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Cutaneous autoimmunity in immunodeficiency: Central role of FOXP3 and regulatory T-cell dysfunction

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ABSTRACT

Regulatory T cells (Tregs), orchestrated by the master transcription factor FOXP3, are pivotal for maintaining immune tolerance in the skin, a complex barrier tissue constantly exposed to environmental antigens and commensal microbiota. Dysfunction of the FOXP3–Treg axis underlies a spectrum of primary immunodeficiencies (PIDs) characterized by prominent cutaneous autoimmunity, including eczematous dermatitis, erythroderma, psoriasiform lesions, and alopecia. This review synthesizes the specialized cutaneous immune microenvironment integrating keratinocytes, dendritic cells, and tissue-resident Tregs and delineates the transcriptional, epigenetic, and signaling mechanisms governing FOXP3 stability and Treg function. Particular emphasis is placed on Treg plasticity, whereby inflammatory cues drive conversion to pro-inflammatory ex-Tregs exacerbating Th17/Th2 skewing and cytokine imbalance. We examine prototypic FOXP3 mutations in IPEX syndrome alongside related Tregopathies (CTLA4, LRBA, DOCK8, STAT3 GOF, WAS), highlighting shared and distinct cutaneous phenotypes driven by microbiota dysbiosis, barrier disruption, and failed tissue repair. Mechanistic integration reveals self-amplifying inflammatory loops in the skin. Finally, we discuss the evolution of therapies from conventional immunosuppression and hematopoietic stem cell transplantation to precision strategies, including Treg adoptive transfer, CAR-Tregs, FOXP3 gene editing, cytokine biologics, and microbiome modulation. A mechanism-based, tissue-specific approach is essential to restore durable immune tolerance in FOXP3-related cutaneous immunopathology.

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Introduction

Autoimmune manifestations in primary immunodeficiencies (PIDs) constitute a well-established paradox in immunology, in which impaired host defense coexists with pathological self-reactivity due to defective immune tolerance mechanisms (1, 2). Among affected organs, the skin serves as both a physical barrier and an immunologically active interface, making it particularly susceptible to dysregulated immune responses in immunodeficient states (3, 4). Clinical observations and cohort studies consistently show that cutaneous autoimmunity, including eczematous dermatitis, psoriasiform inflammation, vitiligo, and alopecia, often presents as an early and prominent manifestation of immune dysregulation syndromes (2, 5).

The maintenance of peripheral immune tolerance is critically dependent on regulatory T cells (Tregs), a specialized subset of $CD4^+$ T lymphocytes defined by stable expression of the transcription factor FOXP3 (6, 7). Tregs suppress autoreactive immune responses through multiple coordinated mechanisms, including secretion of inhibitory cytokines such as IL-10 and TGF-β, engagement of immune checkpoint pathways such as CTLA-4, and metabolic disruption of effector T-cell function (8, 9). Beyond systemic immune regulation, Tregs exhibit tissue-adapted phenotypes that are essential for maintaining local immune homeostasis in barrier tissues, particularly in the skin (10, 11). Within the cutaneous microenvironment, Tregs regulate keratinocyte proliferation, modulate immune responses to commensal microbiota, and contribute to wound healing and tissue repair processes (11, 12).

Disruption of the FOXP3–Treg axis is a central mechanistic link between immunodeficiency and autoimmunity, particularly in tissues with continuous antigen exposure, such as the skin (7, 13). Loss-of-function mutations in FOXP3, as seen in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, cause a profound deficiency of functional Tregs and lead to severe, early-onset autoimmune disease with prominent cutaneous involvement (14, 15). Beyond complete FOXP3 deficiency, partial impairment of Treg function due to defects in pathways such as IL-2/STAT5 signaling, CTLA-4-mediated co-inhibition, or epigenetic regulation also predisposes to inflammatory and autoimmune skin diseases across multiple inborn errors of immunity (16, 17). Notably, experimental evidence indicates that Treg dysfunction involves not only quantitative deficiency but also functional instability and phenotypic plasticity, allowing conversion into pro-inflammatory effector-like cells under specific inflammatory conditions (18, 19).

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The skin microenvironment further amplifies the consequences of Treg dysfunction because it is continuously exposed to environmental antigens, commensal microbiota, and mechanical stress, all of which require tightly regulated immune responses to preserve tissue integrity (10, 20). In this context, failure of FOXP3-dependent regulatory mechanisms leads to exaggerated Th1- and Th17-mediated responses, dysregulated cytokine production, and sustained epithelial inflammation characteristic of autoimmune skin disease (21, 22). These processes are reinforced by local factors, including barrier dysfunction, microbial dysbiosis, and altered interactions between immune and non-immune skin cells such as keratinocytes and fibroblasts (23, 24). Consequently, cutaneous autoimmunity in primary immunodeficiency should be interpreted not merely as a secondary complication, but as a direct manifestation of tissue-specific failure of immune regulation (13, 25).

Despite significant advances in Treg biology and immunodermatology, current literature remains fragmented, frequently emphasizing either systemic immunological mechanisms or descriptive classifications of dermatological conditions without integrating these perspectives into a unified mechanistic framework (26, 27). Moreover, many existing reviews rely heavily on secondary sources and descriptive summaries of cytokines and disease associations, with limited critical evaluation of primary mechanistic studies, thereby reducing conceptual clarity and translational relevance (27, 28).

In this review, we adopt a focused and mechanism-driven perspective centered on the FOXP3–Treg axis as the principal determinant of cutaneous immune tolerance in primary immunodeficiency. Rather than broadly cataloging autoimmune skin diseases, we synthesize molecular, cellular, and clinical evidence to delineate how defects in Treg development, stability, and function translate into skin-specific immune pathology. We further examine how tissue-resident immune networks, cytokine environments, and microbial interactions modulate disease expression, and we discuss emerging diagnostic and therapeutic strategies targeting these pathways. By narrowing the conceptual scope and emphasizing mechanistic integration, this review aims to provide a coherent framework for understanding and managing autoimmune skin manifestations associated with immunodeficiency. These processes reflect the transition from regulatory to inflammatory states illustrated in Figure 1.

Skin immune homeostasis and the role of regulatory T cells

Skin immune regulatory environment

The skin is a highly specialized immunological niche where continuous exposure to environmental antigens requires tightly controlled immune responses to maintain tissue integrity while preventing inappropriate inflammation (4, 29). This balance is achieved through coordinated interactions between structural cells and immune populations that collectively establish a state of tissue-specific immune tolerance (12). Disruption of this equilibrium is a central driver of inflammatory and autoimmune skin disease (21).

Keratinocytes, the predominant epithelial cell type in the epidermis, are not merely structural components; they also actively regulate cutaneous immunity by sensing

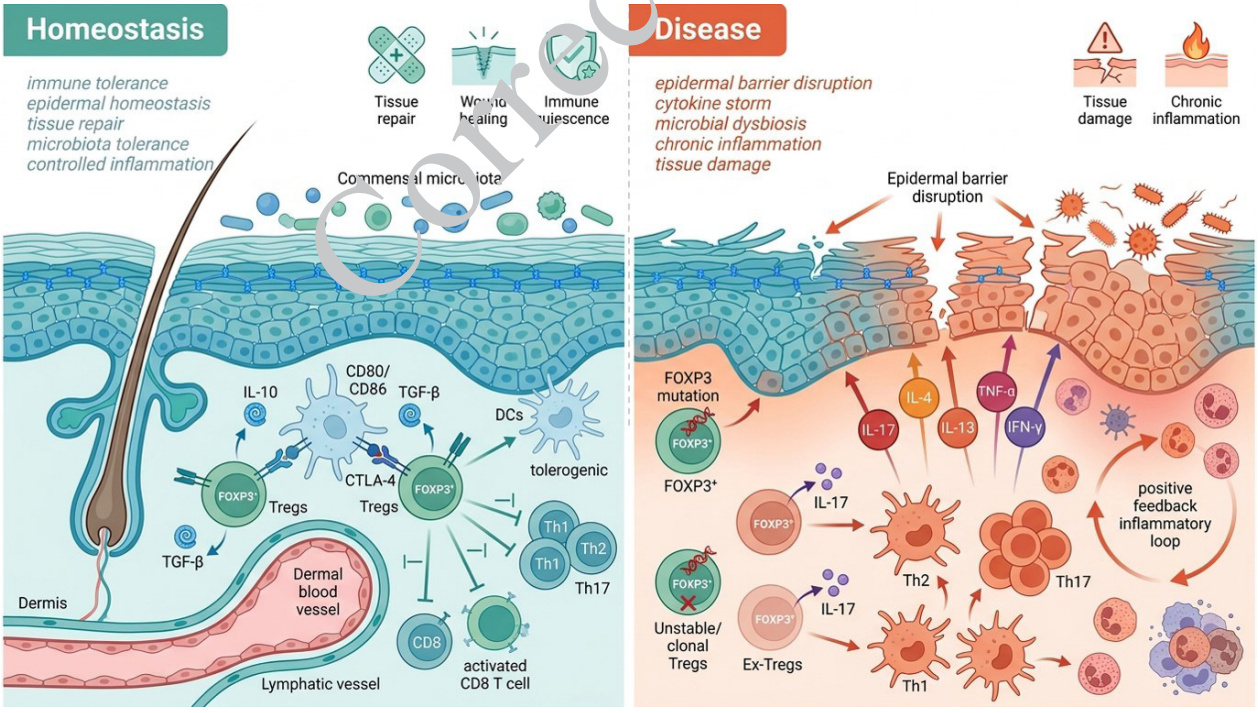


Figure 1. FOXP3-dependent regulation of cutaneous immune homeostasis and its disruption in disease

FOXP3$^+$ regulatory T cells (Tregs) retain immunological tolerance in the skin under physiological conditions by producing anti-inflammatory cytokines such as IL-10 and TGF-β, which suppress effector T-cell activation and preserve tissue homeostasis. Coordinated interactions among Tregs, dendritic cells, and keratinocytes provide a controlled immunological system that prevents excessive inflammation, preserves epidermal barrier integrity, and supports a stable commensal microbiota. Conversely, under pathological situations, mutations or instability in FOXP3 limit Treg functionality and disrupt immune control. This can cause Tregs to become dysfunctional or transform into effector-like cells (ex-Tregs) and promote the proliferation of pro-inflammatory T helper subsets, including Th17 and Th2 cells, which produce cytokines such as IL-17 and IL-4. This induces inflammation, undermines epithelial barrier integrity, leads to microbial dysbiosis, and ultimately establishes a self-perpetuating inflammatory cycle that exacerbates tissue damage and sustains chronic cutaneous immune activation

Treg, regulatory T cell; ex-Treg, former FOXP3$^+$ regulatory T cell that has lost stable FOXP3 expression and acquired effector-like characteristics

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environmental stimuli and producing immunomodulatory signals (30, 31). Upon stimulation, keratinocytes secrete a broad spectrum of cytokines and chemokines, including IL-1, IL-6, TNF-α, and thymic stromal lymphopoietin (TSLP), which orchestrate the recruitment and activation of immune cells (32, 33). In homeostatic conditions, however, keratinocytes contribute to immune tolerance by producing anti-inflammatory mediators and maintaining barrier integrity, thereby limiting excessive immune activation (34). Importantly, keratinocyte-derived signals have been shown to influence Treg recruitment and function within the skin, highlighting their role in shaping local regulatory networks (35).

Dendritic cells (DCs) constitute a second critical component of the skin immune regulatory environment, acting as professional antigen-presenting cells that bridge innate and adaptive immunity (36). Distinct subsets of cutaneous DCs, including Langerhans cells in the epidermis and dermal DCs, exhibit context-dependent functions that can either promote immune activation or induce tolerance (37, 38). Under steady-state conditions, tolerogenic DCs facilitate the induction and maintenance of $FOXP3^+$ Tregs through mechanisms involving antigen presentation in the absence of co-stimulation, as well as secretion of immunoregulatory cytokines such as IL-10 and TGF-β (39, 40). Conversely, inflammatory signals can reprogram these cells toward immunogenic phenotypes, thereby contributing to the breakdown of tolerance (41).

The skin's tissue tolerance is further reinforced by signals from the commensal microbiota, local metabolic conditions, and epithelial–immune cell interactions (23, 42). Commensal microorganisms play a fundamental role in calibrating immune responses by promoting regulatory pathways that limit inflammation while preserving antimicrobial defense (43). In parallel, local metabolic cues including nutrient availability and hypoxic gradients modulate immune cell differentiation and function, influencing the balance between effector and regulatory responses (44). Together, these factors help maintain a controlled immune environment that prevents aberrant activation against self-antigens.

Within this regulatory framework, Tregs function as central mediators of immune homeostasis by integrating signals from keratinocytes, DCs, and the microbiota to suppress excessive immune activation (6, 7). The spatial and functional organization of these interactions ensures that immune responses remain proportionate to external challenges while preserving tissue integrity. Importantly, failure of these regulatory circuits—whether due to intrinsic defects in Tregs or dysregulation of the surrounding microenvironment—results in a shift toward pro-inflammatory signaling, ultimately leading to chronic cutaneous inflammation and autoimmunity (45, 46).

Regulatory T-cell biology relevant to the skin

Tregs comprise a heterogeneous population of immunosuppressive $CD4^+$ T cells that are essential for maintaining immune tolerance across both lymphoid and non-lymphoid tissues (7, 47). Two principal subsets of Tregs have been defined based on their developmental origin: thymus-derived Tregs (tTregs), which arise during thymic selection, and peripherally induced Tregs (pTregs), which differentiate from conventional $CD4^+$ T cells in peripheral tissues under tolerogenic conditions (48, 49). These subsets are functionally complementary, with tTregs primarily responsible for enforcing central tolerance to self-antigens. At the same time, pTregs are critical for maintaining tolerance to environmental, dietary, and commensal-derived antigens encountered at barrier surfaces such as the skin (20, 23). The differentiation and maintenance of pTregs are highly dependent on local microenvironmental signals, including transforming growth factor-β (TGF-β), interleukin-2 (IL-2), and retinoic acid, which collectively promote FOXP3 expression and stabilize the regulatory phenotype (50, 51). In contrast, tTregs exhibit a more stable lineage commitment due to epigenetic imprinting at the FOXP3 locus, although their functional specialization remains influenced by peripheral cues (7, 52). Importantly, both subsets contribute to cutaneous immune homeostasis, but their relative roles may differ depending on the nature and context of antigen exposure within the skin (46). Within the skin, a distinct population of tissue-resident Tregs has been identified, characterized by unique phenotypic and functional adaptations that distinguish them from their circulating counterparts (53, 54). Skin-resident Tregs express tissue-homing receptors such as cutaneous lymphocyte antigen (CLA) and chemokine receptors including CCR4 and CCR8, which facilitate their localization and retention within the cutaneous microenvironment (55, 56). These cells are enriched in specific anatomical niches, including hair follicles, where they interact closely with epithelial stem cells and contribute to the regulation of hair cycling and tissue regeneration (46, 57). In addition to their classical immunosuppressive functions, skin-resident Tregs exhibit non-canonical roles in promoting epithelial repair, modulating fibroblast activity, and maintaining barrier integrity (10, 58).

Tissue adaptation of Tregs is a dynamic process driven by local environmental cues that shape their transcriptional and functional profiles (59, 60). In the skin, this adaptation involves the acquisition of tissue-specific transcriptional programs regulated by factors such as BATF, IRF4, and GATA3, which enable Tregs to effectively control type 1, type 2, and type 17 inflammatory responses depending on the context (61, 62). Moreover, skin-resident Tregs display metabolic adaptations that support their survival and function in a nutrient-variable and often hypoxic microenvironment, including reliance on lipid metabolism and oxidative phosphorylation (44, 63). These adaptations are essential for sustaining long-term immune regulation within the tissue. Notably, the functional stability of Tregs in peripheral tissues is not absolute and can be influenced by inflammatory signals present in the local microenvironment (19, 64). Under conditions of chronic inflammation, Tregs may undergo phenotypic reprogramming or exhibit reduced suppressive capacity, contributing to the breakdown of immune tolerance (45, 65). In the skin, this instability has been linked to increased pro-inflammatory cytokine production and impaired control of effector T-cell responses, promoting the development of autoimmune and inflammatory dermatoses (21, 22). Collectively, these findings highlight that Treg biology in the skin is defined not only by lineage origin but also by dynamic interactions with the tissue microenvironment that govern their localization, specialization, and functional stability. Disruption of these tightly regulated processes

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Table 1. Genotype–phenotype correlations between FOXP3 mutations and cutaneous manifestations in IPEX syndrome and related FOXP3-associated disorders

Mutation category	Predominantly affected FOXP3 region	Major molecular defect	Consequences for Treg biology	Remaining suppressive activity	Common cutaneous manifestations	Clinical significance	Suggested original reference
Missense variants	Primarily Forkhead (FKH), Leucine zipper (LZ), or Zinc finger domains	Amino acid substitutions impair DNA binding, cofactor recruitment, or transcriptional activity without completely abolishing protein expression	Reduced suppressive capacity, impaired lineage stability, and altered transcriptional programs	Frequently retained to a variable extent	Eczema, atopic dermatitis-like eruptions, alopecia areata, vitiligo	Clinical phenotype is heterogeneous and depends on mutation location and residual FOXP3 activity	(71)
Nonsense variants	Can occur throughout the coding sequence	Premature stop codons generate truncated proteins or induce nonsense-mediated mRNA decay	Profound impairment of Treg differentiation and regulatory function	Usually absent	Severe eczema, diffuse erythroderma, generalized dermatitis	Commonly associated with early-onset, multisystem autoimmunity characteristic of severe IPEX	(71)
Frameshift variants	Distributed across multiple coding regions	Reading-frame disruption produces unstable or nonfunctional FOXP3 protein	Severe loss of FOXP3-dependent transcriptional regulation and Treg identity	Very limited	Extensive inflammatory dermatitis, erythroderma, severe skin inflammation	Often correlates with aggressive disease course and poor immune regulation	(72)
Splice-site variants	Exon–intron junctions	Abnormal RNA splicing causes exon skipping or altered FOXP3 isoform expression	Variable defects in Treg maintenance depending on the affected transcript	Variable	Chronic eczema and heterogeneous inflammatory skin disease	Clinical manifestations are highly variable because different transcripts may be preserved	(73)
Large deletions or genomic rearrangements	Multiple functional domains	Loss of substantial coding regions abolishes essential structural and functional elements	Major impairment of Treg development, maintenance, and suppressive function	Minimal or none	Severe eczema, generalized erythroderma, extensive inflammatory skin lesions	Frequently associated with profound immune dysregulation and severe IPEX phenotype	(71)
Leucine zipper (LZ)-associated variants	Leucine zipper domain	Defective FOXP3 dimerization and impaired interaction with transcriptional partners	Failure to sustain the regulatory phenotype despite preserved protein expression	Often partially retained	Recurrent eczematous dermatitis and atopic dermatitis-like lesions	Considerable variability exists among affected individuals	(74)
Forkhead (FKH)-associated variants	Forkhead DNA-binding domain	Reduced chromatin occupancy and defective target-gene regulation	Loss of lineage stability together with markedly impaired suppressive function	Low to moderate	Eczema, psoriasis-like dermatitis, alopecia, vitiligo	Frequently associated with severe immune dysregulation owing to defective DNA binding	(74)

represents a key mechanistic pathway linking defects in the FOXP3–Treg axis to cutaneous immune pathology in immunodeficiency states. While initial studies primarily categorized Tregs based on their activation status (naïve, effector, and memory Tregs) or developmental origin (tTregs versus pTregs), recent advancements in single-cell RNA sequencing (scRNA-seq) have greatly enhanced our comprehension of Treg heterogeneity by revealing various transcriptionally and functionally distinct tissue-adapted subsets (66-68). These results indicated that tissue-resident Tregs implement distinct transcriptional programs influenced by local microenvironmental signals rather than being a homogeneous extension of circulating Tregs (66, 69). Skin-resident Tregs play a crucial role in maintaining epithelial immune homeostasis and preferentially expre[s] GATA3. In contrast, BATF serves as a pivotal transcriptional regulator governing tissue-specific Treg differentiation across multiple organs, including skin and viscer[al] adipose tissue (68). Similarly, CCR8 detects highly activated tissue-resident Tregs and facilitates their specific accumulation and retention in non-lymphoid tissues (70). Hair follicle-associated Tregs represent a distinct subset of tissue-specialized populations that directly promote hair follicle stem cell activation and tissue regeneration via local cellular interactions, while also facilitating immune suppression. (Experimental evidence primarily from murine studies). Moreover, new lineage-tracing and migration studies suggest that a dynamic equilibrium including long-lived resident cells, localized proliferative growth, and continuous replenishment from circulating precursor Tregs may maintain tissue Treg pools. This indicates that tissue residence and recirculation constitute a continuum rather than entirely separate states (68). These results indicate that Treg heterogeneity encompasses a spectrum of specialized tissue-adapted populations exhibiting distinct phenotypic, transcriptomic, and functional attributes, beyond the conventional resident-versus-circulating paradigm (Table 1)(Figure 2).

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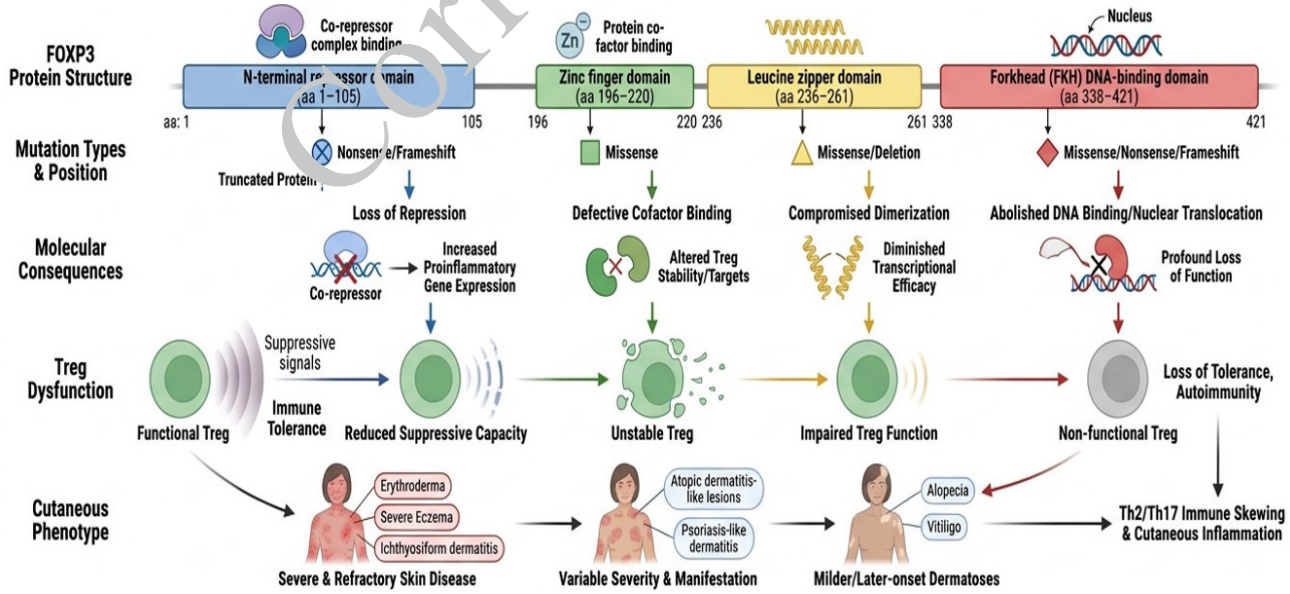


Figure 2. Genotype–phenotype relationship between FOXP3 mutation classes and cutaneous manifestations in IPEX syndrome
Diagrammatic representation of how different classes of FOXP3 mutations missense, nonsense, frameshift, splice-site, and large deletion variants affect particular functional domains of the FOXP3 protein, resulting in different levels of immune tolerance loss, regulatory T-cell stability impairment, altered suppressive activity, and transcriptional dysfunction. The correlation between these molecular deficiencies and the range and intensity of cutaneous symptoms highlights the mechanistic continuity connecting genetics, molecular dysfunction, immunological dysregulation, and clinical skin phenotype. The image also shows how residual FOXP3 activity, modifier genes, epigenetic control, and environmental factors may produce diverse dermatologic presentations within identical mutant classes

Mechanisms of Treg-mediated immune regulation

Tregs maintain immune homeostasis through a coordinated network of suppressive mechanisms that operate at cellular, molecular, and metabolic levels, enabling precise control of immune responses within both lymphoid and peripheral tissues such as the skin (6, 8). Rather than relying on a single pathway, Tregs use multiple complementary strategies, including cytokine-mediated suppression, checkpoint-dependent inhibition, and metabolic regulation, to restrain effector T-cell activity and prevent tissue damage (7, 75). The integration of these mechanisms is particularly critical in barrier tissues, where continuous antigen exposure necessitates dynamic yet tightly regulated immune responses (29).

One of the primary mechanisms of Treg-mediated suppression involves the secretion of anti-inflammatory cytokines, most notably interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and interleukin-35 (IL-35)(9, 76). IL-10 plays a central role in limiting immune activation by inhibiting antigen-presenting cell maturation and reducing pro-inflammatory cytokine production, thereby dampening downstream T-cell responses (77). TGF-β contributes to immune regulation by suppressing effector T-cell proliferation and promoting peripheral Treg differentiation, reinforcing a tolerogenic environment (50). IL-35, a more recently characterized cytokine, further enhances Treg-mediated suppression by directly inhibiting effector T-cell expansion and inducing regulatory phenotypes in conventional T cells (78). In the skin, these cytokine-mediated effects are essential for controlling inflammation induced by commensal microbes and environmental stimuli (23). In addition to soluble mediators, Tregs exert potent immunosuppressive effects through checkpoint signaling pathways that directly modulate the function of antigen-presenting cells and effector T cells (8, 79). Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), constitutively expressed on Tregs, plays a pivotal role by competitively binding to CD80/CD86 on DCs, thereby limiting co-stimulatory signaling required for T-cell activation (80). This interaction can also lead to trans-endocytosis of co-stimulatory molecules from antigen-presenting cells, effectively reducing their immunogenic capacity (81). Additional checkpoint molecules, including PD-1 and LAG-3, contribute to Treg function by attenuating T-cell receptor signaling and promoting a state of functional exhaustion in effector T cells (82, 83). These pathways are particularly relevant in the skin, where local antigen presentation must be tightly regulated to prevent chronic inflammation.

Metabolic control represents a third major axis of Treg-mediated immune regulation, reflecting the critical role of cellular metabolism in shaping immune responses (44, 63). Tregs modulate the metabolic environment through several mechanisms, including high expression of the IL-2 receptor α-chain (CD25), which enables efficient consumption of IL-2 and deprives effector T cells of this essential growth factor (84). Additionally, Tregs express ectoenzymes such as CD39 and CD73, which catalyze the conversion of extracellular ATP into adenosine, a potent immunosuppressive metabolite that inhibits effector T-cell activation via adenosine receptor signaling (85). Tregs also exhibit distinct metabolic programs characterized by preferential reliance on oxidative phosphorylation and lipid metabolism, which support their survival and function in low-glucose or hypoxic environments such as inflamed tissues (86, 87). These metabolic adaptations not only sustain Treg activity but also help suppress competing effector T-cell responses.

Importantly, these suppressive mechanisms do not operate in isolation but are dynamically coordinated in response to environmental cues within the tissue microenvironment (88, 89). In the skin, the integration of cytokine signaling, checkpoint interactions, and metabolic regulation enables Tregs to maintain a delicate balance between immune tolerance and protective immunity (10). Disruption of any of these pathways, whether through genetic defects, inflammatory signaling, or environmental perturbations, can impair Treg function and lead to uncontrolled immune activation, thereby contributing to the development of autoimmune and inflammatory skin diseases (21, 90). Collectively, Treg-mediated immune regulation is a multifaceted process that integrates soluble mediators, cell–cell interactions, and metabolic control to enforce immune tolerance. Understanding how these mechanisms operate within the skin provides critical insight into the pathogenesis of cutaneous autoimmunity in conditions characterized by FOXP3 dysfunction and Treg instability.

Skin-specific interactions

Beyond their canonical immunosuppressive functions, Tregs participate directly in tissue-specific processes in the skin, where they help regulate epithelial stem cell activity, tissue regeneration, and repair (10, 58). These non-classical roles highlight the integration of immune regulation with tissue homeostasis and underscore the importance of Tregs as multifunctional mediators in barrier organs (46). In the skin, such interactions are particularly evident within specialized microenvironments, including the hair follicle niche, sites of tissue injury, and areas undergoing epithelial remodeling.

The hair follicle represents a key immunological niche in which Tregs accumulate and exert localized regulatory functions that extend beyond immune suppression (35, 54). Skin-resident Tregs are highly enriched around hair follicles, where they interact with epithelial stem cells and regulate hair follicle cycling (57). Experimental studies show that Tregs promote hair follicle stem cell activation and differentiation through Jagged1-mediated Notch signaling, facilitating hair regeneration (91) (Animal evidence). This interaction reflects a direct crosstalk between immune cells and epithelial progenitors, indicating that Tregs contribute to tissue maintenance by modulating stem cell behavior rather than solely controlling inflammation (46). Disrupting Treg function within this niche has been associated with impaired hair regeneration and inflammatory hair disorders, highlighting the microenvironment's sensitivity to immune dysregulation (92).

Tregs also play a critical role in wound healing, where they regulate the inflammatory response and promote tissue repair following injury (93, 94). During the early phases of wound healing, Tregs accumulate at sites of tissue damage and limit excessive inflammation by suppressing pro-inflammatory cytokine production and controlling effector T-cell infiltration (95). This regulation is essential to prevent chronic inflammation, which can impair healing and lead

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to tissue damage (96). Beyond immunosuppression, Tregs contribute to repair by producing growth factors such as amphiregulin, which supports epithelial cell proliferation and tissue regeneration (*predominantly animal evidence)* (97). The absence or dysfunction of Tregs has been shown to delay wound closure and exacerbate inflammatory responses, underscoring their dual role in immune regulation and tissue repair (98). Epithelial repair and barrier restoration are further influenced by Treg-mediated interactions with keratinocytes and other structural cells of the skin (30, 31). Tregs can modulate keratinocyte differentiation and proliferation, thereby helping re-establish epidermal integrity after injury or inflammation (10). In addition, Treg-derived cytokines such as IL-10 and TGF-β promote anti-inflammatory signaling pathways in epithelial cells, facilitating inflammation resolution and restoration of tissue homeostasis (77). These interactions are particularly important in conditions characterized by barrier dysfunction, where impaired Treg activity can lead to persistent inflammation and defective tissue repair (34).

Importantly, the tissue-supportive functions of Tregs are tightly linked to their ability to adapt to local environmental cues within the skin microenvironment (88, 89). Signals derived from epithelial cells, commensal microbiota, and inflammatory mediators collectively shape Treg phenotype and function, enabling context-dependent responses that integrate immune regulation with tissue maintenance (42). However, under conditions of chronic inflammation or genetic defects affecting FOXP3 function, these adaptive processes may be disrupted, resulting in impaired tissue repair, aberrant epithelial responses, and sustained inflammation (21, 90). Collectively, these observations show that Tregs are integral to skin homeostasis not only by suppressing immune responses but also by directly participating in tissue regeneration and repair. The integration of immunological and tissue-specific functions positions Tregs as key regulators of the balance between inflammation and regeneration in the skin, and disruption of these processes represents a critical mechanism underlying cutaneous pathology in immunodeficiency states.

FOXP3 as the molecular controller of cutaneous immune tolerance

FOXP3 structure and transcriptional regulation

FOXP3 (Forkhead box P3) is the lineage-defining transcription factor of Tregs and functions as a master regulator of immune tolerance by orchestrating transcriptional programs that suppress effector immune responses (6, 7). Structurally, FOXP3 belongs to the forkhead/winged-helix family of transcription factors and contains several functional domains, including an N-terminal proline-rich repressor domain, a central zinc-finger and leucine-zipper domain involved in protein–protein interactions, and a C-terminal forkhead domain responsible for DNA binding (99-101). These domains enable FOXP3 to act both as a transcriptional activator and repressor through the formation of multi-protein complexes that modulate gene expression in Tregs (102). The transcriptional activity of FOXP3 is highly dependent on its interaction with a diverse set of cofactors that collectively define the regulatory T-cell transcriptional landscape (99, 103). FOXP3 associates with transcription factors such as NFAT, Runx1, and STAT5 to regulate genes involved in immune suppression, including CTLA4, IL2RA (CD25), and TIGIT, while simultaneously repressing genes associated with effector T-cell function such as IL-2 and IFN-γ (13, 104, 105). These interactions allow FOXP3 to integrate signals from T-cell receptor (TCR) activation and cytokine pathways, thereby dynamically modulating Treg function in response to environmental cues (106). Importantly, FOXP3 does not act in isolation but operates within a broader transcriptional network that determines the identity and functional specialization of Tregs in different tissue contexts (88).

FOXP3 expression is tightly regulated at the transcriptional level by signaling pathways that are essential for Treg development and maintenance (107, 108). Among these, IL-2–mediated STAT5 activation plays a central role in inducing and sustaining FOXP3 expression, particularly in peripheral Tregs (108, 109). TCR signaling strength and co-stimulatory signals also influence FOXP3 induction, with intermediate levels of stimulation favoring Treg differentiation over effector T-cell development (110). In addition, transforming growth factor-β (TGF-β) signaling contributes to FOXP3 induction in peripheral tissues, linking environmental cues to the establishment of regulatory programs (50). These regulatory inputs collectively ensure that FOXP3 expression is precisely controlled in response to both intrinsic and extrinsic signals. In the skin, FOXP3-dependent transcriptional programs are further shaped by tissue-specific factors that influence Treg localization, function, and stability (10, 89). Local cytokine environments, microbial signals, and interactions with epithelial cells modulate FOXP3 activity, enabling Tregs to adapt to the unique immunological demands of the cutaneous microenvironment (42). Disruption of FOXP3 structure or transcriptional regulation—whether through genetic mutations or altered signaling pathways—can impair the ability of Tregs to maintain immune tolerance, leading to uncontrolled inflammation and autoimmunity in the skin (14, 111).

Epigenetic regulation and Treg stability

The stability and functional integrity of FOXP3$^+$ Tregs are critically dependent on epigenetic mechanisms that control gene expression independently of DNA sequence (52, 112). Among these, DNA methylation patterns at the FOXP3 locus play a central role in maintaining stable FOXP3 expression and preventing lineage instability (52). A key regulatory region, known as the Treg-specific demethylated region (TSDR), is fully demethylated in stable, thymus-derived Tregs, enabling sustained FOXP3 transcription even in the absence of continuous external signaling (113, 114). In contrast, incomplete demethylation of this region in peripherally induced Tregs is associated with reduced stability and increased susceptibility to phenotypic conversion (115).

Histone modifications further contribute to the epigenetic regulation of Treg identity by modulating chromatin accessibility and transcriptional activity (88). Activating histone marks, such as H3K4me3 and H3K27ac, are enriched at FOXP3 and other Treg-associated genes, facilitating transcription, whereas repressive marks such as H3K27me3 are associated with silencing of effector T-cell genes (116). These epigenetic landscapes are dynamically regulated in response to environmental signals, allowing

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Tregs to adapt their functional programs while preserving lineage identity (117). Importantly, disruptions in these epigenetic mechanisms can compromise Treg stability and lead to loss of FOXP3 expression. Epigenetic regulation also governs the plasticity of Tregs, a phenomenon whereby Tregs can acquire features of effector T cells under inflammatory conditions (90, 118). Pro-inflammatory cytokines such as IL-6 and IL-1β have been shown to destabilize FOXP3 expression and promote the conversion of Tregs into Th17-like or Th1-like cells, thereby contributing to immune dysregulation (65, 119). This plasticity is particularly relevant in the skin, where persistent inflammatory signals can alter the epigenetic landscape of Tregs and impair their suppressive function (120). Consequently, epigenetic instability represents a key mechanism linking environmental inflammation to the breakdown of immune tolerance.

Evidence for a direct lineage alteration remains ambiguous; however, IL-6 is widely recognized as a crucial factor promoting the transformation of Tregs into a Th17-like phenotype (121, 122). Evidence suggests that IL-6 does not induce a global reprogramming of fully committed Treg populations; instead, it primarily facilitates the proliferation and differentiation of a specific subset of peripherally produced, unstable Foxp3$^+$ cells (121, 123). In inflammatory environments, including IL-6, thymus-derived, lineage-stable Treg cells mostly maintain consistent Foxp3 expression, indicating that the IL-6 response is primarily confined to a varied population of cells with incomplete lineage commitment (121). Moreover, not all exFoxp3 cells exhibit a Th17-like phenotype, and some Foxp3$^+$ cells may simultaneously retain Foxp3 expression while releasing IL-17, despite the potential emergence of IL-17-producing Foxp3$^-$ cells after IL-6 exposure (121). These data undermine the reductionist hypothesis that IL-6 always converts Tregs into detrimental Th17-like cells. The data support a more complex model in which authentic Treg cells mostly preserve their lineage identity via mechanisms of epigenetic stability, such as TSDR demethylation, whereas IL-6 preferentially enhances pre-existing unstable Foxp3$^+$ populations (121, 124).

Metabolic pathways are closely intertwined with epigenetic regulation and play a significant role in maintaining Treg stability (44, 63). Cellular metabolites such as acetyl-CoA and S-adenosylmethionine serve as substrates for histone acetylation and methylation, thereby linking cellular metabolism to chromatin remodeling and gene expression (125). In Tregs, metabolic programs that favor oxidative phosphorylation and lipid metabolism support epigenetic states associated with stable FOXP3 expression, whereas shifts toward glycolytic metabolism are associated with reduced suppressive capacity and increased instability (126). These findings highlight how metabolic and epigenetic pathways integrate to control Treg function. In the context of cutaneous immunity, stable FOXP3 expression is essential for maintaining long-term immune tolerance in a tissue exposed to constant environmental challenges (20, 127). Disruption of epigenetic regulation, whether from genetic mutations, inflammatory signals, or environmental stressors, can lead to Treg instability and loss of immune control, contributing to chronic skin inflammation and autoimmune disease (90, 128). Understanding these mechanisms provides critical insight into how FOXP3 dysfunction translates into tissue-specific pathology and identifies potential therapeutic targets to restore Treg stability. Not every fate-mapping dataset has equivalent interpretative significance; nevertheless, lineage-tracing methodologies are widely used to examine Treg plasticity (129). Various fate-mapping systems used in different studies include diverse promoter-driven models, Cre recombinase-based techniques, and reporter alleles, which exhibit considerable variation in recombination efficiency, temporal resolution, and labeling fidelity (129, 130). Reporter designs have evolved from single fluorescent reporters to multicolor and genetic barcoding systems, each offering distinct lineage resolution levels. Inducible systems, such as CreERT2 and MerCreMer, exhibit varied sensitivities to tamoxifen induction (129). Moreover, the precision of lineage labeling may be compromised by inadequate or varied reporter expression, and promoter activity may be more widespread or transient than first seen (129, 131). As a result, methodological variation rather than true biological differences in Treg adaptability may explain disparities across lineage-tracing studies. Therefore, results on lineage instability and ex-Treg generation should be evaluated in light of the specific fate-mapping technique used.

Signaling pathways controlling FOXP3 function

FOXP3 activity is not static but is dynamically regulated by multiple intracellular signaling pathways that integrate environmental cues with transcriptional control of regulatory T-cell (Treg) function (7, 8). These signaling networks modulate FOXP3 expression, stability, and transcriptional activity, thereby determining Treg suppressive capacity under both homeostatic and inflammatory conditions (8). Among these pathways, IL-2/STAT5 signaling, T-cell receptor (TCR) signaling, PI3K–AKT–mTOR signaling, and NF-κB pathways represent key regulators of FOXP3 function (107, 108).

The IL-2/STAT5 axis plays a central role in both the induction and maintenance of FOXP3 expression, particularly in peripheral Tregs (100, 108). Binding of IL-2 to its high-affinity receptor activates STAT5, which directly binds to regulatory elements within the FOXP3 locus and promotes its transcription (132). Sustained IL-2 signaling is essential for maintaining Treg survival and functional stability, and disruption of this pathway leads to impaired FOXP3 expression and loss of suppressive capacity (107). In addition to transcriptional regulation, IL-2 signaling enhances the expression of key Treg-associated molecules such as CD25 and CTLA-4, reinforcing the regulatory phenotype (6). TCR signaling provides another critical input that influences FOXP3 function by modulating the activation and differentiation of T cells (106, 133). The strength and duration of TCR signaling determine the balance between effector T-cell differentiation and Treg induction, with intermediate signaling favoring FOXP3 expression (134). Downstream of TCR engagement, transcription factors such as NFAT and AP-1 cooperate with FOXP3 to regulate gene expression, linking antigen recognition to regulatory function (99). Importantly, dysregulated TCR signaling can impair FOXP3 activity and contribute to Treg instability. The PI3K–AKT–mTOR pathway exerts a critical regulatory effect on FOXP3 function by integrating metabolic and growth signals (44, 63). Activation of AKT negatively regulates FOXP3 by inhibiting the nuclear localization of

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transcription factors such as Foxo1 and Foxo3, which are required for FOXP3 expression (135, 136). Conversely, inhibition of mTOR signaling promotes Treg differentiation and stabilizes FOXP3 expression, highlighting the importance of metabolic signaling in controlling Treg fate (137). These findings demonstrate that FOXP3 activity is closely linked to cellular metabolic states, providing a mechanism by which environmental conditions influence immune regulation.

NF-κB signaling also contributes to the regulation of FOXP3 function through its role in T-cell activation and survival (138, 139). Components of the NF-κB pathway, including c-Rel, have been shown to bind to regulatory regions of the FOXP3 gene and facilitate its transcription during Treg development (140). Additionally, NF-κB signaling influences the expression of genes involved in Treg function, thereby contributing to the establishment of a stable regulatory phenotype (141). However, excessive or dysregulated NF-κB activation under inflammatory conditions can disrupt Treg function and promote immune pathology. Collectively, these signaling pathways form an interconnected network that governs FOXP3 expression and activity, enabling Tregs to respond dynamically to environmental cues. Disruption of these pathways, whether through genetic mutations or inflammatory signals, can impair FOXP3 function and lead to loss of immune tolerance, particularly in tissues such as the skin where immune regulation is tightly balanced (90, 128). Figure 3 summarizes the multi-layered regulation of FOXP3, including structural organization, transcriptional control, epigenetic stabilization, and inflammatory destabilization pathways.

The universality of Treg plasticity as a property of all Tregs remains ambiguous, despite accumulating evidence indicating considerable variability within the Foxp3$^+$ Treg subset (142-144). Available research indicates that Tregs consist of many functionally specialized subpopulations characterized by distinct transcription factors, chemokine receptors, suppressive mechanisms, and tissue-adapted phenotypes. This indicates that heterogeneity is not a consistent suppressing condition but an inherent characteristic of the lineage (142, 145). This variation remains a substantial unresolved issue, since the adaptability seen in experimental conditions may reflect only certain Treg subsets rather than the whole population. Functions involved in tissue repair, migration, inflammatory responses, or follicular control (Tfr) likely experience distinct microenvironmental cues, which may lead to differing capacities for lineage stability or phenotypic flexibility (142). Consequently, studies that broadly reference "Treg plasticity" without acknowledging this variability risk overgeneralizing findings from certain cellular subsets (142, 146). Further research integrating high-resolution single-cell transcriptome and epigenomic profiling with lineage-tracing approaches will be essential to ascertain if plasticity is a trait common to all Tregs or exclusive to certain functional subpopulations (142).

Context-dependent FOXP3 activity in skin immune homeostasis

The functional activity of FOXP3 in Tregs is highly context-dependent and is shaped by the unique microenvironment of the tissue in which Tregs reside (42, 89). In the skin, local cytokines, microbial signals, and cellular interactions modulate FOXP3-dependent regulatory programs, collectively shaping the balance between immune

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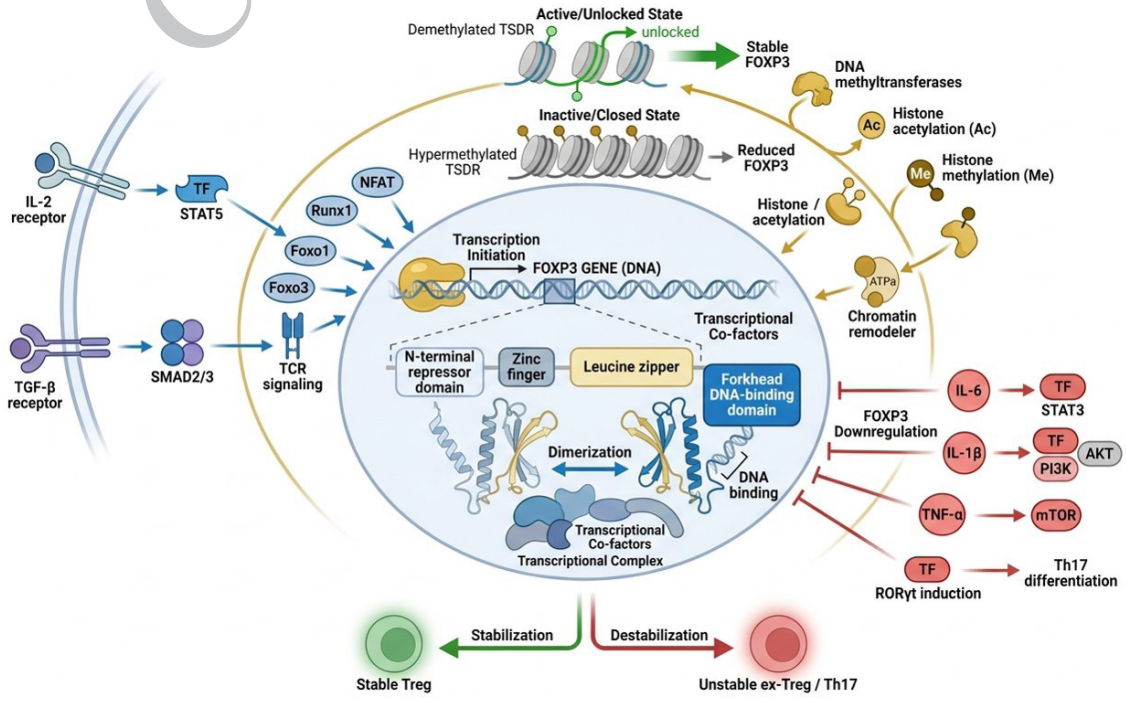


Figure 3. Multi-layered regulation of FOXP3 expression and stability in regulatory T cells
Integrated structural, transcriptional, epigenetic, and signaling processes govern FOXP3 expression and regulatory T-cell stability. FOXP3's functional domains control transcriptional regulation, dimerization, and DNA binding. While TCR-associated transcription factors further strengthen regulatory programs, cytokine-dependent pathways, namely IL-2/STAT5 and TGF-β/SMAD signaling, support FOXP3 transcription and lineage commitment. While remethylation and chromatin remodeling promote lineage instability, epigenetic maintenance via TSDR demethylation maintains steady FOXP3 expression. In contrast, inflammatory pathways mediated by IL-6/STAT3, PI3K–AKT–mTOR signaling, and metabolic stress inhibit FOXP3 activity, promote RORγt-dependent transcriptional programs, and facilitate Treg instability and functional plasticity

tolerance and protective immunity (127). This tissue-specific regulation allows Tregs to adapt their function to the dynamic conditions of the cutaneous environment. One of the key determinants of FOXP3 activity in the skin is the local cytokine milieu, which influences both Treg stability and functional specialization (50, 107). Cytokines such as IL-2 and TGF-β support FOXP3 expression and reinforce regulatory function, whereas pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α can destabilize FOXP3 and promote Treg plasticity (65, 118). This balance is particularly important in the skin, where environmental insults and microbial exposure frequently induce inflammatory responses that must be tightly controlled to prevent tissue damage (20).

Interactions with commensal microbiota further modulate FOXP3 activity by shaping the development and function of skin-resident Tregs (35, 43). Commensal-derived signals promote the expansion of Tregs and enhance their suppressive capacity, thereby contributing to immune tolerance at barrier surfaces (42, 147). Disruption of the skin microbiome, or dysbiosis, can alter these regulatory pathways and impair FOXP3 function, increasing susceptibility to inflammatory skin diseases (24). These findings highlight the importance of host–microbe interactions in regulating FOXP3-dependent immune tolerance. Cellular interactions within the skin microenvironment also play a critical role in modulating FOXP3 activity (30, 31). Crosstalk between Tregs and keratinocytes, DCs, and fibroblasts provides signals that influence Treg localization, activation, and function (10). For example, antigen presentation by tolerogenic DCs supports FOXP3 stability, while keratinocyte-derived factors can either enhance or inhibit Treg function depending on the inflammatory context (36). These interactions ensure Treg activity is precisely tailored to tissue needs. Metabolic programming primarily governs Treg stability by regulating FOXP3 expression and its post-translational modifications (148). Tregs mainly use oxidative phosphorylation (OXPHOS) for energy production, in contrast to conventional effector T cells (148). FOXP3 actively inhibits glycolysis by blocking Myc-dependent transcriptional programs while promoting mitochondrial oxidative pathways (148). This metabolic reprogramming enhances mitochondrial respiration and NAD regeneration, hence fostering conditions conducive to the acetylation-dependent stability of FOXP3 (149). Enhanced FOXP3 acetylation correlates with heightened oxidative metabolism, and inhibition of histone deacetylases (HDACs) further amplifies FOXP3 lysine acetylation, protecting it from proteasomal degradation and augmenting its transcriptional efficacy. Collectively, these metabolic alterations stabilize the FOXP3 protein, thereby directly facilitating the maintenance of suppressive Treg function (148, 150). Furthermore, metabolic intermediates serve as substrates for epigenetic modifications that regulate the stability of Treg lineages (148). Foxp3 establishes a metabolic condition that prioritizes acetylation-dependent chromatin remodeling over glycolytic reprogramming by enhancing mitochondrial oxidative metabolism and concurrently inhibiting glycolysis via Myc suppression (148). Enhanced OXPHOS correlates with elevated NAD production and up-regulated expression of mitochondrial electron transport chain components, both of which facilitate suppressive function and sustain FOXP3 activity (151). In contrast, compromised mitochondrial respiration or altered metabolic flexibility reduces Treg suppressive capacity, highlighting the strong correlation between metabolic state and epigenetic regulation in maintaining Treg identity (148, 151). Importantly, the context-dependent nature of FOXP3 activity also underlies the vulnerability of Tregs to dysfunction under pathological conditions (90, 152). Inflammatory environments characterized by persistent cytokine signaling, metabolic stress, and tissue damage can disrupt FOXP3 expression and impair Treg suppressive function (153). In the skin, such disruptions contribute to the development of chronic inflammatory diseases, including psoriasis and atopic dermatitis, where defective Treg function fails to control pathogenic immune responses (128, 154). Furthermore, genetic defects affecting FOXP3 or its regulatory pathways exacerbate these effects, leading to severe cutaneous autoimmunity in immunodeficiency syndromes (14). Despite compelling evidence from murine models, definitive evidence for Treg plasticity in human skin is still lacking, warranting cautious interpretation of current findings. Overall, FOXP3 activity in the skin is governed by a complex interplay of signaling pathways, environmental factors, and cellular interactions that together determine immune response outcomes. Understanding this context-dependent regulation is essential for elucidating the mechanisms underlying cutaneous immune tolerance and for developing targeted therapeutic strategies to restore Treg function in disease states. These processes reflect the transition from regulatory to inflammatory states illustrated in Figure 1.

FOXP3 mutations and Tregopathies with cutaneous phenotypes

FOXP3 mutations and molecular consequences

Mutations in the FOXP3 gene represent a direct genetic disruption of regulatory T-cell (Treg) lineage specification and function, leading to profound defects in immune tolerance (7, 100). FOXP3 mutations include missense, nonsense, frameshift, and splice-site variants that affect distinct functional domains of the protein, thereby impairing DNA binding, protein–protein interactions, or transcriptional regulatory activity (155, 156). Mutations within the forkhead domain frequently disrupt nuclear localization and DNA-binding capacity, whereas alterations in the leucine-zipper domain impair dimerization and interaction with transcriptional cofactors (99). These structural defects compromise FOXP3's ability to establish and maintain the transcriptional program required for Treg suppressive function.

At the cellular level, FOXP3 mutations result in either quantitative deficiency of Tregs or qualitative defects in their suppressive capacity, depending on the nature of the mutation (157, 158). In severe loss-of-function mutations, Tregs are absent or non-functional, whereas hypomorphic mutations may permit partial FOXP3 expression but lead to unstable or dysfunctional Tregs (159, 160). Importantly, even when Treg numbers appear normal, impaired transcriptional activity of FOXP3 can result in defective suppression of effector T-cell responses and increased production of pro-inflammatory cytokines (161). This highlights that Treg dysfunction in FOXP3-related disease is not solely a matter of cell number but involves profound alterations in functional programming. At the molecular

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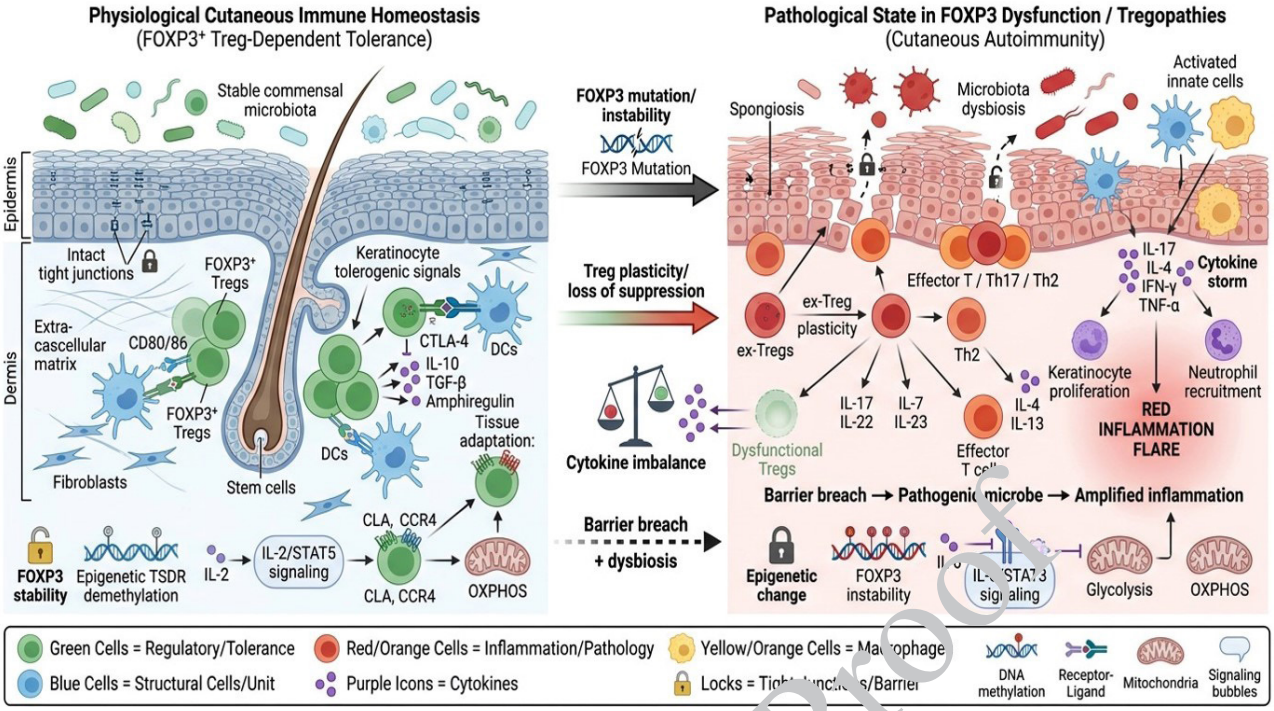


Figure 4. FOXP3-dependent regulation of cutaneous immune homeostasis and its disruption in Tregopathies
Tissue-resident FOXP3$^+$ Tregs preserve immunological tolerance and tissue integrity in the skin under physiological conditions (left panel). They do this by secreting IL-10, TGF-β, and amphiregulin; suppressing antigen-presenting cells through CTLA-4; promoting commensal microbiota tolerance; and supporting activation of hair follicle stem cells and wound healing. FOXP3 expression and Treg lineage stability are guaranteed by IL-2/STAT5 signaling and stable epigenetic control (TSDR demethylation). Reduced Treg numbers and function, acquisition of effector-like phenotypes (ex-Tregs producing IL-17), and unchecked Th2 and Th17 cell expansion are all consequences of FOXP3 mutations or functional instability (caused by inflammatory cytokines like IL-6, epigenetic remodeling, and metabolic changes) in disease (right panel). Eczematous, psoriasiform, or autoimmune skin diseases result from a self-amplifying inflammatory loop, microbial dysbiosis, cytokine imbalance, and epidermal barrier disruption. The image highlights the skin microenvironment's crucial involvement by integrating findings from model systems with processes shown in human IPEX and other Tregopathies

level, FOXP3 mutations disrupt the expression of key target genes involved in immune regulation, including CTLA-4, IL2RA (CD25), and genes controlling metabolic and checkpoint pathways (103, 162). This leads to enhanced effector T cell activation, increased cytokine production, and breakdown of peripheral tolerance (6). Additionally, FOXP3 dysfunction has been linked to increased Treg plasticity, allowing regulatory cells to convert into effector-like phenotypes that further amplify inflammation (118). These molecular consequences are particularly detrimental in barrier tissues such as the skin, where immune responses require tight regulation. The structural and functional heterogeneity of FOXP3 mutations and their downstream effects are summarized in Table 2.

IPEX syndrome as a prototype disease

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is the prototypical disease caused by FOXP3 mutations and provides critical insight into the role of Tregs in human immune homeostasis (14, 72, 168). IPEX is characterized by early-onset, multisystem autoimmunity, including enteropathy, endocrinopathies, and severe cutaneous manifestations (169). Skin involvement is a prominent and often early feature of the disease, typically presenting as eczematous dermatitis, erythroderma, psoriasis-like lesions, or alopecia (170, 171).

IPEX pathogenesis is directly linked to the absence or dysfunction of FOXP3$^+$ Tregs, resulting in uncontrolled activation of autoreactive T cells and widespread tissue inflammation (157). In the skin, this manifests as exaggerated Th2- and Th17-driven immune responses, increased inflammatory cytokine production, and disruption of epithelial barrier integrity (20, 120). Histopathological analyses of skin lesions in IPEX patients reveal dense lymphocytic infiltration, epidermal hyperplasia, and

Table 2. Structural and functional consequences of FOXP3 mutations in human disease

Mutation Type	Affected Domain	Molecular Mechanism	Experimental Validation	Effect on Treg Biology	Clinical Correlates	Refs
Missense	Forkhead (FKH)	Impaired DNA binding and transcriptional targeting	EMSA, reporter assays, ChIP	Reduced suppressive function, unstable lineage	Variable IPEX, eczema	(163)
Missense	Leucine zipper	Defective dimerization	Protein interaction assays	Impaired FOXP3 complex formation	Autoimmunity with skin involvement	(164)
Frameshift/nonsense	Full-length	Truncated protein, loss-of-function	Western blot, knockout models	Absence of functional Tregs	Severe early-onset IPEX	(165)
Splice-site	Multiple domains	Aberrant isoforms	RNA sequencing	Partial loss of stability	Atypical / late-onset disease	(166)
Regulatory variants	Promoter/enhancer	Reduced transcription	Luciferase assays	Decreased FOXP3 expression	Mild or tissue-restricted phenotypes	(167)

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features consistent with chronic inflammation (172). These findings underscore the essential role of Tregs in maintaining cutaneous immune tolerance. Clinical variability in IPEX syndrome reflects the heterogeneity of FOXP3 mutations and their impact on protein function (173). While classic IPEX presents with severe early-onset disease, atypical or milder phenotypes have been described in patients with hypomorphic mutations, indicating that partial preservation of FOXP3 function can modulate disease severity (174). Nevertheless, even in these cases, cutaneous manifestations remain common, highlighting the skin's sensitivity to immune-regulation defects.

Other immunodeficiencies affecting the Treg axis

Beyond FOXP3 mutations, several primary immunodeficiencies disrupt Treg function through defects in pathways that regulate Treg development, stability, or suppressive activity, leading to clinical phenotypes that overlap with FOXP3-related disease (17, 175). These conditions, often referred to as "Tregopathies," provide further evidence that impairment of regulatory pathways is a central mechanism underlying autoimmune skin disease in immunodeficiency (16, 176). Deficiency of dedicator of cytokinesis 8 (DOCK8) is associated with combined immunodeficiency characterized by recurrent infections, allergic disease, and prominent cutaneous manifestations, including eczema and viral skin infections (177, 178). DOCK8 deficiency impairs cytoskeletal dynamics and immune synapse formation, leading to defective Treg survival and function, as well as impaired control of effector T-cell responses *(Human and animal evidence)* (179). The resulting immune dysregulation contributes to chronic skin inflammation and barrier dysfunction (180).

Haploinsufficiency of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) represents another disorder affecting Treg-mediated immune regulation (181, 182). CTLA-4 is a key inhibitory receptor expressed by Tregs, and its deficiency leads to impaired suppression of antigen-presenting cells and enhanced T-cell activation (80). Clinically, CTLA-4 deficiency is associated with lymphoproliferation, autoimmunity, and cutaneous manifestations such as dermatitis and psoriasis-like lesions (183). Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency shares mechanistic overlap with CTLA-4 deficiency, as LRBA is required for the intracellular trafficking and stability of CTLA-4 (184, 185). Loss of LRBA results in reduced CTLA-4 expression and impaired Treg function, leading to immune dysregulation and autoimmune manifestations, including skin involvement (184). These findings highlight the importance of checkpoint pathways in maintaining Treg-mediated tolerance. Gain-of-function (GOF) mutations in signal transducer and activator of transcription 3 (STAT3) also disrupt immune homeostasis by altering the balance between effector and regulatory T-cell responses (186, 187). STAT3 GOF promotes Th17 differentiation while impairing Treg function, leading to chronic inflammation and autoimmunity, often involving the skin (188). Cutaneous manifestations include eczema, psoriasis-like lesions, and recurrent infections, reflecting combined immune dysregulation and barrier impairment. Wiskott–Aldrich syndrome (WAS), caused by mutations in the WAS gene, is characterized by immunodeficiency, thrombocytopenia, and eczema (189). WAS protein is involved in actin cytoskeleton remodeling, and its deficiency affects T-cell activation and Treg function (190). Tregs from WAS patients show reduced suppressive capacity, contributing to autoimmunity and chronic skin inflammation (191). Collectively, these disorders show that disruption of multiple pathways converging on Treg function can produce similar clinical phenotypes characterized by immune dysregulation and cutaneous autoimmunity. This convergence underscores the central role of the FOXP3–Treg axis in maintaining skin immune homeostasis. It also highlights regulatory pathways as therapeutic targets in immunodeficiency-associated skin disease. Tables 3 and 4 provide a comparative overview of Tregopathies and their cutaneous manifestations.

Mechanistic links between FOXP3 dysfunction and skin disease

FOXP3 dysfunction disrupts immune homeostasis through multiple converging mechanisms that collectively drive cutaneous inflammation, positioning the skin as a primary site of disease manifestation in Tregopathies (6, 90). Rather than a single pathogenic pathway, the link between FOXP3 deficiency and skin disease reflects the integration of immune dysregulation, barrier disruption, and altered tissue–immune interactions within the cutaneous microenvironment (20). These mechanisms amplify one another, resulting in persistent inflammation and failure of tissue repair. A central consequence of FOXP3 dysfunction is the loss of suppressive control over effector T-cell responses, leading to exaggerated Th1, Th2, and Th17 immune activation (21, 65). Without effective Treg-mediated regulation, autoreactive T cells expand and produce high levels of pro-inflammatory cytokines such as IFN-γ, IL-4, IL-13, and IL-17, which drive distinct patterns of skin inflammation (202). Th2-skewed responses

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Table 3. Primary immunodeficiencies affecting the Treg axis with cutaneous phenotypes

Disease	Gene	Core Pathway Defect	Mechanism of Treg Dysfunction	Dominant Immune Skewing	Skin Manifestations	Key Experimental Evidence	Ref
IPEX	FOXP3	Transcriptional control	Loss of lineage identity	Mixed Th1/Th2/Th17	Eczema, erythroderma	Scurfy mouse, human	(192)
CTLA4 deficiency	CTLA4	Checkpoint signaling	Reduced co-inhibition	T-cell hyperactivation	Dermatitis, infiltration	Human studies	(193)
LRBA deficiency	LRBA	CTLA4 trafficking	CTLA4 degradation	Hyperactive T cells	Autoimmune skin lesions	Knockout models	(194)
DOCK8 deficiency	DOCK8	Cytoskeleton/synapse	Impaired immune regulation	Th2 bias	Severe eczema, viral infections	Mouse+clinical	(195)
STAT3 GOF	STAT3	Cytokine signaling	FOXP3 antagonism	Th17 dominance	Psoriasiform lesions	Genetic+functional	(196)
WAS	WAS	Actin remodeling	Defective Treg function	Mixed dysregulation	Eczema, vasculitis	Mouse+human	(197)

Table 4. Mechanistic evidence, cutaneous phenotypes, biomarkers, and targeted therapy in Treg-related immunodeficiencies

Disease	Immune Defect	Skin Phenotype Category	Key Biomarkers	Proven Human Evidence vs Inferred	Targeted Therapy	Key References
IPEX (FOXP3)	FOXP3 mutation → Treg absence/dysfunction	Autoimmune + eczematous+alopecia	↓FOXP3⁺ Tregs, ↑IgE, eosinophilia	⋆ ⋆ ⋆ ⋆ ⋆ (direct human genetic disease)	HSCT, sirolimus, biologics	(198)
CTLA4 deficiency	Checkpoint failure (↓CTLA-4)	Autoimmune dermatitis, infiltration	↓CTLA-4 expression	⋆ ⋆ ⋆ ⋆ ⋆ (human monogenic disease)	Abatacept, HSCT	(199)
LRBA deficiency	CTLA-4 trafficking defect	Autoimmune dermatitis	↓CTLA-4 stability	⋆ ⋆ ⋆ ⋆ (human+mechanistic)	Abatacept	(199)
DOCK8 deficiency	Cytoskeleton+immune synapse defect	Eczematous+infectious dermatitis	↑IgE, viral susceptibility	⋆ ⋆ ⋆ ⋆ (human+translational)	HSCT	(199)
STAT3-GOF	Th17 skewing+Treg suppression	Psoriasiform+autoimmune	↑IL-17, STAT3 activation	⋆ ⋆ ⋆ ⋆ (human+cytokine data)	JAK inhibitors, IL-6 blockade	(199)
WAS	Actin cytoskeleton defect	Eczematous+vasculitic	Thrombocytopenia	⋆ ⋆ ⋆ ⋆ (human+functional data)	HSCT, gene therapy	(199)
Th2-dominant IEI dermatitis	Treg dysfunction+Th2 skewing	Allergic/eczema	IL-4, IL-13, IgE	⋆ ⋆ ⋆ (human+mechanistic)	Dupilumab	(200)
Th17/psoriasiform IEI	Treg-Th17 imbalance	Psoriasis-like	IL-17, IL-23	⋆ ⋆ ⋆ (part human, part inferred)	IL-17 / IL-23 inhibitors (caution)	(201)

contribute to eczematous dermatitis by inducing IgE production and eosinophilic inflammation, whereas Th17 and Th1 pathways promote psoriasiform inflammation characterized by keratinocyte hyperproliferation and neutrophil recruitment (203, 204). This dysregulated cytokine environment represents a key mechanistic bridge between FOXP3 defects and diverse cutaneous phenotypes.

In addition to altered adaptive immune responses, FOXP3 dysfunction impacts innate immune regulation within the skin (30, 31). Tregs normally modulate the activity of DCs, macrophages, and innate lymphoid cells, thereby limiting excessive inflammatory signaling (8). Loss of FOXP3-dependent control heightens activation of these innate populations, increases antigen presentation, and amplifies inflammatory cascades (36). In particular, dysregulated dendritic cell activation enhances T-cell priming and perpetuates chronic inflammation within the skin (205). These innate–adaptive interactions contribute to the persistence and severity of cutaneous lesions. Barrier dysfunction represents another critical mechanism linking FOXP3 deficiency to skin disease (34, 206). Tregs play an essential role in maintaining epithelial integrity by regulating keratinocyte function and controlling inflammatory damage (10). Impaired Treg activity disrupts tight junctions, alters keratinocyte differentiation, and increases transepidermal water loss, creating a permissive environment for microbial invasion and sustained inflammation (207). This barrier breakdown further amplifies immune activation by increasing exposure to environmental antigens and microbial products. Microbiome alterations (dysbiosis) further exacerbate the effects of FOXP3 dysfunction by disrupting the balance between commensal tolerance and inflammatory responses (24, 42). Under physiological conditions, Tregs promote tolerance to commensal microorganisms, preventing unnecessary immune activation (35). However, without effective FOXP3-mediated regulation, microbial signals can trigger exaggerated immune responses, leading to chronic inflammation and tissue damage (43). Dysbiosis has been implicated in multiple inflammatory skin diseases and likely contributes to Treg-related cutaneous pathology.

Metabolic dysregulation within the skin microenvironment also contributes to disease progression in the context of FOXP3 dysfunction (44, 63). Tregs regulate local metabolic conditions through cytokine signaling and consumption of key metabolites such as IL-2, thereby limiting effector T-cell expansion (84). Loss of this regulatory control leads to a metabolic environment that favors effector T-cell activation, increased glycolysis, and sustained inflammatory responses (126). These metabolic shifts further reinforce immune dysregulation and tissue damage. Importantly, FOXP3 dysfunction also impairs tissue repair mechanisms that are essential for resolving inflammation and restoring homeostasis (58, 93). As discussed in earlier sections, Tregs contribute to epithelial regeneration and wound healing through production of growth factors such as amphiregulin and through interactions with epithelial stem cells (97, 208). Defective Treg function results in delayed wound healing, impaired epithelial regeneration, and persistence of inflammatory lesions (98). This failure of repair mechanisms represents a critical factor in the chronicity of skin disease associated with Treg dysfunction.

These mechanisms do not operate independently but form a self-reinforcing network in which immune dysregulation, barrier disruption, microbial imbalance, and impaired repair collectively drive chronic cutaneous inflammation (20, 90). As a barrier organ exposed to continuous environmental challenges, the skin is particularly sensitive to such disruptions, explaining the prominence of dermatological manifestations in FOXP3-related disorders and other Tregopathies (127). Overall, FOXP3 dysfunction leads to skin disease through a multifactorial process involving loss of immune regulation, altered tissue homeostasis, and failure of repair mechanisms. Understanding these interconnected pathways provides a framework for identifying therapeutic strategies to restore immune tolerance and tissue integrity in patients with Treg-related disorders. Table 5 summarizes these interconnected mechanisms, highlighting their integration across molecular, cellular, and tissue levels.

Conclusion

FOXP3-dependent Tregs serve as the cornerstone of cutaneous immune tolerance, and their dysfunction represents a unifying mechanism driving autoimmune skin manifestations in primary immunodeficiencies. This review underscores how genetic defects in FOXP3 or converging pathways (CTLA4, LRBA, DOCK8, STAT3 GOF, WAS) disrupt Treg stability, promote plasticity toward pro-inflammatory ex-Tregs, and skew the Treg–Th17 axis, resulting in cytokine imbalance, barrier breakdown,

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Table 5. Integrated mechanisms linking FOXP3 dysfunction to cutaneous inflammation

Mechanistic Axis	Key Molecular Drivers	Cellular Effect	Tissue-Level Outcome	Evidence Type	Ref
Cytokine dysregulation	IL-17, IL-4, IL-13, IFN-γ	Effector T-cell expansion	Chronic inflammation	Human + mouse	(209)
Treg instability	IL-6, STAT3	FOXP3 down-regulation	Loss of tolerance	Experimental	(210)
Barrier disruption	TNF-α, IL-22	Keratinocyte dysfunction	Increased permeability	In vivo	(211)
Microbiota dysbiosis	TLR ligands	Innate activation	Immune amplification	Microbiome studies	(212)
Metabolic shift	Glycolysis ↑	Effector dominance	Sustained inflammation	Metabolic assays	(213)
Repair failure	Amphiregulin ↓	Stem cell impairment	Chronic lesions	Functional models	(214)

microbial dysbiosis, and persistent inflammation in the skin. Tissue-resident Tregs' unique roles in hair follicle regeneration, wound healing, and keratinocyte modulation further explain the prominence of dermatologic phenotypes in these disorders. Beyond quantitative Treg deficiency, qualitative impairments, including epigenetic instability and metabolic reprogramming, amplify pathology through self-reinforcing loops involving keratinocytes, DCs, and the microbiota. While conventional immunosuppression and hematopoietic stem cell transplantation provide symptomatic relief or cure in severe cases, they do not fully address tissue-specific regulatory failure. Emerging precision therapies, such as low-dose IL-2, CAR-Treg adoptive transfer, CRISPR-based FOXP3 editing, and microbiome-directed interventions, promise to restore targeted immune homeostasis with reduced systemic toxicity. Future progress requires deeper integration of single-cell multi-omics, humanized models, and biomarker-driven patient stratification to translate mechanistic insights into durable, mechanism-based treatments. Ultimately, reinforcing FOXP3-mediated tolerance in the skin microenvironment offers the most effective path toward controlling autoimmune dermatoses in immunodeficiency.

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Authors' Contributions

T Y conceived the study, drafted the manuscript, and critically revised it. Y W performed data collection, literature review, and manuscript editing. Z L provided supervision, critical intellectual input, and final approval of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare that they have no competing interests.

Declaration

During the preparation of this manuscript, the authors used an AI-assisted tool (ChatGPT) to support language editing and manuscript organization. The authors reviewed and edited the content after using this tool and take full responsibility for the accuracy, integrity, and final content of the manuscript.

References

1. Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, *et al.* Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency 2015. J Clin Immunol 2015; 35: 696-726.
2. Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. Primary immunodeficiency and autoimmunity: A comprehensive review. J Autoimmun 2019; 99: 52-72.
3. van der Fits L, van der Wel LI, Laman JD, Prens EP, Verschuren MC. Psoriatic lesional skin exhibits an aberrant expression pattern of interferon regulatory factor-2 (IRF-2). J Pathol 2003; 199: 107-114.
4. Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. Nat Rev Immunol 2012; 12: 503-516.
5. Costagliola G, Cappelli S, Consolini R. Autoimmunity in primary immunodeficiency disorders: an updated review on pathogenesis and clinical implications. J Clin Med 2021; 10: 4729.
6. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008; 133: 775-787.
7. Lu LF, Thai TH, Calado DP, Chaudhry A, Kubo M, Tanaka K, *et al.* Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity 2009; 30: 80-91.
8. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol 2008; 8: 523-532.
9. Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, *et al.* The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 2007; 450: 566-569.
10. Boothby IC, Cohen JN, Rosenblum MD. Regulatory T cells in skin injury: At the crossroads of tolerance and tissue repair. Sci Immunol 2020; 5: eaaz9631.
11. Dudda JC, Perdue N, Bachtanian E, Campbell DJ. Foxp3+ regulatory T cells maintain immune homeostasis in the skin. J Exp Med 2008; 205: 1559-1565.
12. Rosenblum MD, Gratz IK, Paw JS, Lee K, Marshak-Rothstein A, Abbas AK. Response to self antigen imprints regulatory memory in tissues. Nature 2011; 480: 538-542.
13. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: Mechanisms of differentiation and function. Annu Rev Immunol 2012; 30: 531-564.
14. Ben-Skowronek I. IPEX syndrome: Genetics and treatment options. Genes (Basel) 2021; 12: 323.
15. Park H, Kim M, Lee K, Kim K, Jeon D, Kim Y, *et al.* Association between anxiety, depression and asthma. J Allergy Clin Immunol Pract 2011; 127: AB42.
16. Abbas AK, Benoist C, Bluestone JA, Campbell DJ, Ghosh S, Hori S, *et al.* Regulatory T cells: Recommendations to simplify the nomenclature. Nat Immunol 2013; 14: 307-308.
17. Szczawińska-Popłonyk A, Popłonyk N, Awdi K. Down syndrome in children: An inborn error of immunity with immune dysregulation. Children (Basel) 2024; 11: 1251.
18. Ohkura N, Sakaguchi S. A novel modifier of regulatory T cells. Nat Immunol 2009; 10: 685-686.
19. Lakkis FG. Immunology: TREG cells in transplantation-a

Corrected Proof

double-edged sword? Nat Rev Nephrol 2014; 10: 185-186.
20. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157: 121-141.
21. Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. Clin Exp Immunol 2004; 135: 1-8.
22. Ruterbusch M, Pruner KB, Shehata L, Pepper M. *In vivo* CD4(+) T cell differentiation and function: Revisiting the Th1/Th2 paradigm. Annu Rev Immunol 2020; 38: 705-725.
23. Scharschmidt TC. Establishing tolerance to commensal skin bacteria: Timing is everything. Dermatol Clin 2017; 35: 1-9.
24. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol 2011; 9: 244-253.
25. Abbas AK, Lichtman AH, Pillai S. Preface. Cellular and Molecular Immunology: Elsevier; 2010. p. v.
26. Di Vincenzo M, Diotallevi F, Piccirillo S, Carnevale G, Offidani A, Campanati A, *et al.* miRNAs, mesenchymal stromal cells and major neoplastic and inflammatory skin diseases: A page being written: A systematic review. Int J Mol Sci 2023; 24: 8502.
27. Gong Y, Tong J, Wang S. Are follicular regulatory T cells involved in autoimmune diseases? Front Immunol 2017; 8: 1790.
28. Eskandari SK, Daccache A, Azzi JR. Chimeric antigen receptor T(reg) therapy in transplantation. Trends Immunol 2024; 45: 48-61.
29. Belkaid Y, Tamoutounour S. The influence of skin microorganisms on cutaneous immunity. Nat Rev Immunol 2016; 16: 353-366.
30. Pasparakis M, Haase I, Nestle FO. Mechanisms regulating skin immunity and inflammation. Nat Rev Immunol 2014; 14: 289-301.
31. Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. Nat Rev Immunol 2004; 4: 211-222.
32. Albanesi C, Scarponi C, Giustizieri ML, Girolomoni G. Keratinocytes in inflammatory skin diseases. Curr Drug Targets Inflamm Allergy 2005; 4: 329-334.
33. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, *et al.* Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol 2002; 3: 673-680.
34. Proksch E, Brandner JM, Jensen JM. The skin: An indispensable barrier. Exp Dermatol 2008; 17: 1063-1072.
35. Scharschmidt TC, Vasquez KS, Truong HA, Gearty SV, Pauli ML, Nosbaum A, *et al.* A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 2015; 43: 1011-1021.
36. Malissen B, Tamoutounour S, Henri S. The origins and functions of dendritic cells and macrophages in the skin. Nat Rev Immunol 2014; 14: 417-428.
37. Clausen BE, Stoitzner P. Functional specialization of skin dendritic cell subsets in regulating T cell responses. Front Immunol 2015; 6: 534.
38. Collin M, Milne P. Langerhans cell origin and regulation. Curr Opin Hematol 2016; 23: 28-35.
39. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, *et al.* A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med 2007; 204: 1757-1764.
40. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. Science 2010; 327: 291-295.
41. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496-509.
42. Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity 2017; 46: 562-576.
43. Naik S, Bouladoux N, Linehan JL, Han SJ, Harrison OJ, Wilhelm C, *et al.* Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. Nature 2015; 520: 104-108.
44. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity 2013; 38: 633-643.
45. Barros L, Ferreira C, Veldhoen M. The fellowship of regulatory and tissue-resident memory cells. Mucosal Immunol 2022; 15: 64-73.
46. Rosenblum MD, Way SS, Abbas AK. Regulatory T cell memory. Nat Rev Immunol 2016; 16: 90-101.
47. Sakaguchi S. Regulatory T cells: Key controllers of immunologic self-tolerance. Cell 2000; 101: 455-458.
48. Benoist C, Mathis D. Treg cells, life history, and diversity. Cold Spring Harb Perspect Biol 2012; 4: a007021.
49. Roncarolo MG, Gregori S, Bacchetta R, Battaglia M, Gagliani N. The biology of T regulatory type 1 cells and their therapeutic application in immune-mediated diseases. Immunity 2018; 49: 1004-1019.
50. Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, *et al.* Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med 2003; 198: 1875-1886.
51. Bordon Y. A new vein of TLR biology. Nat Rev Immunol 2010; 10: 748.
52. Floess S, Freyer J, Siewert C, Baron U, Olek S, Polansky J, *et al.* Epigenetic control of the foxp3 locus in regulatory T cells. PLoS Biol 2007; 5: e38.
53. Gratz IK, Truong HA, Yang SH, Maurano MM, Lee K, Abbas AK, *et al.* Cutting edge: Memory regulatory t cells require IL-7 and not IL-2 for their maintenance in peripheral tissues. J Immunol 2013; 190: 4483-4487.
54. Sanchez Rodriguez R, Pauli ML, Neuhaus IM, Yu SS, Arron ST, Harris HW, *et al.* Memory regulatory T cells reside in human skin. J Clin Invest 2014; 124: 1027-1036.
55. Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS. Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. Nature 1997; 389: 978-981.
56. Fujimi M, Tager AM, Luster AD. Role of CCR4 and CCR8 in antigen specific T helper 2 cell trafficking into allergic lung. J Allergy Clin Immunol 2005; 115: S255.
57. Ali N, Zirak B, Rodriguez RS, Pauli ML, Truong HA, Lai K, *et al.* Regulatory T cells in skin facilitate epithelial stem cell differentiation. Cell 2017; 169: 1119-1129.
58. Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, *et al.* A distinct function of regulatory T cells in tissue protection. Cell 2015; 162: 1078-1089.
59. Miragaia RJ, Gomes T, Chomka A, Jardine L, Riedel A, Hegazy AN, *et al.* Single-cell transcriptomics of regulatory T cells reveals trajectories of tissue adaptation. Immunity 2019; 50: 493-504.
60. Luo CT, Li MO. Transcriptional control of regulatory T cell development and function. Trends Immunol 2013; 34: 531-539.
61. Cretney E, Xin A, Shi W, Minnich M, Masson F, Miasari M, *et al.* The transcription factors Blimp-1 and IRF4 jointly control the differentiation and function of effector regulatory T cells. Nat Immunol 2011; 12: 304-311.
62. Wohlfert EA, Grainger JR, Bouladoux N, Konkel JE, Oldenhove G, Ribeiro CH, *et al.* GATA3 controls Foxp3(+) regulatory T cell fate during inflammation in mice. J Clin Invest 2011; 121: 4503-4515.
63. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, *et al.* Cutting edge: Distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J Immunol 2011; 186: 3299-3303.
64. Schneider A, Long SA, Kita M, Buckner JH. Persistence of FOXP3 expression is impaired in RR-MS Tregs (99.3). J Immunol 2009; 182: 99.3.
65. Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, *et al.* Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. Nat Med 2014; 20: 62-68.
66. Blinova VG, Zhdanov DD. Many faces of regulatory T cells: Heterogeneity or plasticity? Cells 2024; 13: 959.
67. McCallion O, Bilici M, Hester J, Issa F. Regulatory T-cell therapy approaches. Clin Exp Immunol 2023; 211: 96-107.
68. Cheru N, Hafler DA, Sumida TS. Regulatory T cells in peripheral tissue tolerance and diseases. Front Immunol 2023; 14: 1154575.

Corrected Proof

69. Estrada Brull A, Panetti C, Joller N. Moving to the outskirts: Interplay between regulatory T cells and peripheral tissues. Front Immunol 2022; 13: 864628.
70. Santosh Nirmala S, Kayani K, Gliwiński M, Hu Y, Iwaszkiewicz-Grześ D, Piotrowska-Mieczkowska M, *et al.* Beyond FOXP3: A 20-year journey unravelling human regulatory T-cell heterogeneity. Front Immunol 2024; 14: 1321228.
71. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, *et al.* The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001; 27:20- 21.
72. Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova J-L, Buist N, *et al.* X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 2001; 27: 18-20.
73. Joly AL, Seitz C, Liu S, Kuznetsov NV, Gertow K, Westerberg LS, *et al.* Alternative splicing of FOXP3 controls regulatory T cell effector functions and is associated with human atherosclerotic plaque stability. Circ Res 2018; 122: 1385-1394.
74. Chae WJ, Henegariu O, Lee SK, Bothwell AL. The mutant leucine-zipper domain impairs both dimerization and suppressive function of Foxp3 in T cells. Proc Natl Acad Sci U S A 2006; 103: 9631-9636.
75. Shevach EM. Mechanisms of foxp3+ T regulatory cell-mediated suppression. Immunity 2009; 30: 636-645.
76. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. Annu Rev Immunol 2020; 38: 541-566.
77. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19: 683-765.
78. Collison LW, Pillai MR, Chaturvedi V, Vignali DA. Regulatory T cell suppression is potentiated by target T cells in a cell contact, IL-35- and IL-10-dependent manner. J Immunol 2009; 182: 6121-6128.
79. Bluestone JA, Abbas AK. Natural versus adaptive regulatory T cells. Nat Rev Immunol 2003; 3: 253-257.
80. Qureshi OS, Zheng Y, Nakamura K, Attridge K, Manzotti C, Schmidt EM, *et al.* Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. Science 2011; 332: 600-603.
81. Deshane J, Chaplin DD. Follicular dendritic cell makes environmental sense. Immunity 2010; 33: 2-4.
82. Ivanyi J, Plata F. Progess in antimicrobial immunity. In Immune Regulation: Humana Press; 1985. p. 375-378.
83. Workman CJ, Vignali DA. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). J Immunol 2005; 174: 688-695.
84. Pandiyan P, Zheng L, Ishihara S, Reed J, Lenardo MJ. CD4+CD25+Foxp3+ regulatory T cells induce cytokine deprivation-mediated apoptosis of effector CD4+ T cells. Nat Immunol 2007; 8: 1353-1362.
85. Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, *et al.* Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. J Exp Med 2007; 204: 1257-1265.
86. Angelin A, Gil-de-Gomez L, Dahiya S, Jiao J, Guo L, Levine MH, *et al.* Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. Cell Metab 2017; 25: 1282-1293.
87. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. Immunity 2015; 42: 406-417.
88. Bordon Y. Asthma and allergy: The NET effect of respiratory viruses. Nat Rev Immunol 2017; 17: 346-347.
89. Fuchs O. Single-cell transcriptomics: Technology and applications. Single-Cell Omics: Elsevier; 2019. p. 231-251.
90. Bluestone JA. Chance favours the prepared mind. Nat Rev Immunol 2018; 18: 541.
91. Oshimori N, Fuchs E. Paracrine TGF-beta signaling counterbalances BMP-mediated repression in hair follicle stem cell activation. Cell Stem Cell 2012; 10: 63-75.
92. Paus R, Cotsarelis G. The biology of hair follicles. N Engl J Med 1999; 341: 491-497.
93. Nosbaum A, Prevel N, Truong HA, Mehta P, Ettinger M, Scharschmidt TC, *et al.* Cutting edge: Regulatory T cells facilitate cutaneous wound healing. J Immunol 2016; 196: 2010-2014.
94. Zaiss DM, van Loosdregt J, Gorlani A, Bekker CP, Grone A, Sibilia M, *et al.* Amphiregulin enhances regulatory T cell-suppressive function via the epidermal growth factor receptor. Immunity 2013; 38: 275-284.
95. Steenvoorde P, Oskam J. Comments on the paper, "The biosurgical wound debridement: Experimental investigation of efficiency and practicability," by Blake FA *et al.* Wound Repair Regen. 2008; 16: 466.
96. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: Molecular and cellular mechanisms. J Invest Dermatol 2007; 127: 514-525.
97. Zaiss DMW, Gause WC, Osborne LC, Artis D. Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. Immunity 2015; 42: 216-226.
98. Smith AM, Moxon S, Morris GA. Biopolymers as wound healing materials. Wound Healing Biomaterials: Elsevier; 2016. p. 261-287.
99. Ono M, Yaguchi H, Ohkura N, Kitabayashi I, Nagamura Y, Nomura T, *et al.* Foxp3 controls regulatory T-cell function by interacting with AML1/Runx1. Nature 2007; 446: 685-689.
100. Fontenot JD, Rudensky AY, Gavin MA, Rudensky AY. A function for interleukin 2 in Foxp3-expressing regulatory T cells. Nat Immunol 2005; 6: 1142-1151.
101. Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko S-A, *et al.* Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet 2001; 27: 68-73.
102. Li B, Song X, Zhou Z, Wang Q, Shen Y, Greene MI. FOXP3 activation in Treg cells, - atomic level aspects of FOXP3 structure and biochemistry that govern function (89.4). J Immunol 2009; 182: 89.4.
103. Zheng Y, Josefowicz SZ, Kas A, Chu TT, Gavin MA, Rudensky AY. Genome-wide analysis of Foxp3 target genes in developing and mature regulatory T cells. Nature 2007; 445: 936-940.
104. Martinez de Paz A, Josefowicz SZ. Gene regulatory networks STARR-ing B cells. Nat Immunol 2020; 21: 110-112.
105. Wu Y, Borde M, Heissmeyer V, Feuerer M, Lapan AD, Stroud JC, *et al.* FOXP3 controls regulatory T cell function through cooperation with NFAT. Cell 2006; 126: 375-387.
106. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, *et al.* CTLA-4 control over Foxp3+ regulatory T cell function. Science 2008; 322: 271-275.
107. Cao X, Cai SF, Fehniger TA, Song J, Collins LI, Piwnica-Worms DR, *et al.* Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity 2007; 27: 635-646.
108. Soper DM, Kasprowicz DJ, Ziegler SF. IL-2Rbeta links IL-2R signaling with Foxp3 expression. Eur J Immunol 2007; 37: 1817-1826.
109. Zorn E, Nelson EA, Mohseni M, Porcheray F, Kim H, Litsa D, *et al.* IL-2 regulates FOXP3 expression in human CD4+ CD25+ regulatory T cells through a STAT-dependent mechanism and induces the expansion of these cells *in vivo*. Blood 2006; 108: 1571-1579.
110. Hayes SM, Li L, Love PE. TCR signal strength influences alphabeta/gammadelta lineage fate. Immunity 2005; 22: 583-593.
111. Park JW. Revised Pollen Calendar in Korea. Allergy Asthma Immunol Res. 2020; 12: 171-172.
112. Whalley K. Epigenetic regulation of asymmetry. Nat Rev Neurosci 2012; 13: 72.
113. Wilk C, Effenberg L, Abberger H, Steenpass L, Hansen W, Zeschnigk M, *et al.* CRISPR/Cas9-mediated demethylation of FOXP3-TSDR toward Treg-characteristic programming of Jurkat

Corrected Proof

T cells. Cell Immunol 2022; 371: 104471.
114. Floess S, Freyer J, Siewert C, Baron U, Olek S, Polansky J, *et al.* Epigenetic control of the foxp3 locus in regulatory T cells. PLoS Biol 2007; 5: e38.
115. Barbon CM, Yang M, Wands GD, Ramesh R, Slusher BS, Hedley ML, *et al.* Consecutive low doses of cyclophosphamide preferentially target Tregs and potentiate T cell responses induced by DNA PLG microparticle immunization. Cell Immunol 2010; 262: 150-61.
116. Todd JA. Etiology of type 1 diabetes. Immunity 2010; 32: 457-67.
117. Pelling M, Garschagen M. Put equity first in climate adaptation. Nature 2019; 569: 327-329.
118. Zhang Z, Zhou X. Foxp3 Instability Helps tTregs Distinguish Self and Non-self. Front Immunol 2019; 10: 2226.
119. Zhou X, Bailey-Bucktrout S, Jeker LT, Bluestone JA. Plasticity of CD4+ FoxP3+ T cells. Curr Opin Immunol 2009; 21: 281-285.
120. Gudjonsson JE, Kabashima K, Eyerich K. Mechanisms of skin autoimmunity: Cellular and soluble immune components of the skin. J Allergy Clin Immunol 2020; 146: 8-16.
121. Miyao T, Floess S, Setoguchi R, Luche H, Fehling Hans J, Waldmann H, *et al.* Plasticity of Foxp3(+) T cells reflects promiscuous Foxp3 expression in conventional T cells but not reprogramming of regulatory T cells. Immunity 2012; 36: 262-275.
122. Bailey-Bucktrout SL, Bluestone JA. Regulatory T cells: Stability revisited. Trends Immunol 2011; 32: 301-306.
123. Miyao T, Floess S, Setoguchi R, Luche H, Fehling HJ, Waldmann H, *et al.* Plasticity of Foxp3+ T cells reflects promiscuous Foxp3 expression in conventional T cells but not reprogramming of regulatory T cells. Immunity 2012; 36: 262-275.
124. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, *et al.* Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013; 504 446-450.
125. Kaelin WG, Jr., McKnight SL. Influence of metabolism on epigenetics and disease. Cell 2013; 153: 56-69.
126. Bending D, Ono M. FoxP3 partners up. Nat Immunol 2017; 18: 1181-1183.
127. van de Veen W, Wirz OF, Globinska A, Akdis M. Novel mechanisms in immune tolerance to allergen during natural allergen exposure and allergen-specific immunotherapy. Curr Opin Immunol 2017; 48: 74-81.
128. Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. Clin Rev Allergy Immunol 2007; 33: 45-56.
129. Lee SE, Rudd BD, Smith NL. Fate-mapping mice: New tools and technology for immune discovery. Trends Immunol 2022; 43: 195-209.
130. Seibler J, Zevnik B, Küter-Luks B, Andreas S, Kern H, Hennek T, *et al.* Rapid generation of inducible mouse mutants. Nucleic Acids Res 2003; 31: e12.
131. Zhang B, Wu J, Jiao Y, Bock C, Dai M, Chen B, *et al.* Differential requirements of TCR signaling in homeostatic maintenance and function of dendritic epidermal T cells. J Immunol 2015; 195: 4282-4291.
132. Davoodi-Semiromi A, Cheikhi A, Xia C, Litherland S, Clare-Salzler M. Modulation of CD4+Foxp3− T-cells with a JAK-STAT5 kinase inhibitor (131.2). J Immunol 2007; 178: S237.
133. Yang F, Ikeda Y, Guo Z, Bednar KJ. Regulatory T cell heterogeneity: Who they are, where they come from, and where they go. Front Immunol 2026; 17: 1929923.
134. Ohkura N, Sakaguchi S. Foxo1 and Foxo3 help Foxp3. Immunity 2010; 33: 835-837.
135. Ouyang W, Beckett O, Ma Q, Paik JH, DePinho RA, Li MO. Foxo proteins cooperatively control the differentiation of Foxp3+ regulatory T cells. Nat Immunol 2010; 11: 618-627.
136. Kerdiles YM, Stone EL, Beisner DL, McGargill MA, Chen IL, Stockmann C, *et al.* Foxo transcription factors control regulatory T cell development and function. Immunity 2010; 33: 890-904.
137. Gamper CJ, Powell JD. All PI3Kinase signaling is not mTOR: Dissecting mTOR-dependent and independent signaling pathways in T cells. Front Immunol 2012; 3: 312.
138. Sen R. The origins of NF-kappaB. Nat Immunol 2011; 12: 686-688.
139. Gerondakis S, Fulford TS, Messina NL, Grumont RJ. NF-kappaB control of T cell development. Nat Immunol 2014; 15: 15-25.
140. Zhang F, Meng G, Strober W. Erratum: Corrigendum: Interactions among the transcription factors Runx1, RORγ t and Foxp3 regulate the differentiation of interleukin 17–producing T cells. Nat Immunol 2009; 10: 223.
141. Targeting the c-Rel Subunit of NF-κB Inhibits Treg Function in Melanoma. Cancer Discov 2017; 7: OF13.
142. Sawant DV, Vignali DA. Once a Treg, always a Treg? Immunol Rev 2014; 259: 173-191.
143. Huehn J, Siegmund K, Lehmann JC, Siewert C, Haubold U, Feuerer M, *et al.* Developmental stage, phenotype, and migration distinguish naive- and effector/memory-like CD4+ regulatory T cells. J Exp Med 2004; 199: 303-313.
144. Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3+ regulatory T cells. Nat Rev Immunol 2011; 11: 119-130.
145. Koch MA, Tucker-Heard G, Perdue NR, Killebrew JR, Urdahl KB, Campbell DJ. The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nat Immunol 2009; 10: 595-602.
146. Schmidl C, Klug M, Boeld TJ, Andreesen R, Hoffmann P, Edinger M, *et al.* Lineage-specific DNA methylation in T cells correlates with histone methylation and enhancer activity. Genome Res 2009; 19: 1165-1174.
147. Scharschmidt TC, Vasquez KS, Truong H-A, Gearty SV, Pauli ML, Nosbaum A, *et al.* A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 2015; 43: 1011-1021.
148. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, *et al.* Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. Cell Metab 2017; 25: 1282-1293.
149. Beier UH, Wang L, Han R, Akimova T, Liu Y, Hancock WW. Histone deacetylases 6 and 9 and sirtuin-1 control Foxp3+ regulatory T cell function through shared and isoform-specific mechanisms. Sci Signal 2012; 5: ra45.
150. Liu Y, Wang L, Han R, Beier UH, Hancock WW. Two lysines in the forkhead domain of foxp3 are key to T regulatory cell function. PloS One 2012; 7: e29035.
151. Howie D, Cobbold SP, Adams E, Ten Bokum A, Necula AS, Zhang W, *et al.* Foxp3 drives oxidative phosphorylation and protection from lipotoxicity. JCI Insight 2017; 2: e89160.
152. Cully M. Autoimmunity: LKB1 helps T(reg) cells battle exhaustion. Nat Rev Immunol 2017; 17: 592-593.
153. Pola C. Muscular Treg cells. Nat Med 2014; 20: 28.
154. Carbone F, De Rosa V, Carrieri PB, Montella S, Bruzzese D, Porcellini A, *et al.* Regulatory T cell proliferative potential is impaired in human autoimmune disease. Nat Med 2014; 20: 69-74.
155. Levy-Lahad E, Wildin RS. Neonatal diabetes mellitus, enteropathy, thrombocytopenia, and endocrinopathy: Further evidence for an X-linked lethal syndrome. J Pediatr 2001; 138: 577-580.
156. Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome. SpringerReference: Springer-Verlag; 2011.
157. Bacchetta R, Passerini L, Gambineri E, Dai M, Allan SE, Perroni L, *et al.* Defective regulatory and effector T cell functions in patients with FOXP3 mutations. J Clin Invest 2006; 116: 1713-1722.
158. Gambineri E, Hackett M, Añover S, Zhu Q, Ocheltree E, Ochs HD, *et al.* Clinical, laboratory, and molecular evaluation of 105 patients with a phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. J Allergy Clin Immunol 2009; 123: S148.
159. d'Hennezel E, Piccirillo CA. Analysis of human FOXP3+ Treg Cells Phenotype and Function. Methods in Molecular Biology: Humana Press; 2011. p. 199-218.

Corrected Proof

160. d'Hennezel E, Ben-Shoshan M, Ochs HD, Torgerson TR, Russell LJ, Lejtenyi C, *et al*. FOXP3 forkhead domain mutation and regulatory T cells in the IPEX syndrome. N Engl J Med 2009; 361: 1710-1713.
161. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: A paradigm of immunodeficiency with autoimmunity. Front Immunol 2012; 3: 211.
162. Session 02: Regulatory T cells. Immunology 2008; 104: 6-13.
163. Szczawińska-Popłonyk A. Atopic dermatitis in inborn errors of immunity: At the interface of immunodeficiency and immune dysregulation. Immunol Res 2025; 73: 147.
164. Bakhtiar S, Ghosh S, Hauck F. Diseases of Immune Dysregulation. Inborn Errors of Immunity: Definition, Diagnosis, and Management: Springer; 2026. p. 407-88.
165. Gambineri E, Ciullini Mannurita S, Hagin D, Vignoli M, Anover-Sombke S, DeBoer S, *et al*. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol 2018; 9: 2411.
166. Li D, McIntosh CS, Mastaglia FL, Wilton SD, Aung-Htut MT. Neurodegenerative diseases: A hotbed for splicing defects and the potential therapies. Transl Neurodegener 2021; 10: 16.
167. Zong X, Hao X, Xu B, Crawford JC, Wright S, Li J, *et al*. Foxp3 enhancers synergize to maximize regulatory T cell suppressive capacity. J Exp Med 2021; 218: e20202415.
168. Aljubran S, Al najem A. An early successful hematopoietic stem cell transplant (Hsct) for a boy with ipex syndrome. Ann Allergy Asthma Immunol 2024; 133: S171.
169. Spickett GP. Chapter 9 Autoimmune haematological disorders. Oxford Handbook of Clinical Immunology and Allergy: Oxford University Press; 2006.
170. Resnick ES. X-linked Immune Dysregulation with Polyendocrinopathy (IPEX) Syndrome. Allergy and Clinical Immunology: Wiley; 2015. p. 382-7.
171. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. Autoimmun Rev 2005; 4: 253-263.
172. Naguib G, Al-Mashat H, Desta T, Graves DT. Diabetes prolongs the inflammatory response to a bacterial stimulus through cytokine dysregulation. J Invest Dermatol 2004; 123: 87-92.
173. Changelian PS, Moshinsky D, Kuhn CF, Flanagan ME, Munchhof MJ, Harris TM, *et al*. The specificity of JAK3 kinase inhibitors. Blood 2008; 111: 2155-22157.
174. Barzaghi F, Passerini L. IPEX syndrome: Improved knowledge of immune pathogenesis empowers diagnosis. Front Pediatr 2021; 9: 612760.
175. Fisher MS, Sennikov SV. T-regulatory cells for the treatment of autoimmune diseases. Front Immunol 2025; 16: 1511671.
176. Cepika A-M, Sato Y, Liu JM-H, Uyeda MJ, Bacchetta R, Roncarolo MG. Tregopathies: Monogenic diseases resulting in regulatory T-cell deficiency. JAllergy Clin Immunol 2018; 142: 1679-1695.
177. Su HC. Dedicator of cytokinesis 8 (DOCK8) deficiency. Curr Opin Allergy Clin Immunol 2010; 10: 515-520.
178. Gates MG, Atkinson TP. Transient hypereosinophilia and markedly elevated IgE as the presenting feature in DOCK8 (Dedicator of Cytokinesis 8) deficiency. J Allergy Clin Immunol 2012; 129: AB159.
179. Randall K, Lambe T, Johnson A, Kucharska E, Vinuesa C, Treanor B, *et al*. Immunodeficiency and abnormal B cell synapse formation due to DOCK8 mutations in mice. Clin Immunol 2010; 135: S17.
180. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, *et al*. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016; 375: 2335-2348.
181. Maiarana J, Moncada-Velez M, Malbran E, Torre MG, Elonen C, Malbran A, *et al*. Deep immunophenotyping shows altered immune cell subsets in CTLA- 4 haploinsufficiency. Pediatr Allergy Immunol 2023; 34: e13994.
182. Pichler WJ. Drug-induced autoimmunity. Curr Opin Allergy Clin Immunol 2003; 3: 249-253.
183. Hossen MM, Ma Y, Yin Z, Xia Y, Du J, Huang JY, et al. Current understanding of CTLA-4: From mechanism to autoimmune diseases. Front Immunol 2023; 14: 1198365.
184. Sangiorgi E, Capecchi MR. Bmi1 is expressed *in vivo* in intestinal stem cells. Nat Genet 2008; 40: 915-920.
185. Al-Awqati Q. Kidney growth and hypertrophy: The role of mTOR and vesicle trafficking. J Clin Invest 2015; 125: 2267-2270.
186. Suh YW, Horton JC. Papilledema from gain-of-function mutations in the STAT3 gene. Ophthalmic Genet 2019; 40: 165-9.
187. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015; 373: 1640-1648.
188. Kıykım A. STAT1/STAT3 gain of function and mechanisms of immune dysregulation. Turkish J Immunol 2024; 12: 47-52.
189. Ochs HD, Thrasher AJ. The wiskott-aldrich syndrome. J Allergy Clin Immunol 2006; 117: 725-738.
190. Metcalf D. On hematopoietic stem cell fate. Immunity 2007; 26: 669-673.
191. Humblet-Baron S, Sather B, Anover S, Becker-Herman S, Kasprowicz DJ, Khim S, *et al*. Wiskott-Aldrich syndrome protein is required for regulatory T cell homeostasis. J Clin Invest 2007; 117: 407-418.
192. Lee G, Chung H-S, Lee K, Lee H, Kim M, Bae H. Curcumin attenuates the scurfy-induced immune disorder, a model of IPEX syndrome, via inhibiting Th1/Th2/Th17 responses in mice. Phytomedicine 2017; 34: 1-6.
193. Zheng C, Shi Y, Zou Y. T cell co-stimulatory and co-inhibitory pathways in atopic dermatitis. Front Immunol 2023; 14: 1081999.
194. Cámez-Díaz L, Grimbacher B. Immune checkpoint deficiencies and autoimmune lymphoproliferative syndromes. Immunol J 2021; 44: 400-411.
195. Biggs CM, Keles S, Chatila TA. DOCK8 deficiency: Insights into pathophysiology, clinical features and management. Clin Immunol 2017; 181: 75-82.
196. Calautti E, Avalle L, Poli V. Psoriasis: A STAT3-centric view. Int J Mol Sci 2018; 19: 171.
197. Kalekar LA, Rosenblum MD. Regulatory T cells in inflammatory skin disease: From mice to humans. Int Immunol 2019; 31: 457-463.
198. Bacchetta R, Roncarolo MG. IPEX syndrome from diagnosis to cure, learning along the way. J Allergy Clin Immunol 2024; 153: 595-605.
199. Kennedy-Batalla R, Acevedo D, Luo Y, Esteve-Solé A, Vlagea A, Correa-Rocha R, *et al*. Treg in inborn errors of immunity: Gaps, knowns and future perspectives. Front Immunol 2024; 14: 1278759.
200. Tong X, Kim SH, Che L, Park J, Lee J, Kim TG. Foxp3(+) Treg control allergic skin inflammation by restricting IFN-γ-driven neutrophilic infiltration and NETosis. J Dermatol Sci 2024; 115: 2-12.
201. Hardtke-Wolenski M, Landwehr-Kenzel S. Tipping the balance in autoimmunity: Are regulatory t cells the cause, the cure, or both? Mol Cell Pediatr 2024; 11: 3.
202. Visan I. Restricting T cell responses. Nat Immunol 2013; 14:691.
203. Bieber T. Atopic dermatitis. N Engl J Med 2008; 358: 1483-1494.
204. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol 2014; 32: 227-255.
205. Ginhoux F, Guilliams M, Merad M. Expanding dendritic cell nomenclature in the single-cell era. Nat Rev Immunol 2022; 22: 67-68.
206. Kirschner N, Houdek P, Fromm M, Moll I, Brandner JM. Tight junctions form a barrier in human epidermis. Eur J Cell Biol 2010; 89: 839-842.
207. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis

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results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol 2013; 131: 300-313.
208. Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, *et al*. A distinct function of regulatory T cells in tissue protection. Cell 2015; 162: 1078-1089.
209. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol 2007; 25: 821-852.
210. Beres A, Komorowski R, Mihara M, Drobyski WR. Instability of Foxp3 expression limits the ability of induced regulatory T cells to mitigate graft versus host disease. Clin Cancer Res 2011; 17: 3969-3983.
211. Lou H, Lu J, Choi EB, Oh MH, Jeong M, Barmettler S, *et al*. Expression of IL-22 in the skin causes Th2-biased immunity, epidermal barrier dysfunction, and pruritus via stimulating epithelial Th2 cytokines and the GRP pathway. J Immunol 2017; 198: 2543-2555.
212. Liwinski T, Zheng D, Elinav E. The microbiome and cytosolic innate immune receptors. Immunol Rev 2020; 297: 207-224.
213. Soto- Heredero G, Gómez de Las Heras MM, Gabandé-Rodríguez E, Oller J, Mittelbrunn M. Glycolysis–a key player in the inflammatory response. FEBS J 2020; 287: 3350-3369.
214. Zaiss DM, Gause WC, Osborne LC, Artis D. Emerging functions of amphiregulin in orchestrating immunity, inflammation, and tissue repair. Immunity 2015; 42: 216-226.

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