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REVIEW

Tissue-resident memory T cells in the skin

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Abstract

Purpose Tissue-resident memory T (T_{RM}) cells are a newly described subset of memory T cells. The best characterized T_{RM} cells are CD8+ and express CD103 and CD69. These cells are non-recirculating and persist long term in tissues, providing immediate protection against invading pathogens. However, their inappropriate activation might contribute to the pathogenesis of autoimmune and inflammatory disorders. In the skin, these cells have been described in psoriasis, vitiligo, and melanoma among other diseases.

Methods Literature review was done to highlight what is currently known on the phenotype and function of T_{RM} cells and summarizes the available data describing their role in various cutaneous conditions.

Results Resolved psoriatic skin and disease-naïve non-lesional skin contain a population of IL-17-producing T_{RM} cells with shared receptor sequences that recognize common antigens and likely contribute to disease recurrence after cessation of therapy. In vitiligo, T_{RM} cells produce perforin, granzyme B, and interferon-γ following stimulation by interleukin-15 and collaborate with recirculating memory T cells to maintain disease. In melanoma, increased accumulation of T_{RM} cells was recently shown to correlate with improved survival in patients undergoing therapy with immune checkpoint inhibitors.

Keywords Tissue-resident T cells · Psoriasis · Melanoma · Fixed drug eruption · Dermatitis

Introduction

Healthy skin is populated by T cells. Following antigen exposure, naïve T cells differentiate into effector T cells capable of executing immune defense mechanisms. Most of these cells are short-lived and die following the immune response, but some remain and differentiate into memory T cells. Central memory T cells (T_{CM}) traffic through lymphoid tissues while effector memory cells (T_{EM}) circulate through peripheral tissues. Tissue-resident memory T (T_{RM}) cells are a newly identified subset of memory T cells that persist long-term in tissues without recirculating in the blood thus providing a first line of adaptive cellular defense (Fig. 1) [1]. However, increasing evidence suggests that aberrant activation of these cells might contribute to the pathogenesis of autoimmune and inflammatory diseases making them a new therapeutic target [2]. It is estimated that healthy adult skin contains around 20 billion T_{RM} cells [3]. This review summarizes the current data available on the protective and pathogenic roles of T_{RM} cells in cutaneous disease.

Phenotype and functions

T_{RM} cells have variable expression of different markers depending on the tissue of residence and the nature of the pathogen. Therefore, they might exist as different subsets with phenotypic heterogeneity (Table 1). The best characterized T_{RM} cells are CD8+ cells that express CD103 and CD69 [4]. CD103 (α_E integrin chain) binds E-cadherin potentially promoting retention within epithelial tissues [5]. CD69 is a T-cell activation marker and its expression mediates early T cell retention in the skin by blocking sphingosine 1-phosphate receptor 1 (S1PR1)-mediated egress from tissues [6]. The expression of CD69 precedes that of CD103. In fact, the former marker has a major influence on the early lodgment of T_{RM} cells in tissue, whereas the latter is involved in

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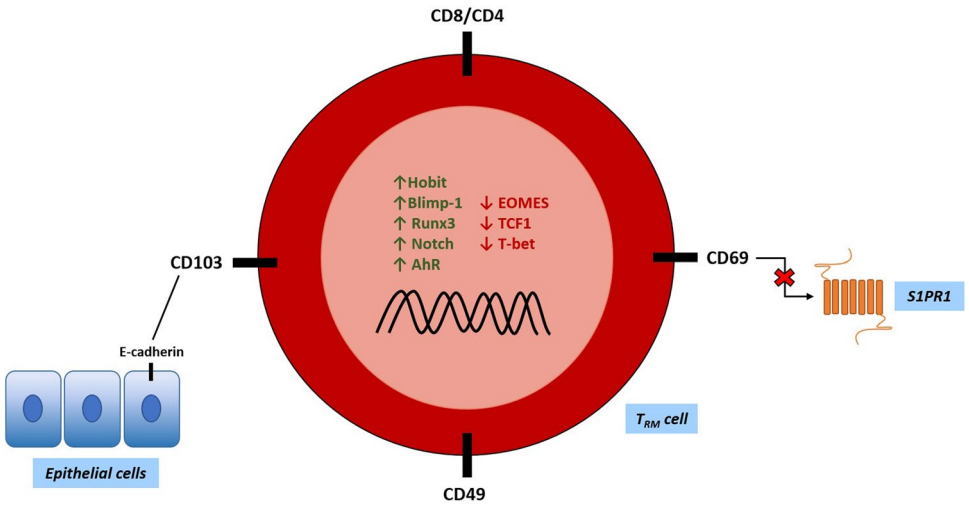

Fig. 1 Tissue-resident memory T (T_{RM}) cell markers and the transcription factors involved in its development and survival. T_{RM} cells are CD4+ or CD8+ T cells with a variable expression of different markers. CD103 binds E-cadherin on epithelial cells. CD69 blocks sphingosine 1-phosphate receptor 1 (S1PR1)-mediated egress from tissues. CD49 (α-subunit of the α1β1 integrin receptor) is another marker with important functional implications. The transcription factors Hobit, B lymphocyte-induced maturation protein-1 (Blimp-1), Runt Related Transcription Factor 3 (Runx3), Notch, aryl hydrocarbon receptor (AhR), eomesodermin (EOMES), transcription factor 1 (TCF1) and T-bet are all involved in the regulation of T_{RM} cell differentiation and survival

Table 1 Phenotype, tissue distribution, and T_{RM} main features in cutaneous conditions

Characteristics of T_{RM} cells		
	Marker	Function
Phenotype	CD4+ or CD8+	Co-receptors of the TCR
	CD103 (αE integrin chain)	Binds E-cadherin to promote retention within epithelial tissues
	CD69	Blocks S1PR1-mediated egress from tissues
	CD49a (α-subunit of the α1β1 integrin receptor)	Pairs with CD29 to form the heterodimer very late antigen-1 which binds to type IV collagen [10]
	CD44	Binds to proteins in the extracellular matrix
Tissue distribution [89]	Barrier tissues	Skin, lung, gut, reproductive tract
	Non-barrier tissues	Brain, liver
Role in cutaneous disease	Fixed drug eruption	CD8+ CD45RA+ CD69+ TRM cells detected in resting lesions release IFN-γ after oral challenge with the causative drug
	Psoriasis	CD103+ CD69+ TRM cells in resolved lesions and disease-naïve non-lesional skin express a psoriasis specific T-cell receptor and secrete IL-17 and IL-22 upon antigenic stimulation
	Vitiligo	CD103+ CD69+ CD49a+ TRM cells express a melanocyte-specific TCR and, in the presence of IL-15, secrete IFN-γ, perforin and granzyme B. TRM cells also secrete CXCL9 and CXCL10 which bind to CXCR3 on TRCM cells to recruit them to the skin
	Eczema	Atopic dermatitis: CD4+ CD8+ CD69+ TRM cells accumulate and can produce significant levels of IL-4, IL-13, IL-17, and IL-22 Contact dermatitis: CD8+ CD69+ CD103+ T cells accumulate during the acute contact hypersensitivity reaction and gradually decrease up to 12 months after challenge
	Melanoma	CD8+ CD103+ TRM expressing a melanoma antigen-specific TCR produce IFN-γ and TNF-α. These cells also express high levels of immune checkpoints and their numbers correlate with improved survival in patients on immune checkpoint inhibitors

T_{RM} cells tissue-resident memory T cells, *TCR* T cell receptor, *S1PR1* sphingosine 1-phosphate receptor, *IFN* interferon, *IL* interleukin, *CXCL* C–X–C motif chemokine ligand, *CXCR* C–X–C chemokine receptor, *T_{RCM}* recirculating memory T cells, *TNF* tissue necrosis factor

their persistence long after reaching the skin. The absence of these surface molecules leads to a decrease, not a complete deletion, of the T_{RM} cell population [7]. CD49 (α-subunit of the α1β1 integrin receptor) is another marker of T_{RM} cells with important functional implications. In the skin, CD8+ CD49a+ T_{RM} cells—which are abundant in vitiligo—produce perforin, granzyme B, and interferon (IFN)-γ following stimulation by interleukin (IL)-15 [8]. However, in the absence of external stimulation, these cells express only low levels of these cytolytic molecules and therefore differ from circulating CD8+ T cells [9]. CD8+ CD49a− T_{RM} cells produce IL-17 and accumulate in psoriasis (Fig. 2) [8]. CD44 is a marker expressed on previously activated CD8+ effector and memory T cells. It is often retained in murine T_{RM} cells and can bind to various proteins in the extracellular matrix [10]. CD4+ T_{RM} cells are less well-studied but increasing evidence shows their potential role in cutaneous disease. These cells mediate protective immunity against skin infections such as leishmaniasis [11] and candidiasis [12]. In a study by Cheuk et al., IL-22-producing CD4+ T_{RM} cells were shown to persist in psoriasis following the clinical resolution of lesions [13].

Several signaling pathways, including the mammalian target of rapamycin (mTOR) pathway, transforming growth factor-β (TGF-β) and IL-15 signaling, are believed to control the development and survival of memory T cells [14]. Specifically, the mTOR signaling pathway is activated early on during the immune response. Rapamycin (mTOR inhibitor) enhances the formation of memory CD8+ T cells in secondary lymphoid tissues but inhibits the formation of CD8+ T_{RM} cells in the intestinal and vaginal mucosa. This inhibitory effect on the mucosal tissues markedly decreased the epithelial damage in a mouse model of cell-mediated intestinal autoimmunity [15]. Dysregulation of the mTOR pathway has been noted in several inflammatory and neoplastic conditions. Interestingly, several inflammatory skin diseases—such as psoriasis, allergic contact dermatitis, and atopic dermatitis—show an increased expression of the mTOR gene [16]. Given the potential role of T_{RM} cells in these conditions (discussed below) and the influence of the mTOR pathway on these cells, targeting the mTOR pathway may alter the T_{RM} cell population and provide a therapeutic benefit in these inflammatory dermatoses [17].

Several transcription factors regulate T_{RM} cell differentiation and survival, including Hobit (Homolog of Blimp-1 in T cells), B lymphocyte-induced maturation protein-1 (Blimp-1) [18], Runt Related Transcription Factor 3 (Runx3) [19], Notch [20], and the aryl hydrocarbon receptor (AhR) [21]. Eomesodermin (EOMES) and transcription factor 1 (TCF1) are upregulated in circulating long-lived memory cells but downregulated in T_{RM} cells [14, 22]. Downregulation of T-bet is also essential but residual expression of this transcription factor is required for IL-15-mediated CD8+ CD103+ T_{RM} cell survival [14]. Interestingly, Notch1 signalling was found to positively correlate with the severity of psoriasis [23] and AhR is believed to regulate immune balance in atopic dermatitis and psoriasis [24]. These effects may partly be mediated by T_{RM} cells.

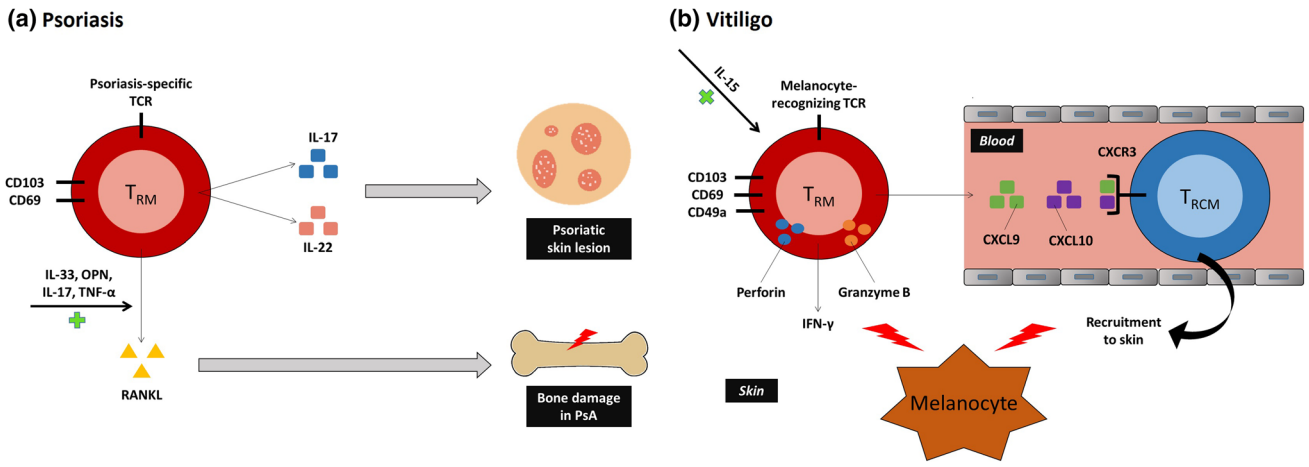

Fig. 2 Role of T_{RM} cells in **a** psoriasis and **b** vitiligo. **a** Resolved psoriatic skin and disease-naïve non-lesional skin contain a population of T_{RM} cells which express CD103, CD69, and a psoriasis specific T-cell receptor (TCR). Upon antigen recognition, these cells secrete interleukin (IL)-17 and IL-22, leading to the appearance of cutaneous lesions. After stimulation by the proinflammatory cytokines IL-33, osteopontin (OPN), IL-17, and tumor necrosis factor (TNF)-α, T_{RM} cells secrete pro-osteoclastogenic factors, such as receptor activator of nuclear factor-B ligand (RANKL), thus contributing to the bone damage in psoriatic arthritis (PsA). **b** In vitiligo, T_{RM} cells express CD103, CD69, CD49a, as well as a melanocyte-specific TCR. In the presence of IL-15, these cells secrete interferon (IFN)-γ, perforin and granzyme B, possibly leading to melanocyte cytotoxicity. In addition, T_{RM} cells secrete C–X–C Motif Chemokine Ligand (CXCL) 9 and CXCL10 which bind to C–X–C chemokine Receptor (CXCR) 3 on the surface of recirculating memory T (T_{RCM}) cells to recruit them to the skin. T_{RM} and T_{RCM} cells then work together to maintain depigmentation

The ultimate role of T_{RM} cells in protective immunity remains to be fully elucidated. These cells possess dendritic projections that extend into the basal cell layer of the epidermis, but not upward towards higher epidermal layers or downward towards the dermis. This dendritic morphology appears to be largely defined by the epidermal location of these cells and might not be a characteristic property of T_{RM} cells. Regardless, these cells can navigate through the basal layer and detect antigens [21, 25]. However, their slow and random movement constrains them to a limited region of skin near the original site of formation [21]. T_{RM} cells may also localize to distinct anatomical clusters containing antigen-presenting cells including the isthmus of the hair follicle [26]. Thus, they could act as a sensing and an alarming system capable of rapidly recruiting immune effectors through the secretion of cytokines and chemokines. Conversely, they might have direct cytotoxic effects allowing them to clear target pathogens [8, 27, 28] and are believed to provide superior protective immune responses against localized infections compared with circulating effector memory T cells [29]. In fact, they upregulate antiviral and antibacterial genes involved in broad-spectrum defense providing cross-protection against antigenically unrelated pathogens [30].

T_{RM} cells have been reported to persist in tissues for variable periods of time. CD8+ T cells can be detected in the nasal tissues up to 3 months following total respiratory tract infection [31], and in the skin up to a year following herpes simplex virus (HSV) infection [21]. Recent studies have shown that following antigen re-encounter, pre-existing T_{RM} cells divide giving rise to secondary T_{RM} cells. Furthermore, the capacity of epidermal T_{RM} niches are very large allowing for the accommodation of multiple T_{RM} cells with different specificities without displacing previously established cells [1, 32, 33].

New T_{RM} cells can also form in inflamed tissues even in the absence of specific antigenic stimulation. In a study by Mackay et al. conducted on mice, HSV-specific T_{RM} cells were detected at sites treated with the contact-sensitizing agent 2,4-dinitrofluorobenzene without direct HSV antigen stimulation. These cells were capable of controlling local HSV infection once the mice were inoculated with the virus. In the absence of persisting antigenic stimulation, circulating CD8+ T cells lose the expression of homing molecules that drive their infiltration into tissues. Once the antigen has been re-encountered, these cells require some time to regain entry into tissues. The persistence of T_{RM} cells in the skin following inflammation has the advantage of providing a fast means of achieving immune protection against peripheral pathogens, even those which have never been encountered before [29].

Fixed drug eruption

Fixed drug eruption (FDE) is characterized by relapse in the same location following the administration of the culprit drug. In resting (pigmented) FDE lesions, there is a predominance of CD8+ CD45RA+ CD69+ T cells in the lesional epidermis [34, 35]. In vitro, following expansion and stimulation, these cells display cytolytic functions against keratinocytes [36]. In vivo, most of them produce IFN-γ within 2–3 h of oral challenge with the causative drug. These results indicate that T_{RM} cells play a major role in FDE. It has been noted that lesions can be induced by other unrelated drugs and trauma, a phenomenon called "polysensitivity". This might be explained by the cross-reactive nature of these immune cells [34].

Psoriasis

Psoriatic lesions preferentially recur in previously affected areas indicating the possible role of immune memory. In a study in mice, grafts of non-lesional normal-appearing skin from psoriatic mice induced active lesions when transplanted into immunodeficient mice [37]. In fact, T cell-associated genes and inflammatory genes- such as IL-17 and IL-22-remain upregulated in resolved lesions three months following treatment with etanercept, a TNF-inhibitor [38]. CD8+ cells expressing CD69 are retained in resolved lesions several months after effective treatment with methotrexate [39]. CD4+ cells producing IL-22 and CD8+ cells producing IL-17 also remain in the epidermis of healed lesions [13]. Most of the IL-17-producing T cells are αβ T cells with unique psoriasis-specific T cell receptor (TCR) sequences that are not found in healthy skin [40]. These shared receptor sequences could be responsible for binding to specific antigens thus triggering the recurrence of inflammatory psoriatic lesions. In fact, several putative antigens have been identified in psoriasis, including the antimicrobial peptide LL37 [41], neolipid antigens [42], and a disintegrin and metalloproteinase with thrombospondin motifs-like protein 5 (ADAMTSL5) produced by melanocyte [43].

In a study by Sérézal et al., stimulation of T cells within skin explants resulted in the upregulation of pathways induced by IFN-γ in both healthy and resolved psoriatic skin. However, IL-17A-driven pathways were only upregulated in resolved psoriatic skin. In addition, a dominant IL-17 tissue response correlated with early relapse following treatment with UVB [44]. In another study, the ratio of IL-17A-producing to IFN-γ-producing CD103+ CD8 T_{RM} cells increased with disease duration in psoriatic

disease-naïve non-lesional skin [45]. These findings suggest that earlier treatment might be associated with a lower risk of disease relapse. Similar to healed skin, never-lesional skin explants from patients with psoriasis also harbor resident CD8+ T cells poised to produce IL-22, and IL-17 and IFN-γ [45, 46]. The latter induces the expression of IFN-α in keratinocytes suggesting a new source of type I interferons capable of initiating new lesions of psoriasis. Keratinocytes from the same skin explants respond to fungal antigens with upregulation of the CCR6 ligand CCL20. Therefore, the accumulation of epidermal CCR6+ T_{RM} cells might be attributed to an exaggerated and genetically determined keratinocyte CCL20 response to microbes [46].

Taken together, these studies suggest that resolved psoriatic skin and disease-naïve non-lesional skin contain a population of IL-17-producing T_{RM} cells with shared receptor sequences that recognize common antigens and contribute to disease recurrence after cessation of therapy.

T_{RM} cells might also be involved in the pathogenesis of psoriatic arthritis (PsA). Proinflammatory cytokines induce the release of pro-osteoclastogenic factors- such as Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL)- from skin-resident T cells, potentially contributing to the bone damage in PsA [47].

Vitiligo

As in psoriasis, vitiligo lesions often recur in the same locations suggesting that autoimmune memory develops at these sites. Stable and active vitiligo perilesional skin contains a population of CD8+ CD69+ T_{RM} cells. These cells persist in the skin for over a year and are particulary enriched within the epidermis [48] The T_{RM} cell infiltrate is characterized by a combination of CD103+ and CD103− cells. These cells have moderate cytotoxic activity and secrete the pro-inflammatory cytokines IFN-γ and tumor necrosis factor-α (TNF-α). CD49 is also expressed in epidermal and dermal CD8+ T_{RM} cells in vitiligo lesional skin. In the presence of IL-15, cells expressing this marker secrete IFN-γ, perforin and granzyme B [8]. These molecules are essential for inducing melanocyte apoptosis in vitiligo [49, 50]. Through their secretion of cytokines and chemokines, T_{RM} cells might therefore have directs cytotoxic effects or play a role in the recruitment of other effector immune cells. Furthermore, these cells might also prevent the replenishment of melanocytes by inhibiting local regulatory T cells (T_{reg}) which are critical for stem cell regeneration in the hair follicle [51].

However, T_{RM} cells alone are not sufficient for the maintenance of vitiligo [48]. Autoreactive recirculating memory T cells (T_{RCM}) have been detected in the blood of vitiligo patients. A recent study by Richmond et al. [52] found that T_{RCM} and T_{RM} cells work together to maintain depigmentation. Both cell types recognize auto-antigens in the skin and produce IFN-γ. Furthermore, T_{RM} cells produce C–X–C Motif Chemokine Ligand (CXCL) 9 and CXCL10. These chemokines bind to C–X–C chemokine Receptor (CXCR) 3 on the surface of T_{RCM} cells, potentially to recruit them to the skin. Interestingly, circulating CXCR3+ CD8+ T_{RCM} cells in vitiligo patients have an enhanced proliferative capacity compared to cells in healthy controls [53]. In animals deficient in CXCL10, T_{RCM} cells were more likely to engraft in the lymph node and less likely to be recruited to the epidermis. Furthermore, blocking T_{RCM} access to the skin, or depleting these cells resulted in reversal of disease. These results highlight the importance of these chemokines and chemokine receptor in vitiligo [54].

Some studies have started looking into T_{RM} cells as a potential therapeutic target in vitiligo. In a mouse model, long-term blockade of the Il-15 receptor with an anti-CD122 antibody was shown to deplete antigen-sepcific T_{RM} cells from the skin, whereas short-term blockade reduced their secretion of IFN-γ. As a result, durable repigmentation occurred. Targeting Il-15 signaling might therefore be an effective and long-lasting treatment strategy for vitiligo [55].

Eczema

In a study of atopic dermatitis (AD), most top abundant T cell clones were shared between lesional and non-lesional skin. The infiltrate was maintained at least 4 months following successful treatment with a topical steroid [56]. Therefore, there is a potential population of pathogenic T_{RM} cells that persists beyond treatment. In another study, CD4+ and CD8+ T_{RM} cells expressing CD69 significantly infiltrated into AD skin compared to normal skin. These cells produced significant levels of the Th2 cytokines IL-4, IL-13, IL-17, and IL-22. Furthermore, thymic stromal lymphopoietin (TSLP), a known trigger for AD, increased the expression of CD69+ T_{RM} cells. The authors concluded that T_{RM} cells might be the main cause of AD recurrence [57, 58].

In a mouse model of allergic contact dermatitis, CD8+ CD69+ CD103+ T cells gradually accumulated in the epidermis during the acute contact hypersensitivity reaction. Their numbers stabilized for around 2 weeks following the resolution of skin inflammation and then gradually decreased up to 12 months after the challenge. 1 month following the initial acute contact hypersensitivity reaction, some of the mice were rechallenged with the same antigen and experienced disease flare-up with a more severe reaction compared to naive skin. The detected T_{RM} cells were shown to express inhibitory checkpoint receptors, such as programmed cell death protein-1 (PD-1) and T cell immunoglobulin and mucin domain 3 (TIM-3). Blocking these

inhibitory checkpoint receptors (ICRs) increased the magnitude and severity of the eczema flare-up [59]. Therefore, these receptors likely prevent excessive activation of T_{RM} cells upon re-exposure to the antigen and are a potential therapeutic target in autoimmune and auto-inflammatory disorders. In another study in mice [60], the number of CD8+ T_{RM} cells increased with the dose and the number of exposures to the allergen. This expansion was mediated by a combination of local proliferation and recruitment from the circulation. In addition, the magnitude of the contact hypersensitivity reaction directly correlated with the number of T_{RM} cells.

Melanoma

T_{RM} cells are increasingly recognized for their role in infectious, autoimmune and auto-inflammatory diseases but their involvement in cancer immunity remains unclear. CD103+ T_{RM} cells accumulate in several human solid tumors—such as lung, liver, and breast cancers—and are often indicative of a good prognosis [61–63]. Similarly, increased accumulation of these cells was recently shown to correlate with improved survival in melanoma patients undergoing therapy with immune checkpoint inhibitors. Local IL-15 expression levels strongly correlates with T_{RM} cell numbers and therefore seems to be essential for their retention in the tumor microenvironment [64]. Another study showed that expression of CD49a by vaccine-induced T_{RM} cells also predicts a prolonged overall and disease-free survival. In addition, in vivo blockade of this marker as well as CD103 significantly impairs control of subcutaneous tumor [65].

Melanoma antigen-specific CD8+ T_{RM} cells generated in vitiligo produce IFN-γ and are critical for protection against melanoma rechallenge. These cells reside mostly around depigmented hair follicles [66]. Furthermore, following the administration of ovalbumin-expressing vaccines, generated CD8+ T_{RM} cells provide effective anti-tumor immunity against OVA-expressing melanoma independently of circulating CD8+ T cells [67]. In cases where some cancer cells resist initial eradication, T_{RM} cells were shown to promote long-term melanoma-immune equilibrium by controlling the outgrowth and spread of these residual tumor cells [68]. In a study by Rosato et al. [69], antiviral memory CD8+ T cells were reactivated by viral peptides injected into the tumors of mouse models of melanoma. Within 12 h, these cells expressed IFN-γ, CD25, and granzyme B. Innate and adaptive immune response mechanisms were activated leading to an arrest in tumor growth. In addition, peptide therapy extended the range of tumors responding to checkpoint blockers. In a study of metastatic melanoma by Boddupalli et al. [70], tumor associated T_{RM} cells were shown to express the highest levels of immune checkpoints among tumor-infiltrating lymphocytes. Another study reported that these immune checkpoints were mainly enriched in T_{RM} cells expressing CD103 and that the use of checkpoint inhibitors expanded the number of this T_{RM} cell population. Taken together, these studies suggest that immune profiling of T_{RM} cells prior to treatment could help design more effective strategies for immune checkpoint blockade in melanoma [64].

The exact mechanism of action for the anti-tumor effects of T_{RM} cells is still unknown. Activated tumor-specific T_{RM} cells produce IFN-γ and TNF-α and promote the maturation of dermal dendritic cells (DCs) and their trafficking to draining lymph nodes. These DCs are required for the expansion of CD8+ T cells which can respond not only to the T_{RM} cell-targeted antigen but also to other tumor-derived neo- and self-antigens [71]. In addition, CD103 was found to concentrate in the synapse formed between immune and tumor cells and initiate E-cadherin-dependent signaling pathways which enhance the effector functions of cytotoxic T lymphocytes [72]. Effective tumor eradication likely involves an interplay between multiple immune cells and a higher density of peritumoral T_{RM} cells.

Others

T_{RM} cells possibly play a role in many other skin diseases. These cells persist in the skin following the resolution of cutaneous viral infections such as HSV and vaccinia virus and provide rapid viral clearance upon reinfection [73, 74]. In murine models of graft-versus-host disease, T_{RM} cells were detected in the epidermis, dermis, intestinal tract, and spleen [75]. In cutaneous T-cell lymphoma (CTCL), low-dose alemtuzumab depleted all circulating and recirculating T cells including central and effector memory T cells but spared T_{RM} cells. It effectively treated leukemic-CTCL but not mycosis fungoides (MF) indicating that T_{RM} cells might contribute to the pathogenesis of the latter [76]. In fact, T cells isolated from MF lesions strongly express C–C chemokine receptor (CCR) 4 but not L-selectin (CD62L) or CCR7. This phenotype is suggestive of T_{RM} cells [77]. In a study of actinic keratoses, a 4-day course of calcipotriol plus 5-fluorouracil treatment induced TRM formation and lowered the risk of development of squamous cell carcinoma development after a follow-up period of 3 years [78].

Discussion and conclusion

In the coming years, it will be critical to develop better techniques for detecting T_{RM} cells in tissues and determine with better accuracy the factors involved in their generation, metabolism and survival. The identification of diseases with

T_{RM} cell involvement will allow for the development of new and improved therapies. However, many important points should be kept in mind when designing new treatment strategies. T_{RM} cells are heterogeneous, and different subsets with distinct expressions of surface markers and effector functions are likely involved in different diseases and/or anatomical locations. Therefore, a T_{RM} cell-targeted treatment that works for one disease may not work for another. In addition, special attention should be given to the potential cross-talk between the different T_{RM} cell subtypes and between T_{RM} cells and other cells of the immune system [79]. The interplay between environmental factors and TRM cells should also be kept in mind [80]. For instance, following ultraviolet radiation (UVR), skin-resident T cells are activated and protect keratinocytes from UVR-induced DNA damage [81]. T_{RM} cells may have been one of the unrecognized targets of phototherapy in several skin diseases. Similarly, it is likely that the local microbiome has an influence on the generation, compartmentalization, diversity, and function of these cells [80].

In disorders where T_{RM} cells play a protective role, vaccination can be used as a tool to amplify the immune response. T_{RM} cells have been generated in various sites by the local delivery of vaccine vectors [82]. Conversely, other approaches have focused on inducing inflammation in target tissues to recruit T cells generated at remote sites. This vaccine protocol termed 'prime and pull' relies on two successive steps: the first is the administration of the vaccine parenterally, and the second is the application of a chemokine to the target tissue thus attracting immune cells [83, 84]. Another therapeutic strategy is to release T_{RM} cells from immune checkpoints. The number of T_{RM} cells correlates with improved survival in melanoma patients undergoing therapy with immune checkpoint inhibitors [64]. In fact, among tumor-infiltrating lymphocytes, T_{RM} cells seem to be particularly rich in immune checkpoints [70] and the use of checkpoint inhibitors leads to a significant expansion of these cells [64]. Therefore, T_{RM} cells may be the major target of immune checkpoint inhibitors [85].

In diseases where T_{RM} cells play a pathogenic role, the long-lived nature of these cells becomes a problem. Early treatment might be critical to prevent their accumulation during disease flare-up. Maintenance therapy is also necessary for the same reason. However, the side effects that could appear following the blockade of these cells should be carefully assessed. Although not fully elucidated yet, T_{RM} cells rely on multiple cytokines and chemokines for their development, survival, and activation. These include TGF-β, TNF-α, IL-33, type I interferons, IL-15, and others. Possible future treatments could target these factors [51, 55] or the markers expressed on these cells, such as ICRs [59, 86]. A unique characteristic of T_{RM} cells is their dependence on exogenous lipid uptake for survival. In fact, cells lacking the fatty-acid-binding proteins 4 and 5 (FABP4 and FABP5) died prematurely. Furthermore, the administration of pharmacologic agents that block lipid metabolism (etomoxir or trimetazidine) was shown to decrease the survival of these cells [87, 88]. Therefore, the oxidative metabolism of exogenous fatty acid is essential for the survival of T_{RM} cells. Furthermore, targeting the metabolic pathways of these cells appears to be a promising therapeutic strategy.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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