



Role of tissue-resident memory T cells in the pathophysiology of allergic contact dermatitis

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Purpose of review

We bring updated knowledge on tissue-resident memory T cells (T_{RM}), underlining their major role in the recurrence and the severity of allergic contact dermatitis (ACD).

Recent findings

ACD is a frequently encountered skin disease. It is defined as a delayed-type hypersensitivity reaction initiated by the recruitment of antigen-specific T cells into the skin of sensitized patients. ACD lesions tend to develop on already-exposed areas and worsen over time. That clinical observation has raised questions on the contribution of T_{RM} to ACD recurrence and severity. T_{RM} are memory T cells that persist in peripheral tissues, such as the skin, without recirculating through the blood. These cells provide effective immune memory against pathogens, but they may also participate in the development or exacerbation of numerous inflammatory diseases, including skin allergies. Recent works have demonstrated a major role for T_{RM} in ACD pathophysiology.

Summary

In ACD, T_{RM} accumulate preferentially at the allergen contact site during the sensitization phase. Thereafter, these cells cause a rapid and intense response to any new allergen exposure. They also play a key role in flare-ups of ACD and the chronicity and severity of the disease. These aspects suggest that T_{RM} may have an interest as therapeutic targets.

Keywords

allergic contact dermatitis, pathophysiology, tissue-resident memory T cells

INTRODUCTION

Allergic contact dermatitis (ACD) is a T-cell-mediated skin disease [1]. ACD manifests as eczema flare-ups following cutaneous exposure to an allergen. Exacerbations usually occur at the same sites and tend to worsen over time [2]. Studies inspired by that clinical observation have demonstrated a key role for tissue-resident memory T cells (T_{RM}) in ACD recurrence and severity [3]. With this review, we first provide an overview on the pathophysiology of ACD and thereafter describe the general characteristics of T_{RM} and their contribution to ACD flare-ups. Finally, we will discuss the diagnostic and therapeutic vistas opened by the discovery of the roles of these cells in ACD.

ALLERGIC CONTACT DERMATITIS PATHOPHYSIOLOGY

ACD is a delayed-type hypersensitivity (i.e., a type IV reaction as defined by Gell and Coombs), characterized by the recruitment and activation of allergen-specific effector (Teff) and memory (Tmem)

T cells into the skin of previously sensitized patients. ACD follows three distinct phases:

Sensitization: Teff and Tmem differentiation

The sensitization phase is clinically silent but results in the development of specific Teff upon antigen presentation by dendritic cells (DC) [4]. The penetration and accumulation of the allergen in the skin activate innate immunity and the release of pro-inflammatory mediators, such as interleukin (IL)-1 β

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KEY POINTS

- T_{RM} play fundamental roles in ACD chronicity, severity, and flare-ups.
- Antigen-specific T_{RM} accumulate into the skin in parallel with the number of allergen exposures and the intensity of clinical reaction.
- Targeting pathological T_{RM} by depletion, modification of their residency capacities, or limiting their activation should be investigated as a promising option for the treatment of ACD.

or IL-18 by keratinocytes [5,6]. Inflammation is a prerequisite for the activation and migration of DC to the draining lymph nodes, where they present the antigen to naive CD8+ and CD4+ T cells *via* major histocompatibility complex class I or class II molecules respectively, or CD1 molecules [7–9]. Antigen-specific-T cells are then activated, proliferate, and differentiate into Teff and Tmem, able to recirculate into the skin. [10,11]. A new encounter with the antigen will activate these Teff and Tmem and result in skin inflammation.

Elicitation: activation of Teff

Elicitation occurs in sensitized patients 24–48 h after a renewed contact with the antigen. After cutaneous barrier penetration, the antigen is captured by the DC and presented to the antigen-specific T cells generated during the sensitization phase. These latter induce a rapid and effective inflammatory response and contribute to the recruitment of other circulating T cells [4]. Several studies highlighted the role of cytotoxic CD8+ T cells [12]. Their activation results in keratinocyte apoptosis and is accompanied by the release of pro-inflammatory cytokines that amplify skin inflammation [13,14]. Furthermore, unconventional lymphocytes, monocytes/macrophages, neutrophils, eosinophils, or mast cells, accumulate in ACD lesions, further worsening the inflammatory process [15–18].

This leads to the establishment of the ACD lesion.

Resolution: establishment of Tmem in the skin

The duration of the inflammatory reaction depends on the allergen persistence in the skin and involves regulatory processes. ACD lesion remission involves regulatory T cells (Treg) and the IL-10 they produce [19–21], increased

expression of co-inhibitory molecules by resident immune cells [22], and the release of anti-inflammatory cytokines.

During the resolution phase, Teff are progressively replaced by a large population of Tmem, which enable a faster and more effective immune response upon allergen reexposure [23]. Although the various Tmem share certain characteristics, they are not a homogenous population. Indeed, a number of subsets, distinguishable by their circulatory and functional properties, have been identified.

- (1) Central memory T cells (T_{CM}) circulate in the lymphoid organs. They have no direct effector activity, but rather the ability to proliferate and differentiate rapidly into effector cells in response to a secondary antigen challenge [24–26].
- (2) Effector memory T cells (T_{EM}) circulate in the blood and peripheral tissues. Upon antigen recognition, they rapidly acquire effector capacities, with limited proliferation [24–26].
- (3) More recently, a third population was identified, i.e., tissue-resident memory T cells (T_{RM}). These cells survive for several months within the peripheral tissues (notably epithelial barriers) of the organism without recirculating after the resolution of inflammation and are able to provide an extremely rapid response after new antigen exposure. [3,27,28].

TISSUE-RESIDENT MEMORY T CELLS (T_{RM})

T_{RM} were first described in cutaneous infection models. They are a heterogeneous group of T lymphocytes that, in contrast to T_{CM} and T_{EM} , do not migrate or recirculate outside of their resident tissues [29]. They thus provide rapid and durable immune responses against pathogenic agents in peripheral tissues (skin, lung, gut, nerves, etc.). TRM comprise CD8+ and CD4+ T cells that differ phenotypically and functionally from their circulating counterparts [30].

Immunological characteristics of skin- T_{RM}

Because of their tissue residency and distinct functions, T_{RM} have specific characteristics. Transcriptionally, such factors as Hobit, Blimp-1, Runx3, Notch, and the aryl hydrocarbon receptor (AhR) are strongly upregulated in T_{RM} and mediate their differentiation and survival [31–33]. In contrast, the EOMES, TCF1, and T-box transcription factors are downregulated in T_{RM} , compared to circulating Tmem [34].

Two phenotype markers, CD69 and CD103, are conventionally used to differentiate T_{RM} from other circulating T cells [35]. These two surface proteins play a key role in T_{RM} biology by favoring their retention and survival within the concerned tissue. CD49 is another important marker for T_{RM} , expressed upon IL-15 stimulation, and associated with T_{RM} cytotoxic function [production of granzyme B (GrB), perforin, and interferon gamma (IFN γ)] [36].

The molecular mechanisms behind T_{RM} differentiation have not been completely elucidated. There are three important steps in the development of these cells:

- (1) Penetration into cutaneous tissue – The ability of Teff to penetrate and accumulate in the skin via the expression of the chemokine receptor CXCR3 is a prerequisite for the later establishment of memory cells [30].
- (2) Local retention – Preventing T cells from recirculating into the blood is a key factor in the development of T_{RM} . Egress can be hampered by the reduction of the molecules needed for it, such as CCR7 [37] or S1PR1, which is dependent on CD69 expression [38]. CD103 also appears to play a role by facilitating T_{RM} adhesion to epithelial cells via the E-cadherin ligand [30].
- (3) Micro-environmental signal responses – TGF β , TNF α , IL-33, IL-7, and IL-15 contribute to the environmental signals favoring T_{RM} differentiation [30,39,40[¶]].

Other mechanisms that may contribute to T_{RM} survival are currently being explored, for example, the upregulation of BCL2 (an apoptosis regulator) [41] or AhR [33]. Finally, the expression of fatty acid-binding protein 4 (FABP4) and 5 (FABP5), which ease the absorption of cutaneous lipids needed for T_{RM} metabolism, also appear vital for their survival [42].

Immunosurveillance and skin protection

Peripheral tissues like skin are in direct contact with the environment and thus constantly exposed to pathogenic organisms. Because of their strategic position within the peripheral tissues where they can initiate a rapid immune response, T_{RM} provide a first-line barrier against infections. T_{RM} act as a detection and alarm system able to rapidly recruit immune effectors by secreting cytokines and chemokines like IFN γ , IL-2, IL-17, and TNF α . By secreting GrB and perforin, they also provide direct cytotoxic activity against targeted pathogens [43]. Several studies have shown that T_{RM} induce

an immune response to infections superior to that of circulating T cells [44]. The T_{RM} resulting from a skin infection are not only local; they also disseminate throughout the skin [45]. T_{RM} thus favor organism-wide immunosurveillance. However, authors have reported more rapid viral control at infection-nonnaive vs infection-naive sites, suggesting that T_{RM} develop preferentially at the site of initial infection [44]. Thus, there does appear to be a clear correlation between local T_{RM} density at a particular site and the specific level of protection therein [46].

Beyond the immunosurveillance they provide, T_{RM} are also able to tame excessive responses to avoid tissue damage. These regulatory mechanisms involve co-inhibitory molecules (e.g., PD-1, LAG-3, TIM-3 and 2B4) [30] and anti-inflammatory cytokines (e.g., IL-10 and TGF β) that stimulate Treg [47].

Thus, under normal conditions, T_{RM} play an essential role as a sentinel within cutaneous tissue. They contribute to immune stimulation and favor rapid and effective responses to re-encountered pathogens while preserving tissue integrity.

T_{RM} pathogenesis

However, certain T_{RM} can become pathological and participate in the development of autoimmune or allergic inflammatory disease. That role was first identified in the setting of fixed drug eruptions (FDE), an allergic reaction that reoccurs in a same location each time the allergenic drug is administered. Studies revealed that CD8⁺CD69⁺CD103⁺ T cells in FDE lesions were able to secrete IFN γ very rapidly upon renewed drug challenge [48]. This suggested that T_{RM} are the main effector cells driving the pathology.

T_{RM} involvement has furthermore been demonstrated in psoriasis [49–51], vitiligo [52], mycosis fungoides [53], and atopic dermatitis [54]. Clinical characteristics of these pathologies reflect T_{RM} biology:

- (1) Because T_{RM} do not recirculate, the inflammatory lesions they induce tend to be clearly circumscribed and highly persistent. The lesions may disappear under efficacious anti-inflammatory treatments, but will often reoccur at the same site when the treatment is stopped and/or an antigen is reencountered.
- (2) Furthermore, T_{RM} -mediated inflammation is extremely rapid upon antigen reexposure.
- (3) Finally, the progressive accumulation of T_{RM} in skin repeatedly exposed to antigens can result in progressive worsening of inflammation over time.

T_{RM} IN ALLERGIC CONTACT DERMATITIS: PATHOPHYSIOLOGY AND CLINICAL IMPLICATIONS

Several studies have shown that T_{RM} are involved in the pathophysiology of ACD. Most underline a major role for CD8+ T_{RM} [3,55,56[■],57[■]] and a recent study highlighted an important role for CD4+ T_{RM} in delayed hypersensitivity mouse model [59].

During the sensitization phase, antigen-specific T_{RM} and T_{CM} are generated in equal number from a shared precursor cell; they share the same receptor repertoire and recognize the same antigen [55]. T_{RM} domiciliate in the skin tissue under the influence of TGFβ and IL-15, and furnish a rapid (<24 h) and intense immune response. In contrast, the response furnished by circulating T_{CM} is more delayed (>48–72 h) and attenuated. T_{RM} gather preferentially at the site of contact and their activation is dependent on the allergen's presence [56[■]]. They release IFNγ and IL-17, leading to increased production of IL-1β, a key cytokine in ACD lesion development, by keratinocytes [3]. How long T_{RM} persists in skin tissue in the absence of antigen stimulation is currently unknown, although some studies have suggested that they diminish progressively over at least one year [56[■],58[■]].

Allergen reexposure causes a more severe ACD flare-up at antigen-nonnaive compared to antigen-naive sites. This response has been observed in both preclinical dinitrofluorobenzene-induced ACD murine models and in patch-test studies in sensitized patients [3,55,56[■],57[■],58[■]]. The tendency of T_{RM} to accumulate in tissues exposed repeatedly to antigens may explain why ACD worsens over time, with more severe lesions appearing more rapidly with each exposure. Indeed, Schmidt *et al.* showed that clinical response correlated with epidermal T_{RM} levels, and IFNγ and IL-17 expression [3]. Similarly, Gadsboll *et al.* demonstrated a clinical correlation between reaction intensity and epidermal CD8+ T_{RM}, and a correlation of this latter with the applied allergen dose and the number of exposures [57[■]].

These observations may explain, for example, why one skin zone is affected but not another in nickel allergy, or why traces of highly allergenic compounds like paraphenylenediamine reactivate eczema at zones where T_{RM} may have accumulated. T_{RM} abundance varies from one zone to another and in proportion to the frequency of allergen exposure. This contrasts with T_{CM}, the abundance of which appears unaffected by exposure frequency [55].

A recent study showed that allergens can persist within the skin for more than a month after contact [56[■]], which favors the formation and accumulation of T_{RM} at the exposure site, even after the lesion has healed. Persistent T_{RM} are hyporeactive due to

the expression of co-inhibitory molecules, including PD1, TIM3, and 2B4. This attenuates their activation and prevents excessive recurrences at low-dose allergen exposure. Indeed, the use of PD1 and TIM3 antagonists exacerbates the inflammatory reaction with increased production of IFNγ and GrB [56[■]]. Thus, the presence of these strong regulatory mechanisms may be explained by the persistence of the allergen in the skin, which contributes to maintaining the expression of inhibitory receptors.

Consequently, T_{RM} appear to be key players in ACD recurrence.

Diagnostic insights

As compared to the roles of T_{EM} and T_{CM} in the pathophysiology of ACD, that of T_{RM} could explain why epicutaneous tests performed on the back, usually far from the sensitization site, show delayed and often low-intensity responses and why trace antigen reactions can be symptomatic only at previously exposed sites. These observations suggest the possibility of false-negative skin tests due to too-low concentrations of the considered antigen, and especially a possible interest for performing skin tests on the previously affected areas, as is done currently for FDE.

Also, the identification of qualitative and/or quantitative biomarkers of T_{RM} could prove useful for patient stratification, improve clinical management of the disease, and empower a personalized medicine approach to it. Finally, novel technological tools need to be developed to enable the detection of T_{RM} in routine clinical practice.

Therapeutic perspectives

For decades now, skin T_{RM} have been targeted fortuitously by topical corticosteroids. These latter bring lesions under control efficaciously and rapidly but do not prevent recurrences once they are discontinued. Recent work of our team suggests that topical corticosteroids temporarily modulate T_{RM} activation, but do not deplete them, which may explain a very rapid relapse after treatment discontinuation.

T_{RM} depend on numerous cytokines and chemokines for their development, survival, and activation, and thus potential therapies targeting these factors, or the markers expressed by T_{RM} are currently being explored. For example, targeting IL-15 with anti-CD122 (a subunit of IL-15 receptor) monoclonal antibodies has been shown to be effective in murine model of vitiligo [59]. Short-term treatment with anti-CD122 inhibits T_{RM} production of IFNγ, and long-term treatment depletes T_{RM} from skin lesions. [59].

Gamradt *et al.* showed that the expression of inhibitory checkpoint receptors by T_{RM} controls their reactivation and limits ACD flare-ups during low-concentration allergen exposure. They also reported that the long-term persistence of the allergen in the epidermis appeared to play a role in the modulation and expression of these co-inhibitory molecules [56[■]]. The molecular network favoring the acquisition and expression of these inhibitory receptors by T_{RM} remains to be explored. Studying the capacities of PD1, TIM3 ou 2B4 antagonists for the prevention of T_{RM} reactivation would appear particularly pertinent. Also, desensitization protocols using very low antigen doses may be useful. The development of new therapeutic strategies to prevent the reactivation of T_{RM} via their inhibitory receptors could help restore tolerance in allergic patients.

T_{RM} survival and function also depends on the absorption of exogenous lipids and their oxidative metabolism. Thus, pharmacological agents blocking lipid metabolisms, such as etomoxir or trimetazidine, strongly reduce T_{RM} survival [42]. The T_{RM} in ACD are also influenced by the mTOR pathway [60], and targeting it may enable the alteration of T_{RM} production and provide therapeutic benefit [61]. Thus, targeting T_{RM} metabolic or activation pathways would appear to be a therapeutic strategy worth exploring in ACD.

Finally, T_{RM} are essential for infection prevention and crucial components of the adaptive immune response. It appears thus vital to be able to distinguish protective T_{RM} from their pathological counterparts and to carefully study any adverse effects of treatments aimed at these latter. Respecting these precautions, approaches aimed at eliminating pathological T_{RM} (by depletion or modification of residency capacities) or preventing or limiting their activation hold great promise for the treatment of ACD.

CONCLUSION

The discovery of T_{RM} in the pathophysiology of ACD has contributed important knowledge on the natural history of the disease. T_{RM} play fundamental role in ACD chronicity, severity and flare-ups. A better understanding of their nature will empower the ability to target T_{RM} , which may ultimately enrich the armamentarium against ACD. The challenge is to target specifically the pathological T_{RM} while preserving the individual's immunological balance.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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