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Resident Cutaneous Memory T Cells and Psoriasis

Mariana Marques Barreto Lopes Pires

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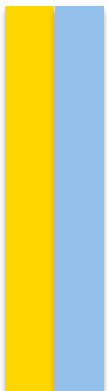

Resident Cutaneous Memory T Cells and Psoriasis

Artigo de Revisão Bibliográfica

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Junho de 2025

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Resumo

A psoríase é uma doença inflamatória crónica comum, que afeta primariamente a pele e se associa a diversas comorbilidades, perda de qualidade de vida e redução da esperança média de vida. Atualmente, os fármacos biológicos dirigidos contra a IL-23 ou a IL-17 constituem a estratégia terapêutica mais eficaz utilizada na prática clínica para o tratamento da psoríase. No entanto, estes fármacos ainda não conseguem alcançar uma remissão duradoura da doença, sendo que mesmo o fármaco mais eficaz desta classe induz a remissão da doença durante uma média de apenas 30 semanas após a interrupção do tratamento. O facto de as lesões psoriáticas tipicamente recidivarem nos mesmos locais originalmente afetados suporta a hipótese de que a recidiva da doença poderá ser causada por agentes locais de memória imunológica que resistem aos tratamentos atuais.

Nos últimos anos, as células T de memória residentes na pele, uma subpopulação de células T de memória não circulantes, têm sido apontadas como as mais plausíveis responsáveis pela recidiva da psoríase, devido ao seu perfil de produção de citocinas e à sua capacidade de persistir na pele durante anos após a resolução clínica das lesões. Estas células desempenham primariamente um papel de vigilância imunológica, mas, quando ativadas, são capazes de produzir citocinas pró-inflamatórias, como a IL-17, IL-22 e IFN-γ, centrais na patogénese da psoríase. Os estudos mais recentes sobre este tema têm-se focado em compreender o papel das células T_{RM} como mediadoras da recorrência da psoríase e o efeito das terapias atuais e emergentes nesta população de células.

Nesta revisão, iremos explorar os mecanismos de sobrevivência, residência e ativação das células T de memória residentes na pele, o seu papel na patogénese da psoríase e o seu potencial como alvos terapêuticos no desenvolvimento de tratamentos mais eficazes, ou mesmo de uma cura, para esta doença.

Palavras-chave

Psoríase, recorrência, células T de memória, memória imunológica

Abstract

Psoriasis is a common immune-mediated chronic inflammatory skin disease associated with several comorbidities, lower quality of life, and reduced life expectancy. Currently, biologics targeting IL-23 or IL-17 are the most effective therapeutic strategies used in clinical practice for the management of psoriasis. However, these still fail to achieve lasting disease remission, with even the most effective drug of this class inducing disease remission for an average of only 30 weeks after treatment withdrawal. The fact that psoriatic lesions tend to recur at the same sites that were originally affected supports the hypothesis that disease relapse could be caused by local agents of immunologic memory that are resistant to current treatments.

In recent years, skin-resident memory T cells, a subpopulation of non-circulating memory T cells, have been pointed out as the most likely culprits, due to their profile of cytokine production and their ability to persist in the skin for years after clinical resolution of psoriatic lesions. Skin-resident memory T cells primarily play a role of immune surveillance, but, when activated, they are able to produce proinflammatory cytokines, such as IL-17, IL-22 and IFN-γ, central in the pathogenesis of psoriasis. Recent research has focused on understanding the role of T_{RM} cells as mediators of disease recurrence and comprehending the effect of current and emerging therapies in this cell population.

In this review, we will explore the mechanisms of T_{RM} cell survival, residence, and activation, their role in the pathogenesis of psoriasis, and their potential as therapeutic targets in the development of more effective treatments, or even a cure, for this disease.

Keywords

Psoriasis, recurrence, memory T cells, immunologic memory

Abbreviations

AhR - aryl hydrocarbon receptor
AMPs - antimicrobial peptides
APC - antigen-presenting cells
Bcl-2 - B cell lymphoma 2
CD - cluster of differentiation
CCR - C-C chemokine receptor
CLA - cutaneous lymphocyte-associated antigen
CXCL - C-X-C motif chemokine ligand
CXCR - C-X-C chemokine receptor
DC - dendritic cells
DNA - deoxyribonucleic acid
FFA - free fatty acid
IL - interleukin
JAK/STAT - Janus kinase/signal transducer and activator of transcription
LC - Langerhans cells
PASI - psoriasis area severity index
PDE-4 - phosphodiesterase 4
RNA - ribonucleic acid
ROCK2 - rho-associated protein kinase 2
RORγt - retinoic-acid-receptor-related orphan receptor gamma-t
T_{CM} - central memory T cells
T_{EM} - effector memory T cells
T_{MM} - migratory memory T cells
T_{RM} - tissue-resident memory T cells
Tc - T cytotoxic
TCR - T cell receptor
TGF - transforming growth factor
Th - T helper
TNF - tumour necrosis factor
VEGF - vascular endothelial growth factor

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Introduction

Background on psoriasis as a chronic inflammatory skin disease

Psoriasis is a common immune-mediated chronic inflammatory skin disease that may present heterogeneously.[1,2] Cutaneous psoriasis can be divided into four main subtypes: chronic plaque psoriasis, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis, according to the macroscopic presentation of the skin lesions.[2] Chronic plaque psoriasis, the most common subtype, is characterized by well-demarcated, indurated, erythematous, scaly plaques that affect primarily the scalp, trunk and extensor surfaces.[3,4] Despite the cutaneous manifestations being the most common, psoriasis should be understood as a multisystemic chronic inflammatory disorder associated with a substantial socioeconomic burden and various comorbidities, such as psoriatic arthritis, metabolic syndrome, cardiovascular disease, psychosocial disorders, and even a reduced life expectancy when compared to persons without psoriasis.[5,6,7]

Psoriatic lesions result from the activation and subsequent differentiation of CD4+ T cells into Th17 cells, due to the production of IL-23 by Langerhans cells and other epidermal dendritic cells. Th17 cells release cytokines, namely IL-17A, IL-17F and IL-22, which play a crucial role in the pathogenesis of psoriasis, by inducing epidermal acanthosis and stimulating keratinocytes to produce IL-8, TNF-α, CXCL10 and VEGF. These stimulate angiogenesis and the recruitment of neutrophils, further exacerbating the inflammatory response.[8]

Due to the key role that the IL-23/Th17 pathway and TNF signalling play in the pathogenesis of psoriasis, biologics that target IL-23, IL-17 and TNF-α are widely employed in clinical practice for the treatment of this pathology. [7] Biologic agents are the most effective systemic therapies for chronic plaque psoriasis[9], with up to 79,4% of patients treated with the most effective agents of this group achieving PASI 90.[10] However, most patients experience relapse after withdrawal of this medication upon clinical cure.[3] In fact, psoriatic lesions tend to recur at the same sites that were originally affected[8], supporting the hypothesis of a local immunologic memory that persists in the skin, despite the disappearance of macroscopic signs of inflammation.[4]

Overview of resident memory T cells and their significance in the immune system

Recently, the role played by skin-resident memory T cells in the pathogenesis of psoriasis has gained increasing interest.[3] Tissue-resident memory T cells are a subpopulation of non-circulating memory T cells that express specific homing markers that enhance their ability to remain in peripheral tissues.[11]

After a primary exposure to a given pathogen, antigen-presenting cells present its antigens to naïve T cells, inducing their activation, monoclonal proliferation and differentiation into effector T cells, which then migrate into infection sites.[12] After the active phase of inflammation, the remaining effector T cells differentiate into memory T cells. According to their function and pattern of migration and tissue residence, memory T cells can be classified into one of three populations: central memory T cells, effector memory T cells, or tissue-resident memory T cells.[7] At the skin level, two main lineages of tissue-resident memory T cells can be identified: CD4+ T_{RM} cells and CD8+ T_{RM}

cells. The latter predominates in the epidermis and is the most abundant subpopulation infiltrating the skin of patients with psoriasis.[13]

Skin-resident memory T cells primarily play a role of immune surveillance, but, when activated by re-exposure to a specific antigen, they can function as effector T cells, locally acting as a first-line adaptive cellular immune response against pathogens.[14]

The hypothesis on the role of TRM cells in psoriasis pathogenesis

Although the exact mechanism of T_{RM} cell involvement in psoriasis recurrence is not yet fully comprehended, studies show that these cells remain in the skin of psoriatic patients for months to years following the clinical resolution of psoriatic lesions and that, in response to certain triggers, they produce IL-17, IL-22 and IFN-ɣ, which is why they are thought to mediate disease recurrence.[14] In fact, Cheuk et al. identified a subset of cytotoxic CD8+ T_{RM} cells and demonstrated a direct correlation between the number of these cells in the epidermis of psoriatic patients and the degree of inflammation in a relapse of the disease.[15] Additionally, biologics targeting IL-23, which, on average, are associated with a longer remission of psoriasis, are also those that have the greatest effect in reducing the number of T_{RM} cells in the skin of these patients.[16]

Thus, the most recent evidence suggests that memory T cells residing in the skin play a fundamental role in the recurrence of psoriasis, and further research is necessary on this topic to understand the effect that a therapy targeting this cell population would have on the progression of psoriasis. This review focuses on the current knowledge about the involvement of T_{RM} cells in the pathophysiology of psoriasis and their potential as therapeutic targets in the development of novel therapies.

Methods

A search in PubMed for the articles relevant to this topic was conducted, using the following search strategies:

1. ("Psoriasis"[MeSH] OR "psoriasis"[All Fields]) AND ("Memory T Cells"[MeSH] OR "Memory T Cells"[All Fields])
2. ("Psoriasis"[MeSH] OR "psoriasis"[All Fields]) AND ("Immunologic Memory"[MeSH] OR "Immunologic Memory"[All Fields]).

The abstract of each article retrieved was then analysed to evaluate its relevance to the topic. Only the articles addressing the role of tissue-resident memory T cells in the pathogenesis of psoriasis relapse or in its treatment were further analysed.

The first search strategy retrieved a total of 214 articles. From these, 86 were selected to include in the narrative review. The second search strategy retrieved 125 articles. After analysing their abstracts and excluding the articles common to both search strategies, 10 additional articles were included. Additionally, a manual search for other relevant studies was performed, namely the bibliographic references of previously selected articles. After this search, 16 more articles were included.

The complete content of the selected articles was further analysed. In the presence of articles that presented duplicate information, we selected those with broader and/or more recent data, excluding studies that did not present novel content. Data on skin-resident memory T cells and their implication on the relapse of psoriatic lesions as well as potential therapeutic strategies to target these cells was manually extracted, and a narrative synthesis was then elaborated. The collected data referred to the mechanisms of skin-resident T cell retention in the skin, the activation and proliferation of these cells in psoriatic lesions, their contribution to the inflammatory milieu of psoriasis and the emerging therapeutic strategies aimed at modulating T_{RM} cell function.

Resident Memory T Cells: An Overview

Memory T cells can be found in peripheral blood and lymphoid tissues, but also in virtually all barrier tissues in the human body, such as the skin, lungs, intestine, and genital mucosa, and even non-barrier tissues, such as the central nervous system and liver.[17,18] These cells represent the most numerous lymphocyte population in the human body for most of one's lifetime.[17] In the skin of an adult person alone, there are approximately 20 billion memory T cells.[19]

Memory T cells are a population of antigen-specific long-lived T cells, essential for rapid and long-lasting immune protection against the antigen/pathogen they are specific for.[20] Studies show that the assignment of T cells to the memory lineage occurs early after the first episode of infection by a given pathogen.[21] In response to infection, CD8+ T cells undergo monoclonal expansion and differentiation into antigen-specific effector cells. During the phase of resolution of the inflammatory response, effector CD8+ T cells originate two cellular populations: killer cell lectin-like receptor subfamily G member 1 (KLGR1)^{high} interleukin-7 receptor (IL-7R)^{low} short-lived effector cells (SLECs) and KLGR1^{low} IL-7R^{high} memory precursor effector cells (MPECs). SLECs rapidly undergo apoptosis, leading to the progressive decrease of this cellular pool, while MPECs differentiate into the different subtypes of memory T cells.[3,15,19] The fate of T cell differentiation into SLEC or MPEC is determined by the degree of inflammation and duration of antigen exposure. The magnitude of pro-inflammatory cytokine stimulation (namely IL-12) during CD8+ T cell priming determines a gradient of T-bet expression, in a dose-dependent manner, that dictates effector CD8+ T cell differentiation.[22] Exposure to high amounts of T-bet determines the formation of KLGR1^{high} IL-7R^{low} short-lived effector cells, whereas CD8+ effector T cells expressing lower amounts of T-bet become long-lived MPECs.[22] Generally, in acute infection, MPEC formation predominates, while in chronic or latent infection, the continued exposure to pathogenic antigens and synthesis of inflammatory cytokines favours the formation of SLECs.[23]

Recirculating memory T cells: subtypes, functions and characteristics

Memory T cells in human skin can be divided into recirculating memory T cells and non-recirculating, or resident, memory T cells.[19]

There are two main phenotypically and functionally different populations of recirculating memory T cells: central memory T cells and effector memory T cells. Central memory T cells express CCR7 (a lymph node homing C-C chemokine receptor) and L-selectin (essential for the migration and re-

entry of lymphocytes along the vascular endothelium and into secondary lymph nodes), making them largely restricted to the lymphoid organs and peripheral blood. Clark et al. demonstrated the existence of a subset of T_{CM} cells with tropism for the skin that expressed both skin-homing receptors (CLA/CCR4) and central memory markers (CCR7/L-selectin).[24] T_{CM} cells have a high capacity of proliferation and survival. Effector memory T cells exhibit a very low or absent expression of CCR7 and L-selectin, thus having the ability to migrate between the blood and multiple peripheral organs, and have a reduced proliferative capacity when compared to T_{CM} cells.[7] Despite their nomenclature, the effector capacity is not restricted to effector memory T cells, as all subsets of memory T cells have the capacity to produce effector cytokines. The synthesis of effector cytokines associated with a Th1, Th17 and Th22 response is generally higher in T_{EM} cells, while T_{CM} cells produce mostly cytokines associated with a Th2 immune response.[19] In 2015, Watanabe et al. reported the existence of another subset of recirculating memory T cells identifiable in human skin, referred to as migratory memory T cells. These cells express both skin-homing receptors and CCR7 but, unlike skin-tropic T_{CM} cells, do not express L-selectin. They are eliminated from the skin by alemtuzumab therapy and can be isolated in peripheral blood, suggesting that they are recirculating memory T cells, but approximately one third of these cells coexpresses CD69, a T_{RM} marker. This led to the hypothesis that these cells might be in a transitional state, between T_{CM} and T_{RM}. T_{MM} cells show an intermediate pattern of cytokine production, between those of T_{CM} and T_{EM} cells.[19]

T_{RM} cells: characteristics and mechanisms of skin-residence and longevity

Non-recirculating memory T cells are a population of memory T cells that reside in peripheral non-lymphoid tissues and do not have the capacity to migrate through the bloodstream to other sites.[18] These cells act primarily as peripheral immune sentinels. Upon reactivation by cognate antigen, they exert effector functions, becoming directly cytotoxic and able to induce the recruitment of other immune cells, which leads to a much faster immune response against reinfection by a known pathogen.[25] At the skin level, there are two main subtypes of tissue-resident memory T cells: CD4+ T_{RM} cells, and CD8+ T_{RM} cells. Studies on the implications of skin-resident memory T cells in the pathogenesis of psoriasis have predominantly focused on CD8+ CD103+ T_{RM} cells, since these represent the majority of T_{RM} infiltration in psoriatic lesions.[3]

Skin-resident memory T cells are characterised by low migration and long-term survival.[14] The process of T_{RM} cell residence in peripheral tissues is twofold: initially, these memory T cells must migrate to their peripheral target tissue (homing) and, once they are taken up by said tissue, they must be retained there in order not to egress back to the lymph nodes (retention).[14] The homing of T_{RM} cells to peripheral tissues is a chemokine-dependent process, since the profile of chemokine-receptors expressed by each population of tissue-resident memory T cells defines their target tissue. Campbell et al. demonstrated that local factors of the microenvironment where these cells were initially produced determine their chemoattractant pattern, targeting the resulting T_{RM} cells to the same nonlymphoid site where the antigen they are specific for was previously encountered.[26] Skin-resident memory T cells exhibit a skin-homing phenotype, with chemoattractants such as CCR4, CCR8, CCR10, CXCR3, CXCR6 and CLA.[3,14,18] CCR4, CCR8, CCR10 allow memory T cells to migrate to the skin.[27,28,29] CLA binds to E-selectin and P-selectin, enabling memory T cells to enter the skin, while CXCR3 is essential for T_{RM} cell precursors to enter the epidermis.[3,30] CXCR6 intervenes in T_{RM} formation at the skin level.[31] Skin-resident memory T cells express multiple surface markers

that are believed to be responsible for their retention in the skin.[14] Both subtypes of skin-resident memory T cells consistently lack CCR7 and L-selectin, but express CD69, a C-type lectin that downregulates sphingosine-1-phosphate receptor 1, inhibiting the efflux of T_{RM} cells from peripheral tissues.[18] While most CD8+ T_{RM} cells are CD103+, the majority of CD4+ T_{RM} cells do not express this marker.[19] CD103 is the αE subunit of the heterodimeric integrin $\alpha E\beta 7$, which binds to E-cadherin, expressed in all epidermal cell layers, but not in the dermis, which enhances T_{RM} cell adhesion to epithelial cells in the epidermis.[3,32] The expression of CD103 by T_{RM} cells is increased by keratinocyte contact and by TGF-β stimulation, in line with the fact that the vast majority of CD103+ T_{RM} cells, both the CD4 and CD8 subtypes, are located in the epidermis, while CD103- T_{RM} cells predominate in the dermis.[19] Therefore, most T_{RM} cells in the epidermis are CD8+ CD103+, while CD4+ CD103- T_{RM} cells are the most frequent in the dermis.[8] CD49a, originally known as very late antigen 1, is an integrin that further contributes to the retention of T_{RM} cells in the skin, by binding to type IV collagen in the extracellular matrix. This marker also has important functional implications: CD49a+ CD8+ skin-resident memory T cells mainly produce IFN-γ, whereas CD49a+ CD8- skin-resident memory T cells predominantly account for IL-17 secretion, being an important factor in the etiopathogenesis of psoriasis.[33]

The T_{RM} cell population in the skin remains stable for months to years, even in the absence of antigenic stimulation.[34] Local microenvironment factors play an important role in skin-resident memory T cells' longevity. For instance, keratinocytes produce IL-7 and IL-15, which stimulate the activation of the JAK/STAT 5 signalling pathway, enhancing STAT5 phosphorylation and activation. Activated STAT5 increases the expression of antiapoptotic genes, such as Bcl-2, increasing T_{RM} cell survival.[14,18] Additionally, as previously stated, keratinocytes play a key role in CD103 expression by skin-resident memory T cells. The $\alpha E\beta 7$ integrin also upregulates Bcl-2 expression, further contributing to their longevity.[8] The metabolic reprogramming that memory T cell precursors undergo to originate T_{RM} cells adapted to survive in the skin is essential to the longevity of these cells.[34] The skin is relatively poor in nutrients such as glucose, but it is a lipid-rich environment.[35] When compared to any other memory T cell population, skin-resident memory T cells overexpress molecules that promote the uptake and metabolism of exogenous free fatty acids, such as fatty acid binding protein 4 and 5, CD36 and lipoprotein lipase, which enables them to have a much more efficient lipid metabolism, using fatty acids as their primary source of energy. [34] Studies show that skin-resident memory T cells made unable to metabolize FFAs are incapable of long-term survival.[14]

T_{RM} Cells in Psoriasis: Pathogenic Mechanisms

The pathogenesis of psoriasis is complex, but the central role of T-cells is well established, with several studies proving skin-resident T cells to be more effective in disease maintenance than circulating T cells.[36,37] In fact, the inhibition of T cell migration into the skin, using biologics targeting E-selectin or CD11, proved ineffective in resolving psoriatic lesions, which suggests that psoriasis maintenance doesn't depend on the migration of T cells into the skin.[13] However, the transplantation of xenografts of non-lesional skin of psoriatic patients into immunodeficient mice was shown to be sufficient to induce the formation of psoriatic lesions in the absence of circulating T cells, while inhibition of T cell function prevented disease development. This suggests that psoriasis is a T_{RM} cell-dependent disease, as these cells appear to be both sufficient and necessary

for its development.[38,39] Additionally, it suggests that non-lesional skin is poised towards psoriasiform inflammation.[2] Interestingly, Matos et al. demonstrated the existence of specific populations of oligoclonally expanded αβ T_{RM} cells in lesional skin of psoriatic patients, that persist in the skin and maintain IL-17A production even after clinical resolution of lesions. These cells were present, at a lower level, in non-lesional skin of psoriatic patients. T cell receptor Vβ and Vα gene usage and amino acid sequences of TCRβ CDR3 and TCRα CDR3 in these cell populations were analysed and compared to those of T cell populations in the skin of healthy controls and patients with other skin diseases, such as atopic dermatitis or pityriasis lichenoides. This revealed an overlap of putative pathogenic clones between psoriatic patients, while none of the putative pathogenic clones were present in the skin of healthy controls or in the skin of patients with other skin diseases.[40] In this section, we will explore the pathogenic mechanisms of T_{RM} cells in the pathogenesis of psoriasis.

Activation and proliferation of T_{RM} cells in psoriatic lesions - the role of cytokines, chemokines and antigen-presenting cells

Several elements of the skin microenvironment, such as cytokines, antigen-presenting cells and keratinocytes, contribute to the maintenance of T_{RM} cells in the skin of psoriatic patients, playing a key role in disease recurrence.[13] The local pool of epidermal and dermal dendritic cells undergoes marked changes during inflammation in psoriatic skin, increasing in number and acquiring a pro-inflammatory profile, with increased IL-12 and IL-23 expression. Particularly relevant is the fact that even after clinical resolution of psoriatic lesions, DC maintain altered gene expression profiles.[41] In clinically healed psoriatic skin, Langerhans cells share similar locations with epidermal T cells and, when compared to healthy individuals, exhibit increased production of IL-15 and IL-23, essential for T_{RM} cell maintenance and survival.[36,38] Regarding their dermal counterparts, TNF-producing and IL-23p19-producing pools of dermal dendritic cells have been identified in psoriatic patients and shown to persist after treatment.[42] Several autoantigens derived from skin components have been implicated in the pathogenesis of psoriasis, such as neolipid antigens, antimicrobial peptides, ADAMTSL5 (A disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like 5), PLAG4D (phospholipase A2 group 4D) and keratin 17, and they are thought to play a role in the maintenance of T_{RM} cell function by DC.[13,36] Of interest, cationic antimicrobial peptides, including LL-37 and human beta-defensins 2 and 3, form complexes with self-DNA/ RNA, activating plasmacytoid dendritic cells and TNF and nitric oxide releasing dendritic cells, leading to the formation of key inflammatory cytokines IL-23 and TNF-α.[13,43] This evidence suggests that the crosstalk between DC and T_{RM} cells contributes to the inflammatory memory that remains in the skin of psoriatic patients after remission of cutaneous lesions.[44]

Contribution to the inflammatory milieu of psoriasis

T_{RM} cells directly contribute to the inflammatory milieu of psoriasis by producing pro-inflammatory cytokines and recruiting other immune cells. CD8+ T_{RM} cells can be divided into two functionally different subtypes: CD8+ CD49- T_{RM} cells, the main responsible for IL-17A production, and CD8+ CD49- T_{RM} cells, which mainly produce IFN-γ.[3,45] IL-17A acts directly on keratinocytes, increasing

their proliferation and the production of proinflammatory cytokines, chemokines, and antimicrobial peptides. AMPs are produced by keratinocytes in response to injury and cytokine stimulation, and act as chemotactic agents for T cells and neutrophils.[1] Additionally, as previously stated, AMPs, such as LL-37, activate DC to produce IL-23, which binds to IL-23R on T_{RM} cells, leading to its own upregulation, as well as upregulation of the transcription factor RORγt and activation of STAT3, assigning these cells to the Th17 or Tc17 lineage and further increasing IL-17 production. In this way, the IL-23/IL-17 pathway creates a positive feedback loop that perpetuates psoriasiform inflammation.[2] The role of IFN-γ in psoriasiform inflammation is not as well established as the role of the IL-23/IL-17 axis.[1] However, studies show that IFN-γ levels are elevated in psoriatic skin, in correlation with disease severity, as IFN-γ induces chemokine production and promotes T-cell migration into lesional epidermis.[46] IL-17A-producing CD8+ CD49- T_{RM} cells are considered to be the major mechanism driving psoriasis recurrence. Interestingly, Sézéral et al. demonstrated that skin-resident T cell stimulation resulted in upregulation of IFN-γ-dependent pathways both in healthy skin and in clinically resolved psoriatic skin, while IL-17A-driven pathways were only upregulated in resolved psoriatic skin. Moreover, studies show that the ratio of IL-17A-producing to IFN-γ-producing CD103+ CD8+ T_{RM} cells in psoriatic skin increases in correlation to disease duration.[33]

Even though CD8+ T_{RM} cells make up the majority of the T cell infiltrate in psoriatic lesions, CD4+ T_{RM} cells also contribute to psoriasiform inflammation, through IL-22 synthesis.[47] IL-22 leads to excess proliferation and abnormal differentiation of keratinocytes and induces the production of granulocyte chemokines (such as CXCL1, CXCL5 and CXCL8), leading to the recruitment of granulocytes that amplify psoriatic inflammation.[3]

T_{RM} Cells and Psoriasis Treatment

Current treatments targeting the pathways associated with T_{RM} cells

Biological therapies

Biologics have significantly improved psoriasis treatment and are currently considered the most effective therapeutic weapons against this disease.[3] A meta-analysis compared the results of sixty phase 2, 3 or 4 randomized clinical trials on the efficacy of several biologic drugs in obtaining reductions of PASI assessment of 90% (PASI 90). Data concerning TNF-α inhibitors (etanercept, adalimumab, certolizumab pegol and infliximab), anti-IL-17 agents (secukinumab, ixekinumab and brodalimumab) and anti-IL-23 agents (tildrakizumab-asmn, guselkumab and risankizumab-rzaa) was compared. Risankizumab-rzaa, guselkumab, brodalumab and ixekizumab were the most effective biologics at obtaining PASI 90, both at short- and long-term therapy, with risankizumab-rzaa achieving the highest PASI 90 rates of all.[10] Despite their significant efficacy, biologics still fail to prevent psoriasis relapse, and, in recent years, it has been postulated that targeting skin-resident memory T cells could be key to finding a cure for this disease.[3] In fact, studies show that, while the reduction in the number of neutrophils is responsible for a faster response to therapy, the length of remission is associated with the decrease in the number of T cells and DC in the skin.[36] Given the essential role of IL-23 in the maintenance of skin-resident memory T cells, IL-23 antagonists are the most effective biologics at depleting T_{RM} cells from psoriatic skin, whereas IL-17 inhibition has a greater effect on the neutrophil infiltrate.[3] In fact, the ECLIPSE study analysed the frequency of T_{RM}

cell populations in biopsy specimens from psoriatic patients, before and after treatment with guselkumab or secukinumab, demonstrating that guselkumab, unlike secukinumab, was associated with a significant decrease in the number of CD8+ T_{RM} cells.[4] This aligns with the fact that biologics directed against IL-17 elicit a faster clinical response, but those directed against IL-23 account for the longest remission periods.[36,44] For IL-23 antagonists, studies show a median time of disease recurrence after treatment withdrawal of 30 weeks for risankizumab, 23 weeks for guselkumab and 16 to 20 weeks for tildrakizumab, while IL-17 antagonists ixekizumab and bimekizumab induce disease remission for a median of 20 weeks and brodalumab for only 11 weeks.[4]

Recently, the potential benefit of early treatment initiation has also gained attention, based on the rationale that disease duration positively correlates with the amount of T_{RM} cells in the skin of psoriatic patients.[44] This raises the hypothesis that earlier biologic use may reduce the accumulation of T_{RM} cells in the skin previous to treatment initiation and, therefore, facilitate the clearance of these cells from the skin, improving clinical response to treatment. [44] Interestingly, the GUIDE study compared the time necessary for skin clearance between two groups of patients with moderate to severe plaque psoriasis, treated with guselkinumab. One initiated treatment within the first two years of disease onset (short disease duration (SDD)), while the other initiated treatment at least two years after disease onset (long disease duration (LDD)). On average, SDD patients achieved disease remission faster, with a median of 141 days for SDD patients and 200 days for LDD patients. Additionally, at 28 weeks, more SDD patients than LDD patients achieved an absolute PASI score of 0 (51,8% vs. 39,4%). This study suggests that in fact, early treatment initiation elicits a higher and faster response to treatment.[48]

Topical treatments

Kurihara et al. demonstrated that topical therapies for psoriasis, such as calcipotriol, betamethasone dipropionate and a compound formulation combining both active principles, reduce the number of T_{RM} cells in lesional epidermis, with the combination ointment depleting skin-resident memory T cells to the greatest degree.[49] However, a subset of CD8+ T_{RM} cells persists in the basement membrane zone of the epidermis even after clearance of skin lesions, proving resistant to all the topical therapies currently used in the treatment of psoriasis.[7]

Emerging therapeutic strategies aimed at modulating T_{RM} cell function

Biologics have revolutionized the treatment of psoriasis and currently represent the most effective therapeutic strategy against this disease. However, due to their high cost, adverse effect profile, complexity of administration and inability to prevent disease relapse, there has been increasing interest in new treatment strategies, such as orally administered drugs (namely Janus kinases inhibitors, rho-associated protein kinase 2 inhibitors, retinoic-acid-receptor-related orphan receptor gamma-t agonists, and phosphodiesterase 4 inhibitors) and topical treatments (namely aryl hydrocarbon receptor agonists).[50]

Aryl hydrocarbon receptor agonists

Aryl hydrocarbon receptor is a transcription factor that has been implicated in the pathogenesis of psoriasis. In 2022, topinarof, a topical aryl hydrocarbon receptor agonist was approved by the FDA for the treatment of psoriasis.[16] This drug was shown to induce long-term psoriasis remission (averaging 4.5 months) following treatment withdrawal. In fact, *in vitro* studies demonstrated that topiranof significantly reduced T_{RM} activation and proliferation in the skin.[51]

JAK/STAT inhibitors

Janus kinases are cytoplasmic tyrosine kinases, essential for intracellular signalling downstream of the surface receptor they are associated with.[52] Upon ligand recognition by a cell-surface receptor, JAKs phosphorylate signal transducer and activator of transcription proteins (STATs), allowing them to translocate to the nucleus and regulate gene expression.[52,53] The JAK family comprises four proteins: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), while the STAT family consists of seven: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.[54] Type 1 and type 2 cytokine receptors, such as the IL-7, IL-15, IL-23, IL-22, IFN-α, IFN-β, and IFN-γ receptors, often depend on the JAK-STAT pathway for signal transduction. [54] For instance, the IL-23 receptor is associated with JAK2, TYK2 and STAT3, while the IL-15 is associated with JAK 1 and 3 and STAT5.[55] This explains the critical role of the JAK/STAT pathway in psoriatic inflammation and the growing interest in JAK-STAT inhibitors as therapeutic weapons in the management of this disease.[50]

Currently, only deucravacitinib, a selective TYK2 inhibitor, has been approved by the FDA for the treatment of chronic plaque psoriasis, but many JAK/STAT inhibitors have shown promising results in clinical trials.[53,56] Upadacitinib is a JAK-1 inhibitor approved to the treatment of psoriatic arthritis. Even though there have been no clinical trials evaluating its efficacy in psoriasis, in a phase 3 clinical trial on its efficacy in psoriatic arthritis over 50% of patients achieved PASI75 in a year.[57] Tofacitinib inhibits JAK1 and JAK3. A phase 3 clinical trial on its efficacy in plaque psoriasis showed improvement of skin lesions in the majority of subjects. Brepocitinib, a TYK2 and JAK1 inhibitor, is also being studied for psoriasis treatment, with phase I and II clinical trials revealing dose-dependent efficacy, with significant PASI score improvements.[50] These drugs block IL-15 and/or IL-23 signalling, essential for T_{RM} maintenance and survival, but further studies are necessary to determine their effect on this cell population.[52]

ROCK2 inhibitors

Inhibition of rho-associated protein kinase 2 decreases the production of proinflammatory cytokines, such as IL-17 and IL-23, while increasing the regulatory immune response.[54] One study demonstrated that oral administration of belumosudil (KD025), a ROCK2 inhibitor, attained a 50 % reduction in PASI scores in 46 % of patients with psoriasis vulgaris. This treatment was also shown to reduce epidermal thickness and T-cell infiltration.[50]

RORγt inhibitors

Retinoic-acid-receptor-related orphan receptor gamma-t is a transcription factor essential for the development and function of IL-17 producing cells. Even though this medication is not yet used in clinical practice in the management of psoriasis, VTP-43742, an oral inhibitor of the RORγT protein, is currently being evaluated in a phase 3 clinical trial for the treatment of this disease, with a 23 to 29% reduction in PASI score after 4 weeks of treatment.[54]

PDE-4 inhibitors

Phosphodiesterase 4 degrades the phosphodiester bond of cyclic adenosine monophosphate (cAMP), converting it into adenosine monophosphate (AMP). cAMP mediates signal transduction, leading to the production of anti-inflammatory cytokines. However, its inactivation by PDE-4 results in the increase of pro-inflammatory mediators, such as IL-12, IL-23, TNF-α and IFN-γ.[53] So far, two drugs of this family have been approved for the treatment of psoriasis: oral apremilast, in 2014, and topical roflumilast, in 2022.[50]

Phase 2 and 3 clinical trials show effectiveness of once-daily application of 0,3% roflumilast cream in the treatment of plaque psoriasis. The phase 3 double-blind randomized clinical trials DERMIS-1 and DERMIS-2 showed efficacy at achieving IGA status "clear" or "almost clear" of 48% after 8 weeks of treatment and 45% after 52 weeks.[58,59] Additionally, topical roflumilast demonstrated a favourable safety and tolerability profile, with few mild to moderate side effects, such as transient gastrointestinal symptoms, headache, insomnia, and application-site reactions.[60] More recently, studies evaluating the efficacy and safety of oral roflumilast in the treatment of moderate-to-severe psoriasis showed promising results.[61]

Vaccination strategies to induce tolerance in T_{RM} cells

Vaccines modulating skin-resident memory T cell function are increasingly recognized as potential therapeutic weapons against skin infections and skin cancers.[62,63] Interestingly, a study demonstrated that vaccination-induced T_{RM} cells were able to infiltrate tumours and markedly suppress the growth of B16F10 melanoma, independently of recirculating memory T cells.[63] Recently, it has been postulated that vaccination strategies targeting these cells could also be employed in the treatment of other tissue-based diseases, such as psoriasis. This approach would target the root cause of disease recurrence, instead of the proinflammatory mediators of disease, hopefully proving more efficient at preventing psoriasis relapse. Several factors influence the likelihood of vaccines generating tissue-resident memory T cells, including the route of immunization, as orthotopic administration of vaccines is associated with more marked T_{RM} cell production than systemic or distal routes.[64,65]

So far there have been very few studies on the use of vaccines for the treatment of psoriasis. Most studies have been conducted using microbial-based vaccines, and those with more rigorous methodologies showed no clinical benefit. A study using a virus-like particle of the bacteriophage Qβ linked to the TNF-α protein or a peptide derived from its N terminus resulted in the formation of anti-TNF-α antibodies, that proved effective in reducing clinical inflammation in a murine model of rheumatoid arthritis.[66] This technology has never been applied to a psoriasis model and is far

from ready for human use, but it is thought that immunization against proinflammatory cytokines involved in psoriatic inflammation, such as TNF-α, IL-17, IL-22, or IL-23, could be a promising advancement in the treatment of this disease. [64,65]

Overall, clinically applicable vaccination strategies that effectively generate T_{RM} cell responses are largely unexplored, and more research is necessary to understand if this could be a viable approach to the treatment of psoriasis.

Future research directions and challenges

The central role of T_{RM} cells in the recurrence of psoriasis is increasingly well established, as well as the correlation between a treatment's ability to deplete skin-resident memory T cells and the duration of disease remission it induces. Currently, further clinical research is necessary to understand how these cells can be targeted in clinical practice, in order to prevent psoriasis relapse. The challenge lies in depleting pathogenic T_{RM} cells from lesional and non-lesional skin, without compromising local and systemic immunity. It is vital to have a comprehensive understanding of T_{RM} cell survival and proliferation mechanisms, their exact role in the inflammatory milieu of psoriasis, and the differences between pathogenic and non-pathogenic T_{RM} cells, to allow for the development of a therapy that selectively targets psoriasis-specific T_{RM} cell clones.

Another possible goal of future research would be to gain a deeper understanding of the metabolic network of psoriasis. As previously stated, skin-resident memory T cell metabolism is dependent on exogenous free fatty acids and, when deprived of these nutrients, these cells lose their long-term survival capacity. Therefore, it has been postulated that modulating T_{RM} cell lipid metabolism could be an effective way of targeting these cells. An eventual metabolic therapy raises concern due to the possibility that it would not selectively target pathogenic T_{RM} cells and could instead disrupt the skin's immune microenvironment to a greater extent. Nonetheless, additional research into the metabolic programs of skin-resident memory T cells is needed to understand whether these programs could be manipulated to modulate T_{RM} cell function and longevity.

Conclusion

T_{RM} cells are a subpopulation of memory T cells, characterized by their capacity of long-term survival and residence in non-lymphoid tissues, such as the skin. These cells originate from antigen-specific circulating effector T cells and maintain antigen specificity. Upon reactivation by cognate antigen, they exert effector functions, initiating a much faster immune response against it. However, in recent years, they have also been implicated in the pathogenesis of several immune-mediated diseases.

Recent research has heavily focused on understanding the role that T_{RM} cells play in the pathogenesis of psoriasis and on exploring their potential as therapeutic targets. It is currently known that, at the skin level, there are two main subtypes of T_{RM} cells: CD4+ T_{RM} cells and CD8+ T_{RM} cells. CD8+ CD49- T_{RM} cells have a central role in psoriatic inflammation. These cells mainly produce IL-17, directly inducing keratinocyte proliferation. IL-17 also stimulates keratinocytes to produce proinflammatory cytokines, chemokines and AMPs, that act as chemotactic agents for T cells and

neutrophils and further activate dendritic cells to produce IL-23. Ultimately, this further stimulates T_{RM} cell function, creating a positive feedback loop that perpetuates psoriasiform inflammation.

Additionally, studies show that T_{RM} cells can remain in the skin of psoriatic patients for months to years following the clinical resolution of psoriatic lesions, and that the degree of T_{RM} cell clearance from the skin positively correlates with the duration of disease remission induced by a given treatment. Therefore, targeting T_{RM} cells represents a promising future approach for improving therapeutic outcomes of psoriatic patients, as it appears that by eliminating all pathogenic T_{RM} cell clones from the skin it would be possible to prevent disease relapse.

To conclude, in recent years, significant advancements have been made towards a deeper understanding of the critical role of T_{RM} cells in the pathogenesis of psoriasis and the impact of different treatments on this cell population. However, further research is necessary to identify the specific molecular targets and inflammatory pathways at which treatment should be directed to allow for selective destruction of pathogenic T_{RM} cell clones, without compromising systemic immunity, and in a way that is applicable to clinical practice. In light of current knowledge, it can be postulated that such treatment would inhibit psoriasis relapse, representing a possible cure for the disease.

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