REVIEW ARTICLE

Tissue-resident memory T cells and their biological characteristics in the recurrence of inflammatory skin disorders

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The skin is the largest organ of the body. The establishment of immunological memory in the skin is a crucial component of the adaptive immune response. Once naive T cells are activated by antigen-presenting cells, a small fraction of them differentiate into precursor memory T cells. These precursor cells ultimately develop into several subsets of memory T cells, including central memory T (T_{CM}) cells, effector memory T (T_{EM}) cells, and tissue resident memory T (T_{RM}) cells. T_{RM} cells have a unique transcriptional profile, and their most striking characteristics are their long-term survival (longevity) and low migration in peripheral tissues, including the skin. Under physiological conditions, T_{RM} cells that reside in the skin can respond rapidly to pathogenic challenges. However, there is emerging evidence to support the vital role of T_{RM} cells in the recurrence of chronic inflammatory skin disorders, including psoriasis, vitiligo, and fixed drug eruption, under pathological or uncontrolled conditions. Clarifying and characterizing the mechanisms that are involved in skin T_{RM} cells will help provide promising strategies for reducing the frequency and magnitude of skin inflammation recurrence. Here, we discuss recent insights into the generation, homing, retention, and survival of T_{RM} cells and share our perspectives on the biological characteristics of T_{RM} cells in the recurrence of inflammatory skin disorders.

Keywords: Tissue-resident Memory T cells; Skin inflammatory disorders; Recurrence; Psoriasis

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INTRODUCTION

Our body is covered by barrier tissues, such as the skin and the external mucosa. The entry of pathogens through these barrier tissues stimulates dendritic cells (DCs) that underlie the mucosal epithelium and the skin. DCs capture incoming antigens and subsequently migrate to local draining lymph nodes for antigen presentation to naive T cells.[1] Once activated, naive T cells proliferate and transform into effector T cells that migrate to B cell areas or to inflamed tissues. Among activated naive T cells, a small fraction differentiate into the memory T cell precursors. Based on effector function, proliferative capacity, and migration potential, these precursor memory cells ultimately develop into several subsets of memory T cells, including central memory T (T_{CM}) cells, effector memory T (T_{EM}) cells, and tissue resident memory T (T_{RM}) cells.[2] In addition to peripheral barrier tissues, nonbarrier tissues, such as the brain, sensory ganglia, liver, bone marrow, and adipose tissue, have also been reported to contain memory T cells.[3–5]

While T_{RM} cells have only been described for two decades, our understanding of them and interest in them are increasing. T_{RM} cells are not just memory T cells that are located in peripheral tissues. They have a unique transcriptional profile that differs from that of T_{CM} cells or T_{EM} cells. For instance, T_{RM} cells do not express CD62L (L-selectin) or CCR7 (a lymph node homing receptor). They express C-type lectin CD69, CD103 (an E-cadherin receptor), and CD49a depending on the T_{RM} subset and peripheral tissues.[6] Moreover, in contrast to recirculating memory T cells, skin T_{RM} cells show strong enhancement of genes that facilitate extracellular free fatty acid (FFA) acquisition/metabolism and mitochondrial oxidative metabolism,[7–9] which suggests their prominent ability to adapt to the local skin microenvironment.

Apart from long-term survival (longevity), low migration in peripheral tissues is likewise a striking characteristic of T_{RM} cells. T_{CM} cells target and survey the lymph node and then egress and return to the blood after infection.[10] T_{EM} cells survey nonlymphoid peripheral tissues and egress from peripheral tissues to blood vessels via the lymphatic system, while T_{RM} cells do not. Generally, T_{RM} cells never recirculate through the blood once they take up residence in peripheral tissues, and a recent study of T_{RM} cells in secondary lymphoid organs indicated that T_{RM} cells in the skin or mucosa can give rise to T_{RM} cells within draining lymph nodes.[11–13]

T_{RM} cells are heterogeneous and can be divided into $CD8^+$ and $CD4^+$ subsets. $CD8^+$ T_{RM} cells play an irreplaceable role in peripheral tissues, in which they enhance immune responses. For instance, $CD8^+$ T_{RM} cells in skin lesions in psoriasis, a common chronic inflammatory skin disorder, have been demonstrated to generate IL-17 to promote local skin inflammation.[14] The features of $CD4^+$ T_{RM} cells are much more unclear, but recent evidence has indicated that they play a critical role in in situ protective immunity against skin infections (e.g. *Leishmania* and *Candida*

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albicans infections) and in mucosal sites, such as the lung, small intestine, and female reproductive tract.[15–19]

T_{RM} cells are known to act as rapid on-site security alarms and provide immune protection against pathogen infections.[20] In addition, evidence has suggested that T_{RM} cells also develop after sensitization to otherwise harmless environmental antigens or self-antigens.[21] Given their biology and behavior (long-term survival and low migration), aberrantly activated T_{RM} cells have been strongly implicated in the recurrence of chronic inflammatory skin diseases[22], including psoriasis,[23] fixed drug eruption (FDE),[24] mycosis fungoides (MF),[21] vitiligo,[25] and allergic contact dermatitis (ACD).[26] Here, we discuss recent insights into the generation, homing, retention, and survival of T_{RM} cells. In fact, these points are not stand-alone processes of T_{RM} cells. We discuss them separately for the purpose of better understanding. We also share our perspectives regarding the biological characteristics of skin T_{RM} cells in the recurrence of inflammatory skin disorders.

GENERATION OF T_{RM} CELLS

The generation of antigen-specific T_{RM} cells is essential for rapid and long-lasting immunological protection. It is now known that the commitment to the memory lineage occurs early after infection,[27,28] when a fraction of naive T cells activated by local DCs differentiate into memory T cell precursors. These precursors can be divided into distinct subsets according to the expression of the receptors CD127 and KLRG1 (killer cell lectin-like receptor subfamily G member 1).

CD127 is an IL-7 receptor α-chain. In humans, the IL-7/CD127 interaction promotes the differentiation, survival, and homeostasis of T cells. It is enhanced in rheumatoid arthritis, inflammatory bowel disease, and inflammatory skin diseases, including psoriasis and atopic dermatitis.[29] CD127 is considered a marker of memory precursor cells; however, it has been indicated that the IL-7/CD127 interaction alone is not sufficient for the formation of $CD8^+$ memory T cell precursors.[30,31] Another receptor, KLRG1, is an inhibitory cell surface receptor expressed on subsets of NK cells and memory T cells. It inhibits immune responses by regulating the senescence and development of NK and T cells.[32] In humans, E-cadherin, a calcium-dependent adhesion molecule on skin keratinocytes and DCs, is the ligand for KLRG1. The inhibition of KLRG1 function by blocking E-cadherin has been shown to result in a significant enhancement of Akt phosphorylation and T-/cell receptor (TCR)-induced proliferative activity in highly differentiated $CD8^+$ T cells.[33]

It has been shown that $KLRG1^{dim}/CD127^{low}$ and $KLRG1^{dim}/CD127^{high}$ cells give rise to long-lived T cells, while short-lived T cells are derived from $KLRG1^{high}/CD127^-$ cells.[1,34] T_{RM} cells, like long-lived T_{CM} cells have been demonstrated to be derived from $KLRG1^{dim}$ cells, while T_{EM} cells are derived from $KLRG1^{high}$ cells.[34,35] Moreover, recent studies in humans and mice with ACD have demonstrated that skin T_{RM} cells and lymph node T_{CM} cell clones share overlapping TCR complementarity determining region 3 (CDR3) sequences.[26,36] This was supported by an in vivo experiment on the generation of T_{RM} cells in human skin-engrafted mice. The experiment demonstrated that, compared with other memory subsets, injected T_{CM} cells enter grafted skin in larger numbers, giving rise to more T_{RM} cells.[2] In addition, $CD8^+$ T_{CM} cells have been demonstrated to differentiate into functional $CD69^+CD103^-$ T_{RM} cells following viral clearance in the skin to act as the major tissue-resident population.[37] These data suggest that at least some T_{RM} cells and T_{CM} cells are derived from a common naive T cell precursor after skin immunization. They also suggest that T_{RM} cells are probably generated after successful tissue homing and tissue residency.

Published results have indicated that specific priming signals from DCs may differentially affect these two identical TCR CDR3 memory T cell precursors to generate T_{CM} and T_{RM} cells. For instance, a study showed that optimal T_{RM} cell generation can be promoted by dendritic cell natural killer lectin group receptor 1 $(DNGR\text{-}1)^+$ DCs during viral infection and skin immunization. $DNGR\text{-}1^+$ DCs provide unique signals associated with IL-15 and the transcription factor T-bet, and favor longer cell retention in the lymph nodes.[38]

In addition to the expression of CD127 and KLRG1, the expression of the chemokine receptor CX3CR1 has been recently reported by Gerlach and colleagues to define distinct memory $CD8^+$ T cell subsets following viral infection; T_{CM} cells are $CX3CR1^-$ cells, T_{EM} cells are $CX3CR1^{hi}$ cells, and T_{RM} cells are $CX3CR1^{-/low}$ cells.[10] The authors also identified another distinct memory subset called T_{PM} ($CX3CR1^{int}$) that predominantly surveys peripheral tissues with unique phenotypic, homeostatic, and migratory properties.

At present, several signaling pathways, including TCR stimulation affinity, the mTOR pathway, and IL-15 signaling, have been suggested to control the differentiation fate of naive $CD8^+$ T cells into short-lived effector cells or memory precursor T cells.

(1) The fine changes in the magnitude of affinity between TCR and major histocompatibility complex (MHC) can lead to markedly different downstream consequences in memory T cell generation and function.[39,40] There is strong evidence that T_{RM} precursor cells receive TCR signals with a different affinity from that of other subsets.[41] It has been shown that TCR stimulation affinity is inversely associated with the establishment of functional $CD8^+$ T_{RM} cells in the brain. Lower stimulation confers greater functionality to brain T_{RM} cells.[42] Moreover, the transcriptome of lung T_{RM} cells has been demonstrated to depend on the TCR-MHC interaction.[43] However, whether this process is the same for T_{RM} cells in the skin and the molecular mechanisms by which TCR-MHC induces events to optimize skin T_{RM} cell formation require further exploration.

(2) The mammalian target of rapamycin (mTOR) pathway is a central regulator that links diverse environmental stimuli, immune signals, and nutrient metabolism.[44] It is clear that the effect of rapamycin on mTORC1/2 is magnitude-dependent. mTORC1 is sensitive to routine rapamycin inhibition, and prolonged rapamycin treatment inhibits mTORC2 assembly.[45] The mTOR signaling pathway is activated in the early phase of the immune response and shut down or turned off as time passes. It has been suggested to play a key role in the generation of T_{RM} cells.[46,47] It has been demonstrated that rapamycin enhances the formation of $CD8^+$ memory T cells in the circulation and secondary lymphoid tissues,[47] but it inhibits the formation of $CD8^+$ T_{RM} cells in the intestinal and vaginal mucosa.[46] The inhibition of functional $CD8^+$ T_{RM} cells in the mucosa by rapamycin can protect a mice from lethal $CD8^+$ T cell-mediated intestinal autoimmunity.[46] These findings suggest an opposing role of the mTOR pathway in the generation of resident a d nonresident $CD8^+$ memory T cells, most likely due to the various levels of rapamycin in different microenvironments.

(3) IL-15 is an important homeostatic cytokine, and many types of cells in various peripheral tissues, including the skin, can produce IL-15. Therefore, T_{RM} cells have the advantage of receiving IL-15 signals more frequently and more robustly than circulating T cells.[47] IL-15 has been closely linked to the generation of T_{RM} cells, but it is not indispensable.[47,48] Within $CD8^+$ memory T cell populations, both IL-15-dependent and IL-15-independent (e.g., in the lung) populations have been described. IL-15 activates mTOR signaling, and the inhibition of mTOR can lead to a predominantly IL-15-independent memory population.[49]

Table 1. The phenotype, tissue distribution, and other immune characteristics of T_{CM}, T_{EM}, and T_{RM} cells

Subset	Phenotype	Tissue distribution	Migration	Proliferation	Cytokine	Ref.
T_{CM}	CD62L^{+}, CCR7^{+}, CD69$^{+/-}$, CD103 (Integrin αE)$^{-}$, CD11a$^{+/-}$, KLRG1^{-}, CD127 (IL-7R)$^{+}$, CX3CR1^{-}	Lymph nodes, Spleen, Blood	High	Prompt	Poor	10,34,35,76,77
T_{EM}	CD62L^{-}, CCR7^{-}, CD69$^{+/-}$, CD103 (Integrin αE)$^{-}$, CD11a$^{+/-}$, KLRG1^{+}, CD127 (IL-7R)$^{+/-}$, CX3CR1^{+} Skin: CLA^{+}, CCR4^{+}, CCR8^{+}, CCR10^{+} Gastrointestinal tract: CCR9^{+}, Integrin α4β7^{+}	Spleen, Lymph nodes, Blood, Gastrointestinal tract, Lung, Liver, Skin, Reproductive tract	High	Slow	Prompt	10,34,35,76,77
T_{RM}	CD62L^{-}, CCR7^{-}, CD69^{+}, CD103 (Integrin αE)$^{+/-}$, CD11a^{+}, KLRG1^{-}, CD127 (IL-7R)$^{+/-}$, CX3CR1$^{+/-}$, CD49a (Integrin α1) $^{+/-}$ Skin: CLA^{+}, CCR4^{+}, CCR8^{+}, CCR10^{+} Gastrointestinal tract: CCR9^{+}, Integrin α4β7^{+} Lung: CCR6^{+}, BLT-1^{+}, Integrin α1β1^{+}	Skin, Gastrointestinal tract, Lung, Liver, Reproductive tract	Low	Poor	Prompt	1,10,34,35,53–62,76,77

Despite this progress, we still have not completely uncovered the link(s) between the phenotype of T_{RM} cells and the corresponding signals, especially the possible crosstalk among TCR, mTOR, and IL-15. Therefore, information regarding the signals that regulate the generation of T_{RM} cells is not sufficient, and there is still a long road ahead.

HOMING OF T_{RM} CELLS

Distinct subsets of mature memory T cells are recruited to different tissues. T_{CM} cells are mainly recruited to lymphoid tissues by the expression of the lymph node homing receptors CD62L and CCR7. T_{EM} cells are spread throughout diverse peripheral tissues by homeostasis. T_{RM} cells are recruited to peripheral tissues, where they initially encounter pathogens or attacks.[12]

Evidence has indicated that the homing of T_{RM} cells to peripheral target tissues is a chemokine-dependent but antigen-independent process within tissue-draining lymph nodes.[50–52] Depending on the expression of tissue-specific receptors (Table 1), subsets of T_{RM} cells can home to specific tissues. For instance, in patients with psoriasis, atopic dermatitis, or ACD, most T_{RM} cells that infiltrate skin lesions express CCR10, a skin homing receptor,[53,54] T_{RM} cells that are recruited to the gut express integrin α4β7, CXCR3, and CCR9,[55] T_{RM} cells that enter the kidney have enhanced E/P-selectin expression promoted by TGF-β,[56,57] BLT-1, CCR6, and α1β1 integrin (VLA-1) are lung homing addressins,[58] and CCR5 and CXCL10 are brain homing addressins.[59,60] However, this is not always the case. For instance, integrin α4β7^{+} T_{RM} cells have also been found in certain skin contact hypersensitivity responses;[61] P-selectin is likewise important for the homing of CD4^{+} T_{RM} cells to the gut, and CXCR3 also plays a key role in the homing of T_{RM} cells to the HSV-infected skin and vagina.[62]

In addition to epithelial cells in the skin and mucosa, other types of cells (e.g., neutrophils) are also capable of producing chemokines for T cell recruitment. It has been demonstrated that, during influenza virus infection, neutrophils that are recruited to the infected sites early on leave behind long-lasting chemokine CXCL12-containing trails that are critical for virus-specific CD8^{+} T cell recruitment.[63] In psoriasis, a chronic inflammatory skin condition, neutrophils have been suggested to be involved in skin lesion initiation.[64–66] It is now clear that the skin influx of neutrophils is the early stage of psoriatic initialization. Neutrophil influx results in the formation of Munro's microabscesses (psoriasis vulgaris, Fig. 1) in the epidermis stratum corneum or spongiform pustules of Kogoj in the stratum spinosum (pustular psoriasis).[67] It seems that there is a link between the homing of T_{RM} cells to psoriatic lesions and early neutrophil influx. However, whether neutrophils in psoriatic lesions leave behind chemokine-containing trails for T_{RM} cell homing similar to generated during influenza virus infection and the type of chemokine(s) involve require more studies.

It has been demonstrated that repeated skin infections can lead to the progressive accumulation of protective T_{RM} cells not only in infection sites but also in uninvolved (normal-appearing) skin.[12] In addition to infections, physical stimuli can also provoke memory T cell accumulation and even reactivation. The Koebner phenomenon is an example in dermatological practice. It represents the development of isomorphic inflammatory skin lesions (e.g., psoriasis) in the uninvolved (normal-appearing) skin following various traumas (e.g., surgical incision, tattooing, insect bites, tape stripping, and needle acupuncture, Fig. 2).[68,69] These isomorphic lesions are always historically identical to those that arise spontaneously. Although the specific mechanism has not been completely elucidated, extensive studies have shown that nonlesional skin in inflammatory dermatosis is clearly distinct from normal skin with respect to the increased expression of immune-related genes,[70,71] and certain T cell-related cytokines and adhesion molecules have been suggested to be involved in the Koebner phenomenon in the skin.[72,73] In general, the time required for koebnerization is several days. Thus, it is rational to speculate that there may be a potential link between the homing/accumulation of T_{RM} cells in normal-appearing skin following those stimuli and the Koebner phenomenon, which requires further investigation.

All of these data and observations further enhance our understanding of memory T cell homing. However, the factors that promote aberrant chemokine production for T_{RM} cell homing to peripheral skin tissues need to be elucidated and would likely helpful for relieving the recurrence of chronic inflammatory skin diseases.

RETENTION OF T_{RM} CELLS

Once T_{RM} cells are taken up by peripheral tissues, they do not recirculate back to the lymph nodes and; like T_{EM} cells, they equilibrate in the blood. T_{RM} cells can persist for months (e.g., in the lung) or years (e.g., in the skin), even though the pathogens are undetectable.[12,74] Although the molecular mechanisms responsible for the retention of T_{RM} cells are not fully understood, CD69, integrins (CD49a, VLA-1, CD103, αvβ6, and αvβ8), CCR7, the CCL27-CCR10 axis, and aryl hydrocarbon receptor (AhR) have been suggested as key factors in the process.

In humans and mice, CD69 is expressed by the majority of CD4^{+} and CD8^{+} T_{RM} cells in multiple sites, including the skin.[75] It is an early marker of TCR-mediated activation. Effector T cells and circulating memory T cells express CD69 upon activation, but its expression is downregulated afterwards; however, T_{RM} cells in peripheral tissues express CD69 constitutively.[76,77] These distinct CD69 expression patterns distinguish tissue residents from

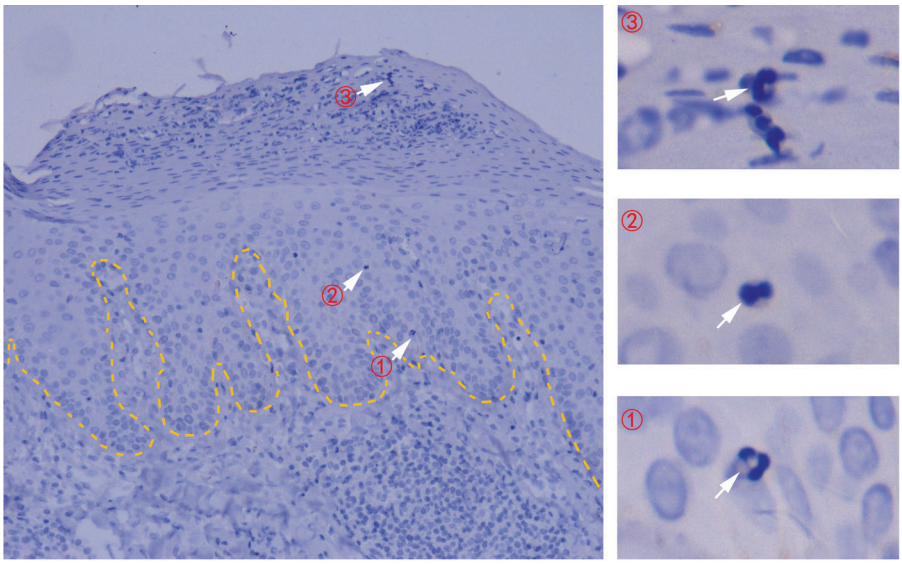

Fig. 1 Epidermal influx (① → ② → ③) of neutrophils from the peripheral blood in the early stage of psoriatic lesion initialization. Neutrophils form Munro's microabscesses (③) when they reach the epidermis stratum corneum. The dotted line indicates the border between the epidermis and the dermis. Routine hematoxylin-eosin staining of psoriatic lesions at ×400 magnification are shown

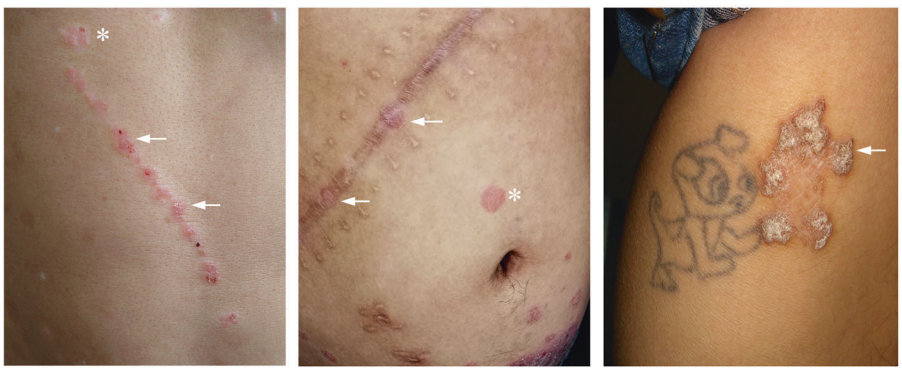

Fig. 2 Clinical images of the Koebner phenomenon. Psoriatic lesions develop in uninvolved (normal-appearing) skin at the site traumas. The accumulation and reactivation of memory T cells at these sites have been suggested to occur. Left, new linear psoriatic lesions occurred along scratches on the abdomen; Middle, new psoriatic lesions occurred on a scar from abdominal surgery; Right: psoriatic lesions occurred at the site of tattoo removal by medical laser on the leg. Asterisks, original psoriatic lesions; arrows, psoriatic lesions induced by trauma

circulating memory populations. Human $CD69^+$ T_{RM} cells are transcriptionally and phenotypically distinct from $CD69^-T_{RM}$ cells. They exhibit a core gene signature including homing, residency, proliferative turnover, and activation elements with key homology with mouse T_{RM} cells. This core signature associated with the $CD69^+$ subset (e.g., PD-1, CRTAM, CXCR6, DUSP6, and CD101) is conserved across $CD4^+$ and $CD8^+$ T_{RM} lineages and multiple peripheral tissues.[75]

The main mechanism by which CD69 participates in the retention of T_{RM} cells is the inhibition of the cell-surface expression and function of S1PR1 (sphingosine 1-phosphate receptor type 1).[77,78] S1P is a downstream target of Kruppel-like factor 2 (KLF2) and mTOR, and it is a vital lipid second messenger involved in T cell egress from peripheral tissues.[28,79] It has been demonstrated that $CD8^+$ T_{RM} cells lack S1PR1 expression, and the forced expression of S1PR1 or genetic deletion of CD69 prevents the retention of T_{RM} cells in peripheral tissues.[41,77]

CD49a (integrin α1) and VLA-1 (α1β1 integrin heterodimer) are involved in collagen binding and can mediate the retention of T_{RM} cells in mucosal tissues via attachment to the extracellular matrix. Blocking antibody treatment or genetic deficiency of VLA-1 decreases the number of T_{RM} cells in the lung.[80–82]

CD103 (integrin αE) is paired with integrin β7, and it is often enhanced in inflammatory diseases, particularly in those in which T cells infiltrate epithelial tissues.[83] In the skin, it has been verified that $CD103^+$ T_{RM} cells reside in both the epidermis and dermis, while $CD103^-$ T_{RM} cells prefer the dermis.[2,7] Similar to the CD49a-collagen interaction, CD103 confers substrate specificity for cell adhesion to E-cadherin (epithelial cadherin), as does KLRG1 (Fig. 3). However, the CD103 binding site on E-cadherin has been suggested to be distinct from the KLRG1 binding site.[84] Moreover, KLRG1-E-cadherin inhibits effector T cell function, whereas the binding of CD103 to E-cadherin enhances cell–cell interaction and adhesion.[85] The expression of CD103 and KLRG1 has been demonstrated to be mutually exclusive. TGF-β may play certain roles in this process, as it is known to induce CD103 but downregulate KLRG1 expression on $CD8^+$ T cells.[85,86]

CD103 and CD49a are not merely biomarkers of certain subsets of T_{RM} cells. They confer substrate specificity for cell adhesion and define different subsets of T_{RM} cells in certain tissues.[6,14,87] Their relationship, especially whether they can compensate for one another, is unknown, and more research is needed. For instance, $CD103^+$ T_{RM} cells can reside in the tissues of the adult central nervous system, in which E-cadherin is not expressed.[11] This

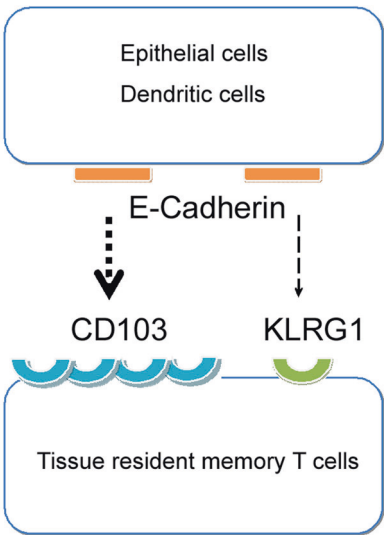

Fig. 3 CD103 on TRM cells is the main receptor for E-cadherin from epithelial cells or DCs. The interaction between CD103 and E-cadherin enhances cell–cell adhesion and the residence of T_{RM} cells

suggests that E-cadherin is likely not the sole ligand of CD103 in T_{RM} cells or that there are other compensatory molecules responsible for the residence of T_{RM} cells in nonepithelial tissues.

Other integrins (e.g., αvβ6 and αvβ8) that are expressed by interfollicular keratinocytes in the skin have also been reported to maintain the residence of T_{RM} cells in the skin by activating latent TGF-β. The treatment of the skin with ultraviolet irradiation (a therapeutic regimen against chronic skin inflammation) can decrease their expression on keratinocytes and that of the active form of TGF-β, which leads to reduced skin retention of T_{RM} cells and skin inflammation.[88]

Chemokines have also been suggested to regulate the tissue retention of memory T cells. The lymph node homing receptor CCR7 is involved in egress from the skin, and its cooperation with S1PR1 in accelerating the egress of T_{RM} cells has been suggested.[1,41] Therefore, the downregulation of CCR7 may be an additional mechanism by which T_{RM} cells are retained in the skin. CCR10 and its ligand CCL27 is the most skin-specific chemokine receptor/ligand pair implicated in inflammatory skin diseases. This pair is thought to regulate not only homing (as mentioned above) but also the retention of skin T_{RM} cells.[57] It has been reported that the level of CCL27 is not only increased during skin inflammation but also remains high several weeks after allergen skin challenges. In parallel with increased CCL27 expression, large numbers of $CD4^+CCR10^+$ T_{RM} cells exist in ACD lesions that have returned to normal clinically weeks after challenge.[89] These results suggest that the CCL27-CCR10 axis is one of the main mechanisms of the retention of T_{RM} cells in ACD.

Aryl hydrocarbon receptor (AhR), a member of the helix-loop-helix transcription factor family, is also associated with the retention of T_{RM} cells in the skin.[90] AhR is thought to mediate the toxic reaction of chemical substances at barrier sites, such as the skin and gut. It is clear that AhR participates in crucial biological processes, including innate and adaptive immune responses, in vivo.[91] The activation of AhR can inhibit the inflammatory reaction, and its antagonism promotes this process in skin lesions.[92–95] An animal model of psoriasis with AhR deficiency exhibits more severe pathological characteristics than those of wild-type animals.[93] Studies have shown that $CD8^+$ T_{RM} cells express a higher level of AhR than T_{CM} and T_{EM} cells.[96] In a mouse model of dinitrofluorobenzene-induced skin inflammation, AhR knockout in $CD8^+$ cells does not alter the number of $CD8^+$ cells recruited to the skin lesions, but they disappear only a few days later.[90,97] This suggests that AhR contributes to the skin retention or survival of T_{RM} cells, which is similar to the roles of AhR in the maintenance of liver-resident natural killer cells.[98] In addition, it has been demonstrated that treatment with the potent exogenous AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin can transiently increase CD69 expression.[99] However, the exact role of AhR and the biochemical mechanism underlying AhR-mediated T_{RM} cell retention require further investigation.

Overall, the above studies show that the distinct regulators of T_{RM} cell retention may be promising intervention targets for T_{RM} cells and suggest that they are probably tissue-specific. However, a recent investigation identified the transcription factors Hobit and Blimp1 as universal central regulators that instruct the retention of T_{RM} cells in the skin, gut, liver, and kidneys of mice.[100] These findings are suggestive of the complexity of T_{RM} cell retention regulation.

SURVIVAL OF T_{RM} CELLS

There is limited understanding of the molecular mechanisms and signaling processes that regulate T_{RM} cell survival and apoptosis. It has been suggested that T_{RM} cell survival in skin tissues is mainly regulated by the local microenvironment, even in the absence of antigen presentation.[101] A combination of retention in the skin and local inflammatory signaling by IL-7, IL-15, or TGF-β has been suggested to be required for the survival and homeostasis of skin T_{RM} cells.[101–103] Tissue-specific instruction is involved in the survival of T_{RM} cells. Skin keratinocytes, DCs, and fibroblasts may play critical roles in this process because they sense environmental danger signals (e.g., microbial agents) and are the major source of IL-7, IL-15, TGF-β, and IL-17 polarizing cytokines.[104,105]

It has been demonstrated that the local proliferation of T_{RM} cells in the skin in response to local antigen challenge can maintain the survival of a stable pool of tissue-resident memory T cells.[106] Multiple interrelated signaling pathways, including the Notch, JAK/STAT5, PI3K/Akt, and Wnt signaling pathways, have been suggested to be involved in the survival of T_{RM} cells in peripheral tissues.

Notch is a transcriptional regulator involved in T cell development and the formation of memory T cells. It controls the survival of T_{CM} cells by regulating Akt phosphorylation and glucose uptake.[107] Recent genetic and pharmacological experiments have provided compelling evidence that Notch signaling is also required for the survival of T_{RM} cells. Notch-deficient mice have decreased expression of CD103 on $CD8^+$ T_{RM} cells in their airways.[108] Moreover, the activator of Notch signaling, Delta-like ligand, can induce the expression of IFN-γ mRNA in T_{RM} cells but not in T_{EM} cells. Although most T_{RM} cell-specific gene expression is not dependent on Notch signaling, the inhibition of Notch can affect the expression of a few T_{RM} cell-specific genes, including *Itgae*, *Acer2*, *Tmem37*, *Rplp2*, and *Arl5c*.[108,109] Among these specific genes, *Itgae* encodes CD103, and its downregulation by Notch inhibition leads to the lower surface intensity of CD103 on T_{RM} cells; Acer2 hydrolyzes the sphingolipid ceramide into sphingosine and FFAs. Exogenous FFA consumption has been demonstrated to be critical for the long-term survival of skin T_{RM} cells. The T cell-specific deletion of the lipid transport molecules fatty-acid-binding proteins 4 and 5 (FABP4/5) impairs exogenous FFA uptake by skin $CD8^+$ T_{RM} cells and greatly decreases their long-term survival in vivo, while having no effect on the survival of T_{CM} cells.[8,9] These findings suggest that Notch signaling controls the survival of T_{RM} cells at least in part by regulating their metabolic functions.

In response to IL-7 and/or IL-15, long-lived memory T cells rapidly activate JAK/STAT5, as do effector T cells. However, the phosphorylation levels of STAT5 are much higher than the levels

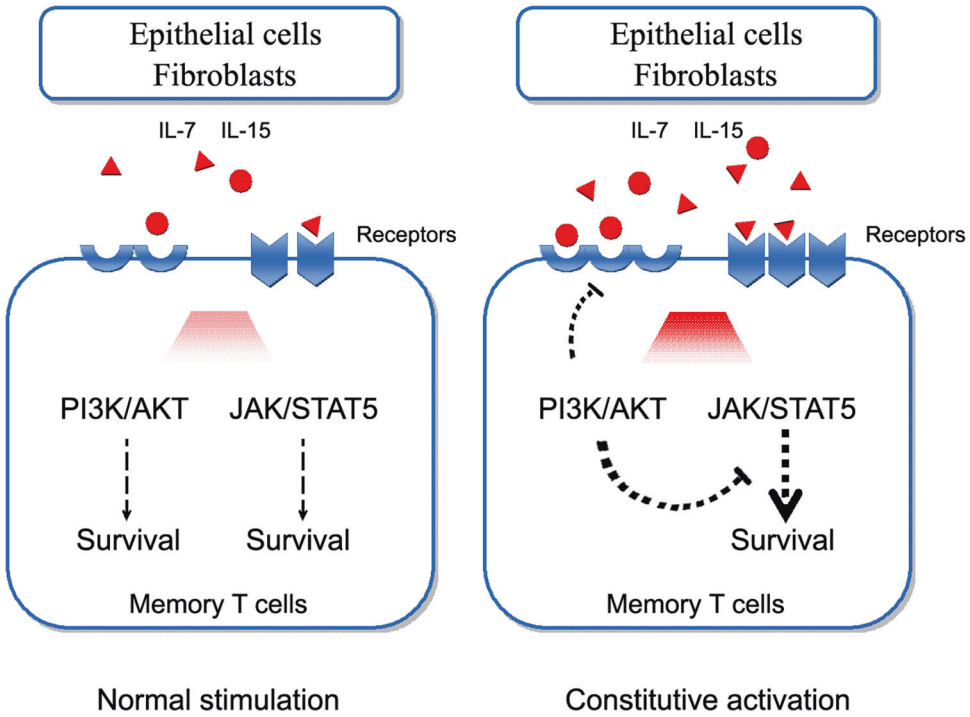

Fig. 4 The balance of PI3K/Akt signaling, the maintenance of JAK/STAT5 signaling, and their complex interplay in the survival of T_{RM} cells. The activation of both PI3K/Akt signaling and JAK/STAT5 signaling support T_{RM} cell survival (left). However, the constitutive activation of PI3K/Akt represses IL-7/IL-15 receptor expression and STAT5 phosphorylation (right)

of STAT5.[110] Constitutive STAT5 activation has been demonstrated to profoundly enhance antiapoptotic Bcl-2 expression and memory T cell survival.[111,112] The forced expression of the active form of STAT5 prolongs the survival of what would otherwise be short-lived terminally differentiated effector T cells.[113] PI3K/Akt signaling has been shown to be activated more robustly in long-lived memory precursor T cells than in short-lived effector cells, and the functional suppression of PI3K/Akt can lead to defective $CD8^+$ memory T cell formation in vivo.[111,114] However, constitutive PI3K/Akt activation does not enhance memory $CD8^+$ T cell survival but rather represses IL-7 and IL-15 receptor expression, STAT5 phosphorylation, and Bcl-2 expression (Fig. 4).[111,115,116] This suggests that the survival of memory T cells likely depends on optimally balanced PI3K/Akt signaling, the maintenance of JAK/STAT5 signaling, and their complex interplay. However, whether this is true for the survival of skin T_{RM} cells requires further investigation.

The Wnt pathway is evolutionarily conserved and promotes stem cell self-renewal. It has been suggested to be involved in the maintenance of the longevity of mature memory $CD8^+$ T cells via downstream transcription factors (e.g., TCF-1).[117,118] TCF-1 is highly expressed in naive T cells, downregulated in effector T cells, and upregulated in T_{CM} cells. TCF-1-deficient memory $CD8^+$ T cells are progressively lost over time and show decreased levels of antiapoptotic Bcl-2 and Eomes. The forced expression of Eomes can partly rescue TCF-1-deficient $CD8^+$ T_{CM} cells from time-dependent fade.[118–120] These findings suggest that canonical Wnt signaling plays a critical role in T_{CM} cells in vivo.

However, in T_{RM} cells, the role of Wnt signaling seems to not be identical to that in T_{CM} cells. It has been demonstrated that the downregulation of T-box transcription factors (Eomes and T-bet) is crucial for IL-15 and TGF-β signaling in $CD8^+$ T_{RM} cell survival,[121] which is supposed to be different from that of T_{CM} cells. In particular, Eomes should be nearly eliminated for optimal $CD8^+$ T_{RM} cell development, and residual T-bet expression is sufficient for IL-15-mediated long-term survival in a range of different tissues.[122] TGF-β has been shown to promote the development of pulmonary T_{RM} cells via a signaling pathway that does not require downstream Smad4.[123] It plays an important role in the down-regulation of Eomes and T-bet.[41] Furthermore, the TGF-β and Notch pathways undergo intensive crosstalk, and along with optimally balanced PI3K/Akt and/or JAK/STAT5 signaling, they most likely constitute the integrated mechanisms involved in the survival of T_{RM} cells.

T_{RM} CELLS IN THE RECURRENCE OF INFLAMMATORY SKIN DISORDERS

The skin is the largest organ of the body. It contains a large number of T cells, reaching up to 2×10^{10} cells or twice the number in the blood.[124] Common T cell subsets, e.g., Th17 and Th22 cells, are associated with the severity of inflammatory skin diseases.[125–127] The inhibition these cells has been proven to be an effective treatment temporarily, but it fails to prevent disease recurrence. This suggests that other T cell subsets may be directly responsible for the recurrence of inflammatory skin disorders.

It has long been known that the recurrence of cutaneous chronic inflammation, especially psoriasis and FDE, frequently occurs in previously affected sites (Fig. 5). Therefore, immunological memory has been proposed to be involved in flare-up reactivity and the chronicity of inflammatory disorders.[128] With respect to the striking characteristics of T_{RM} cells (long-term survival and low migration in peripheral tissues), it has been suggested that skin T_{RM} cells may actively participate in the recurrence of inflammatory skin disorders.[21]

Psoriasis

Psoriasis is a common chronic inflammatory skin disorder that usually appears on the skin as red patches covered with white scales. Genetic predisposition and environmental factors that affect the immune system (e.g., stressful events and skin trauma) are involved in triggering psoriasis.[129]

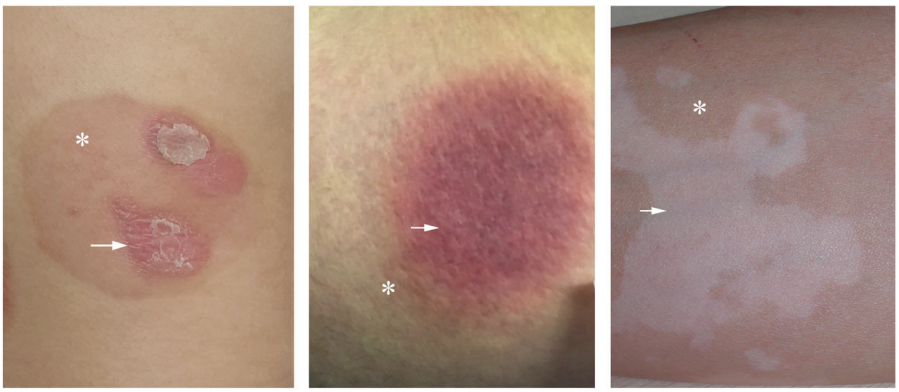

Fig. 5 The recurrence of cutaneous chronic inflammation frequently occurs in previously resolved sites. Therefore, immunological memory is proposed to be involved. Left, psoriatic lesions on the trunk recurred at previously resolved sites; Middle, recurrent fixed drug eruption on the buttock; Right, recurrent vitiligo lesions on the upper extremity. Arrow, recurrent lesions; asterisks, previously resolved areas

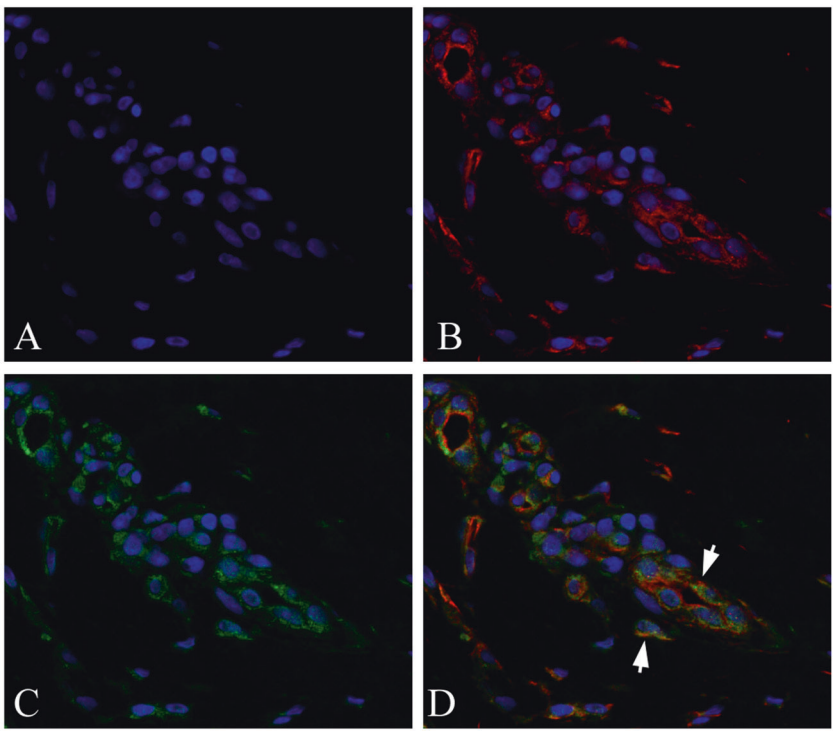

Fig. 6 Immunofluorescence staining of sections from resolved psoriatic areas. (a) DAPI staining; (b) DAPI and CD8 staining; (c) DAPI and CD69 staining; (d) DAPI, CD8 and CD69 staining. The yellow in the merged image indicates $CD8^+CD69^+$ T_{RM} cells in the resolved psoriatic areas (arrows)

The primary onset of psoriatic lesions is often followed by recurrence in previously resolved sites, and the recurrence rate is approximately 90% (unpublished data, Zhu Shen). The immune memory maintained by local resident memory T cells has been suggested to play major roles in its development and flare-ups.[130] For instance, T cells in lesional skin but not peripheral blood maintain the psoriatic phenotype in an SCID xenotransplantation mouse model.[131] Moreover, immunodeficient mice can develop psoriatic skin lesions when normal-appearing skin is grafted from psoriatic patients.[130] $CD8^+$ T cells in psoriatic lesions are highly activated and express large amounts of CD69 and CD103. In contrast, few T cells constitutively express these proteins in the peripheral blood.[23,132] Furthermore, it is clear that T_{EM} cells interact with the vascular addressin E-selectin and are trafficked to the skin during infection or attack. However, the inhibition of T_{EM} cell infiltration by blocking E-selectin is not an effective treatment for psoriasis.[133] More importantly, recent studies have shown that $TCR\alpha\beta^+$ resident T cells accumulate in psoriatic resolved sites, even in normal-appearing skin, and that they are capable of producing IL-17 and IFN-γ to trigger psoriasiform responses.[104,134,135] These findings support the important role of lesion-resident T cells in psoriasis development.

It has been demonstrated that psoriatic T_{RM} cells are retained in resolved lesions even for months after effective treatment with methotrexate (MTX), anti-TNF-α, or IL-12/23 biotherapy.[23,136] For instance, after routine MTX treatment (12.5 mg/week) for 8 weeks, the level of inflammatory infiltrates is reduced; however, the persistence of $CD8^+$ T cells that express CD69 in resolved skin lesions has been observed.[136] Our unpublished data have also shown that a high number of $CD8^+CD69^+$ T_{RM} cells remains in

resolved psoriatic lesions (Fig. 6). In addition to its function in T_{RM} cell retention, CD69 has been demonstrated to control the secretion of IL-22, which contributes to psoriasis development.[137] Furthermore, CD69 has been demonstrated to be coexpressed with FABP4 and FABP5, two vital molecules highly expressed in psoriatic lesions, by $CD8^+$ T_{RM} cells enriched in human psoriatic lesions. FABP4 and FABP5 are involved in exogenous FFA acquisition/metabolism and long-term T_{RM} cell survival, as discussed above.[8,9,138] These results demonstrate that a large number of T_{RM} cells remain in resolved sites of psoriasis.

Psoriatic T_{RM} cells are heterogeneous and functional. It has been reported that psoriatic $CD8^+$ T_{RM} cells can produce IL-17A upon ex vivo stimulation, and $CD4^+$ T_{RM} cells respond with IL-22 production for as long as 6 years after TNF-α inhibition.[23] Both $CD8^+CD103^+$ and $CD8^+CD49a^-$ subsets of T_{RM} cells from psoriatic lesions predominantly generate IL-17 responses.[14,23] Furthermore, our unpublished data have demonstrated that the intradermal injection of culture supernatant from stimulated $CD8^+CD69^+$ T_{RM} cells isolated from clinically resolved psoriatic tissues into a mouse model of imiquimod-induced psoriasiform dermatitis can significantly reactivate psoriasis-like histological phenotypes (e.g., inflammatory infiltrates and epidermic hyperplasia). These data demonstrate that T_{RM} cells in resolved skin lesions are functional and capable of producing cytokines that are known to be critical for psoriasis development, which further supports the role of T_{RM} cells in psoriasis recurrence.

The CCL27-CCR10 axis has been suggested to be pivotal for the retention of T_{RM} cells. However, it does not seem to be vital for the retention of T_{RM} cells in psoriasis recurrence because the CCR10 level is sharply reduced in resolved sites compared with neighboring psoriatic lesions. Moreover, CCL27 expression is lower in psoriatic lesions than in perilesional skin (unpublished data, Zhu Shen),[139,140] most likely because of the negative feedback of IL-17, INF-γ, or TNF-α in the lesions.[141,142]

Similar to those of CCR10, the levels of IL-7 and its receptor CD127 are sharply reduced (over 10-fold) in resolved sites compared with neighboring psoriatic lesions (unpublished data, Zhu Shen). IL-15 is an important proinflammatory cytokine and has important roles in psoriasis.[143,144] It has been demonstrated to be required for the formation and maintenance of $CD103^+$ T_{RM} cells in the skin epidermis following HSV infection.[7] Our unpublished data have shown that the IL-15 level in resolved sites remains as high as that in neighboring recurrent psoriatic lesions and can be upregulated by experimental Koebner phenomenon. In addition, MTX plus a neutralizing IL-15 antibody can decrease CD69 expression and the number of $CD8^+CD69^+$ T_{RM} cells in psoriatic organ cultures (unpublished data, Zhu Shen). This suggests the important role of IL-15 in the survival of T_{RM} cells in psoriasis recurrence.

These findings demonstrate the persistence of immunological memory in psoriatic resolved sites, and T_{RM} cells are one of the vital subsets of resident memory T cells in psoriatic lesion recurrence. This suggests that targeting T_{RM} cells is a novel potential therapeutic strategy for decreasing psoriasis recurrence; however, more evidence, especially from psoriatic animal modes, is needed.

Fixed drug eruption

Adverse reactions to medications are common in dermatological practice. FDE is a localized variant of systemic medication-induced cutaneous adverse reactions. It usually presents with a single or a small number of erythematous or violaceous plaques, even those that are bullous or necrotic. FDE is characterized by rapid recurrence months or even years later in susceptible patients when a medication of the same or similar structure is taken again.[145] It occurs in exactly the same location as the first instance (Fig. 5) or in previously traumatized sites, such as insect bite, burn scars, and venipuncture sites (the Koebner phenomenon discussed above).[24,146]

In resolved FDE lesions, histological staining has shown the predominance of an intraepidermal population of $CD8^+$ memory T cells that is capable of producing IFN-γ and TNF-α upon activation.[21,24,147,148] These T cells constitutively express the cutaneous lymphocyte-associated antigens CD11a, CD69, and CD103 but not CD62L or CCR7.[24,147,149] Moreover, the rate of production of IFN-γ is much faster (3 h after challenge) than that of their peripheral counterparts.[24,149]

The clinical and pathologic features observed in FDE lesions can be explained by the presence of $CD8^+$ T_{RM} cells. For instance, these T cells can transiently acquire a natural killer-like phenotype upon clinical challenge with the causative medication and release cytotoxic granules that lead to the epidermal damage seen in FDE lesions;[150] the influx of regulatory T cells into the epidermis in fully evolved lesions has been suggested to limit the harmful immune reactions of these $CD8^+$ T_{RM} cells.[147] Moreover, IL-15 derived from lesional keratinocytes can maintain the survival of these T_{RM} cells, even without antigenic stimulus over a prolonged period.[24,150] The above evidence suggests that aberrantly activated T_{RM} cells are one of the major effector cells in FDE recurrence.

Drug eruptions represent a wide spectrum of cutaneous reactions. Unlike mild FDE, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are potentially life-threatening and at the extremely severe end of the drug eruption spectrum. Skin T_{RM} cells have been suggested to play a key role in the pathogenesis of SJS and TEN;[151] however, more direct evidence is needed.

Vitiligo

Vitiligo is a chronic skin disorder characterized by skin depigmentation (Fig. 5), and it is clinically characterized by pale to white patches on the skin. Psychological stress, skin damage (the Koebner phenomenon mentioned above), a family history of vitiligo, and other concomitant autoimmune conditions are triggers. Vitiligo prominently recurs in the same site after treatment is discontinued, suggesting the involvement of immunological memory.[25]

In vitiligo, an abnormal immune reaction has been demonstrated to attack the melanocytes of the skin. Recently, melanocyte-specific autoreactive T_{RM} cells in vitiligo lesions have been described, and T_{RM} cells have been suggested to cooperate with T_{CM} cells to maintain vitiligo in a mouse model.[25,152] Research has demonstrated that, in skin lesions of patients with vitiligo, $CD8^+CD49a^+$ T_{RM} cells constitutively express perforin and granzyme B and thus exhibit a strong cytotoxic phenotype.[14] More recent studies have shown that stable and active perilesional skin in vitiligo is enriched with a subset of $CD8^+$ T_{RM} cells that express CD69, CD103, and CXCR3. They are functional and exhibit the increased production of IFN-γ and TNF-α and moderate cytotoxic activity.[153]

Likewise, IL-15 has been reported to promote the survival of T_{RM} cells in vitiligo. IL-15-deficient mice reportedly exhibit the impaired formation of T_{RM} cells. Targeting IL-15 signaling with an antibody against CD122 (subunit of IL-15 receptor) can reverse established vitiligo in mice by inhibiting the production of IFN-γ by T_{RM} cells or even depleting T_{RM} cells in skin lesions.[154] These studies not only emphasize the involvement of T_{RM} cells in vitiligo recurrence but also provide novel potential therapeutic strategies for diseases involving T_{RM} cells.

Atopic dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic inflammatory skin condition. AD often involves scaly and red rashes on the cheeks, scalp, or flexion of the arms and legs. It is characterized clinically by waves of recurrence in the above areas. Both genetic and stimulating factors, e.g., scratching, infections, dry skin, colds, and stress, play important roles in AD development.[155]

AD recurrence is accompanied by uncontrolled immune activation, and immune memory has been suggested to be

involved.[138,156] It has been shown that TCR diversity is similar in lesional and nonlesional skin. Most top expanded lesional T cell clones are also present in nonlesional skin, and they are largely maintained even after months of treatment with topical glucocorticoids. This suggests the presence of potentially pathogenic T_{RM} cells in lesional and nonlesional skin in AD.[157]

Recently, thymic stromal lymphopoietin (TSLP), an triggering factor for AD, has been reported to increase CD69 expression and the number of $CD69^+$ T_{RM} cells in AD.[158] It has been demonstrated that, as in psoriasis, $CD69^+$ T_{RM} cells in AD skin lesions express considerable molecules related to tissue residency. Moreover, both $CD4^+CD69^+$ and $CD8^+CD69^+$ T_{RM} cells are enriched with various potentially pathologic cytokine genes, e.g., IL-4, IL-13, IL-17, and IL-22, which indicates that these multifunctional T_{RM} cells might be the main cause of AD recurrence.[159]

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a classic example of a T cell-mediated hypersensitivity reaction in the skin. Red, pruritic, swollen erythema or blisters occur 24 to 48 h after the skin comes in contact with an irritant or allergen. The lesions may persist for weeks after exposure stops and will recur upon future exposure.[160,161]

The damage to skin cells caused by ACD depends on the rapid activation of a subtype of specific T cells. There is emerging evidence to suggest the contribution of T_{RM} cells to ACD flare-ups.[162,163] It has been shown the response to ACD challenge in both mice and humans sensitized to contact allergens (2,4-dinitrofluorobenzene and nickel) is dramatically increased at sites previously challenged by these allergens. Furthermore, the response magnitude is correlated with the accumulation of T_{RM} cells that are capable of producing IL-17A and IFN-γ in the skin.[163] It has been demonstrated that a large number of $CD4^+CCR10^+$ T_{RM} cells exist in ACD lesions that have clinically returned to normal 21 days after allergen challenge. This is likely associated with local skin immunological memory and rapid recall responses in previously challenged sites.[89]

Mycosis fungoides

Mycosis fungoides (MF) is a skin-limited variant of cutaneous T cell lymphoma. It may be clinically and histologically manifested as an inflammatory skin disorder in its early stages. MF usually begins as eczematous patches and proceeds to plaques and nodules that are infiltrated by T cells. These early inflammatory lesions are often stable for years and are therapeutically responsive to topical glucocorticoids, phototherapy, and low-dose irradiation. However, they usually recur in previously affected sites once therapy is withdrawn.[164]

It has been demonstrated that immune cells that are trafficked to the skin play crucial roles in MF. Recent studies have suggested that MF is a malignancy of distinct memory T cell subsets.[21] T cells isolated from MF skin lesions do not express CD62L (L-selectin) or CCR7 (a lymph node homing receptor), but they strongly express CCR4 and a cutaneous lymphocyte-associated antigen, which is a phenotype that is suggestive of skin T_{RM} cells.[165] This is consistent with the formation of fixed patches or plaques on the skin in MF. However, the factors that drive these skin T_{RM} cells into malignancy are not well known.

PERSPECTIVES

The long-term survival and low migration of skin T_{RM} cells combined with their potent effector functions are evidence of their potential roles in the recurrence of inflammatory skin disorders. However, more studies regarding the direct contribution of T_{RM} cells to skin inflammation recurrence are needed. Moreover, further investigations are needed to uncover more mechanisms underlying the biology of T_{RM} cells, including common mechanisms and distinct mechanisms. At present, there are several vital points that require more attention.

First, T_{RM} cells are heterogeneous, and subsets of T_{RM} cells that are involved in the recurrence of inflammatory skin disorders are most likely distinct in the expression of surface markers and biological behaviors. For instance, the main T_{RM} cells involved in vitiligo are $CD8^+CD49a^+$ T_{RM} cells that constitutively express perforin and granzyme B; however, T_{RM} cells in psoriasis are $CD8^+CD49a^-$ and predominantly generate IL-17.[14] Moreover, special anatomical niches, e.g., the hair follicles on the scalp and the folds of the inframammary region, are likely other important determinants of the diversity of subsets in the skin. T_{RM} cells are a crucial component of the adaptive immune response. To avoid the complete collapse of the immune defense system against infections, disease specificity and/or anatomical position should be considered when intervening with the biological functions of distinct subsets of T_{RM} cells. Therefore, the identification of distinct subsets of skin T_{RM} cells will be helpful for determining precise intervention strategies in the future.

Second, attention should be paid to the crosstalk between subsets of T_{RM} cells from different skin compartments (the dermis and epidermis) in the development of skin inflammation. Are they cooperative or antagonistic? In addition, recent studies have suggested that γδ T cells and innate lymphocyte cells can also form long-lived resident memory-like subsets upon local inflammation or infection.[166–168] Is there crosstalk between these unconventional T_{RM} cells and the conventional αβ ones we reviewed here? The clarification of this crosstalk will contribute to our understanding of the overall immunological balance and lay the foundation for the development of therapeutics on the whole.

Third, attention should also be paid to the interactions between the skin microbiome (bacteria, fungi, viruses, archaea and skin mites) and the training of skin T_{RM} cells. Skin T_{RM} cells are exposed to the skin microbiome and their antigens for life. How the composition of the skin microbiome and whether certain species of the skin microbiome impact the training of skin T_{RM} cells are not known, but much can be learned from the gastrointestinal tract.[156] This may open up new avenues for topical therapeutic strategies.

Next, skin T_{RM} cells have the prominent ability to adapt to the local environment, at least through FFA consumption and mitochondrial oxidative metabolism. We know that the majority of chronic skin inflammation is concomitant with metabolism-related disorders (e.g., diabetes mellitus). Do skin T_{RM} cells obtain more robust survival energy under such conditions? Are there any differences between skin T_{RM} cells in skin inflammation only and those in metabolic disorders? The answers to these questions will provide new clinical therapeutic strategies from a new perspective of cell survival energy.

Finally, further studies with animal models are needed to establish whether the manipulation of T_{RM} cells or their molecular pathways involved in recruitment, retention, and long-term survival may help to control inflammatory disease continuation and/or recurrence. In fact, manipulating T_{RM} cells is a challenging task because it is difficult to deplete T_{RM} cells in animal models with antibodies against surface markers. Encouragingly, the exploration of the manipulation of molecular pathways involved in the biological behavior of T_{RM} cells is already underway. For example, MTX plus a neutralizing IL-15 mAb has been demonstrated to manipulate CD69 expression and $CD8^+CD69^+$ T_{RM} cells in psoriatic organ cultures, although MTX alone failed (unpublished data); S1PR1 modulators are being developed to control autoimmune and inflammatory diseases including psoriasis and inflammatory bowel disease.[169,170]

In conclusion, skin T_{RM} cells have been suggested to play vital roles in the recurrence of inflammatory skin disorders. Clarifying and characterizing the mechanisms underlying the roles of skin T_{RM} cells will provide new perspectives for controlling chronic

inflammation and promising strategies for reducing the frequency and magnitude of skin inflammation recurrence.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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