Journal of Dermatological Science 95 (2019) 2–7

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Invited Review Article

Protective and pathogenic roles of resident memory T cells in human skin disorders

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ARTICLE INFO

Article history:
Received 9 May 2019
Received in revised form 1 June 2019
Accepted 3 June 2019

Keywords:
resident memory T cell
skin disorders

ABSTRACT

The human skin is populated by recirculating T cells and skin-sessile resident memory T cells (T_{RM}). Skin T_{RM} are constructed during immune responses against antigens that the host immune system encounters in the skin. T_{RM} persist in the same sites for a long time and play important protective roles in skin immune responses in collaboration with other skin-composing cells such as dendritic cells and keratinocytes. These T_{RM} with strong effector functions possibly also engender skin inflammatory disorders. Since human skin T cells, especially T_{RM}, are phenotypically distinct from T cells in the blood circulation, T cells residing in the skin should be directly investigated, without presuming from the activities of blood T cells, in order to understand the functional characteristics of skin T cells in skin disorders. This review summarizes the features of human skin T_{RM} and reviews the immunopathological involvement of T_{RM} in human skin disorders such as infectious disease, inflammatory skin disease, and malignant skin tumors.

1. Introduction

Memory T cells are generated once the immune system encounters pathogens and provide a rapid response against the same pathogens at the time of reexposure. These memory T cells are driven by a variety of foreign and internal antigens and are classified into subpopulations such as central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) according to their motility and function. In the past decade, many reports have been published on a new subset of memory T cells named resident memory T cells (T_{RM}). T_{RM} are constructed from T cells entering the peripheral tissues. T_{RM} do not recirculate and stay for a long time in epithelial barrier tissues such as those of the gut, lung, reproductive tract, and skin, through which the host is constantly exposed to pathogens (Fig. 1) [1–3]. T_{RM} can react against the specific pathogens that each tissue frequently encounters without recruiting other immune cells from the bloodstream [4,5], suggesting their role as a front-line barrier in terms of protective immunity. T_{RM} are also found in nonbarrier tissues such as those of the central nervous system, endocrine system, liver, and kidneys, and a functional skew of these T_{RM} may be involved in tissue-specific autoimmune disorders. Since the phenotypic characteristics of skin T_{RM} are distinct from those of blood T cells, the activities of skin T cells should be investigated directly to reveal their roles in the healthy condition and in various skin diseases. This review summarizes the characteristics of skin T_{RM} in humans and reviews the involvement of T_{RM} in skin immunopathology from the viewpoint of human skin disorders.

2. Characteristics of human skin T_{RM}

There are three frequently reported key markers of skin T_{RM}, which are also common in various tissues: CD69, αE integrin (CD103), and α1 integrin (CD49a). All of these markers are not necessarily expressed in T_{RM}, and little is known about the functioning of these markers.

CD69 is a glycoprotein and regarded as a marker of recent T-cell activation in the lymph nodes. However, even though the existence of CD69-expressing T cells has been reported in all the tissues in which T_{RM} cells were identified [6–8], most of the T_{RM} cells in these tissues were not recently activated by antigens. CD69 is now coming to be recognized as a retention marker of peripheral tissues also. CD69 contributes to downregulation of the G protein-coupled receptor for sphingosine 1 phosphate (S1P1) [9]. T cells expressing S1P1 are guided out of tissue into the lymph nodes and then into the blood depending on the gradients of S1P, expression levels of which are low in tissues, intermediate in lymph nodes, and high in blood [10]. T_{RM} expressing CD69 do not express S1P1 and are thus considered not to exit from peripheral tissues because of a lack of sensing S1P gradients. However, absence of CD69 results in only a decrease, not a complete depletion, of the T_{RM} population [1],

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https://doi.org/10.1016/j.jdermsci.2019.06.001

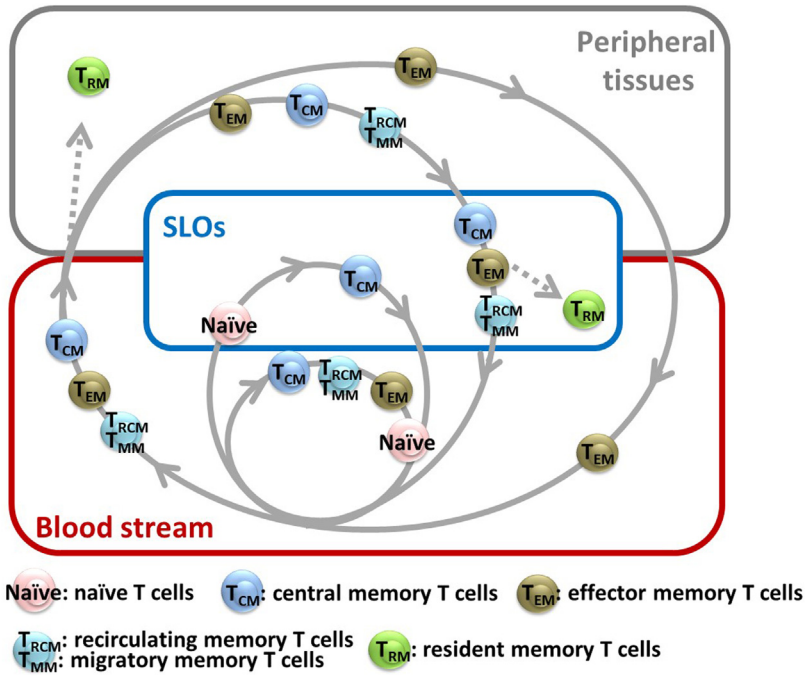

Fig. 1. Mobile profile of memory T-cell subsets.
Central memory T cells (T_{CM}) recirculate in a similar manner to that of naïve T cells and recirculate to and from the blood and secondary lymphoid organs (SLO). A subpopulation of T_{CM} also expresses tissue-tropic markers and can enter into the peripheral tissues. Effector memory T cells (T_{EM}) usually recirculate from the blood and peripheral tissues without entering the SLOs. However, a part of T_{EM} can enter the lymphatics from the peripheral tissues and return to the blood circulation through the SLOs. This population might be overlapped with the populations reported as recirculating memory T cells (T_{RCM}) or migratory memory T cells (T_{MM}). Resident memory T cells (T_{RM}) are found both in peripheral nonlymphoid tissues and SLOs. T_{RM} arise from T cells that enter those organs and have a sessile phenotype.

suggesting that CD69 expression is not mandatory for maintenance of the T_{RM} nature.

CD103 is known as a ligand of E-cadherin, a homotypic adhesion molecule expressed by epithelial cells in barrier tissues [11], suggesting that T_{RM} are attached to epithelial cells through the interaction between CD103 and E-cadherin. Supporting this notion, T_{RM} lacking CD103 have been shown to increase their motility in the epidermis of a mouse model. Beyond adhesion, $CD103^+$ T_{RM} are engaged in cytotoxicity via exocytosis of cytolytic granules, and this mechanism is also regarded to be through tight cell-to-cell adhesion. However, as reported for CD69, absence of CD103 leads to a decrease, not a complete deletion, of the T_{RM} population [1]. Thus, retention of T_{RM} within tissue does not absolutely require the binding of T_{RM} to epithelial cells. Actually, $CD103^+$ T_{RM} and $CD103^+$ dendritic cells are found in the dermis. $CD103^-$ T_{RM} populations have has also been reported in human skin [12].

Under normal conditions, CD49a is expressed exclusively on CD8 T cells in the epidermis and has been demonstrated to be a marker of T_{RM} in the epidermis. CD49a binds to type IV collagen, which is expressed in the basement membrane zone. CD49a is required not only for binding to collagen, but also for cell migration along the collagen. This migration is supposed to confine CD49a-expressing cells to the epidermal compartment. Notably, the expression of this molecule is related to the cytokine production profile of the cells. CD49a-expressing T cells are enriched with IFNγ-producing T cells, and CD49a-negative T cells are dominated by IL-17A-producing T cells [13]. CD49a expression on epidermal T cells is demonstrated in one of the Th1/Tc1-mediated skin disorders, vitiligo vulgaris.

In humans, skin T_{RM} reportedly can also be distinguished by surface CCR8 expression [14]. CCR8 expression on skin T cells correlates not only with high expression of the other T_{RM} markers but also with low expression levels of inhibitory receptors such as programmed cell death protein 1, Tim-1, and LAG-3. Interestingly, senescence markers such as CD57 and killer cell lectin-like receptor subfamily G member 1 are not expressed on $CCR8^+$ skin T cells, suggesting the long-lived phenotype of these cells.

3. Human skin T_{RM} in infectious diseases

Research on T_{RM} has focused on barrier functions against infectious antigens in various mouse models. Infection was caused intravenously in the early research on skin T_{RM}, and skin T_{RM} were constructed even with this infection route. However, the skin infection model of vaccinia virus demonstrated that infection via the epidermis is the most effective immunization route to develop skin T_{RM}. Notably, this skin immunization also generates T_{RM} in distant barrier tissues such as those of the lung [4,5]. In mice infected with *Candida albicans* via the skin, CD4 T cells were shown to be recruited to the infected area and to become sessile, with responsible production of IL-17A after pathogen rechallenge [15]. These observations on T_{RM} development against pathogens possibly reflect the construction processes of T_{RM} in human skin.

In humans, within CD8 T_{RM}, CD8αα T_{RM} that localize at the dermal-epidermal junction protect against the reactivation of herpes simplex virus (HSV) [16]. In patients with recurrent HSV-2 infection of the genital skin, the affected skin contains CD8 T cells that persist for months after the lesion has disappeared and the number of HSV-specific T_{RM} in the skin inversely relates with the period free from clinical recurrence. CD4 T cell fraction has also been shown to persist as clusters with macrophages in the genital mucosa after HSV-2 infection [17]. It is difficult to demonstrate the live function of pathogen-specific T_{RM}, but T_{RM} against pathogens are presumed to be generated in barrier tissues such as those of the skin and mucosa in a similar way. Mucosal CD8 T_{RM} specific for

human immunodeficiency virus (HIV)-1 have been demonstrated and the stronger reaction of these cells against HIV-1 was reported to be correlated with natural control of HIV-1 infection [18]. Influenza virus-specific CD8 T_{RM} generated in the nasal mucosa take part in preventing the influenza virus from spreading from the upper respiratory tract to the lung [19]. The developmental process and presumed function of mucosal T_{RM} can probably also be adapted to skin T_{RM} [20].

4. Human skin T_{RM} in immune-mediated skin disorders

4.1. Fixed drug eruption

Human T_{RM} are best investigated in skin disorders. Fixed drug eruption (FDE) characteristically develops in the same site (s) as oval erythematous patches after systemic exposure to particular drugs. IFNγ-producing CD8 T cells persist in the epidermis of resting FDE lesions [21,22], and these T cells are suggested to play a pathogenic role in disease progression. The expression of the CD103 molecule in these intraepidermal CD8 T cells supports the notion that FDE is a T_{RM}-mediated reaction [21] and probably reflects the sessile clinical manifestation of FDE. In addition, the upregulation of ICAM-1 in the keratinocytes of the affected lesions implies the involvement of keratinocytes in the development and activation of the T_{RM} population in FDE [23]. Interestingly, increased numbers of $CD25^+$ CD4 T cells are observed in the active rechallenged epidermis of FDE lesions. This population is regarded to include $FoxP3^+$ regulatory T cells and implied to be related to induction of FDE desensitization [24].

4.2. Psoriasis

One of other disease examples intensively researched from the viewpoint of T_{RM} is psoriasis. Psoriatic skin is known to have a large number of CD8 T cells expressing CD103 in the epidermis [25]. In a mouse model of engrafted human skin, the psoriatic lesion was maintained by injection of psoriatic lesional T cells, not blood T cells, into the grafted specimen [26]. On the other hand, the engrafted mouse model of non-lesional psoriatic skin suggested that blood CD4 T cells are inevitable for psoriatic lesion formation [27]. However, in this experiment with engraftment of psoriatic non-lesional skin and blood CD4 T cells, development of CD8 T cells expressing CD69 was observed in the transplanted skin. The subsequent report demonstrated that the engrafted non-lesional skin from patients with psoriasis spontaneously develops a psoriatic lesion by itself, suggesting that psoriatic lesions can develop solely dependent on the cells existing in the skin without recruitment of circulating cells [28,29]. Going back to the first engrafted mouse model, it can be presumed that $CD69^+$ CD8 T cells in the engrafted skin originated from the skin T_{RM} that have existed in the non-lesional psoriatic skin from the beginning. Furthermore, this psoriatic disease formation in the grafted skin was prevented by neutralizing CD8 [30]. These results demonstrate that skin CD8 T_{RM}, especially epidermal CD8 T_{RM}, play an inevitable role in the lesion formation of psoriasis. In this mouse model, blockade of ICAM-1 also prevented the development of psoriatic lesion [29]. Considering ICAM-1 expression in keratinocytes [31], the efficacy of efalizumab targeting LFA-1, the ligand of ICAM-1, on psoriasis [32] is regarded to be through blocking not only the interaction of T cells with myeloid dendritic cells and extravasation of circulating T cells but also the interaction of activated T cells with keratinocytes. Keratinocytes in never-lesional skin, which has never experienced disease formation, of psoriasis patients are also reported to be involved in accumulation of T_{RM}. Never-lesional keratinocytes are prone to upregulate CCL20 expression under stimulation with psoriasis-related cytokines, which leads to migration of CCR6-expressing IL-17A-generating T cells [33]. Actually, psoriatic never-lesional epidermis is enriched with $CD103^+$ CD8 T_{RM} with the potential of producing IL-17A. In mild psoriasis, relative IL-17A generation from $CD103^+$ CD8 T_{RM} compared to IFNγ expression correlated with disease duration [34]. These observations on CD8 T_{RM} in psoriasis imply that the population of CD8 T_{RM} with an IL-17A-producing profile is constructed in psoriatic skin before disease formation in response to recruiting signals such as CCL20 and ICAM-1 and cytokines such as IL-23 and IL-15 and contributes to future lesion formation (Fig. 2). The emergence of biologics will enable drastic improvement of psoriasis and disease-free status has become a realistic goal. However, even in cleared skin, IL-17A/IL-22-producing T cells remain in the epidermis [13,35]. These T cells show quite similar profiles to those of T_{RM} in never-lesional psoriatic skin. Here again, the relative expression levels of IL-17A to IFNγ and IL-10 in the remaining T cells of the cleared skin turned out to correlate with the duration of remission [35]. It has also been demonstrated that cleared skin after treatment for psoriasis contains T cells with limited diversity in terms of the T cell-receptor repertoire [36]. Notably, the same amino acid sequences of the CDR3 regions in T-cell receptors were shared among the cleared skin from different psoriatic patients, while the same amino acid sequences were not detected in the skin of healthy controls. One possibility for the shared T-cell receptors in psoriatic cleared skin, which are distinct from those in healthy skin, is that these T cells are reactive to specific antigens. For instance, antimicrobial peptide LL37 has been demonstrated to serve as a T-cell autoantigen [37]. These LL37-specific T cells were investigated only from T cells in blood, but frequent expression of skin-homing molecules in these T cells may imply the possibility of these T cells being differentiated into skin T_{RM}. Another molecule, ADAMTS-like protein 5 (ADAMTSL5), which is produced by melanocytes, has also been identified as an activating antigen for epidermal CD8 T cells in psoriasis patients with a particular HLA [38]. These antigen-specific T cells from psoriatic patients produce IL-17A upon antigen

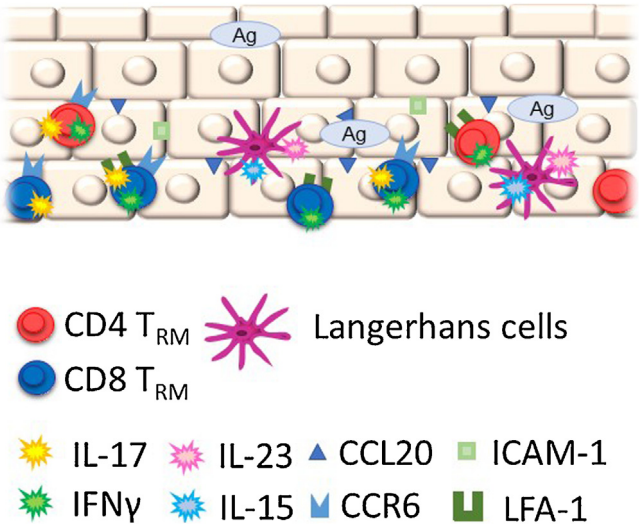

Fig. 2. Accumulation of IL-17A-producing T cells in the epidermis of non-lesional psoriasis.
Keratinocytes of psoriatic non-lesional sites express CCL20 upon psoriasis-related stimulation. Then, CCR6-expressing IL-17A-producing T cells are recruited into the epidermis. ICAM-1 expressed on keratinocytes also takes part in activating the LFA-1-signaling of T cells. Upregulated expression of IL-15 and IL-23 from Langerhans cells is suggested to retain the population of IL-17A-producing epidermal T cells in psoriatic skin. Recognition of possible internal antigens by T cells will also help maintain the epidermal T-cell population. The relative accumulation of IL-17A-producing CD8 T_{RM} is reported to correlate with disease duration and recurrence.

presentation. The accumulation and maintenance of epidermal IL-17A-producing CD8 T_{RM} in psoriatic patients might be explained by the sustained presentation of autoantigens.

4.3. Vitiligo

Much evidence has been accumulated regarding T_{RM} involvement in vitiligo vulgaris. Cytotoxic CD8 T cells take part in destruction of skin melanocytes [39]. Vitiligo lesions frequently recur in the same sites, and this clinical observation supports the idea that autoimmune memory is developed at these sites. Recent studies demonstrated that both stable and active vitiligo perilesional skin is enriched with IFNγ- and TNFα-producing CD8 T_{RM} with expression of CD69, CD103, and CXCR3, including melanocyte-specific CD8 T cells [40]. Epidermal CD8 T_{RM} with CD49a expression is an IFNγ-producing population and is enriched in vitiligo lesions [13]. In rhododendrol (RD)-induced leukodema, CD8 T cells are found more frequently in lesional skin than in normal skin. Melan-A-specific cytotoxic T cells are observed in the blood of a proportion of these cases, indicating the immune reaction of CD8 T cells, including T_{RM} in skin, toward melanocytes in RD-induced leukoderma, also [41]. In a mouse vitiligo model, neutralization of IL-15 receptor with anti-CD122 antibody downregulates IFNγ production from T_{RM} and leads to repigmentation of the lesion [42]. Since expression of CD122 is observed both in human and murine skin T_{RM} and since IL-15 in hair follicle reportedly promotes construction of epidermal T_{RM} [43], it is reasonable to regard T_{RM} as participants in the pathogenesis of vitiligo. Related to malignant melanoma, melanoma antigen-specific T_{RM} with CD103 expression are constructed in autoimmune vitiligo sites and increase the protection against melanoma rechallenge in a mouse model [44]. T_{RM} found in this melanoma-related vitiligo apparently share the same mechanistic function as those found in vitiligo vulgaris.

5. T_{RM} in human skin malignant tumors

5.1. Cutaneous T-cell lymphoma: malignancy of skin T_{RM}

The first report to prove the existence of a sessile T-cell population in human skin was from studies of patients with leukemic cutaneous T-cell lymphoma (L-CTCL) [45]. In that study, low-dose alemtuzumab, an anti-CD52 antibody, was used to treat L-CTCL patients. Alemtuzumab depletes CD52-expressing cells including T cells only in the circulation because this antibody works via ADCC requiring neutrophils or natural killer cells, which exist mostly in the circulation. In these patients, circulating T cells are thus depleted and T cells remaining in the skin are spared. It was also shown that a $CCR7^+$ $CD62L^+$ T_{CM} fraction and $CCR7^+$ $CD62L^-$ migratory memory T cell fraction are depleted from the skin [12], demonstrating that these two populations recirculate from the skin and were depleted by alemtuzumab. The remaining T cells in the skin through alemtuzumab treatment, which are either $CD69^+$ $CD103^+$ or $CD69^+$ $CD103^-$, were proved to be T_{RM} in human skin. The malignant counterpart of the T_{RM} population causes classical mycosis fungoides (MF), where well-demarcated patches, plaques, or tumors develop. In contrast to L-CTCL, most MF patients do not show blood involvement and the malignant clonal T cells are confined to the lesional skin. On the other hand, the malignancy of skin-tropic T_{CM} causes Sézary syndrome, a typical manifestation of L-CTCL with diffuse erythema and the involvement of blood and lymph nodes (Fig. 3) [46]. Notably, the clinical manifestation is reflected by the phenotype of malignant T cells. CCR7 expression on MF cells correlates with subcutaneous involvement of the tumor [47], which also indicates the mobility of these malignant cells.

5.2. Solid skin cancers

Recent research has shed light on tumor-infiltrating lymphocytes (TIL) in various solid tumors. In general, FoxP3 expression of TIL correlates with poor prognosis, and the expression of T_{RM} markers implies a positive outcome [48]. Malignant melanoma is the most intensively explored malignancy in skin from the viewpoint of TIL. The expression of the inhibitory checkpoint molecules CTLA-4 and PD-1 is observed in $CD69^+$ $CD103^+$ TIL of melanoma [49], suggesting TIL as a key target population of immune checkpoint inhibitors. On the other hand, whether the T_{RM}-like TIL with expression of immune checkpoint molecules is a T_{RM} population against the tumor or just the exhausted cell population remains uncertain. The maintenance of T_{RM} reacting with melanoma antigens in the vitiligo lesions, which indicates good prognosis, of melanoma patients [44] at least suggests the protective function of this T_{RM} population against disease development. It has also been reported that T_{RM} induction in actinic keratosis prevents the development of squamous cell carcinoma, demonstrating the antitumor efficacy of TIL with the T_{RM} phenotype [50]. Further functional analyses are needed.

6. Conclusion

Skin T_{RM} seem to have been unknowingly targeted in the long history of dermatological treatments. Skin-tropic treatments ranging from topical corticosteroids to phototherapies and radiation therapies have all led to the remission of what are now recognized as T_{RM}-mediated disease conditions. Revisiting the previous observations related to various skin conditions will further help us understand the potential roles of T_{RM} in human skin.

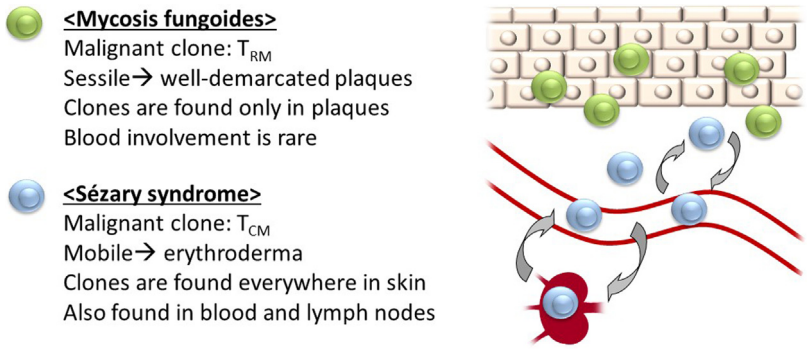

Fig. 3. Malignant T-cell clones in CTCL.
Malignant clonal T cells in mycosis fungoides are T_{RM}. The well-demarcated plaques correlate with the sessile phenotype of T_{RM} clones. On the other hand, malignant clonal T cells in Sézary syndrome are T_{CM}. Diffuse erythema and blood Sézary cells correlate with the mobile phenotype of T_{CM} clones.

Funding sources

None.

Acknowledgements

I would like to thank Dr. Flaminia Miyamasu of the Medical English Communication Center of the University of Tsukuba for native English language support.

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