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Regulatory T cells in inflammatory skin disease: from mice to humans

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Abstract

The skin is the largest organ in the body and one of the primary barriers to the environment. In order to optimally protect the host, the skin is home to numerous immune cell subsets that interact with each other and other non-immune cells to maintain organ integrity and function. Regulatory T cells (Tregs) are one of the largest immune cell subsets in skin. They play a critical role in regulating inflammation and facilitating organ repair. In doing so, they adopt unique and specialized tissue-specific functions. In this review, we compare and contrast the role of Tregs in cutaneous immune disorders from mice and humans, with a specific focus on scleroderma, alopecia areata, atopic dermatitis, cutaneous lupus erythematosus and psoriasis.

Keywords: immune regulation, skin repair, tolerance, Treg therapies, Tregs

Introduction

The immune system is constantly engaging with the outside environment. In order to prevent and contain life-threatening infections, it must recognize foreign pathogens, mount productive responses and react more vigorously when attacks are repeated. It has become increasingly appreciated that an equally important function of the immune system is to regulate inflammation. The 'regulatory arm' serves to limit collateral damage in the face of exuberant and fulminant immune responses. Thus, the stimulatory and regulatory arms of the immune system have co-evolved to efficiently fight infection in tissues while maintaining organ integrity and function. When this delicate balance is disrupted, the result is recurrent infections, chronic tissue inflammation or both.

Regulatory T cells (Tregs) are loosely defined by high expression of both Foxp3 and the high-affinity IL-2 receptor (1, 2). It was first shown that transfer of splenocytes depleted of $CD4^+CD25^{high}$ cells into athymic nude mice resulted in pronounced tissue inflammation. Co-transfer with $CD25^+CD4^+$ T cells prevented this phenotype (2). Soon after, it was discovered that Scurfy mice, which develop severe spontaneous autoimmunity, have a mutation in the *Foxp3* gene (3), and mutations in human *FOXP3* were shown to be responsible for the IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, a disease similar to that seen in Scurfy mice (3–5).

The similarities between the phenotype of patients with the IPEX syndrome and Scurfy mice led several groups to functionally interrogate the role of Foxp3 in the immune system. This transcription factor was shown to be essential for Treg development, maintenance and function (1, 6), and selective ablation of Tregs by targeting *Foxp3* resulted in lethal systemic inflammation (7). These studies and many others firmly establish a critical role for $CD4^+CD25^+Foxp3^+$ Tregs in establishing and maintaining immune regulation in both mice and humans.

Although the importance of Tregs in maintaining immune homeostasis is now well accepted, exactly how these cells function remains an active area of investigation. Initially thought to be a homogenous cell lineage predominantly residing in primary and secondary lymphoid organs, Tregs have emerged as a largely diverse, dynamic and adaptable population, that stably reside in both lymphoid and non-lymphoid tissues (8). In recent years, it has become increasingly appreciated that Tregs establish and maintain immune homeostasis in a tissue-specific manner (9). That is, Tregs residing in different tissues utilize different mechanisms that are dependent to a large extent on the tissues themselves and the nature of the inflammation to which each tissue is predisposed.

Currently, we are only beginning to fully understand the biology of Tregs in tissues. In this review, we focus on how Tregs regulate immune responses in skin. We discuss the unique phenotype of Tregs in this tissue and their association with cutaneous autoimmune and chronic inflammatory skin diseases.

Overview of Tregs in skin

In both mice and humans, Tregs constitute between 20 and 80% of $CD4^+$ T cells in skin at steady-state. These cells accumulate in skin during a defined window of neonatal life (10). In skin, both Tregs and commensal bacteria localize to hair follicles (HFs) (11, 12) and the frequency of Tregs fluctuates with the HF cycle. These cells also are quantitatively reduced in skin of germ-free mice (11).

HF epithelial cells express the chemokine CCL20, which plays a role in driving CCR6-expressing Tregs to accumulate in skin during neonatal life (13). Interestingly, CCL20 expression is reduced in HF epithelium in germ-free mice but expression is increased in human fetal skin explants upon exposure to commensal bacteria (13). These results suggest that HFs and skin commensal bacteria help establish Tregs in skin early in life.

Tregs circulating in peripheral blood express several other skin-homing receptors. Peripheral blood of healthy humans contains a large percentage of Tregs that express a carbohydrate modification of P-selectin glycoprotein ligand-1 (Psgl-1) called cutaneous lymphocyte antigen (CLA) and the skin-homing receptor CCR6 (14, 15). Similar to circulating Tregs in humans, Tregs in murine spleen express Psgl-1 that facilitates Treg homing to inflamed skin (16). Another skin-homing receptor is CCR4 (17). The ligands for CCR4 are CCL17 and CCL22 which are expressed by dermal endothelial cells and myeloid cells, respectively (18, 19). CCR4 deficiency confers a competitive disadvantage for Tregs to accumulate in skin and lungs of mice (20). Finally, ~80% of Tregs in murine skin express the master transcription factor for the T-helper 2 (T_H2) subset, Gata3 (21). Whether Gata3 expression influences chemokine-receptor expression that enables Tregs to effectively migrate to or within skin is currently unknown.

Taken together, both mouse and human studies support the notion that Tregs migrate to skin via expression of unique chemokine receptors and this process is influenced by HF biology and commensal microbes. Whether these processes play a role in human skin and if alterations in these pathways contribute to human skin disease remain to be determined.

Tregs in scleroderma

Diffuse systemic scleroderma (SSc) is an autoimmune disorder characterized by excessive fibrosis in barrier tissues such as skin, gut and lungs [reviewed in (22)]. Interestingly, these are the non-lymphoid organs that house the majority of the body's Tregs in the steady-state (9). A critical event in the development of skin fibrosis is the aberrant activation of fibroblasts (23). Pathologic fibrosis is thought to be very similar to wound healing, occurring in three phases: initiation, inflammatory and fibrotic (23). Following an injury, a reparative inflammatory response is activated, which in turn leads to the differentiation of resting fibroblasts to extracellular matrix (ECM) component-producing myofibroblasts (24). Excess deposition of ECM components such a collagen and fibronectin eventually leads to fibrosis (25, 26).

The major immune cells that have been studied in the context of fibrosis are T_H2 cells and macrophages. In addition, the cytokine TGF-β (transforming growth factor β) is well established to play a central role in augmenting fibroblast activation and ECM deposition (27, 28). T_H2 cytokines such as interleukin 13 (IL-13) and IL-4 can drive the differentiation and proliferation of fibroblasts (29, 30). The role of Tregs in tissue fibrosis has been controversial. In specific contexts, Tregs can express TGF-β and, in other contexts, they suppress T_H2 immune responses, rendering them with the potential to both augment and inhibit fibroblast activation (22). These seemingly opposing actions of Tregs on fibroblast biology have yet to be fully resolved.

Several observational studies in humans have found decreased frequencies of Tregs in peripheral blood of SSc patients when compared with healthy controls and other cutaneous autoimmune diseases (31, 32). Some studies have also reported increased frequencies of Tregs in both peripheral blood and skin lesions during the inflammatory and fibrotic phases of disease (33–35). However, these Tregs were shown to be dysfunctional and had reduced suppressive capacity (36).

The few studies that have examined Tregs in peripheral tissues affected in SSc have been similarly confounding. Fewer Tregs were observed in SSc skin compared with healthy or psoriatic skin lesions and this decrease was associated with a reduction in TGF-β and IL-10 (31). In contrast, a later study showed increased Tregs in the epidermis and dermis of patients with early stage SSc when compared with skin from late-stage SSc patients and healthy controls (37). Additionally, one study that examined Tregs from blood and skin of limited and diffuse SSc patients found that Tregs in skin lesions produced pro-fibrotic T_H2 cytokines like IL-13 and IL-4 (38). Thus, these dysfunctional Tregs could contribute to maintenance or exacerbation of disease. Finally, a study analyzing Tregs in skin lesions of SSc patients found reduced Tregs in the tissue but not in peripheral blood (32).

Overall, these studies correlate quantitatively reduced and/or qualitatively dysfunctional Tregs with SSc; however, consensus and definitive data are lacking. This may be secondary to the methodology used to study these cells, as immunohistochemical or immunofluorescent staining for Foxp3 and CD4 are relatively non-specific markers for Tregs in human tissues (39–41). In addition, human SSc is most likely a highly heterogeneous disease and Tregs may play different roles in different disease subtypes.

Although the literature regarding Tregs in scleroderma warrants further elucidation, there are several clinical results suggesting that Treg augmentation may be a viable therapy for SSc. In a recent clinical trial, patients suffering from chronic graft-versus-host disease (GVHD) were treated with low-dose IL-2 to preferentially boost Tregs. Clinical manifestations of specific subtypes of chronic GVHD closely resemble that of scleroderma. Augmenting Tregs led to a decrease in skin fibrosis in some patients in these studies (42, 43). Interestingly, enhanced Treg engraftment and increased Treg numbers correlated with reduced skin fibrosis in SSc patients undergoing autologous hematopoietic stem cell transplantation to treat this disease (44). Taken together, these findings suggest that Tregs may play a significant role in reducing or even reversing tissue fibrosis in humans.

Tregs in alopecia areata

In mice, Tregs localize to the bulge region of the HF and their frequency in skin is tightly correlated with the HF cycle (11, 45). There is increased accumulation of Tregs during the telogen (resting) phase of HF cycle and they decrease during the anagen (growth) phase. Tregs are in close proximity with HF stem cells (HFSCs) and play a major role in facilitating the telogen to anagen transition, a process mediated by HFSCs (11, 45). A subset of Tregs expresses the notch ligand Jag1, and this pathway plays a role in the activation and differentiation of HFSCs in mice (11). Similarly, in human skin, Tregs localize around the HF bulge and the relative percentage of these cells is increased in skin with higher hair density (12).

Several studies have implicated Tregs in the pathogenesis of alopecia areata (AA), a relatively common autoimmune disease that is characterized by an arrest in HF cycling induced by excessive pro-inflammatory cytokine production [reviewed in (46)]. Genome-wide association studies (GWAS) in AA have revealed single-nucleotide polymorphisms in regions encoding Treg signature genes such as CD25, the ikaros family member Eos (IKZF4), cytotoxic T-lymphocyte antigen 4 (CTLA-4) and Foxp3 (47, 48). Compared with healthy controls, there is markedly reduced frequency of Tregs around the HF in AA skin (49). Clinically, Treg augmentation with low-dose IL-2 administration has been used as a therapy for AA patients resistant to conventional treatments. Following an increase in Treg frequency, successful hair regeneration was achieved in 80% of the patients undergoing this therapy, although this study only included five patients (50).

Taken together, studies from mice and humans provide multiple levels of evidence implicating Tregs in HF biology, AA pathogenesis and a novel potential avenue of therapy for this disease. However, the underlying mechanisms that render Tregs dysfunctional in AA patients and why/how this appears to be restricted to the skin are currently unknown.

Tregs in atopic dermatitis

Atopic dermatitis (AD) is a prevalent inflammatory skin disease that can affect both children and adults. It results from abnormalities in the epidermal barrier and associated chronic aberrant cutaneous inflammation. T_H2 cells and type 2 cytokines (e.g. IL-4 and IL-13) play a major role in disease pathogenesis (51, 52).

Tregs have been shown to attenuate skin inflammation in several mouse models of AD (53–55); however, their role in human AD is less clear. A recent study showed that retinoic acid receptor-related orphan receptor α (RORα)-expressing Tregs in skin were important in suppressing type 2 cytokines from type 2 innate lymphoid cells (ILC2s) in a model of AD (55). Another study showed that IL-4 production from ILC2s blocks the function of Tregs to promote food allergy (56). Finally, the introduction of a specific mutation in the *Foxp3* locus in mice that is identical to a mutation found in humans results in uncontrolled T_H2 responses, T_H2 cytokine production from Tregs and pronounced skin and lung inflammation, similar to that seen in IPEX patients harboring this mutation (57). Thus, in mouse models, a consensus is emerging that Tregs suppress type 2 inflammation in skin to prevent or attenuate allergic responses and AD-like disease.

The strongest evidence in humans that Treg dysfunction predisposes to the development of AD comes from patients with the IPEX syndrome. These patients have dysfunctional Tregs because of mutations in the *FOXP3* gene (4) and suffer from autoimmune enteropathy, anemia and polyendocrinopathy as well as spontaneous severe allergic disorders such as food allergy and allergic airway disease (5, 58). Strikingly, the major skin manifestation in IPEX patients is an eczematous dermatitis that closely resembles severe AD (59).

The role of Tregs in AD that is not associated with the IPEX syndrome is, however, less clear. Several studies have shown an increase in Tregs in blood from AD patients (60, 61) and others have shown that these cells produce T_H2 cytokines, potentially contributing to disease progression instead of regulating inflammation (62). Because activated T effector cells (Teff cells, i.e. non-Tregs) transiently express Foxp3, it is unclear if the T cells that produce T_H2 cytokines, as observed in AD patients, are bona fide Tregs. Comprehensive phenotypic and mechanistic studies interrogating Tregs in AD skin during flares and remission are necessary to better illuminate the role of Tregs in this disease.

Tregs in cutaneous lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease that commonly affects the skin, in which case it is termed cutaneous lupus erythematosus (63). Although the exact etiology is unclear, SLE is strongly associated with autoantibody production, some of which is directed toward antigens that are widely expressed in skin (64).

As in most autoimmune diseases, Tregs have been implicated in the pathogenesis of SLE; however, many mouse models of SLE do not have overt skin manifestations. The NZB × NZW F1 strain is a common model to study SLE-like disease in mice (65–67). These animals spontaneously develop lupus-like symptoms such as lymphadenopathy, splenomegaly, circulating anti-dsDNA autoantibodies and glomerulonephritis but no skin pathology. Compared with nonautoimmune BALB/c mice, (NZB × NZW) F1 mice have a reduced frequency of Tregs throughout their life (68–70).

Because sun exposure is thought to play a major role in driving the skin pathology in patients with SLE (71), it is interesting to speculate that (NZB × NZW) F1 mice do not develop skin disease because they have never been exposed to sunlight. However, skin pathology is observed in the MRL/MPJ-lpr/lpr (MRL/lpr) mouse strain, another common model of spontaneous SLE (67). These mice carry a loss-of-function mutation in the Fas-receptor gene and develop skin lesions (72). After an initial increase in Treg frequencies, there is a rapid decline in Tregs in the MRL/lpr mice with age and this decline follows a concomitant development of SLE symptoms with a sharp increase in Teff cells (73, 74).

Currently, it is unknown why some mouse models of SLE develop cutaneous manifestations, whereas others do not. However, overall, the majority of studies in these strains suggest that disease development is not due to an inherent defect in Tregs, but an imbalance between Teff cells and Tregs in diseased tissues.

IL-2 production is compromised and expression of the high-affinity IL-2-receptor α-chain (CD25) is lower on T cells in SLE patients (75). This is consistent with genetic polymorphisms in the IL-2 pathway associated with SLE (76). Because IL-2 is essential for Treg development, maintenance and function, it is possible that this defect leads to an imbalance between Teff cells and Tregs in some patients with SLE. Consistent with this, Tregs have been shown to be both quantitively and qualitatively defective in peripheral blood of patients with active SLE (77, 78). However, like most studies attempting to quantify Tregs in the peripheral blood of patients with autoimmune diseases, there have been conflicting reports. A number of studies show reduced Treg frequencies in SLE (77, 78), few suggest no change (79) and others have shown increased Tregs (80).

These seemingly conflicting results may be secondary to differing methodologies and/or how Tregs are defined in each study. However, it is most likely that this is secondary to the fact that SLE is a highly heterogenous disease and that defects in Tregs may only play a role in a subset of these patients. It is currently unknown whether SLE patients who harbor defects in the IL-2 pathway and/or reduced Treg to Teff cell ratios have an increased propensity to develop skin manifestations.

As deficiency in IL-2 production is thought to contribute to SLE, several clinical trials are underway to improve disease outcome with low-dose IL-2 therapy. In one small clinical trial, low-dose IL-2 treatment led to a 40% increase in Tregs with a marked amelioration of skin eruptions, myositis and arthritis. In addition, the serum anti-dsDNA antibody titer was decreased after four cycles of treatment (81, 82). Thus, augmenting Tregs through the IL-2 pathway may be a promising approach to treat specific subsets of SLE patients.

Another approach that is being considered is adoptive Treg cell therapy. Here, Tregs are isolated from the peripheral blood of patients with autoimmune disease, expanded to high numbers *ex vivo* and these highly activated cells are adoptively transferred back to the same patient. Interestingly, this approach has recently been attempted in an SLE patient with cutaneous manifestations (83). This patient maintained stable disease throughout the 24-week follow-up period with no clinical flares. Mechanistic studies performed on skin showed a stable increase in activated Tregs, with an associated reduction in the interferon γ (IFN-γ) pathway and an increase in the IL-17 pathway. The significance and reproducibility of these findings are currently unknown, given that only one patient completed the trial. However, this is the first evidence that adoptive Treg therapy may stably alter the inflammatory milieu in diseased tissues of patients with SLE.

Tregs in psoriasis

Psoriasis is a common inflammatory skin disease characterized by hyper-proliferation of keratinocytes and a pronounced infiltrate of immune cells (84). It is well established from studies in mice and humans that the IL-23/IL-17 axis of inflammation plays a dominant role in this disease (85–87). In mice, topical application of Imiquimod (IMQ), a Toll-like receptor 7 (TLR7)/TLR8 ligand, leads to psoriasis-like skin inflammation that recapitulates some elements of the human disease (85). In this model, Tregs can restrain skin inflammation (88). IMQ treatment results in a significant increase in Treg frequency compared with untreated mouse skin, as seen in human psoriasis (88). Treg accumulation is important for disease resolution, as Treg depletion after IMQ treatment results in exacerbated skin inflammation (88). Treatment with the vitamin D3 analog, maxacalcitol, reduced IMQ-induced psoriasiform skin inflammation by inducing Tregs, which was concomitant with a reduction in IL-17/IL-23 production (89). Taken together, these and other studies suggest that Tregs play a role in attenuating psoriasiform skin inflammation in mice.

Studies in adult and pediatric psoriasis patients reveal an imbalance between Tregs and T_H17 cells (90). Although both cell types are increased, the ratio of T_H17 cells to Tregs is higher in both blood and skin of patients with psoriasis (91). Additionally, Tregs isolated from psoriatic plaques are unable to suppress T_H17 responses (86). A recent study analyzed psoriatic plaques from different anatomical locations to understand the molecular differences between scalp, palmoplantar and conventional plaque psoriasis (92). This analysis revealed an increase in Tregs across all psoriatic subtypes, but there were distinct differences in IL-17, IL-22 and IFN-γ production (92).

Thus, although Treg numbers are increased in psoriatic skin lesions, they are clearly not capable of resolving inflammation. To this end, it has been proposed that instead of being able to suppress immune responses, Tregs in psoriatic skin actually contribute to the pathogenesis of the disease (93). Several studies have revealed that subsets of Tregs in skin of psoriasis patients produce IL-17-family cytokines (93–96). Interestingly, Tregs and T_H17 cells are closely related, with similar ontogenies and transcriptional profiles (97).

High expression of the TNF-receptor superfamily members, CD27 and OX40, on Tregs in skin plays a role in suppressing Treg differentiation toward T_H17 cells (98). Tregs that lack CD27 and OX40 expression have high levels of IL-17A as well as the T_H17 master transcription factor RORγt. Furthermore, in skin of psoriasis patients, CD27 expression on Tregs inversely correlates with IL-17A production from these cells (98). A similar finding was observed in skin of patients with hidradenitis suppurativa, a skin disease that is also associated with exuberant T_H17-mediated inflammation (99, 100).

Taken together, these studies implicate Tregs in the pathogenesis of psoriasis; however, a comprehensive analysis of the extent to which these cells are dysfunctional in the skin of these patients has yet to be reported.

Concluding remarks and future directions

Tregs clearly establish and maintain immune homeostasis in both murine and human tissues. Quantitative and/or qualitative defects in these cells have been implicated in the pathogenesis of several autoimmune diseases. Pharmacologic Treg augmentation and adoptive Treg therapy are exciting new approaches to treat these disorders. Given the diversity of functions that Tregs perform and the overall heterogeneity of this immune cell subset, it would appear that we have only scratched the surface in elucidating the molecular pathways that we can target to functionally manipulate these cells for therapeutic benefit.

However, a deeper understanding of how Tregs function in human tissues is important and necessary. Many of the mechanistic studies focusing on the function of these cells in skin have been performed in mice. Although these results are informative, it is worth noting that there are fundamental differences between mouse and human skin. For example, the epidermis in normal mouse skin is ~2–3 cell layers thick, whereas the epidermis in human skin is ~4–5 times this thickness. In addition, several tissue-resident immune cells that are present in mouse skin, for example dendritic epidermal T cells (DETCs) and dermal γδ T cells, are present at very low frequencies or entirely absent in human skin (101).

Mice also have fur, whereas humans do not. HF morphogenesis is quite different between mouse and human skin. The active growth phase of the HF cycle lasts only ~2–3 weeks in mice with a high degree of synchronicity, whereas HF cycling in human skin is highly asynchronous and mosaic, with the growth phase lasting several years (102).

All of these factors are likely to influence Treg biology and may play a profound role in differences observed in this cell subset between the two species. To this end, recent single-cell transcriptomic analysis comparing Tregs in murine and human skin revealed very little overlap in gene expression outside of the 'core' Treg transcriptional signature (103).

In summary, skin is a highly immunologically active organ that is home to a large percentage of the body's Tregs. Multiple lines of investigation suggest that dysfunction in these cells contributes to cutaneous autoimmunity and chronic skin inflammation in both mice and humans. A better understanding of the mechanisms utilized by Tregs in human skin will undoubtedly advance our knowledge of how and why these cells become dysfunctional in disease states, as well as enabling the development of novel targeted therapies aimed at augmenting skin Tregs to restore the immune balance in this tissue.

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