Immune Netw. 2024 Oct;24(5):e33
https://doi.org/10.4110/in.2024.24.e33
pISSN 1598-2629·eISSN 2092-6685

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Review Article

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Th Pathways in Immune-Mediated Skin Disorders: A Guide for Strategic Treatment Decisions

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OPEN ACCESS

Received: Apr 11, 2024
Revised: Jun 6, 2024
Accepted: Jun 19, 2024
Published online: Aug 14, 2024

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Conflict of Interest
The authors declare no potential conflicts of interest.

ABSTRACT

In recent years, there have been significant breakthroughs in the identification of immunological components of skin diseases and in the development of immunomodulatory drugs. Novel therapies create exciting prospects for personalized care. This article provides an overview of the role played by Th1, Th2, Th17, and follicular Th pathways in the most common skin diseases. Additionally, it elucidates the impact of current and upcoming treatments on each of these signaling cascades. Skin diseases predominantly influenced by a single dominant Th pathway such as psoriasis and atopic dermatitis are well-suited for biologics. However, in many other disorders a complex interplay between different immune pathways exists. This can lead to inconsistent efficacy of biologics based on individual patient profiles. In case of activation of several Th pathways, it may be more suitable to consider conventional therapies or JAK inhibitors. Increasing immunological insights have transitioned from laboratory research to practical applications, a trend that is expected to continue growing in the future.

Keywords: Helper T cell; Alopecia areata; Vitiligo; Atopic dermatitis; Psoriasis

INTRODUCTION

A large part of skin diseases is immune-mediated and affects millions of people worldwide. The broad diversity of immunological reactions in the skin leads to an impressive variety in disease presentations (1). It is important to take the pathophysiology of the different skin disorders into account when selecting immunomodulating or immunosuppressive treatments. In recent years, the therapeutic arsenal has become increasingly targeted by the inhibition of specific parts of the immune system. However, while some skin diseases can be directly linked to the activation of a specific Th pathway, in other skin disorders multiple Th lineages are simultaneously activated (2). This highlights the need to understand the immunological balance in different skin diseases to optimize the therapeutic approach (3).

In this review, we summarize the involvement of the different Th cell pathways for the most common inflammatory skin disorders. Additionally, we clarify how immunomodulating treatments for skin diseases affect these Th pathways.

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Abbreviations

AD, atopic dermatitis; AHR, aryl hydrocarbon receptor; BTK, Bruton's tyrosine kinase; FcRn, neonatal Fc receptor; GC, glucocorticosteroids; ICD, irritant contact dermatitis; IL-15R, IL-15 receptor; MC, mast cell; MMP-9, matrix metalloproteinase-9; OX40L, OX40 ligands; PDE4, phosphodiesterase 4; PGE2, prostaglandin E2; Tfh, follicular Th cells.

Author Contributions

Conceptualization: Speeckaert R; Writing - original draft: Speeckaert R, Belpaire A; Writing - review & editing: Speeckaert R, Belpaire A, Lambert J, Speeckaert M, van Geel N.

Th1 PATHWAY

The Th1 response leads to the attack and destruction of other skin cells. This represents the immune response needed to clear intracellular pathogens (e.g., viral infections) or tumoral cells. However, in case the Th1 response is overactive, normal skin cells can become targets for destruction (4,5). Typical examples are vitiligo and alopecia areata. Th1 lymphocytes differentiate from naive T cells under the influence of IL-12, IFN-γ, and to a lesser extent IL-27 (**Fig. 1**). In contrast, IL-4, IL-10, and TGF-β limit the conversion of naive T cells to the Th1 lineage (6). Th1 lymphocytes produce IFN-γ and TNF-α. IFN-γ activates both adaptive and innate immune cells such as cytotoxic T cells, dendritic cells, macrophages, NK-cells and innate lymphoid cells. It plays a crucial part in antiviral protection and is capable to directly inhibit viral replication (7). IFN-γ is induced by other cytokines such as IL-12, IL-15, IL-18, IFN-α, and IFN-β (8).

IL-2 is produced by Th1 cells and stimulates the proliferation of T- and B-lymphocytes. This is important for the clonal expansion of T lymphocytes reacting against specific Ags. Along with IL-15, IL-2 governs the life and death of lymphocytes (9). IL-2 ensures a sufficient number of specific T lymphocytes is produced to mount an effective targeted immune response. Importantly, IL-2 is responsible for the development of IFN-γ producing resident memory T cells which reside in the skin for long periods (10). While high levels of IL-2 induce inflammation, low IL-2 levels dampen immune activation by maintaining the fitness of regulatory T cells and eliminating self-reactive T cells by activation-induced cell death (10,11). IL-15 maintains IFN-γ producing tissue resident memory T cell responses and NK cells against invading pathogens (11).

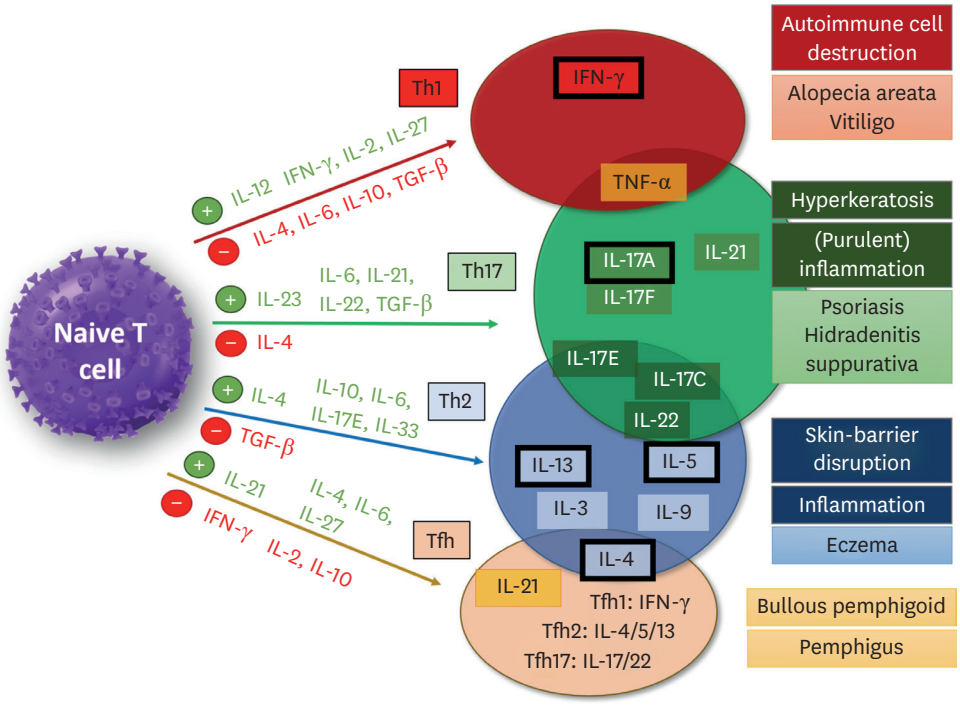

Figure 1. Differentiation of naive T cells into Th1, Th2, Th17, and Tfh cells.

https://doi.org/10.4110/in.2024.24.e33

Th2 PATHWAY

The original function of the Th2 pathway was to eradicate our skin from parasites (12). This is accomplished by producing cytokines that induce itch including IL-4, IL-13, and IL-31. Additionally, the skin barrier is impaired by these cytokines allowing for the decreased adherence of parasites in the epidermis and faster removal by friction or scratching. IL-4 and IL-5 downregulate filaggrin and are therefore directly responsible for the decreased cell-cell adherence of keratinocytes leading to spongiosis and an impaired skin barrier (13). IL-4 is the main cytokine stimulating the development of Th2 lymphocytes although IL-6, IL-10, IL-17E (=IL-25), and IL-33 are costimulatory in contrast to IL-13 (**Fig. 1**). When compared to IL-4, IL-13 is more prevalent in the skin of lesional atopic dermatitis (AD) (14). TGF-β inhibits the conversion of naive T cells into Th2 lymphocytes (15). As parasite elimination has become mostly redundant in developed countries, inhibition of this pathway is in generally considered safe and does not lead to an immunosuppressed state. Both IL-4 and IL-13 act on sensory neurons increasing itch signaling and induce IgE production by plasma cells. Additionally, both cytokines regulate mast cells (MCs) and can contribute to skin fibrosis (16). Besides IL-4 and IL-13, Th2 cells also produce IL-5 which is the key cytokine stimulating the development and maintenance of eosinophils. Other Th2 cytokines include IL-3, IL-9. While AD is the archetypical example, other skin disorders carry also a partial Th2 signature mostly when pruritus and/or skin fibrosis is present or in case of eosinophilia (17).

Th17 PATHWAY

The primary function of the Th17 pathway is to protect outside tissues such as the skin, the pulmonary system and mucosae against extracellular pathogens (18). The defense involves thickening the epidermal layer leading to acanthosis and hyperkeratosis and purulent inflammations resulting in pustules. The strongest cytokine of the Th17 family includes IL-17A, with IL-17F displaying similar but less potent capabilities (**Fig. 2**). The main function of these cytokines is to ensure protection against fungal and yeast (especially candida) infections. IL-17A plays a crucial part in regulating occludin, Reg3g, and mucin 1 preserving the integrity of the bowel mucosa while IL-17F does not (19). IL-17F has a 50% homology with IL-17A, while this is only 27% and 16% for IL-17C and IL-17E (=IL-25), respectively (20,21). The different cytokines of the IL-17 family are highly synergetic with each other but also with TNF-α, IL-22, and IL-1β (22).

IL-17 mediated skin disorders are characterized by hyperkeratosis and/or pustular inflammation. The most recognized examples are psoriasis, hidradenitis suppurativa, and pityriasis rubra pilaris (22). IL-17A is directly linked to the inflammatory signs including erythema and pustules. IL-17E induces proliferation of keratinocytes resulting in hyperkeratosis (23). IL-23 is the central cytokine in the late differentiation and maintenance of Th17 lymphocytes. IL-6, IL-21, IL-22, and TGF-β are additional stimulatory factors of Th17 differentiation, while IL-4 has an inhibitive effect (24).

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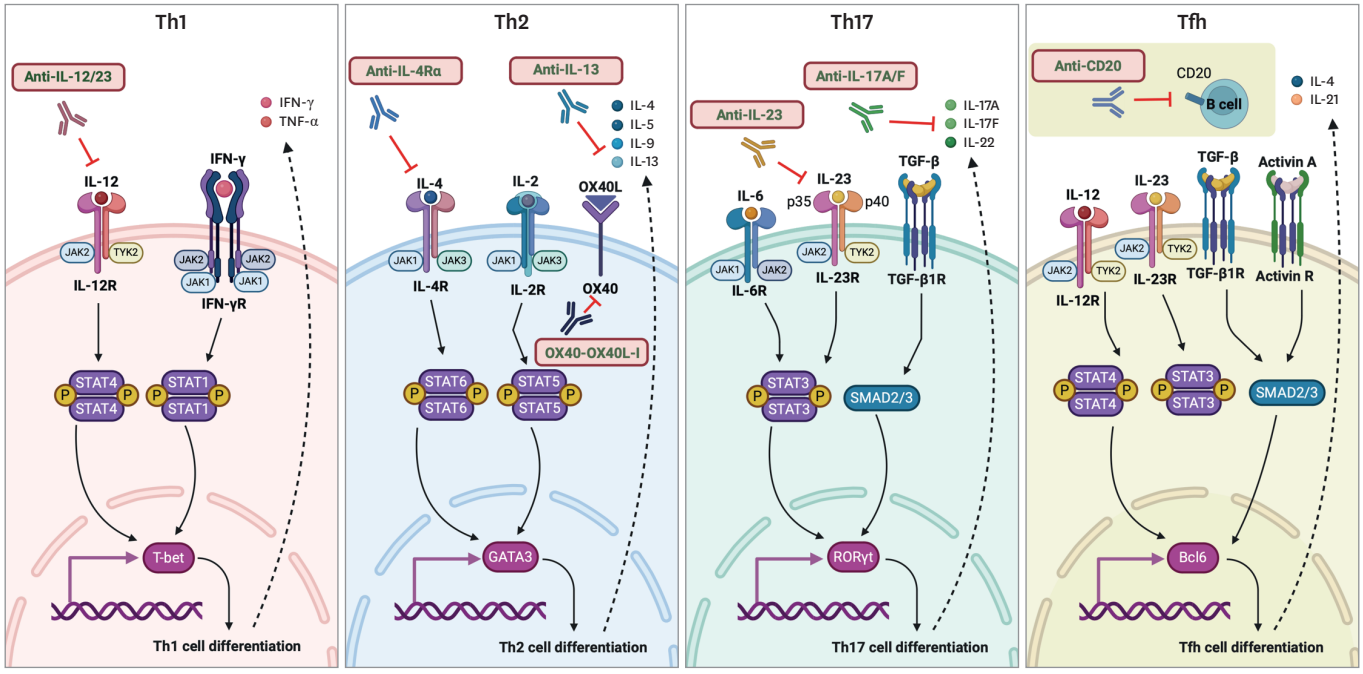

Figure 2. This image illustrates the differentiation and function of four T cell subsets: Th1, Th2, Th17, and Tfh, showcasing their respective signaling pathways, master transcription factors, and cytokine expression. Th1 cells are depicted with IL-12R and IFN-γ receptor activation leading to TNF-α and IFN-γ expression. Th2 cells show IL-2 and IL-4 receptor signaling activating GATA3 for IL-4, IL-5, IL-9, and IL-13 expression. Th17 cells highlight IL-6, IL-23, and TGF-β signaling to RoRγt for IL-17A, IL-17F, and IL-22 expression. Tfh cells display IL-12, IL-23, TGF-β, and activin receptor signaling to Bcl6, promoting IL-21 production and B cell co-stimulation. Inhibitors targeting specific pathways in each subset are also depicted.
SMAD, suppressor of mothers against decapentaplegic; Roryt, retinoic acid receptor-related orphan receptor gamma t; GATA3, GATA binding protein 3; Bcl6, B-cell lymphoma 6.

CYTOKINES AT THE CROSSROADS BETWEEN THE Th17 AND Th2 PATHWAY

IL-17C and IL-17E work at the crossroads of the Th17 and Th2 pathway and can be elevated in disorders affecting both pathways. In contrast to IL-17A and F which are primarily produced by immune cells such as Th17 cells, IL-17C is released by keratinocytes (25). Nonetheless, IL-17C exerts a similar pro-inflammatory and antibacterial function and results in a psoriasiform inflammatory response. Besides psoriasis, IL-17C is increased as a non-essential cytokine in atopic and contact dermatitis. It is involved in psoriasiform skin lesions in inflammatory bowel disease under anti-TNF-α treatment and in recurrent aphthous ulcers. IL-17E was originally described as a Th2 cytokine (26). Mice infused with IL-17E develop a Th2 profile with increased IL-4, IL-5, IL-13, serum IgE and blood eosinophilia. Its role in psoriasis is therefore controversial and may be linked to specific phenotypes such as erythroderma and scalp psoriasis (27).

FOLLICULAR Th CELLS (Tfh)

Tfh are specialized CD4 cells located in the lymph nodes, tonsils, and spleen. They play a critical role in assisting B lymphocytes to produce Abs. Nonetheless, T cells bearing features of Tfh can be found in the circulation, especially in patients with autoimmune disorders (28). In the skin, Ab-mediated diseases are tightly linked with blistering disorders. The deposition

of Abs in the epidermal layer can cause inflammation leading to the splitting of the skin and formation of bullae. Tfh produce IL-21, although cytokines of Th1/Th2/Th17 cells are released including IL-4, IL-6, IL-17, and IFN-γ which has led to the classification of Tfh1, Tfh2, and Tfh17 cells (29). Bullous skin disorders exhibit besides evidence of Tfh activation frequently various degrees of Th1, Th2, and/or Th17 cytokines.

SKIN DISEASES ACCORDING TO Th1/Th2/Th17/Tfh SIGNALING

Predominant Th1

In both vitiligo and alopecia areata, IFN-γ levels are increased and IFN-γ induced chemokines CXCL9 and CXCL10 play a crucial role (**Table 1**) (30,31). Mice models have clearly shown the central role of IFN-γ in the pathogenesis of both vitiligo and alopecia areata (5, 32). The soluble IL-2 receptor is high in both disorders and associated with disease activity (33,34). Similarly, several studies found elevated IL-15 and IFN-α levels in vitiligo and alopecia areata. JAK inhibitors offer high efficacy in both conditions further confirming Th1 signaling as the most promising treatment target (35). Increased IL-17 levels have been reported although a link with disease activity is less clear and inhibition of IL-17 is in both conditions not beneficial (36). The Th2 axis has been suggested to play a role in alopecia areata, especially in a subgroup with high IgE levels where IL-4R inhibition can be considered as a therapeutic option (37).

Lichenoid inflammations such as lichen planus, lichen sclerosus and lichen planopilaris all present with a strong Th1 response. Th1 cytokines IFN-γ, TNFα, IL-2, and Th17 cytokines (IL-17, IL-22) are linked to lichen planus. Diseases with interface dermatitis, indicating an immune-mediated loss of keratinocytes, are typically associated with a strong Th1 response (38). Nonetheless, an important role of the Th17 pathway has been shown in lichen planus by

Table 1. The involvement of the Th pathways in different skin diseases

Skin disease	Th1	Th2	Th17	Tfh	Innate immunity
Acne	+	/	+++	/	+++
Atopic dermatitis	+	++++	/	++	++
Alopecia areata	++++	++	*	?	++
Bullous pemphigoid	/	+++	+	++++	++
Dermatomyositis	+++	+++	++	+	++
Eosinophilic fasciitis	++	+++	++	/	+++
Graft-versus-host disease	++	++	++	++	+
Granuloma annulare	++	++	/	/	+++
Hidradenitis suppurativa	+	/	+++	/	+++
Lichen planopilaris	+++	+	/	/	/
Lichen planus	+++	+	++	++	+
Lichen sclerosus	+++	+	/	/	/
Lupus	+++	++	++	++	+++
Morphea	++	+++	+	+	+
Pemphigus	+	+	+	++	+
Prurigo nodularis	+	+++	++	/	+
Pyoderma gangrenosum	+++	/	++	/	+++
Rosacea	++	/	++	/	++
Psoriasis	++	/	++++	/	+++
Sarcoidosis	+++	/	++	/	++
Vasculitis	++	+	++	++	+++
Urticaria	+	++	+	+++	+++
Vitiligo	++++	/	*	+	++

Pathway increased: ++++, very strong; +++, strong; ++, moderate; +, limited; /, no; ?, unknown.

https://doi.org/10.4110/in.2024.24.e33

cases with improvement to ustekinumab and guselkumab (39). Tfh cells are also active with high IL-21 levels which may be of particular importance in bullous and mucosal lichen planus (40,41). Some studies point to the Th2 cytokine IL-4 in oral lichen planus (42). In lichen sclerosus, Th1 and Th2 signals are pronounced with inhibition of Th17 (43,44). Despite a strong IFN-γ response in lichen sclerosus, cases have been published showing improvement when targeting the Th2 pathway with dupilumab. It is believed that Th1 inflammation is the primary acute inflammation followed by Th2 signaling resulting in fibrosis (45).

Lupus has a complex inflammatory response with Th1 and Th17 cytokines and some Th2 activation despite low levels of IL-2, IL-4, and TGF-β1 (46). Tfh are associated with disease activity and autoantibody production (47). Dermatomyositis which presents similar to lichen planus, and lupus with interface dermatitis produces Th1 cytokines including IFN-γ and TNF-α. However, the Th2 pathway is also activated with IL-4 release (48). Additionally, Il-1β, IL-6, and TGF-β are increased (49).

A skewed Th1 cytokine profile is found in sarcoidosis with low levels of Th2 related factors. Th17 lymphocytes seem present although this mainly concerns a special subset of Th17 lymphocytes that has acquired the capacity to produce IFN-γ (=Th17.1 lymphocytes) (50-52).

A strong innate immune response with neutrophils can be found in pyoderma gangrenosum which is also characterized by a shifted Th1/Th2 and Th17/Th2 balance in favor of Th1 and Th17 (53). Proneutrophilic markers including IL-8, and TNFα are strongly increased together with neutrophil attracting chemokines CXCL1/2/3, CXCL16 and RANTES illustrating the more innate immune nature of pyoderma gangrenosum (54).

Granuloma annulare displays Th1 cytokines including TNFα, IFN-γ, IL-1β, IL-12, and Th2 cytokines. A surprising high level of IL-4 was detected. Th17 and Th22 signals are also upregulated (55). Different types of biologics have been proven to improve granuloma annulare including anti-TNFα, anti-IL12/23 and anti-IL4/13 (56). Granuloma annulare is likely a heterogeneous condition with several patient-dependent immune pathways and a strong contribution of the innate immune cells such as macrophages.

Predominant Th2

AD is characterized by a strong Th2 response, linked with increased IL-13, IL-4, and IL-5 levels. IL-31 is produced by Th2 cells and increased in AD contributing to the intense pruritus associated with AD (57). Th17 and Th22 cells are involved in acute AD, while chronic AD is characterized by recruitment of Th1 lymphocytes leading to a mixed immune cell infiltrate (58). Racial differences further complicate the picture with Asian AD phenotypes exhibiting higher Th17 activation (59). The immune response in allergic contact dermatitis depends on the allergen with differential activation of Th2, Th1, and/or Th17 axes (60). Irritant contact dermatitis (ICD) is less Th2-skewed with an innate immune activation due to toxic effects on keratinocytes. ICD presents with by a mixed non-specific infiltrate of lymphocytes, neutrophils, macrophages and MCs (60,61).

Activated MCs are key players in the release of histamine, leukotrienes, and prostaglandins that cause urticaria, which is primarily an innate immune disorder characterized by itching, localized oedema, and skin redness. Nonetheless, urticaria can be considered to carry a Th2 signature as IL-4 and IL-13 promote IgE synthesis. The Th2 immune response appears stronger in acute compared to chronic urticaria (62).

While the early events of morphea are driven by the Th1/Th17 pathway, the Th2 pathway is also involved in skin fibrosis. Nonetheless, Th17 effector cytokines can remain present for several years (63).

IL-4 and IL-13 have been documented in prurigo nodularis although less pronounced compared to AD. These cytokines recruit eosinophils and MCs and interact with IL-31 leading to pruritus. IL-4 and IL-13 activate itch-sensitive neurons through IL-4Rα (64). The 'itch cytokine' IL-31 is produced by Th2 cells. The excessive keratinocyte proliferation in prurigo nodularis is partly due to increased IL-17 and Th17 cells in lesional skin (65). Th22 cells are believed to participate in the epidermal proliferation and inflammation of prurigo nodularis (66).

Predominant Th17

Th17 cells are crucial in the pathogenesis of psoriasis. IL-23 is essential for the maintenance and late stage differentiation of Th17 cells (67). Both IL-17 and IL-23 inhibition demonstrate impressive efficacy. IL-17A, IL-17F, IL-17C, and TNF-α have been consistently found to be elevated in psoriasis skin. However, other cell types such as neutrophils and Th22 lymphocytes contribute also to the pathogenesis (68). Increased IFN-γ levels have been documented which may promote inflammation, keratinocyte proliferation and Th17 differentiation (69,70). However, anti-IFN-γ treatment did not improve psoriasis suggesting a low Th1 involvement (68).

Acne carries a predominant Th17 profile (71). Proprionibacterium acnes promotes a mixed Th17/Th1 inflammation (72). Similarly, rosacea is characterized by a strong Th17 and Th1 response. IL-6, IL-17, IL-20, and IL-22 are all increased, while IFN-γ and TNF-α are similarly elevated. There is a difference between rosacea subtypes with papulopustular rosacea exhibiting a higher Th17 polarization compared to phymatous and erythematotelangiectatic rosacea. However, innate immune cells such as neutrophils, MCs and macrophages play also major role. Papulopustular rosacea contains the highest number of macrophages (73). The Th2 pathway seems less activated in rosacea although some flares of rosacea under dupilumab have been described possibly due to demodex proliferation induced by a weakened Th2 defense (74).

Predominant Tfh

As blister formation based on anti-BP180 and anti-BP230 is the main pathogenic mechanism of bullous pemphigoid, Tfh are likely to have an important contribution. Serum IL-21 is increased in patients with bullous pemphigoid and the frequency of circulating Tfh correlates with anti-BP180 titers. Depletion of Tfh and neutralization of IL-21 inhibits T cell-induced B cell activation in bullous pemphigoid (75). Besides, bullous pemphigoid shows signs of Th2 and to a lesser extent Th17 activation. IL-4, IL-5, and IL-13 are implied in Ab formation, pruritus and eosinophil recruitment (76). In bullous pemphigoid, serum concentrations of IL-17 and IL-23 have prognostic relevance. Th17 cytokines stimulate the production of matrix metalloproteinase-9 (MMP-9) by neutrophils. The protease MMP-9 facilitates dermo-epidermal division (77).

Increased Tfh, high IL-21 levels and Th17 cells are typical for pemphigus (78). Tissue-resident memory T cells having a follicular helper-like phenotype are responsible for the maintenance and relapse of the disease (79). Several subsets of IL-17A+ T cells subsets were discovered in pemphigus patients with Tfh17 lymphocytes having a strong capacity for Dsg3 and Dsg1 production by memory B cells in pemphigus vulgaris and foliaceus, respectively (80). Additionally, Tfh2 cells are reported to play a pathogenic role in pemphigus vulgaris (81).

https://doi.org/10.4110/in.2024.24.e33

Tfh have rarely been investigated in large cell vasculitis. Increased circulating Tfh were identified in granulomatosis with polyangiitis which improves in patients receiving rituximab (82). In small vessel vasculitis such as Henoch-Schönlein, increased IL-21 values and circulating follicular T cells are present which decrease after successful treatment (83). In most forms of vasculitis, the Th17 signal is strong while the contribution of Th1 and Th2 depends on the type and duration of the vasculitis (84).

CONVENTIONAL IMMUNOSUPPRESSANTS/ IMMUNOMODULATORS

Steroids are the broadest acting choice for dampening inflammatory responses. Glucocorticosteroids (GC) act on almost all types of cells and especially immune cells. GC is a small lipophilic hormone that can rapidly reach most of the target cells. GC bind to an intracellular GR receptor resulting in various signaling cascades leading to the inhibition of both innate immune cells such as neutrophils, Ag presenting cells, Th1, Th2, Th17, and Tfh (85,86). Calcineurin inhibitors such as cyclosporine and tacrolimus are potent and relative selective inhibitors of T cells. They have minimal effects on already activated cytotoxic T cells, granulocytes and macrophages (87). Calcineurin inhibitors restrict the phosphorylation of the NFAT family. Inhibition of IL-2 results in decreased T-cell receptor induced proliferation. Furthermore, a broad range of cytokines including IL-3, IL-4, TNF-α, Il-17, IL-21, and IFN-γ are decreased. Tacrolimus is more potent than cyclosporin with a better safety profile. Nonetheless, despite frequent topical application, data on oral tacrolimus are more limited compared to oral cyclosporine due to its longer historical use. Methotrexate was originally developed as an anti-folate chemotherapeutic. However, its immunomodulating effects are unlikely to originate from the folate pathway. The anti-inflammatory action has more recently been attributed to inhibition of the JAK1/2 pathway (88). Methotrexate suppresses pSTAT5 phosphorylation (88). It inhibits cytokines across all Th pathways including IL-4, IL-13, IL-17, IFN-γ, TNF-α, and GM-CSF (89). Mycophenolate mofetil exerts primarily a cytostatic effect on activated lymphocytes and also reduces a broad range of cytokines across all Th pathways. Mycophenolate mofetil prevents the differentiation of B cells into plasma cells and IL-21 stimulated B cells making it an attractive option for bullous disorders. Furthermore, mycophenolate mofetil reduces the expression of CD40L and inducible costimulator of T cells. This inhibits the IgG production of B cells induced by T cells (90,91). Azathioprine inhibits purine synthesis and modulates rac1 which induces T cell apoptosis in the presence of CD28 (92). This leads to a broad immunosuppressing activity affecting all Th subsets. Dimethyl fumarate has a complex mode of action resulting in antioxidative and immunomodulatory effects. It has inhibitory effects on dendritic cell maturation and an impact on T cell differentiation, T cell activity and apoptosis. Findings in multiple sclerosis and psoriasis indicate a downregulation of Th1 and Th17 activity without suppression of Th2 lymphocytes (93). Tfh are suppressed by dimethyl fumarate in multiple sclerosis patients (94). Nonetheless, dimethyl fumarate has in dermatology rarely been tested outside the field of psoriasis. Dapsone has primarily an anti-neutrophilic action with limited influence on Th subsets. The physiologic concentrations of hydroxychloroquine are in the blood too low to affect T or B cell proliferation although drug concentrations in tissues may be higher (95). Nonetheless, in inflammatory cases hydroxychloroquine alters the Th1/Th2 balance in favor of the latter and may also reduce Th17 activity. Additionally, in collagen-induced arthritis hydroxychloroquine inhibits the generation of Tfh by blocking IL-12 and IL-21 signaling (96). Hydroxychloroquine has effects on innate immune cells such as MCs by decreasing their

long-term survival and accumulating non-functional tryptase (97). A decreased activity of neutrophils and especially the formation of neutrophilic extracellular traps can be beneficial in several autoimmune diseases including lupus and vasculitis (95).

BIOLOGICS

The Th17 pathway has currently the widest choice in biologics that suppress several upstream and downstream cytokines. The development of Th17 cells can be reduced by inhibiting IL-23 using risankizumab, guselkumab, and tildrakizumab. Ustekinumab targets both IL-23 and IL-12. Nonetheless, despite inhibiting IL-12 it is considered to mainly impact the Th17 pathway with very limited impact on Th1 cell differentiation. The available anti-IL17A biologics are secukinumab and ixekizumab, while bimekizumab targets both IL-17A and IL-17F. Brodalumab is an IL-17RA inhibitor blocking the signaling of IL-17A, IL-17F, IL-17C, and IL-17E (98). IL-1 inhibition can improve Th17-related diseases (e.g., hidradenitis suppurativa), although no biologic targeting IL-1 has been FDA-approved in dermatology (99). More recently, also for the Th2 pathway several biologics were formulated. Dupilumab blocks the IL-4Rα receptor inhibiting both IL-4 and IL-13. Tralokinumab and lebrikizumab are IgG4 monoclonal Abs binding selectively to IL-13. Although Tfh are not directly inhibited by anti-CD20 monoclonal Abs such as rituximab, treatment with rituximab decreases the number of Tfh and IL-21 levels (100). Blocking IgE Abs (e.g., omalizumab) decreases the activity of MCs, especially in the context of urticaria with an indirect effect on Th2 and Tfh cells (101).

ARYL HYDROCARBON RECEPTOR (AHR) AGONISTS

The AHR operates as a ligand-activated transcription factor that orchestrates both positive and negative responses generating pro-inflammatory and anti-inflammatory effects depending on the immune environment (102,103). Activation of AHR through its specific ligands influences the differentiation of T cells and the functionality of Tregs and Ag-presenting cells. AHR regulates the production of cytokines including IL-10, IL-21, and IL-22, and is involved in the differentiation of regulatory T cells and Th17 cells (104). Activation of AHR, through specific agonists like topical tapinarof in psoriasis, reduces skin inflammation and leads to early clinical improvements with 41% complete disease clearance (105). AHR signaling downregulates the Th1 pathway by enhancing IL-10 production and CD39 expression by regulatory T1 cells which induces broad immunosuppressive activities (106). In AD, the IL-13/IL-4-JAK-STAT6 pathway suppresses AHR's role in promoting the transcription of skin barrier proteins like fillagrin, loricrin, and involucrin (107).

PROSTANOIDS

Prostanoids, specifically prostaglandin E2 (PGE2), play a pivotal role in the immune regulation of inflammatory skin conditions, such as AD. It can both inhibit and provoke inflammatory responses by affecting the balance of Th1/Th17 and regulatory T cells, influencing cytokine production and eosinophil infiltration (108,109). In general, prostanoids suppress Th1-mediated immunity and inhibit IFN-γ. This explains the use of topical prostaglandins in alopecia areata and vitiligo. PGE2 induces Th2 cytokines IL-4, IL-5, and IL-13 and promotes IL-17 and IL-22 production with increased Th17 activity (110,111).

SMALL MOLECULES

Phosphodiesterase 4 (PDE4) inhibitors

Inhibition of PDE4, leads to intracellular cyclic adenosine monophosphate production which inhibits proinflammatory signals (e.g., IL-6, IL-8, IL-13, TNF-α, IL-17, IL-22, and IL-23), while anti-inflammatory cytokines such as IL-10 increase. 4 types of PDE4 exist of which PDE4B and PDE4D are the predominant drivers of inflammation with limited additional contribution of PDE4A (112). Apremilast, the first orally administered PDE4 inhibitor approved for psoriasis inhibits all 4 isoforms of PDE4 (113). Apremilast, mainly acts on innate immune cells and to a lesser extent on lymphocytes (114). Nonetheless, a reduction of Th1 and Th17 molecules have been reported with apremilast such as IL-2, IL-12, IL-23, and TNF-α (115). The development of topical formulations like roflumilast for psoriasis and crisaborole for AD has significantly mitigated the common gastrointestinal side effects associated with oral apremilast by minimizing systemic absorption (116). Other PDE inhibitors exist including orismilast, notable for its selectivity towards PDE4B and PDE4D subtypes (112).

JAK inhibitors

The JAK family consists of 4 members: JAK1, JAK2, JAK3, and Tyk2. All cytokine receptors are associated with one or more JAKs for their downstream signal transduction through STAT dimerization, translocation to the nucleus and transcription (117). Although targeted, all JAKs are responsible for the signaling of a relatively broad range of cytokines. JAK1 is responsible for Th1 cytokines (e.g., IFN-γ, IL-2, IL-15, IL-27), Th2 cytokines (e.g., IL-4, IL-5, IL-13), the follicular Th cytokine IL-21 and a broad range of other cytokines (such as IFN-α, IFN-β, LIF, OSM, IL-6, IL-7, IL-9, IL-10, IL-19, IL-20, IL-22, IL-27, IL-28, IL-29, IL-35). JAK2 signals also the key Th1 cytokine IFN-γ, the Th2 cytokine IL-13, the Th17 cytokine IL-23 and other cytokines (e.g., IL-6, LIF, OSM, IL-10, IL-19, IL-20, IL-22, and IL-27). JAK3 involves a more restricted number of cytokines of the Th1 pathway, IL-2 and IL-15, the Th2 pathway, IL-4, the Tfh IL-21, and other cytokines including IL-7, and IL-9. Tyk2 has a more limited scope involving IFN-α, IFN-β, LIF, OSM, IL-6, IL-10, IL-11, IL-12, IL-19, IL-20, IL-22, IL-27, and IL-23. Regarding innate immunity, JAK1/2 and Tyk2 affect the activity of Ag presenting cells such as monocytes and dendritic cells. JAK1 and Tyk2 decrease the signaling of NK cells, while JAK2 decreases cytokine signaling affecting neutrophil function and survival. JAK3 seems only to have an indirect effect on innate immune cells (118). JAK1 selective inhibitors include upadacitinib, abrocitinib, and povorcitinib, while anti-JAK1/JAK2 inhibitors are ruxolitinib and baricitinib. Ritlecitinib is an anti-JAK3 blocker. Anti-Tyk2 inhibition is carried out by deucravacitinib and tofacitinib is a panJAK inhibitor.

TEC inhibition

Tyrosine-protein kinase TEC is expressed by hematopoietic liver and kidney cells and regulates Th cell activities. TEC modulates cytokine receptor signaling, lymphocyte surface Ags and integrins. TEC kinase is upregulated in activated T cells and especially in Th2 cells. In contrast, without TEC kinase Th17 cells are increased in number and higher levels of IL-17A, IL-17F are detectable. Ritlecitinib is an example of a JAK3/TEC inhibitor (119).

IL-1 inhibition

Anakinra and lutikizumab (ABT-981) are anti-IL1A/1B drugs being explored for in several immune-mediated diseases, including HS. By targeting two forms of interleukin-1 (IL1α and IL1β) inflammatory responses are dampened (120,121). IL-1 is involved in promoting Th17

https://doi.org/10.4110/in.2024.24.e33

cell differentiation with less clear effects on Th1, Th2, and Tfh. IL-1 drives innate immunity and regulates the long-term memory of innate immune cells (122).

UPCOMING THERAPEUTIC DEVELOPMENTS

PD-1 agonists

Instead of blocking inhibitory signals, enhancing the immune system's capacity to identify and eliminate cancer cells, PD-1 agonists activate the PD-1 pathway, aiming to regulate autoimmune diseases by dampening the immune response to self-tissues. Given the frequent development of vitiligo and other skin eruptions in patients receiving anti-PD1 therapy, PD-1 agonists may improve several immune-mediates skin disorders (123). JNJ-4703 is currently undergoing phase II clinical trials for the treatment of AD (124).

Bruton kinase

Bruton's tyrosine kinase (BTK) a crucial enzyme within the TEC family of kinases. BTK stimulates the activity of various immune cells, including B cells, MCs, macrophages, and basophils, by mediating signals from receptors like the B-cell receptor and the IgE receptor FcεRI in MCs (125,126). Autoimmune diseases see BTK facilitating the activation and differentiation of autoreactive B cells into cells that produce autoantibodies, correlating BTK expression with the severity of autoimmune conditions, especially bullous skin disorders (127). In allergic responses, BTK is key to the process where allergens trigger IgE crosslinking on MCs and basophils, leading to the release of inflammatory mediators (128). Additionally, BTK contributes to other inflammatory mechanisms such as IgG-mediated activation of monocytes and migration of neutrophils (129). Next-generation BTK inhibitors, including fenebrutinib, remibrutinib, rilzabrutinib, and tirabrutinib are under research for their potential in treating chronic spontaneous urticaria and pemphigus (130).

IL-21 receptor inhibitors

IL-21 plays a crucial part in driving CD4+ T cells towards a Th17 profile and enhances the expression of CXCR5 on T cells, which is pivotal for the development of Tfh and the formation of germinal centers (131). The primary sources of IL-21 include Th17 and Tfh cells, and to a lesser degree, NK cells (132). The production of IL-21 can be stimulated by several cytokines like IL-6, IL-7, and IL-15 through the activation of STAT3, although IL-4 does not seem to induce its production. Intriguingly, IL-21 can also augment its own expression through a positive autocrine feedback loop (133).

Emerging research suggests IL-21's involvement in the pathogenesis of various inflammatory skin diseases such as AD, lichen planus, psoriasis and classical autoimmune diseases including (lupus erythematosus), pemphigus, Sjögren's syndrome, and systemic sclerosis (134).

Anti-IL22 receptor

IL-22 is highly present in severe AD skin. In chronic AD a conversion of Th2 signaling to a mixed activation of Th1, Th22, and Th2 takes place. IL-22 induces skin acanthosis. Anti-IL-22 blockade showed only clinical efficacy in patients with severe AD. In these patients, IL-22 inhibition downregulated Th1, Th2, Th17, Th22 signaling leading to a broad immune dampening response (135).

Anti-IL31

The 'itch' cytokine IL-31 is produced by immune cells (Th cells, dendritic cells, and monocytes/macrophages) and skin cells (fibroblasts, keratinocytes). While histamine leads to acute itch, IL-31 is more produced in AD. It stimulates keratinocyte proliferation which is clinically seen by lichenification which represents a combined Th2, Th17, and Th1 signaling (136).

Anti-OX40/OX40 ligands (OX40L)

Anti-OX40 and anti-OX40L inhibitors such as rocatinlimab and amlitelimab are developed for AD. OX40 is a co-stimulatory T cell receptor which is mainly expressed by effector and regulatory T cells. The ligand of OX40 is found on macrophages, activated B cells, endothelial cells and activated Ag presenting cells. The binding of OX40L to OX40 induces Th1 and Th2 proliferation and survival, cytokine production, and development of memory T cells. This signaling is crucial for memory Th2 responses and subsequent IL-4, IL-13, and IL-22 production. OX40 is expressed upon IL-33 production by keratinocytes but also by other cytokines such as TNF-α, IFN-γ, and PGE2 (137). OX40/OX40L regulates Tfh differentiation which is likely to play a role in several autoimmune disorders such as lupus (138).

IL-2 mutein

IL-2 activates both Tregs as inflammatory immune cells which has triggered research to increase Treg specificity. Mutant proteins of IL-2 having decreased affinity for CD122 exhibit more Treg inducing capacity with less effect on other immune cells (139). Tregs can inhibit all Th pathways although IFN-γ production by Th1 cells, and IL-17 by Th17 cells can be more efficiently inhibited compared to Th2 cells.

Anti-IL-15/IL-15 receptor (IL-15R)

Neutralizing IL-15 or the IL-15R is a promising strategy to inhibit IFN-γ producing memory T cells. Its potential seems to primarily be in Th1-mediated disorders. Mice experiments showed reversal of vitiligo in mice using IL-15 blockade (140). Data of human trials in dermatology remain currently unavailable.

Anti-neonatal Fc receptor (FcRn)

The FcRn regulates the transport, distribution, and persistence of IgG. As a therapeutic, anti-FcRn can decrease the half-life of pathogenic Abs, similar to plasma exchange and immunoabsorption (141). Anti-FcRn has been shown to decrease desmoglein-specific B cells in pemphigus (142). Nipocalimab is being tested for lupus.

DISCUSSION

Cutaneous inflammatory disorders are extremely varied and display different contributions of immune pathways. Having insights into the immune balance of each skin disease and the working mechanisms of possible treatments can be extremely helpful for the treatment of recalcitrant and complex cases. It also provides an opportunity to look into the future for possible therapeutic approaches. Biologics are likely the best choice for skin diseases with one dominant immune pathway. Biologics can offer impressive results with limited side effects due to their restricted collateral damage on immunity. However, to date we still lack a biologic approach targeting the Th1 pathway for the treatment of alopecia areata, vitiligo and other Th1 dominant disorders. While inhibition of the Th2 (e.g., AD) and the Th17 pathway (e.g., psoriasis) can be done without severely hampering our body's defense against life-

threatening pathogens or diseases, it remains unclear whether this approach is feasible for the Th1 pathway given its crucial role in antiviral and antitumoral protection. Nonetheless, given the redundancy of most signaling pathways targeted treatment has been shown to be remarkably safe even if key signaling cascades are blocked (14,18).

As can be seen in **Table 1**, a substantial number of skin diseases exhibit a combined upregulation of multiple Th lineages (e.g., bullous pemphigoid, dermatomyositis, eosinophilic fasciitis, graft-versus-host disease, pus, morphea…). This can lead to an inconsistent efficacy of biologics depending on the patient profile. Clinical and laboratory signs can point to activity of certain Th pathways. The loss of skin cells or interface dermatitis points to a Th1 dominance, while pruritus, skin fibrosis, eosinophils and high IgE values reflect Th2 activation. In contrast, pustular inflammation, and hyperkeratosis reflect Th17 and/or Th22 signaling. Small molecules such as JAK inhibitors offer significant advantages in terms of potency over conventional immunosuppressants if multiple Th pathways are increased. Although clinical trials have yet to provide a clear picture of the in vivo differential effectiveness of JAK1, JAK2, JAK3, or Tyk2 inhibition depending on the immune infiltrate, an estimate can be derived based on their inhibitory cytokine profile (**Table 2**). JAK1 and JAK2 inhibition seem most potent to inhibit Th1 disorders, while blocking JAK3 or Tyk2 might lead to less long-term adverse effects by not directly targeting IFN-γ (117).

Unexpected or 'paradoxal' phenomena during immunotherapy can in part be explained by the contribution of a network of cytokines regulating the differentiation of naive T cells. Additionally, Th17 cells retain stem cell-like properties and can transdifferentiate to acquire a Th1, Th2 or Treg-like phenotype depending on the changed immune environment by treatments. Additionally, cytokines (including IL-4) also have, besides the capacity to induce one Th lineage (e.g., Th2), an inhibiting effect on other immune cell subsets (e.g., Th1, Th17). Due to the complex interaction with other driving cytokines (e.g., reciprocal inhibitory effect of IL-4 and TGF-β on each other) a positive or negative influence on the development and evolution of inflammatory skin disorders can be seen depending on the immune environment. An example is the use of dupilumab for alopecia areata, which is only effective in case of an atopic background illustrated by high IgE levels (143). Further research to understand the synergistic and antagonistic interactions between cytokines and their impact on immune cell behavior is crucial given the fast-growing therapeutic arsenal in dermatology. In other circumstances such as with IL-22R inhibition, the treatment is only effective in a particular state of the disease (e.g., severe AD) which can be seen clinically by lichenification, severe pruritus and epidermal hyperplasia reflecting a mixed Th2, Th1, Th17 and Th22 response (136). One may choose to target only the key cytokine causing the most disturbing complaint such as itch by blocking IL-31. This may not necessarily clear the entire diseased skin but improve the quality of life considerably (144).

Future study design may look further than skin (disease), but take into account the concept of 'multimorbidity', with endpoints in several organ diseases at the same time, with common pathogenetic origin (145). A limitation of this review is the non-exhaustive list of therapeutic targets covered, considering the large number of drug targets currently under investigation in dermatology.

https://doi.org/10.4110/in.2024.24.e33

Table 2. Inhibition of the Th1, Th2, Th17, Tfh pathways according to the immunomodulating drug

Drug type	Th1	Th2	Th17	Tfh	Innate immunity
Classic immunomodulating drugs/immunosuppressants					
Corticosteroids*	+++	+++	+++	++	+++
Ciclosporin (PSO, AD)	++	++⁺	++⁺	++	+⁺
Tacrolimus (AD)	++⁺	++⁺	++⁺	++	+⁺
Methotrexate (PSO)	++⁺	++	++	++	+⁺
Mycophenolate mofetil	++	+⁺	+⁺	+++	+⁺
Azathioprine	++	++	++	++	+⁺
Fumaric acid (PSO)	++	/	++	+++	+⁺
Anti-inflammatory drugs					
Dapsone (DH)	⁺	/	⁺	/	++
Hydroxychloroquine (SLE)	+	/	+	+	++
Biologics					
Anti-IL-1			+		++
Anti-IL-4Rα (AD, PN)	/	++++	/	++⁺	/
Anti-IL13 (AD)	/	++++	/	/	/
Anti-IL17A (PSO)	/	/	++++	/	⁺
Anti-IL17A/IL17F (PSO)	/	/	++++⁺	/	⁺
Anti-IL17RA (PSO)	/	+	++++⁺	/	⁺
Anti-IL23 (PSO)	/	/	++++	/	/
Anti-IL12/23 (PSO)	⁺	/	++++	/	/
Anti-IL31 (AD, PN)	/	++	+	/	/
Anti-IgE (URT)	/	+	/	+⁺	+++
Anti-CD20 (PEMPH)	/	/	/	+++†	/
PDE4 inhibitors					
Apremilast (PSO)	+	+	++	/	++
Roflumilast (SD)	+	+	++	/	++
JAK inhibitors					
JAK1 (AA, VIT)	++++	+++	+++	++	+⁺
JAK2 (AA, VIT)	++++	+++	+++	+⁺	+⁺
JAK3 (AA)	+++	+++	+++	++	/
Tyk2 (PSO)	++⁺	+	+++	+	+⁺
Estimated influence of new therapeutics with limited data					
AHR agonists (PSO, AD)	++(+?)	++(+?)	+++	++	++
Anti-FcRn	/	/	/	++++	/
Anti-Il-1a/1b	+	/	++	++	++
Anti-IL-15/IL-15R	+++	/	/	/	+
Anti-IL21R	/	+++	++	+++	++
Anti-IL22R	/	+++	++		++
Anti-OX40	++⁺	+++	+	++⁺	++
Bruton kinase inhibitors	/	++	+	+++†	++
IL-2 mutein	+++	+	++⁺	++	+
PD-1 agonists	+++	++	++	/	++
Prostanoids	++	/	/	/	++

Between brackets: FDA or EMA approved indication.
Inhibition: ++++, very strong; +++, strong; ++, moderate; +, limited; /, no; ?, unknown.
PSO, psoriasis; DH, dermatitis herpetiformis; SLE, systemic lupus erythematosus; PN, prurigo nodularis; URT, urticaria; PEMPH, pemphigus; SD, seborrheic dermatitis; AA, alopecia areata; VIT, vitiligo; FDA, Food and Drug Administration; EMA, European Medicines Agency.
*FDA- and EMA approved for a wide range of inflammatory skin conditions; †These drugs directly target B lymphocytes with indirect influence on Tfh cells.

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