. Front Immunol 2022;13:967055. doi: 10.3389/fimmu.2022.967055.
7. Asada N, Ginsberg P, Gagliani N, Mittrucker HW, Panzer U. Tissue-resident memory T cells in the kidney. Semin Immunopathol 2022;44:801–811. doi: 10.1007/s00281-022-00927-7.
8. FitzPatrick MEB, Provine NM, Garner LC, Powell K, Amini A, Irwin SL, *et al*. Human intestinal tissue-resident memory T cells comprise transcriptionally and functionally distinct subsets. Cell Rep 2021;34:108661. doi: 10.1016/j.celrep.2020.108661.
9. Amsen D, van Gisbergen K, Hombrink P, van Lier RAW. Tissue-resident memory T cells at the center of immunity to solid tumors. Nat Immunol 2018;19:538–546. doi: 10.1038/s41590-018-0114-2.
10. Craig DJ, Creeden JF, Einloth KR, Gillman CE, Stanbery L, Hamouda D, *et al*. Resident memory T cells and their effect on cancer. Vaccines (Basel) 2020;8:562. doi: 10.3390/vaccines8040562.
11. Wu X, Wu P, Shen Y, Jiang X, Xu F. CD8(+) resident memory T cells and viral infection. Front Immunol 2018;9:2093. doi: 10.3389/fimmu.2018.02093.
12. Mizukawa Y, Yamazaki Y, Shiohara T. In vivo dynamics of intraepidermal CD8+ T cells and CD4+ T cells during the evolution of fixed drug eruption. Br J Dermatol 2008;158:1230–1238. doi: 10.1111/j.1365-2133.2008.08516.x.
13. Shah F, Patel S, Begum R, Dwivedi M. Emerging role of tissue resident memory T cells in vitiligo: From pathogenesis to therapeutics. Autoimmun Rev 2021;20:102868. doi: 10.1016/j.autrev.2021.102868.
14. Leijten EF, van Kempen TS, Olde Nordkamp MA, Pouw JN, Kleinrensink NJ, Vincken NL, *et al*. Tissue-resident memory CD8+ T cells from skin differentiate psoriatic arthritis from psoriasis. Arthritis Rheumatol 2021;73:1220–1232. doi: 10.1002/art.41652.
15. Iborra S, Martinez-Lopez M, Khouili SC, Enamorado M, Cueto FJ, Conde-Garrosa R, *et al*. Optimal generation of tissue-resident but not circulating memory T cells during viral infection requires crosspriming by DNGR-1(+) dendritic cells. Immunity 2016;45:847–860. doi: 10.1016/j.immuni.2016.08.019.
16. Osman M, Park SL, Mackay LK. Tissue-resident memory T (T_{RM}) cells: Front-line workers of the immune system. Eur J Immunol 2023;53:e2250060. doi: 10.1002/eji.202250060.
17. Herndler-Brandstetter D, Ishigame H, Shinnakasu R, Plajer V, Stecher C, Zhao J, *et al*. KLRG1(+) effector CD8(+) T cells lose KLRG1, differentiate into all memory T cell lineages, and convey enhanced protective immunity. Immunity 2018;48:716–729.e8. doi: 10.1016/j.immuni.2018.03.015.
18. Joshi NS, Cui W, Chandele A, Lee HK, Urso DR, Hagman J, *et al*. Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. Immunity 2007;27:281–295. doi: 10.1016/j.immuni.2007.07.010.
19. Parga-Vidal L, van Aalderen MC, Stark R, van Gisbergen K. Tissue-resident memory T cells in the urogenital tract. Nat Rev Nephrol 2022;18:209–223. doi: 10.1038/s41581-021-00525-0.
20. Forster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: Balancing immunity and tolerance. Nat Rev Immunol 2008;8:362–371. doi: 10.1038/nri2297.
21. Liu G, Wang Z, Li S. Corrigendum: Heterogeneity and plasticity of tissue-resident memory T cells in skin diseases and homeostasis: A review. Front Immunol 2024;15:1460250. doi: 10.3389/fimmu.2024.1460250.
22. Goodman SL, Picard M. Integrins as therapeutic targets. Trends Pharmacol Sci 2012;33:405–412. doi: 10.1016/j.tips.2012.04.002.
23. Corgnac S, Boutet M, Kfoury M, Naltet C, Mami-Chouaib F. The emerging role of CD8(+) tissue resident memory T (T_{RM}) cells in antitumor immunity: A unique functional contribution of the CD103 integrin. Front Immunol 2018;9:1904. doi: 10.3389/fimmu.2018.01904.
24. Lamb CA, O'Byrne S, Keir ME, Butcher EC. Gut-selective integrin-targeted therapies for inflammatory bowel disease. J Crohns Colitis 2018;12:S653–S668. doi: 10.1093/ecco-jcc/jjy060.
25. Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka K, Dowgiert RK, *et al*. The vast majority of CLA+ T cells are resident in normal skin. J Immunol 2006;176:4431–4439. doi: 10.4049/jimmunol.176.7.4431.
26. Campbell JJ, Haraldsen G, Pan J, Rottman J, Qin S, Ponath P, *et al*. The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. Nature 1999;400:776–780. doi: 10.1038/23495.
27. McCully ML, Ladell K, Andrews R, Jones RE, Miners KL, Roger L, *et al*. CCR8 expression defines tissue-resident memory T cells in human skin. J Immunol 2018;200:1639–1650. doi: 10.4049/jimmunol.1701377.
28. Homey B, Alenius H, Müller A, Soto H, Bowman EP, Yuan W, *et al*. CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. Nat Med 2002;8:157–165. doi: 10.1038/nm0202-157.
29. Matos TR, Gehad A, Teague JE, Dyring-Andersen B, Benezeder T, Dowlatshahi M, *et al*. Central memory T cells are the most effective precursors of resident memory T cells in human skin. Sci Immunol 2022;7:eabn1889. doi: 10.1126/sciimmunol.abn1889.
30. Qiu Z, Chu TH, Sheridan BS. TGF-beta: Many paths to CD103(+) CD8 T cell residency. Cells 2021;10:989. doi: 10.3390/cells10050989.
31. Chen W. TGF-beta regulation of T cells. Annu Rev Immunol 2023;41:483–512. doi: 10.1146/annurev-immunol-101921-045939.
32. Christo SN, Evrard M, Park SL, Gandolfo LC, Burn TN, Fonseca R, *et al*. Discrete tissue microenvironments instruct diversity in resident memory T cell function and plasticity. Nat Immunol 2021;22:1140–1151. doi: 10.1038/s41590-021-01004-1.
33. Schenkel JM, Fraser KA, Casey KA, Beura LK, Pauken KE, Vezys V, *et al*. IL-15-independent maintenance of tissue-resident and boosted effector memory CD8 T cells. J Immunol 2016;196:3920–3926. doi: 10.4049/jimmunol.1502337.
34. Adachi T, Kobayashi T, Sugihara E, Yamada T, Ikuta K, Pittaluga S, *et al*. Hair follicle-derived IL-7 and IL-15 mediate skin-resident memory T cell homeostasis and lymphoma. Nat Med 2015;21:1272–1279. doi: 10.1038/nm.3962.
35. Pan Y, Tian T, Park CO, Lofftus SY, Mei S, Liu X, *et al*. Survival of tissue-resident memory T cells requires exogenous lipid uptake and metabolism. Nature 2017;543:252–256. doi: 10.1038/nature21379.
36. Pan Y, Kupper TS. Metabolic reprogramming and longevity of tissue-resident memory T cells. Front Immunol 2018;9:1347. doi: 10.3389/fimmu.2018.01347.
37. Sowell RT, Rogozinska M, Nelson CE, Vezys V, Marzo AL. Cutting edge: Generation of effector cells that localize to mucosal tissues and form resident memory CD8 T cells is controlled by mTOR. J Immunol 2014;193:2067–2071. doi: 10.4049/jimmunol.1400074.
38. Zhou M, Guo C, Li X, Huang Y, Li M, Zhang T, *et al*. JAK/STAT signaling controls the fate of CD8(+)CD103(+) tissue-resident memory T cell in lupus nephritis. J Autoimmun 2020;109:102424. doi: 10.1016/j.jaut.2020.102424.
39. Milner JJ, Toma C, Yu B, Zhang K, Omilusik K, Phan AT, *et al*. Runx3 programs CD8(+) T cell residency in non-lymphoid tissues and tumours. Nature 2017;552:253–257. doi: 10.1038/nature24993.
40. Dean JW, Helm EY, Fu Z, Xiong L, Sun N, Oliff KN, *et al*. The aryl hydrocarbon receptor cell intrinsically promotes resident memory CD8(+) T cell differentiation and function. Cell Rep 2023;42:111963. doi: 10.1016/j.celrep.2022.111963.
41. Li C, Zhu B, Son YM, Wang Z, Jiang L, Xiang M, *et al*. The transcription factor Bhlhe40 programs mitochondrial regulation of resident CD8(+) T cell fitness and functionality. Immunity 2019;51:491–507.e7. doi: 10.1016/j.immuni.2019.08.013.
42. Mackay LK, Minnich M, Kragten NA, Liao Y, Nota B, Seillet C, *et al*. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. Science 2016;352:459–463. doi: 10.1126/science.aad2035.
43. Zitti B, Hoffer E, Zheng W, Pandey RV, Schlums H, Perinetti Casoni G, *et al*. Human skin-resident CD8(+) T cells require RUNX2 and RUNX3 for induction of cytotoxicity and expression of the integrin CD49a. Immunity 2023;56:1285–1302.e7. doi: 10.1016/j.immuni.2023.05.003.
44. Park SL, Christo SN, Wells AC, Gandolfo LC, Zaid A, Alexandre YO, *et al*. Divergent molecular networks program functionally distinct CD8(+) skin-resident memory T cells. Science 2023;382:1073–1079. doi: 10.1126/science.adi8885.

45. Parga-Vidal L, Behr FM, Kragten NAM, Nota B, Wesselink TH, Kavazovic I, *et al*. Hobit identifies tissue-resident memory T cell precursors that are regulated by Eomes. Sci Immunol 2021;6:eabg3533. doi: 10.1126/sciimmunol.abg3533.
46. Fernandez-Gallego N, Sanchez-Madrid F, Cibrian D. Role of AHR ligands in skin homeostasis and cutaneous inflammation. Cells 2021;10:3176. doi: 10.3390/cells10113176.
47. Fisicaro P, Barili V, Montanini B, Acerbi G, Ferracin M, Guerrieri F, *et al*. Targeting mitochondrial dysfunction can restore antiviral activity of exhausted HBV-specific CD8 T cells in chronic hepatitis B. Nat Med 2017;23:327–336. doi: 10.1038/nm.4275.
48. Gebhardt T, Wakim LM, Eidsmo L, Reading PC, Heath WR, Carbone FR. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. Nat Immunol 2009;10:524–530. doi: 10.1038/ni.1718.
49. Jiang X, Clark RA, Liu L, Wagers AJ, Fuhlbrigge RC, Kupper TS. Skin infection generates non-migratory memory CD8+ T(RM) cells providing global skin immunity. Nature 2012;483:227–231. doi: 10.1038/nature10851.
50. Cheuk S, Schlums H, Gallais Serezal I, Martini E, Chiang SC, Marquardt N, *et al*. CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin. Immunity 2017;46:287–300. doi: 10.1016/j.immuni.2017.01.009.
51. Hombrink P, Helbig C, Backer RA, Piet B, Oja AE, Stark R, *et al*. Programs for the persistence, vigilance and control of human CD8(+) lung-resident memory T cells. Nat Immunol 2016;17:1467–1478. doi: 10.1038/ni.3589.
52. Steinbach K, Vincenti I, Kreutzfeldt M, Page N, Muschaweckh A, Wagner I, *et al*. Brain-resident memory T cells represent an autonomous cytotoxic barrier to viral infection. J Exp Med 2016;213:1571–1587. doi: 10.1084/jem.20151916.
53. Ariotti S, Hogenbirk MA, Dijkgraaf FE, Visser LL, Hoekstra ME, Song JY, *et al*. T cell memory. Skin-resident memory CD8(+) T cells trigger a state of tissue-wide pathogen alert. Science 2014;346:101–105. doi: 10.1126/science.1254803.
54. Klicznik MM, Morawski PA, Hollbacher B, Varkhande SR, Motley SJ, Kuri-Cervantes L, *et al*. Human CD4(+)CD103(+) cutaneous resident memory T cells are found in the circulation of healthy individuals. Sci Immunol 2019;4:eaav8995. doi: 10.1126/sciimmunol.aav8995.
55. Saluzzo S, Pandey RV, Gail LM, Dingelmaier-Hovorka R, Kleissl L, Shaw L, *et al*. Delayed antiretroviral therapy in HIV-infected individuals leads to irreversible depletion of skin- and mucosa-resident memory T cells. Immunity 2021;54:2842–2858.e5. doi: 10.1016/j.immuni.2021.10.021.
56. Iijima N, Iwasaki A. T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells. Science 2014;346:93–98. doi: 10.1126/science.1257530.
57. Shi LQ, Lian N, Sun JT, Liu LH, Chen M. Association between the systemic treatment of psoriasis and cardiovascular risk. Chin Med J (Engl) 2021;134:518–520. doi: 10.1097/CM9.0000000000001249.
58. Bhushan M, Bleiker TO, Ballsdon AE, Allen MH, Sopwith M, Robinson MK, *et al*. Anti-E-selectin is ineffective in the treatment of psoriasis: A randomized trial. Br J Dermatol 2002;146:824–831. doi: 10.1046/j.1365-2133.2002.04743.x.
59. Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, *et al*. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med 2003;349:2004–2013. doi: 10.1056/NEJMoa030002.
60. Conrad C, Boyman O, Tonel G, Tun-Kyi A, Laggner U, de Fougerolles A, *et al*. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med 2007;13:836–842. doi: 10.1038/nm1605.
61. Francis L, Capon F, Smith CH, Haniffa M, Mahil SK. Inflammatory memory in psoriasis: From remission to recurrence. J Allergy Clin Immunol 2024;154:42–50. doi: 10.1016/j.jaci.2024.05.008.
62. Fenix K, Wijesundara DK, Cowin AJ, Grubor-Bauk B, Kopecki Z. Immunological memory in imiquimod-induced murine model of psoriasiform dermatitis. Int J Mol Sci 2020;21:7228. doi: 10.3390/ijms21197228.
63. Whitley SK, Li M, Kashem SW, Hirai T, Igyarto BZ, Knizner K, *et al*. Local IL-23 is required for proliferation and retention of skin-resident memory T(H)17 cells. Sci Immunol 2022;7:eabq3254. doi: 10.1126/sciimmunol.abq3254.
64. Cheuk S, Wikén M, Blomqvist L, Nylén S, Talme T, Ståhle M, *et al*. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. J Immunol 2014;192:3111–3120. doi: 10.4049/jimmunol.1302313.
65. Mashiko S, Edelmayer RM, Bi Y, Olson LM, Wetter JB, Wang J, *et al*. Persistence of inflammatory phenotype in residual psoriatic plaques in patients on effective biologic therapy. J Invest Dermatol 2020;140:1015–1025.e4. doi: 10.1016/j.jid.2019.09.027.
66. Vo S, Watanabe R, Koguchi-Yoshioka H, Matsumura Y, Ishitsuka Y, Nakamura Y, *et al*. CD8 resident memory T cells with interleukin 17A-producing potential are accumulated in disease-naive nonlesional sites of psoriasis possibly in correlation with disease duration. Br J Dermatol 2019;181:410–412. doi: 10.1111/bjd.17748.
67. Cheung KL, Jarrett R, Subramaniam S, Salimi M, Gutowska-Owsiak D, Chen YL, *et al*. Psoriatic T cells recognize neolipid antigens generated by mast cell phospholipase delivered by exosomes and presented by CD1a. J Exp Med 2016;213:2399–2412. doi: 10.1084/jem.20160258.
68. Arakawa A, Siewert K, Stöhr J, Besgen P, Kim SM, Rühl G, *et al*. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015;212:2203–2212. doi: 10.1084/jem.20151093.
69. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, *et al*. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 2007;449:564–569. doi: 10.1038/nature06116.
70. Herster F, Bittner Z, Archer NK, Dickhöfer S, Eisel D, Eigenbrod T, *et al*. Neutrophil extracellular trap-associated RNA and LL37 enable self-amplifying inflammation in psoriasis. Nat Commun 2020;11:105. doi: 10.1038/s41467-019-13756-4.
71. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957–970. doi: 10.1056/NEJMra1505557.
72. Liu Y, Wang H, Taylor M, Cook C, Martínez-Berdeja A, North JP, *et al*. Classification of human chronic inflammatory skin disease based on single-cell immune profiling. Sci Immunol 2022;7:eabl9165. doi: 10.1126/sciimmunol.abl9165.
73. Cook CP, Taylor M, Liu Y, Schmidt R, Sedgewick A, Kim E, *et al*. A single-cell transcriptional gradient in human cutaneous memory T cells restricts Th17/Tc17 identity. Cell Rep Med 2022;3:100715. doi: 10.1016/j.xcrm.2022.100715.
74. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet 2015;386:74–84. doi: 10.1016/S0140-6736(14)60763-7.
75. Frisoli ML, Essien K, Harris JE. Vitiligo: Mechanisms of pathogenesis and treatment. Annu Rev Immunol 2020;38:621–648. doi: 10.1146/annurev-immunol-100919-023531.
76. Boniface K, Jacquemin C, Darrigade AS, Dessarthe B, Martins C, Boukhedouni N, *et al*. Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3. J Invest Dermatol 2018;138:355–364. doi: 10.1016/j.jid.2017.08.038.
77. Maouia A, Sormani L, Youssef M, Helal AN, Kassab A, Passeron T. Differential expression of CXCL9, CXCL10, and IFN-gamma in vitiligo and alopecia areata patients. Pigment Cell Melanoma Res 2017;30:259–261. doi: 10.1111/pcmr.12559.
78. Rashighi M, Agarwal P, Richmond JM, Harris TH, Dresser K, Su MW, *et al*. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. Sci Transl Med 2014;6:223ra23. doi: 10.1126/scitranslmed.3007811.
79. Mackay LK, Rahimpour A, Ma JZ, Collins N, Stock AT, Hafon ML, *et al*. The developmental pathway for CD103(+)CD8+ tissue-resident memory T cells of skin. Nat Immunol 2013;14:1294–1301. doi: 10.1038/ni.2744.
80. Pham JP, Wark K, Woods J, Frew JW. Resident cutaneous memory T cells: A clinical review of their role in chronic inflammatory dermatoses and potential as therapeutic targets. Br J Dermatol 2023;189:656–663. doi: 10.1093/bjd/ljad303.
81. Richmond JM, Strassner JP, Zapata L Jr., Garg M, Riding RL, Refat MA, *et al*. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. Sci Transl Med 2018;10:eaam7710. doi: 10.1126/scitranslmed.aam7710.
82. Fonseca R, Beura LK, Quarnstrom CF, Ghoneim HE, Fan Y, Zebley CC, *et al*. Developmental plasticity allows outside-in immune responses by resident memory T cells. Nat Immunol 2020;21:412–421. doi: 10.1038/s41590-020-0607-7.
83. Cho YT, Lin JW, Chen YC, Chang CY, Hsiao CH, Chung WH, *et al*. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. J Am Acad Dermatol 2014;70:539–548. doi: 10.1016/j.jaad.2013.11.015.
84. Mizukawa Y, Yamazaki Y, Teraki Y, Hayakawa J, Hayakawa K, Nuriya H, *et al*. Direct evidence for interferon-gamma produc-

tion by effector-memory-type intraepidermal T cells residing at an effector site of immunopathology in fixed drug eruption. Am J Pathol 2002;161:1337–1347. doi: 10.1016/s0002-9440(10)64410-0.
85. Mizukawa Y, Shiohara T. Fixed drug eruption: A prototypic disorder mediated by effector memory T cells. Curr Allergy Asthma Rep 2009;9:71–77. doi: 10.1007/s11882-009-0011-8.
86. Shiohara T, Mizukawa Y, Teraki Y. Pathophysiology of fixed drug eruption: The role of skin-resident T cells. Curr Opin Allergy Clin Immunol 2002;2:317–323. doi: 10.1097/00130832-200208000-00005.
87. Iriki H, Adachi T, Mori M, Tanese K, Funakoshi T, Karigane D, *et al*. Toxic epidermal necrolysis in the absence of circulating T cells: A possible role for resident memory T cells. J Am Acad Dermatol 2014;71:e214–e216. doi: 10.1016/j.jaad.2014.07.013.
88. Herrera A, Cheng A, Mimitou EP, Seffens A, George D, Bar-Natan M, *et al*. Multimodal single-cell analysis of cutaneous T-cell lymphoma reveals distinct subclonal tissue-dependent signatures. Blood 2021;138:1456–1464. doi: 10.1182/blood.2020009346.
89. Rindler K, Jonak C, Alkon N, Thaler FM, Kurz H, Shaw LE, *et al*. Single-cell RNA sequencing reveals markers of disease progression in primary cutaneous T-cell lymphoma. Mol Cancer 2021;20:124. doi: 10.1186/s12943-021-01419-2.
90. Rindler K, Bauer WM, Jonak C, Wielscher M, Shaw LE, Rojahn TB, *et al*. Single-cell RNA sequencing reveals tissue compartment-specific plasticity of mycosis fungoides tumor cells. Front Immunol 2021;12:666935. doi: 10.3389/fimmu.2021.666935.
91. Park SL, Buzzai A, Rautela J, Hor JL, Hochheiser K, Effern M, *et al*. Tissue-resident memory CD8(+) T cells promote melanoma-immune equilibrium in skin. Nature 2019;565:366–371. doi: 10.1038/s41586-018-0812-9.
92. Murray T, Fuertes Marraco SA, Baumgaertner P, Bordry N, Cagnon L, Donda A, *et al*. Very late antigen-1 marks functional tumor-resident CD8 T cells and correlates with survival of melanoma patients. Front Immunol 2016;7:573. doi: 10.3389/fimmu.2016.00573.
93. Edwards J, Wilmott JS, Madore J, Gide TN, Quek C, Tasker A, *et al*. CD103(+) tumor-resident CD8(+) T cells are associated with improved survival in immunotherapy-naive melanoma patients and expand significantly during anti-PD-1 treatment. Clin Cancer Res 2018;24:3036–3045. doi: 10.1158/1078-0432.CCR-17-2257.
94. Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, *et al*. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: A multi-institutional retrospective study. J Dermatol 2017;44:117–122. doi: 10.1111/1346-8138.13520.
95. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, *et al*. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: A systematic review and meta-analysis. J Clin Oncol 2015;33:773–781. doi: 10.1200/JCO.2014.57.4756.
96. Nakashima C, Ishida Y, Nakagawa K, Irie H, Hirata M, Kataoka T, *et al*. Identification of CD49a+ CD8+ resident memory T cells in vitiligo-like lesions associated with nivolumab treatment for melanoma. J Eur Acad Dermatol Venereol 2020;34:e79–e82. doi: 10.1111/jdv.15970.
97. Libera J, Wittner M, Kantowski M, Woost R, Eberhard JM, de Heer J, *et al*. Decreased frequency of intestinal CD39(+) gammadelta(+) T cells with tissue-resident memory phenotype in inflammatory bowel disease. Front Immunol 2020;11:567472. doi: 10.3389/fimmu.2020.567472.
98. Zhao Y, Dong P, He W, Zhang J, Chen H. γδ T cells: Major advances in basic and clinical research in tumor immunotherapy. Chin Med J 2024;137:21–33. doi: 10.1097/CM9.0000000000002781.
99. Zakeri N, Hall A, Swadling L, Pallett LJ, Schmidt NM, Diniz MO, *et al*. Characterisation and induction of tissue-resident gamma delta T-cells to target hepatocellular carcinoma. Nat Commun 2022;13:1372. doi: 10.1038/s41467-022-29012-1.
100. Laidlaw BJ, Zhang N, Marshall HD, Staron MM, Guan T, Hu Y, *et al*. CD4+ T cell help guides formation of CD103+ lung-resident memory CD8+ T cells during influenza viral infection. Immunity 2014;41:633–645. doi: 10.1016/j.immuni.2014.09.007.
101. Bishu S, El Zaatari M, Hayashi A, Hou G, Bowers N, Kinnucan J, *et al*. CD4+ tissue-resident memory T cells expand and are a major source of mucosal tumour necrosis factor alpha in active Crohn's disease. J Crohns Colitis 2019;13:905–915. doi: 10.1093/ecco-jcc/jjz010.

How to cite this article: Chen XB, Zheng YX, Man XY, Li W. Tissue-resident memory T cells and their function in skin diseases. Chin Med J 2025;138:1175–1183. doi: 10.1097/CM9.0000000000003499