Review

Skin-Resident Memory T Cells: Pathogenesis and Implication for the Treatment of Psoriasis

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Abstract: Tissue-resident memory T cells (T_{RM}) stay in the peripheral tissues for long periods of time, do not recirculate, and provide the first line of adaptive immune response in the residing tissues. Although T_{RM} originate from circulating T cells, T_{RM} are physiologically distinct from circulating T cells with the expression of tissue-residency markers, such as CD69 and CD103, and the characteristic profile of transcription factors. Besides defense against pathogens, the functional skew of skin T_{RM} is indicated in chronic skin inflammatory diseases. In psoriasis, IL-17A-producing $CD8^+$ T_{RM} are regarded as one of the pathogenic populations in skin. Although no licensed drugs that directly and specifically inhibit the activity of skin T_{RM} are available to date, psoriatic skin T_{RM} are affected in the current treatments of psoriasis. Targeting skin T_{RM} or using T_{RM} as a potential index for disease severity can be an attractive strategy in psoriasis.

Keywords: skin-resident memory T cells; human; psoriasis; cytokines; autoantigens; treatment

1. Introduction

Once the immune system encounters antigens, memory T cells are generated from the naïve T cells and facilitate a prompt response to the re-exposure of the same antigens. Two populations of memory T cells have been defined from human blood circulation: effector memory T cells (T_{EM}) and central memory T cells (T_{CM}) [1]. T_{EM} are also dominant in peripheral non-lymphoid tissues and T_{CM} have an affinity for secondary lymphoid organs [2,3]. Furthermore, research on murine infectious disease models has revealed that a subpopulation of T_{EM} found in peripheral tissues remain in the same tissues for long periods without recirculation after cure of infection [4–6]. These findings led to the establishment of the new population of memory T cells, tissue-resident memory T cells (T_{RM}).

T_{RM} are superior to their circulating memory counterparts in their ability to provide the local adaptive cellular defense [7–11]. They can respond to the local antigen re-exposure without the recruitment of circulating T cells to the tissue [12]. In addition, recent studies suggest T_{RM} also contribute to systemic immune responses upon subsequent exposure to specific antigens by proliferating and baring circulating populations, such as T_{CM} and T_{EM} [13,14].

The existence and functional activities of T_{RM} were initially investigated in barrier tissues, such as the gut [6,15], skin [4,5,12,16,17], respiratory tract [18,19], and reproductive tract [20,21], in the context of local defense against pathogens in infectious diseases. However, their roles are now recognized in various conditions, including cancer immunity, tissue-specific autoimmune diseases, and chronic inflammatory diseases both in barrier and non-barrier tissues [22].

Skin T_{RM} are among the intensively studied T_{RM} populations not only in murine models but also in humans. The human skin contains an estimate of 20 billion T cells,

doubling those in the circulation [23], and over half of these T cells show the T_{RM} pheno-type [24]. Besides infectious diseases, the involvement of skin T_{RM} has been reported in allergic contact hypersensitivity [25]; fixed drug eruption [26]; cutaneous malignancies, including malignant melanoma [27,28] and cutaneous T-cell lymphoma [24,29]; and chronic inflammatory diseases, such as vitiligo, alopecia, and psoriasis [30,31].

In this review, we provide an overview of the general characteristics of T_{RM}. Then, narrowing our focus to skin T_{RM} in humans, we summarize the involvement of skin T_{RM} in cutaneous disorders, especially psoriasis. We also mention the possibility of engaging T_{RM} as a disease index and treatment target in psoriasis. Since CD8$^+$ T_{RM} are the best-characterized population, we focus on CD8$^+$ T_{RM} and describe this population as T_{RM} in this review unless otherwise mentioned.

2. The Characteristics of T_{RM}

T cells in the neonatal murine skin are predominant with dendritic epidermal T cells (DETCS) with restricted antigenic specificity [32], and neonatal human skin holds only a few T cells [24]. Thus, T_{RM} are assumed to develop from circulating T cells according to repeated antigen exposure. In the local inflammation caused by specific antigens, the robustly expanded effector T cells emerge in the circulation and the affected tissues, and both T_{CM} and T_{RM} are assumed to arise from a part of these effector T cells [25,33].

The general characteristics of T_{RM} across the tissues include the loss of migration and the gain of retention. The development and maintenance of these characteristics in T_{RM} are driven by complex factors, such as cytokine and chemokine receptors, the other cell-surface molecules being responsible for tissue homing and retention, and transcription factors (Figure 1).
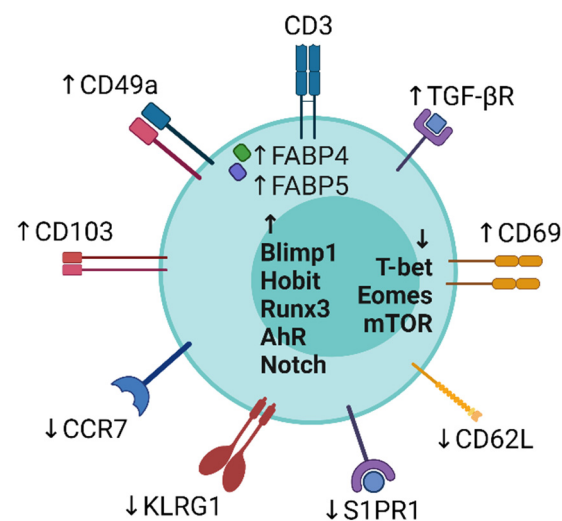

Figure 1. A. Surface markers, intracellular molecules, and transcription factors of T_{RM}. The expression levels of these molecules on T_{RM} are shown by upward arrows (increased expressions) and downward arrows (decreased expressions). Created with BioRender.com (accessed on 21 August 2021).

2.1. Cell Surface Molecules

While homing molecules including chemokine receptors are diverse depending on the target peripheral tissues, the molecules related to tissue retention seem to be shared among various tissues. In general, T_{RM} lack the expression of the secondary lymphoid homing molecules CC-chemokine receptor 7 (CCR7) and L-selectin, which are expressed on T_{CM} and naïve T cells [1]. The tissue retention molecules CD69 and CD103 (αE integrin) are widely recognized as the markers for T_{RM}. CD103 is a ligand of E-cadherin that is expressed on epithelial cells [34], and CD69 interferes with sphingosine-1-phosphate (S1P) receptor-1, which allows the cells to exit from peripheral tissues by sensing the density of S1P [35]. CD69 also reportedly regulates the uptake of L-tryptophan and the intracellular quantity

of L-tryptophan-derived activator of the aryl hydrocarbon receptor (AhR) [36], which is reportedly involved in the persistence of T_{RM} [32]. These functions would explain at least partially the importance of these molecules in tissue retention. However, their expression varies, possibly depending on the tissues and the causes of T_{RM} development. T_{RM} lacking CD103 expression have been described in some peripheral tissues and secondary lymphoid organs [37,38] and CD103$^+$ T_{RM} can be found in the dermis and adult central nervous system where E-cadherin is absent, implying that binding to E-cadherin is not required for the persistence of T_{RM} in peripheral tissues [24,39]. Although CD69 is expressed on the majority of T_{RM} in various peripheral tissues, T_{RM} negative for CD69 expression are also noted [33]. We thus have to take into account that these two molecules are not able to cover T_{RM} universally.

2.2. Transcription Factors

Transcriptional regulation is also presumably common among T_{RM} in various tissues. For instance, the expression of AhR is increased in skin T_{RM} as compared with naïve T cells and splenic T cells, possibly favoring the maintenance of skin T_{RM} [32]. Rapamycin inhibits the formation of T_{RM} in the intestinal and vaginal mucosa, highlighting a positive link of mammalian target of rapamycin and the downstream transcription factors with the formation of T_{RM} [40]. The maintenance of lung T_{RM} may be related to Notch signaling, including the upregulation of the downstream transcription factor RBPJ [41]. The augmented uptake of exogenous lipids accompanied by the upregulation of fatty acid binding proteins (FABPs) 4 and 5 is one of the characteristic processes involved in the generation and maintenance of skin T_{RM} [42]. Hypoxia-inducible factor-1α, which is a transcription factor in the downstream of FABP5 signaling, reportedly promotes the residency and anti-tumor function of tumor-infiltrating T cells in the murine malignancy model [43]. The downregulation of T-box transcription factors T-bet and EOMES [44] and the upregulation of Blimp-1, Hobit [45], and Runx3 [46,47] have also been reported to be involved in the differentiation and/or maintenance of T_{RM}.

2.3. Skin-Homing Molecules

In addition to the shared characteristics of various T_{RM}, skin T_{RM} are shown to have their own homing molecules. As one of skin's homing molecules, cutaneous lymphocyte-associated antigen (CLA) binds to E-selectin and P-selectin and allows the cells to migrate into skin [23]. The chemokine receptors CCR4, CCR8, CCR10, CXCR3, and CXCR6 are also regarded as important skin-homing and/or retention molecules for at least some skin T cells [16,48–52].

2.4. Fate Decision of T_{RM}

How the fate of T_{RM} differentiation is decided remains an unsolved question. T_{RM} reportedly derive from circulating T cells lacking high expression of the killer cell lectin-like receptor subfamily G member 1 (KLRG1), which is regarded as a terminal differentiation marker [16,47]. Another report demonstrates that the effector T cells with enriched expression of T_{RM}-associated genes, such as *Itgae* (CD103), *Itga1* (CD49a), *Cd101*, *Ahr*, and *Fabp5*, already exist as memory precursor cells and preferentially differentiate into T_{RM} [53], suggesting that the fate of T_{RM} is at least partially decided in the early stage of adoptive immune memory formation. On the other hand, the time-course single-cell RNA-sequencing analysis in a murine model with lymphocytic-choriomeningitis-virus infection revealed that the transcriptional characteristics of T_{RM} can be detected from gut-infiltrating T cells at the earliest 4 days after infection, and the characteristics are distinct from those found in splenic T cells [54], implying that the T_{RM} differentiation program is initiated after the cells enter the specific peripheral tissues. Further elucidation of the T_{RM} differentiation mechanism will require further research.

3. Human Skin T$_{RM}$

In general, human T$_{RM}$ and murine T$_{RM}$ share core transcriptional, phenotypic, and functional profiles, including the almost global expression of CD69 and dominant CD103 expression in CD8 fractions [45,55–57]. In patients with cutaneous T-cell lymphoma (CTCL), the treatment with alemtuzumab, which depletes circulating T cells and spares the T$_{RM}$, does not result in serious infection [58], implying the role of skin T$_{RM}$ in protective immunity. The T$_{RM}$ phenotype of the malignant cells in CTCL is related to the clinical manifestation of well-demarcated lesions, suggesting that the sessile property of T$_{RM}$ also exists in humans [24]. In vitro experiments suggest skin T$_{RM}$ maintain the production of IL-17A and IFN-γ in reaction with pathogen challenges through aging [59]. Using transcriptomic and functional data, human T$_{RM}$ are found to abolish their senescent phenotype and survive for over 10 years in specific circumstances [46], replicating the longevity of T$_{RM}$ in humans.

However, T$_{RM}$ in humans are presumably more diverse and widely distributed. For instance, CD4$^+$ T$_{RM}$ are found in both the epidermis and dermis in humans, although murine skin CD4$^+$ T$_{RM}$ are predominantly found in dermis [17,24,60,61]. T$_{RM}$ are also found in secondary lymphoid organs, such as the spleen, lymph nodes, and tonsils in humans [55,56].

The factors that may cause the difference between human skin T$_{RM}$ properties and those observed in laboratory mice may include the following: (1) the thick epidermis with abundant niche for T$_{RM}$ [24,62]; (2) the low density of hair follicles that express cytokines important for T$_{RM}$ migration and survival, including IL-7 and IL-15 [63,64]; (3) the frequent exposure to foreign antigens; (4) the small population of $\gamma\delta$T cells with the lack of DETC in the human epidermis [65] (however, we do not know whether the recently identified $\alpha\beta\gamma\delta$T cell population in fetal skin can replace DETC) [66]. The longer survival period of human T$_{RM}$ compared to murine life span [46] may also cause difficulty in adapting the findings in murine models to human biology.

The involvement of skin T$_{RM}$ is highlighted in chronic inflammatory disorders and cutaneous malignancies. In the lesional skin of alopecia areata, T$_{RM}$ with the ability to produce granzyme B are dominant and related to disease prognosis, implying their involvement in the pathogenesis [67]. Intraepidermal IFN-γ-producing T$_{RM}$ are enriched in the cured sites of fixed drug eruption [26], suggesting the contribution of this fraction to the reproducible property. In patients with atopic dermatitis, cutaneous T$_{RM}$ with the production of IL-4 and IL-13 are also indicated to be involved in the disease pathogenesis [68]. Dermal T$_{RM}$ are increased with the production potential of perforin, granzyme B, and IFN-γ in vitiligo [30,69], which are presumably specific for melanocyte antigens. In malignant melanoma, skin T$_{RM}$ provide protection against tumor regrowth and are involved in vitiligo formation, suggestive of their specific reactivity against melanoma antigens [70]. Better understanding of cutaneous T$_{RM}$ will pave the way for novel management and treatment of skin diseases.

The methodologies for evaluating skin T$_{RM}$ are summarized in Table 1. In the translational research field, one of the most popular methods for analyzing T$_{RM}$ is fluorescence-activated cell sorting (FACS) analysis. However, conducting this method from biopsied skin specimens is not practical in the daily clinical settings considering the burden for both patients and clinicians. Immunohistochemistry (IHC) and/or immunofluorescence (IF) for T$_{RM}$-related molecules, such as CD3, CD8, CD69, and CD103, on the residual biopsy specimens carried out for diagnosis is probably more feasible to date. To establish non-invasive methods for predicting the activities of skin T$_{RM}$, such as analyzing tape-stripped or surface-swabbed samples, will require further research.

4. Skin T$_{RM}$ in the Pathogenesis of Psoriasis

Psoriasis, hereafter referred to as plaque psoriasis, is an immune-mediated chronic inflammatory skin disorder characterized by well-demarcated persistent scaly indurated erythematous plaques. The contributions of environment [71], hereditary predisposition [72],

and autoantigens [73] are implied to be involved in disease development. Circulating T cells were previously regarded as responsible for the lesion formation in psoriasis. However, the inhibition of E-selectin, which is required for T-cell migration from the blood stream to skin, was noted to be ineffective [74]. Another blocking strategy of T-cell migration by the biologics targeting CD11a also did not show dramatic efficacy [75]. However, in a humanized murine model where psoriatic nonlesional skin specimens are grafted to immunodeficient mice [76], the healthy-appearing nonlesional skin grafts spontaneously develop psoriatic disease, suggesting that the cells residing in the nonlesional skin are sufficient for the development of psoriatic disease. These results have led to the theory that T_{RM} may play a crucial role in the pathogenesis of psoriasis.

The fate of skin T_{RM} is affected by the skin microenvironment, and in psoriasis, this is also the case. Several skin-constituting factors have been reported to support the development and persistence of IL-17A-producing T_{RM} in psoriasis. Keratinocytes in disease-naïve sites of psoriasis upregulate the expression of chemokines, such as CCL20 upon stimulation by skin commensal fungi [77]. Since CCL20 is a ligand for CCR6, which is a signature molecule of IL-17A-producing T cells, the activated keratinocytes in the disease-naïve sites of psoriasis are to recruit IL-17A-producing T cells to the disease-naïve sites, leading to the accumulation of IL-17A-producing T_{RM} [77]. In turn, IL-17A from T_{RM} stimulates keratinocytes to express CCL20, further accelerating the recruitment of $CCR6^+$ cells [78]. In the resolved skin, the continuous production of IL-23 and IL-15 from Langerhans cells presumably support the maintenance of IL-17A-producing T_{RM} in the epidermis [79]. The reduced repertoire of IL-17A-producing T cells in the resolved skin, which has been observed in different psoriatic patients, implies the existence of common antigens that drive the accumulation of psoriatic T_{RM} [80]. Several potential autoantigens have been reported in psoriasis (Figure 2). For example, cationic antimicrobial peptide LL-37 produced by various cells including keratinocytes binds self-DNA and triggers the activation of plasmacytoid dendritic cells (pDC) and TNF/iNOS-producing dendritic cells (TIP-DC) [81,82]. A disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTSL5) in complex with HLA-C*06:02 on the surface of melanocytes confers epidermal $CD8^+$ T-cell response [83]. Neo-lipid antigens generated by phospholipase A2 group 4D (PLA2G4D) from mast cells and keratinocytes trigger the CD1a-reactive T cells to produce IL-17A and IL-22 [84]. Keratin 17, a human epidermal keratin that shares a sequential homology with streptococcal M protein, is recognized by HLA-Cw*0602-restricted IFN-γ-producing $CD8^+$ T cells [85,86]. Taken together, these results suggest the synchronizing roles of the skin microenvironment in the development and persistence of pathogenic cutaneous T_{RM}.

In the lesional skin of patients with psoriasis, T_{RM} consist of both CD4 and CD8 fractions, which synchronize the elevated immune response by the increased expression of inflammatory cytokines, such as IL-17A, IL-22, and IFN-γ [62,80,87,88]. While IL-17A-producing $CD4^+$ T_{RM} also exist in healthy skin, the enrichment of $CD8^+$ T_{RM} producing IL-17A in the epidermis is one of the characteristics of psoriasis [87,88]. In disease-naïve skin that has never experienced disease formation, IL-17A production is augmented by T_{RM} [77], and the increase in IL-17A-producing $CD8^+$ T_{RM} at the dispense of IFN-γ-producing T_{RM} occurs according to disease duration [88].

IFN-γ-producing T_{RM} are also dominant in the epidermis and express the complex of CD49a–CD29, also known as very late antigen 1 (VLA-1) or α1β1 integrin [76]. $CD49a^+$ T_{RM} are involved in the pathogenesis of psoriasis. The number of epidermal $CD8^+CD49a^+$ T_{RM} correlates with the severity of the disease [89], and an experimental blockade of CD49a in mice transplanted with psoriatic skin reduces the disease formation [76]. However, since the blockade of whole $CD8^+$ T cells almost completely prevents disease development in the similar psoriatic skin-engrafted murine model [90], $CD49a^+$ T_{RM} with IFN-γ production are not likely the key population for disease development, while the $CD8^+$ T cell population likely includes a critical fraction for disease pathogenesis. In fact, $CD8^+$ T_{RM} without the expression of CD49a are defined as an IL-17A-producing T_{RM} subset [30].
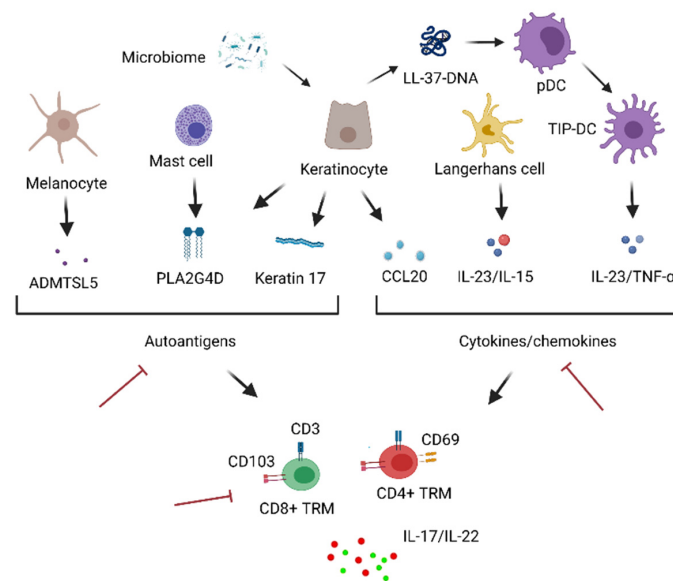
Figure 2. Development of T_{RM} in psoriasis. T_{RM} are activated by either autoantigens or cytokines/chemokines. Autoantigens include ADMTSL5 on the surface of melanocytes, PLAG4D from mast cells and keratinocytes, and keratin 17 from keratinocytes. Antimicrobial peptide LL-37, also from keratinocytes, binds to self-DNA to activate pDC and TIP-DC, leading to the production of IL-23/TNF-α. IL-23/15 from Langerhans cells and CCL20 from keratinocytes also activate T_{RM}. These stimulated T_{RM} produce proinflammatory cytokines, such as IL-17A and IL-22, the hallmarks of psoriasis. The development of pathogenic T_{RM} can be inhibited by stopping pathways related to T_{RM} activation or directly inhibiting the activity of T_{RM} (red inhibition icon). Created with BioRender.com (assessed on 21 August 2021).

Successful treatment with an IL-17A-targeting biologics results in a decreased number of IL-17A-producing T_{RM} in resolved skin, but the frequency of these cells is not altered within the remaining T cells [91]. Another study on residual psoriasis after the use of biologics revealed a decrease in keratinocyte proliferation. However, the percentage of IL-17A-producing CD103$^+$ T_{RM} was not significantly reduced after the treatments [92]. Similarly, a new normal in the persistence of IL-17A-producing T_{RM} with CCR6 and IL-23R expression in the resolved skin has been established [62,80]. IL-17A-producing CD8$^+$ T_{RM} and IL-22-producing CD4$^+$ T_{RM} remain in the psoriatic epidermis for as long as six years after starting the successful TNF-α-targeting treatment [62]. Taken together, these findings highlight the essential standing point of IL-17A-producing T_{RM} as one of the pathogenic populations of skin T_{RM} in psoriasis.

5. Targeting Skin T_{RM} in the Management of Psoriasis

Regardless of the persistence of this population by various treatments in psoriasis, many of the current and upcoming therapeutics in clinical practice presumably exert an indirect influence on cutaneous IL-17A-producing T_{RM}. Since the remission period after successful treatments inversely correlates with the relative IL-17 signaling of the resolved skin compared to IL-10 and IFN-γ signaling [93], the relative reduction, if not elimination, of IL-17A-producing T_{RM} may be of help in controlling psoriatic disease activity.

Biologics targeting the IL-17 pathway reportedly reduce IL-17 signaling and the amount of T cells in the lesion [94]. Furthermore, the biologics targeting IL-23 decrease this fraction from the lesion more strongly compared to those targeting IL-17A [95]. Ultraviolet irradiation leads to the diminishment of IL-17A-producing T cells in skin [96], and this T-cell fraction includes T_{RM}. Topical vitamin D analogues and corticosteroids reportedly reduce the lesional IL-17A-producing T_{RM}, possibly including pathogenic T_{RM} [97,98]. Retinoic acid prevents Th17 differentiation and possibly promotes the properties of regulatory T cells [99,100]. As the oral phosphodiesterase 4 inhibitor (PDE4i) diminishes the pro-

inflammatory cytokine production from circulating T cells [101], the function of both topical and systemic PDE4i could be revisited from the perspective of skin T_{RM}. An AhR agonist modulates the Th17 property of T cells, and the efficacy of its topical form possibly affects IL-17A-producing T cells in skin, including T_{RM} [102].

Proof-of-concept approaches that directly and exclusively target pathogenic populations of T_{RM} should be subjected to further studies. The candidate strategies might include the inhibition of the pathways involved in IL-15 signaling to perturb the survival of pathogenic T_{RM} and the blockade of the pathways processing fatty acids to suppress the lipid metabolism of pathogenic T_{RM}. Targeting the transcription factors specified for differentiation and maintenance of pathogenic T_{RM} is also an attractive strategy. However, although the risk of targeting these populations of T_{RM} is unknown, it may cause the loss of local immune memory against pathogens in the skin. Since the characteristic cell surface molecules and transcription factors found in T_{RM} properties can be overlapped with the sessile properties of other cell types, such as innate lymphoid cells and B cells [103,104], the strategies targeting T_{RM} might also affect the other tissue-sessile immunity. Specific treatment targets for psoriatic dysfunctional T_{RM}, excluding the other T_{RM} and skin-resident immune cells, would be ideal.

6. Conclusions

Extensive studies with rigorous methodologies have broadened our knowledge on T_{RM} in general and those residing in the skin in particular (Table 1). The involvement of skin T_{RM} in the pathogenesis of skin diseases is also being elucidated. Several key points are highlighted below:

- T_{RM} originate from circulating T cells, do not recirculate, and provide the first line of adaptive cellular defense in the residing tissues.
- The functional skew of skin T_{RM} is indicated in chronic skin inflammatory diseases.
- In psoriasis, IL-17-A-producing CD8$^+$ T_{RM} may be among the pathogenic populations in the skin.
- Pathogenic populations of skin T_{RM} can be targeted in the current and future treatments of psoriasis. Skin T_{RM} can also serve as a potential index of the disease.

Further studies on T_{RM} will advance the management of not only psoriasis but other diseases in which this subset of T cells plays a role.

Table 1. Several major findings related to methodologies used in research on humans.

Key Findings	Major Methodologies	
A role of skin T_{RM} in protective immunity in humans	FACS	[58]
Skin T_{RM} with the potential of producing cytokines are infiltrated in the lesion of patients with GVHD	FC, single-cell TCR sequencing, and IF	[46]
Cells residing in nonlesional skin are sufficient, and the recruitment of circulating cells is not necessary for the development of psoriatic disease	Transplantation, FC, quantitative RT-PCR, and IHC	[76]
CD8$^+$ T_{RM} producing IL-17A in the epidermis is one of the characteristics in psoriasis	FC and IHC	[87]
The increase in IL-17A-producing CD8$^+$ T_{RM} during the distribution of IFN-γ-producing T_{RM} occurs according to psoriasis duration	FC and IF	[88]
The successful treatment with IL-17A-targeting biologics results in a decreased number of IL-17A-producing CD8$^+$ T_{RM} in resolved psoriatic skin, but the frequency of these cells is not altered	FC, IHC, and IF	[91]
IL-17A-producing CD8$^+$ T_{RM} and IL-22-producing CD4$^+$ T_{RM} remain in the psoriatic epidermis for as long as six years after starting the successful TNF-α-targeting treatment	FC, quantitative RT-PCR, and IF	[62]

FC: flow cytometry, TCR: T-cell receptor, RT-PCR: reverse transcription polymerase chain reaction, IF: immunofluorescence, IHC: immunohistochemistry.

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