Psoriasis is a chronic T-cell-associated inflammatory disease with an estimated global prevalence of 2–3%. The disease has a strong genetic component, and over 40 regions of the genome and more than 400 single-nucleotide polymorphisms associated with psoriasis have been identified. The major genetic determinants and variations associated with the disease include polymorphisms in the genes coding for major histocompatibility complex (MHC), interleukin (IL)-2, IL-21, IL-23 receptor (IL-23R) and IL-36R antagonist (IL-36RN). Genetic variation accounts for 50–70% of psoriasis susceptibility, while the remaining disease risks are attributed to environmental effects such as infection (e.g. streptococcal infection), medication [e.g. imiquimod, interferon (IFN)-α] or trauma.

Psoriasis, characterized by thickening and scaling of the epidermis due to increased proliferation of keratinocytes, can manifest as various phenotypes (comprehensively reviewed in Greb et al. and Raychaudhuri et al.). The most common
subsection is psoriasis vulgaris, also known as plaque psoriasis. It is characterized by defined erythematous plaques with loosely adherent silvery white scales and commonly affects the elbows, knees, scalp and trunk. Guttae psoriasis, the second-most common subtype, is characterized by small erythematous papules over the trunk and extremities.6,7

The formation of inflammatory psoriatic plaques is caused by infiltration of inflammatory cells into the skin, including CD4+ and CD8+ T cells, innate lymphoid cells, macrophages, mast cells, neutrophils, natural killer (NK) cells and NKT cells.8–12 The pathogenesis of psoriasis is driven by the dys-function of T-cell subsets including T-helper (Th)1 cells, Th2, Th17, Th22 and regulatory T cells (Tregs) and the resulting aberrant release of the corresponding cytokines including IFN-γ, tumour necrosis factor (TNF)-α, IL-23 and IL-17 family members,13 suggesting a dysfunction of regulatory mechanisms.

During immune homeostasis, CD4+ CD25high Forkhead box P3+ (Foxp3+) Tregs maintain self-tolerance by controlling effector T-cell activation.14 Although the exact functions of Tregs in psoriasis pathogenesis remain mostly unknown, there is some evidence that Tregs can ameliorate disease in vivo in preclinical mouse models of psoriasis. Stockenhuber et al. have shown that Foxp3+ Tregs can control psoriasiform inflammation by restraining IFN type I (IFN-I)-driven CD8+ T-cell responses.15 Further, Ma et al. observed a reduced psoriasis-like phenotype on intraperitoneal injection of CD4+ CD45RBhigh cells containing Foxp3+ Tregs in a scid/scid mouse model.16 Additionally, Hartwig et al. demonstrated that Foxp3+ Tregs prevented hyperinflammation by suppressing the infiltration of granulo-cyte–macrophage colony-stimulating factor-producing CD4+ T cells into skin lesions.17 These studies emphasize that Tregs may play an important role in psoriasis pathogenesis.

In this review, we discuss the role of Tregs in psoriasis, including the cause and impact of Treg dysfunction, impaired Th17/Treg balance, and the potential therapeutic application of Tregs (see Figure 1).

Regulatory T cells

Foxp3-expressing Tregs, most of which are CD4+ CD25+ (IL-2 receptor α-chain+), are a subpopulation of T lymphocytes committed to suppress immune responses and preserve immune homeostasis.14 The absence of Foxp3-expressing Tregs leads to the development of severe autoimmunity.18

Based on their origin, natural Tregs can be divided into thymus-derived Tregs (tTregs) and peripherally derived Tregs (pTregs).19 While tTregs develop in the thymus following T-cell receptor (TCR) recognition of self-antigens, pTregs differentiate from naïve CD4+ T cells following the recognition of nonself antigens.20 The markers Helios21 and neuropilin-122,23 were suggested to distinguish pTregs from tTregs; however, controversies exist regarding specificity.24–27 Hypomethylation of Treg signature genes is crucial for Treg transcriptional activity and stable functionality.28–33 Few studies differentiate between tTregs and pTregs; however, several studies suggest that pTregs can acquire a Treg-specific demethylation pattern similar to tTregs.28,29,34 In addition, Tregs can be induced in vitro by stimulating naïve CD4+ T cells using IL-2 and transforming growth factor (TGF)-β3,10,35 These in vitro-induced Tregs (iTregs) have phenotypical similarities to natural Tregs, but differ, for example, in Treg-specific demethylation pattern and stability.28,29

Tregs can mediate their suppressive function through different routes: cell–cell interaction, production of suppressive cytokines such as IL-10, TGF-β1 and IL-35, and direct cytotoxic action.36 Tregs retain lineage stability and suppressive function during various inflammatory stimuli,37 but gain effector phenotypes and lose Foxp3 expression in certain circumstances.38–40 One example is Treg plasticity to a Th17-like phenotype upon IL-6 exposure,41,42 a pro-inflammatory cytokine highly expressed in psoriasis.43,44

Regulatory T cells in the skin

Tissue-resident Tregs are heterogeneous populations with continuous exposure to localized antigenic challenges.45 Increasing evidence shows that they differ from their counterparts in circulation and secondary lymphoid organs in phenotype, transcriptome and metabolism, with tissue-specific adaptation closely linking to environmental and physiological signals.55–59 Single-cell transcriptomics by Miragaia et al. further suggests that transcriptomic adaptation of Tregs starts as early as during the transition from lymph node to tissue.49 Skin-resident Tregs play an important role in maintaining cutaneous immune homeostasis.51,52 They further modulate other important processes in the skin including wound healing, hair-follicle regeneration and adaptive immune tolerance to skin commensals.52

Frequencies of regulatory T cells in the skin

Although only about 3% of peripheral blood mononuclear cells (PBMCs) and about 5–15% of peripheral CD4+ T cells are CD4+ CD25+ Tregs,53–58 over 60% of circulating CD4+ CD25high Foxp3+ Tregs express the skin-homing receptors cutaneous lymphocyte antigen (CLA) and CCR6.59–61 In the skin, Foxp3+ Tregs represent approximately 20% of CD4+ T cells with more than 95% of them expressing the memory T-cell marker CD45RO.58

Localization and function of regulatory T cells in skin homeostasis

In mouse and human skin, Tregs localize primarily to hair follicles.58,62 Mouse studies have shown that the development of hair follicles and the colonization of commensal microbes facilitate Treg accumulation in neonatal skin.63 Meanwhile, a wave of highly activated Tregs populating the skin during the first weeks of life is crucial for the establishment of tolerance to commensal microbes.64 Furthermore, Tregs are found to enrich skin wounds and promote wound healing.65

A potential link between Tregs and skin immune homeostasis can be found in patients suffering from immune dysregulation
Polyendocrinopathy enteropathy X-linked (IPEX) syndrome. IPEX syndrome is caused by mutations of the FOXP3 gene resulting in absent or dysfunctional Tregs, and patients commonly present with cutaneous manifestations such as atopic dermatitis or psoriasis. Skin-related side-effects emerging from anti-CCR4 (mogamulizumab)-dependent Treg depletion in T-cell lymphoma treatment further emphasizes the role of Tregs in maintaining skin immune homeostasis.

Regulatory T cells in psoriasis

Frequency and phenotype of regulatory T cells in disease

The link between Treg frequency and psoriatic disease severity is currently disputed. Several authors have reported a decreased percentage of Tregs in peripheral blood of patients with psoriasis but its correlation to disease severity varied, while other cohorts showed no difference in circulating Treg frequency. Zhang et al. observed that patients with moderate-to-severe disease showed a higher frequency of Tregs, which correlated with Psoriasis Area and Severity Index (PASI) scores. A similar result was reported in paediatric patients.

Most studies investigating the infiltration of Tregs into lesional skin demonstrate an increased frequency compared with healthy skin. Zhang et al. further reported that the increase in Tregs in psoriatic skin correlated with PASI scores. While Bovenschen et al. observed a higher frequency of CD4⁺ CD25⁺ Foxp3⁺ Tregs in the dermis compared with the epidermis in patients with plaque psoriasis, Fujimura...
et al. reported the opposite for psoriasis vulgaris. In contrast, Yun et al. observed a decrease of Foxp3+ Tregs in lesional vs. nonlesional skin of patients with acute exacerbation but an increase in patients with chronic disease, irrespective of disease severity. Moreover, Yan et al. reported that Foxp3+ Tregs in lesional skin were increased in plaque psoriasis but decreased in guttate psoriasis when compared with normal skin.

These conflicting results may be a consequence of differing disease states, varying Treg definition, sites of biopsies within psoriatic plaques as well as psoriasis subtypes investigated. It is important to note that Foxp3 expression is not unique to Tregs in humans, as it can be acquired transiently by effector T cells. Overall, these studies highlight Tregs as potential contributors to psoriasis pathogenesis.

**Regulatory T-cell dysfunction in disease**

Recent studies indicate that in most patients with psoriasis Tregs are dysfunctional. Sugiyama et al. found that CD4+CD25high Foxp3+ Tregs isolated from skin lesions or peripheral blood failed to suppress effector T-cell responses and proliferation. In line with these results, Zhang et al. described that Tregs derived from haematopoietic cells of patients with psoriasis were less efficient in controlling CD4+CD25+ T-cell activation than those of healthy individuals. Tregs isolated from the blood of paediatric patients showed similarly impaired suppressive function, which was partly restored after disease remission.

One mechanism by which the Treg suppressive function might be impaired in psoriatic lesions is the pro-inflammatory cytokine milieu. In particular, the exposure to high levels of IL-6 leads to decreased Treg activity. In psoriasis vulgaris, Zhao et al. revealed that microRNA (miR)-210 – which inhibits Foxp3 expression – is increased in CD4+ T cells, resulting in decreased levels of the suppressive cytokines IL-10 and TGF-β and increased levels of the pro-inflammatory cytokines IFN-γ and IL-17A. These findings suggest that miR-210 overexpression contributes to Treg dysfunction in these patients.

Additionally, Wang et al. found that, in CD18 (β2 integrin) knockout mice, which present with a psoriasiform phenotype, Treg dysfunction is the causal factor of effector T-cell hyperproliferation. Yang et al. discovered that dysfunctional Tregs from peripheral blood of patients with psoriasis show phosphorylation, and thus aberrant activation, of the STAT3 pathway as well as expression of the pro-inflammatory cytokines IFN-γ, TNF-α and IL-17A. In this study, STAT3 phosphorylation and subsequent Treg dysfunction was induced by the pro-inflammatory cytokines IL-6, IL-21 and IL-23.

Impairment of the adenosine signalling pathway may cause loss of the Treg suppressive function in psoriasis. Tregs express both CD39 and CD73 and use adenosine signalling for immune suppression. CD39 converts extracellular adenosine triphosphate (ATP) to adenosine monophosphate (AMP), which in the presence of CD73 is degraded into adenosine. Adenosine binds to the adenosine A2A receptor, present on Tregs, leading to enhanced Treg numbers and function. Yan et al. have shown that in Tregs from patients with psoriasis vulgaris, CD73 expression is markedly reduced and the CD73/AMPK pathway is inactive, thus reducing the immunosuppressive function.

In addition to impaired suppressive function, inefficient homing of Tregs to inflamed sites may also impact Treg function in psoriasis. Soler et al. observed not only numerical and functional impairment of Tregs but also a chemotactic deficiency of CCR5+ Tregs resulting in the inability to restrain inflammation in individuals with psoriasis.

Cutaneous microbiome colonization shapes the development of Tregs and can facilitate immune tolerance via the induction of antigen-specific Tregs in lymph nodes and skin. Although microbial dysbiosis is a contributing factor in psoriasis, there are limited data on the influence of cutaneous commensals on psoriatic skin Tregs. While the gut microbiota evidently affects intestinal Tregs in other diseases, further studies are required to investigate the interaction between skin microbiota and Tregs in skin inflammation.

Taken together, there is clear evidence that the suppressive function of circulating as well as skin-resident lesional Tregs is impeded in patients with psoriasis. The recently gained insights into mechanisms causing this dysfunction may benefit the development of new or the repurposing of available drugs for the treatment of psoriasis.

**T-helper 17/regulatory T-cell balance**

Th17 cells are a subset of CD4+ T cells, which express the lineage-specific transcription factor retinoic acid receptor-related orphan receptor γ t (RORγt) and secrete a characteristic profile of cytokines including IL-17A, IL-17F, IL-21 and IL-22. They play an important role in the immunity to extracellular pathogens, and in the pathogenesis of inflammatory and autoimmune diseases, including psoriasis.

In psoriasis, Th17 cells are highly activated and infiltrate into psoriatic lesions. Additionally, IL-23, a Th17-polarizing cytokine, is elevated in lesional skin. Taken together with the therapeutic efficiency of IL-23 and IL-17 blockade, these findings support an essential role of Th17 responses in psoriasis pathogenesis.

Several reports described an imbalance of the Th17 to Treg ratio in psoriasis. Priyadarssini et al. have shown an increase in circulating Th1/Th17 cells but a decrease in Th2 cells and Tregs. Zhang et al. have shown elevated levels of both Th17 cells and Tregs in peripheral blood and lesional skin of patients with psoriasis, and the Th17/Treg ratio in peripheral blood was positively correlated with PASI scores while the Th17/Treg ratio in psoriatic skin lesions showed a negative trend. However, neither healthy control- nor psoriasis patient-derived Tregs were able to regulate IL-17 secretion by CD4+ T cells. A study by Ma and colleagues suggests that the Th17/Treg ratio imbalance in psoriasis vulgaris is regulated via the Notch1 signalling pathway and may be reversible by dual antiplatelet therapy, which decreased the...
percentage of Th17 cells as well as RORC and IL-17A messenger RNA (mRNA) levels.70

Regulatory T-cell plasticity

Induced Tregs (pTregs and iTregs) and Th17 cells share the requirement for TGF-β to develop from their common precursor, naïve T cells, resulting in a constant developmental competition.105,106 Tregs from patients with severe psoriasis have the potential to differentiate to an IL-17A-producing phenotype on stimulation α vivo. This differentiation could be mediated by histone/protein deacetylases.107 One of these, histone deacetylase 1 (HDAC-1), is elevated in psoriatic skin,108 indicating a potential association of histone acetylation with Treg plasticity in psoriasis. Bovenschen et al. further reported the presence of IL-17A+ Foxp3+ CD4+ cells in psoriatic lesions.107 Moreover, STAT3, which exhibits a hyperactive state in psoriasis,86 stabilizes the Th17 phenotype via the expression of IL-23R and RORγt, in turn contributing to the pathogenesis of psoriasis.109

These observations suggest that not only Treg dysfunction but also Treg phenotypic alteration contributes to psoriasis pathogenesis. Moreover, even an increase in Treg frequency may lead to perturbation rather than suppression of disease as a consequence of modified pro-inflammatory profiles.

Impact of existing psoriasis therapies on regulatory T cells

Many current or prospective treatments for psoriasis appear to increase Treg numbers and/or functionality in psoriasis. An overview of how these treatments affect Treg frequency, function and the Th17/Treg balance can be found in Table 1.

Treatment with anti-TNF-α agents (especially etanercept) increases Treg frequency while decreasing IL-6 and IL-22 levels.69,110 This increase in Tregs may correlate with clinical response,69 and infliximab (chimeric monoclonal anti-TNF-α antibody) has further been shown to induce a more diverse TCR repertoire.111 However, Treg suppressive function was not investigated. In a murine psoriasiform model, anti-TNF-α treatment downregulated Th17-related cytokines and chemokines, but neither Treg numbers nor suppressive function were restored.112 Of note, a separate study on TNF-α blockade reported exacerbation of disease via increased pro-inflammatory cytokine secretion and Th17 function, and decreased Foxp3 expression and Treg frequency.113

The folic acid analogue methotrexate acts not only through folate antagonism but also mediates anti-inflammatory effects via adenosine,114 which enhances Treg numbers and function.89,90 In the treatment of psoriasis, methotrexate decreases the frequency of Th1 and Th17 cells while simultaneously promoting the accumulation of Th2 cells and Tregs.115 Further, decreased suppressive function of IL-17-secreting Tregs resulting from reduced CD73 expression could be recovered by methotrexate treatment.91

Vitamin D treatment induces a cytokine profile favouring the differentiation of T cells with suppressive phenotypes.116,117 Further, vitamin D can induce dendritic cells with a tolerogenic phenotype that promotes the differentiation of CD4+ CD25+ Tregs from naïve T cells.118,119 In patients with psoriasis, serum vitamin D levels are positively correlated with serum Treg levels and inversely correlated with PASI scores.120 In a murine psoriasiform inflammation model, the vitamin D3 analogue mexacalcitol downregulated Il17a, Il17f, Il6 and Il13p19 mRNA expression and increased the infiltration of functional Tregs into lesional skin.121

Retinoids, such as acitretin, are commonly used to treat psoriasis. It has been shown that retinoic acid inhibits the induction of Th17 cells while promoting Foxp3 expression and Treg differentiation.122,123

Treatment of psoriasis with phototherapy [narrowband ultraviolet (UV)B, bath–psoralen UVA] increases Treg levels while simultaneously decreasing the percentage of Th17 cells. Interestingly, Treg levels were significantly higher in patients achieving PASI 90. Most importantly, phototherapy seems to increase Treg functionality.73,124

The immunosuppressant drug sotrastaurin, a pan-protein kinase C inhibitor currently in clinical trials for the treatment of psoriasis, inhibits secretion of pro-inflammatory cytokines and effector T-cell function while rescuing Treg suppressive function and preventing Th17 polarization in vitro.125

Biologics such as anti-IL-17A (secukinumab) and anti-IL-23 (p19-specific guselkumab, p40-specific ustekinumab) have been approved for use in psoriasis. In an imiquimod-induced psoriasiform mouse model, both anti-IL-17A and anti-IL-23 were shown to increase Foxp3+ Treg frequency in lesional skin. Adoptive transfer of antibody-treated Tregs further improved psoriasiform inflammation in recipient mice indicating a functional suppressive phenotype.112 Additionally, in a mouse study on allergic rhinitis, intranasally applied anti-IL-17 reduced Th2 and Th17 responses while increasing the percentage of Foxp3+ Tregs in the nasal mucosa.126 Therefore, anti-IL-17 treatment in psoriasis may restore a healthy Th17/Treg balance and thus reduce inflammation and ameliorate disease. Kannan et al. further highlight the driving role of IL-23 in Treg plasticity to a Th17-like phenotype in a murine model of psoriasiform inflammation.127 Taken together, these findings suggest that the inhibition of IL-23 may have a beneficial effect in psoriasis.

Exploiting available biologics and treatments to target regulatory T cells in psoriasis

Several biologics and drugs that have been approved for the treatment of other diseases can modulate Treg frequency and function, thus presenting potential new treatment options.

Tregs require IL-2 for differentiation and immunosuppression. Low-dose IL-2 has been shown to increase Treg frequency in graft-versus-host disease,128 type 1 diabetes,129,130 alopecia areata131 and systemic lupus erythematosus.132,133 This treatment takes advantage of the IL-2 sensitivity of Tregs, which
Table 1 The effect of current and prospective treatments for psoriasis on Treg frequency, function and the Th17/Treg balance

| Therapy Model(s) | Increase of Treg frequency | Effect on Treg function | Improvement of Th17/Treg balance | First author, year, reference |
|------------------|-----------------------------|-------------------------|----------------------------------|------------------------------|
| **Anti-TNF-α (e.g. etanercept, infliximab)** | | | | |
| • Clinical studies of circulating Tregs in patients with arthropathic psoriasis, psoriasis vulgaris and active plaque-type psoriasis | | | • Via downregulation of Th17-related cytokines and chemokines | Quaglino 2009[69] Cordiali-Fei 2014[100] Ma 2010[115] Shimizu 2019[112] |
| • Murine models of psoriasis-like inflammation | | | | |
| **Folic acid analogue (methotrexate)** | | | | |
| • Clinical studies of circulating PBMCs in patients with moderate-to-severe psoriasis | | | | Ohta 2012[89] Priyadarssini 2019[115] Yan 2018[71] |
| **Vitamin D** | | | | Hau 2018[121] Penna 2005[117] Gregori 2001[119] |
| • Murine study on psoriasiform inflammation using a vitamin D3 analogue (maxacalcitol) | | | | |
| • In vitro study on dendritic cell-mediated induction of Tregs | | | | |
| • Murine transplantation model (in combination with mycophenolate mofetil) | | | | |
| **Retinoids** | | | | Mucida 2007[122] Elias 2008[123] |
| • In vitro induction of Tregs | | | | |
| • Murine study | | | | |
| **Phototherapy** | | | | Furushashi 2013[73] Kubo 2017[124] |
| • Clinical studies on circulating Tregs in patients with psoriasis vulgaris, psoriatic arthritis and psoriatic erythroderma | | | | |
| **Pan-protein kinase C inhibitor (sotrastaurin)** | | | | He 2014[125] |
| • In vitro study on circulating PBMCs from patients with psoriasis vulgaris and skin biopsies of healthy individuals | | | | Shimizu 2019[112] Gu 2017[126] |
| **Anti-IL-17A (secukinumab)** | | | | Yang 2016[86] Shimizu 2019[112] Kannan 2019[127] |
| • Murine study of psoriasiform inflammation | | | | |
| • Murine study on allergic rhinitis | | | | |
| **Anti-IL-23 (guselkumab, ustekinumab)** | | | | |
| • In vitro study on circulating PBMCs from patients with psoriasis vulgaris | | | | |
| • Murine studies of psoriasiform inflammation | | | | |

Foxp3, Forkhead box P3; IFN, interferon; IL, interleukin; mRNA, messenger RNA; PBMC, peripheral blood mononuclear cell; Th, T-helper; TNF, tumour necrosis factor; Treg, regulatory T cell
constitutively express the high-affinity IL-2 receptor. However, as IL-2 acts on a broad range of cells, potential side-effects include eosinophilia and an increase in NK cell numbers. To reduce side-effects, the generation of a mutated IL-2 molecule allows activation in a CD25-dependent manner. In a recent phase I–IIa study, patients with a variety of autoimmune diseases were treated with low-dose IL-2. Patients across all diseases, including patients with psoriasis, showed increased Treg frequencies and improved body surface area and PASI scores.

Thus, in the setting of psoriasis, it is plausible to utilize low-dose IL-2 therapy in combination with a therapy that restores Treg functions, e.g. sotrastaurin or phototherapy, to tip the immune balance back towards equilibrium.

Epigenetic programming is crucial for Treg lineage stability and functionality. In patients with psoriasis, HDAC-1 is increased in psoriatic tissue and the histone/protein deacetylase inhibitor Trichostatin A has been shown to block Treg plasticity towards an IL-17 phenotype in vitro. These findings suggest a potential benefit of HDAC inhibitors in the treatment of psoriasis. This is emphasized by HDAC inhibitors increasing Foxp3 expression as well as production and suppressive function of Tregs in mouse models.

In line with the effects of HDAC inhibitors, Schwarz et al. demonstrated a histone acetylation-dependent upregulation of Foxp3 and IL-10 as well as enhanced numbers of skin Tregs on topical treatment or subcutaneous injection of sodium butyrate in a contact-hypersensitivity mouse model. Based on this report, short-chain fatty acids may also have therapeutic potential for the treatment of psoriasis. It further accentuates the importance of the skin lipid profile generated by commensal bacteria in skin immune homeostasis, and that modulating skin lipid profiles may present a viable target for treatment.

Another potential target for psoriasis treatment is the pro-inflammatory cytokine IL-6, which has been shown to impair the suppressive function of Tregs and is upregulated in non-sional and lesional skin of patients with psoriasis. In vitro and murine studies show that IL-6 inhibits the induction of Tregs while favouring a Th17 phenotype, thus promoting inflammation. In rheumatoid arthritis, anti-IL-6 receptor antibodies (tocilizumab) have shown clinical effectiveness and decreased the percentage of Th17 cells while increasing Treg frequency. Such a restoration of the Th17/Treg balance may also prove beneficial for psoriasis where the Th17/Treg balance is similarly disturbed.

Lastly, the first T-cell-based cellular therapies, treating haematological malignancies, have been approved recently. Although these therapies are costly and bear certain risks, Treg-based cell therapies may possess the potential to improve psoriasis pathogenesis by rebalancing the Th17/Treg ratio and suppressing inflammatory T-cell subsets.

**Conclusion and future perspectives**

Recent publications suggest an indispensable role of Tregs in psoriasis. Although the relevance of Treg frequencies remains unclear, attenuated Treg function and disturbed Th17/Treg balance are established in the pathogenesis and exacerbation of psoriasis. Discrepancies in available data, particularly seen in studies on Treg frequencies, not only stem from differences in disease subtypes and sites studied, but also highlight the technological advance over past decades, such as the development of high-dimensional techniques to define Tregs, and thus studies are not always comparable.

While skin Tregs are known to respond to self and nonself antigens, knowledge on specific antigens is lacking. One example is that the recognition of antigens derived from Candida albicans may not only be MHC class II-dependent but also partially depend on CD1a. This raises the possibility of unconventional Treg populations recognizing relatively non-polymorphic human leukocyte antigen-like molecules. Sequencing of the TCR β-chain further suggests that skin memory Tregs and skin memory CD4+ conventional T cells may recognize predominantly different antigens.

Novel high-dimensional technologies, such as single-cell RNA sequencing, have the potential to delineate Treg subsets and inform about TCR repertoires. Knowledge of skin-specific Treg-TCRs, and their diversity in healthy and psoriatic skin, would open up many possibilities, including the identification of specific antigens and the utilization of these TCRs or TCR-transduced cells for therapeutics. The use of chimeric antigen receptor-Tregs has shown promising results in preclinical models of transplantation and autoimmune diseases and may have therapeutic potential, particularly where extracellular targets are relevant.

The restoration of Treg function may have a broad impact on psoriasis pathogenesis. Many treatments influence Treg frequency and, more importantly, functionality. Further study into the underlying mechanisms of Treg dysfunction and the effectiveness of treatments targeting Tregs are required. Such studies will facilitate the utilization of existing therapies and identify new targets for future therapeutics.

**Acknowledgments**

We thank Koshika Yadava for helpful discussions on the manuscript.

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