The Role of Interleukins in the Pathogenesis of Dermatological Immune-Mediated Diseases

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ABSTRACT

Autoimmune inflammatory diseases are primarily characterized by deregulated expression of cytokines, which drive pathogenesis of these diseases. A number of approved and experimental therapies utilize monoclonal antibodies against cytokine proteins. Cytokines can be classified into different families including the interleukins, which are secreted and act on leukocytes, the tumor necrosis factor (TNF) family, as well as chemokine proteins. In this review article, we focus on the interleukin family of cytokines, of which 39 members have been identified to this date. We outline the role of each of these interleukins in the immune system, and various dermatological inflammatory diseases with a focused discussion on the pathogenesis of psoriasis and atopic dermatitis. In addition, we describe the roles of various interleukins in psychiatric, cardiovascular, and gastrointestinal comorbidities. Finally, we review clinical efficacy and safety data from emerging late-phase anti-interleukin therapies under development for psoriasis and atopic dermatitis. Collectively, additional fundamental and clinical research remains necessary to fully elucidate the roles of various interleukin proteins in the pathogenesis of inflammatory dermatologic diseases, and treatment outcomes in patients.

Keywords: Psoriasis; Atopic dermatitis; Interleukin; Cytokine

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Key Summary Points

Pathogenesis of psoriasis and atopic dermatitis is largely driven by a complex cross-regulatory network of interleukins.

Interleukins can drive metabolic and psychiatric comorbidities associated with inflammatory dermatologic conditions.

Continued characterization of pathogenic roles of interleukin proteins will facilitate development of novel biologic therapies.

INTRODUCTION

The immune system comprises various effector cells and associated cytokines that elicit adaptive and innate immune responses against pathogens. While the innate immune response is intrinsic to the human body since birth and is nonspecific, the adaptive immune response develops over time after exposure to an antigen either from a pathogen or a vaccination, and includes the production of specific antibodies against a foreign antigen [1]. Antigen presentation on dendritic cell surface along with the necessary costimulatory molecules can lead to activation of naïve T cells and their proliferation and subsequent differentiation to either CD8+ cytotoxic T cells or CD4+ helper T cells (Th cells) [1]. Thus, dendritic cells act as an important link between the innate and adaptive immune responses.

There are five major subtypes of CD4+ T cells: Th1 cells, Th2 cells, Th17 cells, T follicular helper cells, and regulatory T cells (Treg) [1]. Th1 cells are involved in intracellular immunity and release interferon-γ to activate macrophages. Th2 cells play a crucial role in mucosal and barrier immunity and release interleukins 4 and 5 (IL-4 and IL-5) to recruit eosinophils and basophils. Th17 cells produce Th17 cytokines such as IL-17 and IL-22 that activate stromal cells and epithelial cells, respectively, to produce various chemokines and antimicrobial peptides that recruit neutrophils to eliminate extracellular pathogens. T follicular helper cells interact with naïve B cells and regulate their antibody production capacity. Finally, Tregs suppress innate immunity and T-cell activation thus acting as a safeguard against development of autoimmunity. In addition, Treg pathways exist in close interaction with each other, and have associated feedback and feedforward regulatory mechanisms.

Both innate and adaptive immune cells are able to generate inflammatory mediators to combat infection and amplify or modulate the immune response. These mediators can be categorized into chemokines and cytokines that are secreted and act on other cells that harbor the respective cognate receptors. Cytokines are small proteins important in cell signaling and important in immune-mediated diseases, while chemokines are small cytokines or signaling proteins secreted by cells that induce directional movement of leukocytes, as well as other cell types. Cytokines are the principal determinants of CD4+ T-cell lineage specification [1]. Exposure of a naïve T cell to various combinations of cytokines will allow it to differentiate to any of the five mentioned subtypes above by activating various members of the STAT family of transcription factors as well as other lineage-specific transcription factors.

It has now become abundantly clear that interleukins play critical roles in the pathogenesis of inflammatory dermatologic conditions. In this article, we conducted a literature review to identify interleukins involved in the pathogenesis of dermatologic inflammatory diseases with a focus on psoriasis and atopic dermatitis. We first describe the various known families of interleukins and their main roles in the normal immune response. We then describe important preclinical and clinical data that support pathogenic roles of interleukins not only in psoriasis and atopic dermatitis, but also in a number of associated comorbidities. These include cardiovascular, psychiatric, and gastrointestinal comorbidities. Our last goal in this review article was to highlight emerging anti-interleukin therapies for the treatment of psoriasis and atopic dermatitis.

COMPLIANCE WITH ETHICS GUIDELINES

This article is based on previously conducted studies, and does not contain any new studies with human participants or animals performed by any of the authors.

INTERLEUKIN SUBFAMILIES AND STRUCTURE

The term "interleukin" (between leukocytes) was first coined in Switzerland in 1979 at the second international lymphokine workshop to describe factors that influence function of

leukocytes [2]. A number of nomenclatures have been proposed to classify interleukins based on sequence homology, structural similarity, bound receptors, as well as producing cells. These nomenclatures were adopted by the World Health Organization/International Union of Immunological Societies (WHO/IUIS) in 1990s [3, 4]. However, the advent of next-generation sequencing and continued discovery of additional interleukins increases the complexity of existing nomenclatures. In a recent report, Akdis et al. conducted a comprehensive review of existing interleukin factors and classified them into various families based on sequence homology, evolutionary relationship, common receptor chains, and immunological function [5]. From a structural standpoint, interleukins can be classified into class I or class II helical proteins. Their structural characteristics are described in Table 1 [6, 7]. Table 2 summarizes the main interleukin families, their structure, and main function in the immune

system, their cognate receptors, and producing cells [5, 6, 8–14].

INTERLEUKINS IN PATHOGENESIS OF PSORIASIS AND ATOPIC DERMATITIS

Interleukins produced by innate and adaptive immune cells can form cross-regulatory networks that are the driving force in many dermatologic inflammatory diseases. Table 2 summarizes dermatologic and non-dermatologic diseases in which various interleukins are implicated. In addition, it identifies relevant approved or experimental therapeutics targeting each interleukin. In this section, we discuss the roles of various interleukins in the pathogenesis of two of the most common dermatologic inflammatory diseases, psoriasis (Fig. 1) and atopic dermatitis (Fig. 2).

Psoriasis

In psoriasis, a number of stress triggers—ranging from environmental to genetic—can stimulate innate immune cells and keratinocytes to synthesize tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), IFN-α, IL-6, and IL-1β [15]. These cytokines activate dermal dendritic cells to produce IL-12 and IL-23, which promote differentiation of naïve T cells into Th1 and Th17 cells, respectively. Production of TNF-α and IFN-γ by Th1 cells and IL17A-F and IL-22 by Th17 cells leads to activation and proliferation of keratinocytes, which in turn produce a wide range of proinflammatory cytokines and chemokines that results in the phenotypic manifestations of psoriasis. These inflammatory mediators exist in a positive feedback loop allowing transition from disease initiation to disease maintenance and chronicity [15].

Several additional interleukins have been documented to have complex roles in the pathogenesis of psoriasis. Gene expression profiling of generalized pustular psoriasis and psoriasis vulgaris lesional biopsies revealed elevated IL-1, IL-17A, and IL-36 expression levels compared to biopsies of normal skin [16].

Table 1 Structural characteristics of various interleukins [6, 7]

Structure	Subclassification	Interleukin
Class I: 4 α-helices in an "up-up-down-down" conformation	Short chain	IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-13, IL-15 and IL-21
	Long chain	IL-6, IL-11, IL-12, IL-23, IL-27, and IL-31
Class II: 6–7 α-helices		IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29
β-Trefoil structure made of 12 packed β-sheets		IL-1 family
Neurotrophin-like cysteine-knot fold		IL-17 family

Table 2 List of interleukin family members, their cognate receptors, their source cells, and main functions in immune system [5, 6, 8–14]

Interleukin family	Interleukin (s)	Producing cell(s)	Receptor(s)	Main role in immune system
IL-1 family	IL-1α/β	Macrophages, monocytes, dendritic cells, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial cells	IL-1 type I receptor (IL-1RI)	Potent proinflammatory cytokines, induce Th17 and B cells, induce chemokine production
	IL-1Ra	Monocytes, fibroblasts, endothelial cells, keratinocytes, macrophages, neutrophils	IL-1RI	Inhibits IL-1α/β signaling
	IL-18	Dendritic cells, macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes	IL-18Rα/IL-18Rβ	Enhances NK cell cytotoxicity, promotes Th1 and Th2 immune responses, enhances IFN-γ production
	IL-33	Fibroblasts, macrophages, damaged epithelial cells, dendritic cells	IL-1 receptor-related protein called ST2	Released upon necrosis, inflammation, and cell damage, potent activator of Th2 immune responses
	Il-36α/β/γ/RA	Internal endothelial cells, keratinocytes, skin epithelia	IL-36R	NF-κB activation, activation of other proinflammatory pathways in response to tissue injury or infection, enhance Th17-immune response (inhibited by IL-36RA)
	IL-37	NK cells, monocytes, B cells, keratinocytes, various human tissues	IL-18Rα, single immunoglobulin IL-1 receptor-related protein (SIGIRR)	Inhibits TLR-induced proinflammatory cytokines, suppress dendritic cell activation
	IL-38	Basal epithelia of skin and in proliferating B cells of the tonsil	IL-1R1, IL-36R	Acts similar to IL-36RA, inhibits Th17 immune response, inhibits IL-36 signaling
IL-6 family	IL-6	B and T cells, eosinophils, granulocytes, mast cells, glial cells, keratinocytes, chondrocytes, osteoblasts	IL-6R, gp130	T and B cell proliferation and differentiation, increase chemokine production, induce Th17 cells
	IL-11	Fibroblasts, epithelial cells, endothelial cells, synoviocytes, osteoblasts, bone marrow cells	IL-11Rα, gp130	Stimulates hematopoiesis and platelet production, stimulates Th2 cytokines and inhibits Th1 cytokines

Table 2 continued

Interleukin family	Interleukin (s)	Producing cell(s)	Receptor(s)	Main role in immune system
IL-10 family	IL-10	Monocytes, dendritic cells, Treg cells, B cells, macrophages	IL-10R1 and IL-10R2	Immunosuppressive; inhibits TLR agonist-induced cytokines and chemokine production
	IL-19	Monocytes, macrophages, epithelial cells, endothelial cells	IL-20R1 and IL-20R2	Induces Th2 responses; induces expression of IL-4, 5, 10, and 13
	IL-20	LPS-stimulated monocytes, dendritic cells, epithelial and endothelial cells	IL-20R1/IL-20R2 and IL-22R1/IL-20R2	Regulates hematopoiesis; aid in clearance of bacterial infection via upregulation of psoriasin and β-defensin-2
	IL-22	Th17, Th22 and γδ T cells, activated NK cells	IL-22R1 and IL-10R2	Antimicrobial defense, activate proliferative and anti-apoptotic pathways to prevent tissue damage
	IL-24	B and T cells, monocytes, mast cells	IL-22R1/IL-20R2 or IL-20R1/IL-20R2	Induces expression of IL-6, TNF-α, and IFN-γ in PBMCs, regulates balance between plasma and memory B cells
	IL-26	Memory T cells, Th17 cells, and NK cells	IL-10R2/IL-20R1	Induce proinflammatory cytokines IL-6, IL-8, and TNF-α in epithelial cells, inhibits IgG and IgA production in B cells
	IL-28A (IFN-λ2) IL-28B (IFN-λ3) IL-29 (IFN-λ1)	Dendritic cells, PBMCs, T reg cells, virus-infected cells, monocytes	IL-28R1/IL-10R2	Have antiviral activities against various viruses

Table 2 continued

Interleukin family	Interleukin(s)	Producing cell(s)	Receptor(s)	Main role in immune system
IL-12 family	IL-12p40 and IL-12p70	Monocytes, antigen presenting cells such as macrophages and dendritic cells, neutrophils	IL-12Rβ1 and IL-12Rβ2	Development and maintenance of Th1 cells through induction of IFN-γ, enhance cytolytic activity of NK cells and antimicrobial activity of macrophages
	IL-23	Phagocytic cells, macrophages, activated DCs	IL-23R	Induction and differentiation of Th17 cells, NK cell activation, T-cell proliferation
	IL-27	Antigen-presenting cells such as macrophages and dendritic cells, endothelial cells	WSX-1 (IL-27Ra) and gp130	Development of Th1 cells, antagonizes Th17 cell response
	IL-35	Treg cells, stimulated monocytes, B cells	IL-12Rβ2 and gp130	Reduce proliferation of effector T cells and enhance that of Tregs, induce iTr35 cells, inhibit Th17 immune responses
IL-17 family	IL-17A	Memory CD4+ T cells, Th17 cells, CD8+ T cell, γδ T cells, NK cells, neutrophils	IL-17RA, IL-17RC	Induce expression of proinflammatory cytokines, chemokines, and metalloproteases. Recruits neutrophils
	IL-17F	Similar cell sources as IL-17A; more abundant in the skin compared to IL-17A	IL-17RA, IL-17RC	Similar to IL-17A, it induces chemokines, and proinflammatory cytokines
	IL-17B	Spinal cord cells, testis, small intestines, various nonimmune tissues	IL-17RB	May play a role in fracture healing, embryonic chondrogenesis, and neutrophil recruitment
	IL-17C	Synovial fluid mononuclear cells (SFMC), and PBMCs	IL-17RE	Enhances proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, can induce IL-23
	IL-17D	Skeletal muscle, brain, adipose tissue, heart, lung and pancreas	Not known	Inhibits myeloid progenitor cell proliferation, enhances IL-6, IL-8, LIF, and MMP-3 production
	IL-17E/IL-25	Th2 cells, alveolar macrophages, granulocytes, intestinal epithelial cells, brain endothelial cells	IL-17RA and IL-17RB	Enhances Th2 cell response, inhibits Th1 and Th17 cell response

Table 2 continued

Interleukin family	Interleukin(s)	Producing cell(s)	Receptor(s)	Main role in immune system
Th2 cytokines	IL-5	Th2 cells, eosinophils, mast cells	IL-5Rα and a β chain subunit (CD131) recognized by IL-3 and GM-CSF	Activation, maturation, and survival of eosinophils
	IL-13	Th2 cells, T cells, NKT cells, mast cells, basophils, eosinophils	IL-4Rα and IL-13Rα1	Promotes isotype switching of B cells, inhibits inflammatory cytokines, defends against nematodes
	IL-31	Activated CD4+ Th2 cells, mast cells, monocytes, macrophages, dendritic cells	IL-31RA and oncostatin M receptor β (OSMRβ)	Modulates eosinophil function, induces chemokines in keratinocytes, induces itching upon engaging its receptors on sensory neurons
Chemokines	IL-8	Monocytes, macrophages, neutrophils, endothelial cells	CXC chemokine receptors: IL-8RA and IL-8RB	Recruitment of neutrophils to infection/injury site
	IL-16	T cells, mast cells, eosinophils, monocytes, dendritic cells	CD4	Chemoattractant of CD4+ and CD8+ T cells, monocytes, mast cells and eosinophils
Common γ chain cytokine family	IL-2	CD4+ and CD8+ T cells	IL-2R composed of IL-2Rα, IL-2Rβ, and γc (CD132)	Proliferation and development of effector B and T cells
	IL-4	Th2 and type II innate lymphoid cells (ILC2)	Type I and II IL-4R	Development of Th2 cells from naïve T cells
	IL-7	Stromal and epithelial cells of non-hematopoietic origin	IL-7R composed of IL-7Rα and CD132	Lymphocyte development in the thymus, and naïve T-cell survival
	IL-9	Th2 and Th9 cells	IL-9R composed of IL-9Rα and CD132	Proliferation of CD8+ T cells and mast cells, reduction of Th1 cytokines, enhancing Th2 immune responses
	IL-15	Monocytes, CD4+ T cells, macrophages, dendritic cells	IL-15R composed of IL-15Rα, IL-15Rβ, and CD132	T cell and NK cell activation
	IL-21	T cells and NKT cells	IL-21R	B cell differentiation and activation, NKT cell survival, CD4+ T-cell proliferation, NK cell maturation

Table 2 continued

Interleukin family	Interleukin(s)	Producing cell(s)	Receptor(s)	Main role in immune system
Other interleukins	IL-3	T cells, NK cells, eosinophils, macrophages	IL-3Rα and CD131	Hematopoietic cell differentiation, synergizes with GM-CSF to induce granulocyte–macrophage lineage, enhance macrophage function
	IL-14	Normal T cells and B cells, and cancerous B cells	IL-14R	Enhances B cell proliferation, inhibits antibody production
	IL-32	T cells, NK cells, lung and intestinal epithelial cells	Unknown	Induces monocyte to macrophage differentiation
	IL-34	Splenic cells, neuronal cells	CSF1R	Proliferation of monocytes and macrophages

Interestingly, IL-1 and IL-36 levels were more elevated in pustular psoriasis vs. psoriasis vulgaris. Immunohistochemical analysis showed that IL-36 was particularly expressed in keratinocytes surrounding neutrophilic pustules. Importantly, loss of function mutations in the *IL36RN* gene, which encodes for the IL-36 receptor antagonist, have been linked to pathogenesis of a debilitating form of psoriasis, generalized pustular psoriasis (GPP) in a mechanism that involves unrestrained IL-36 signaling that causes IL-1 activation [17, 18]. Anakinra, an IL-1R antagonist, has been described to improve pustular eruptions in generalized pustular psoriasis patients [19]. In addition, it has also proven effective in a patient with pustular psoriasis driven by *IL36RN* mutations, although it remains unclear what weight IL-1 vs. IL-36 have in pathogenesis of pustular psoriasis [20]. IL-36R inhibition blocks proinflammatory pathways underling GPP, and it has been suggested that IL-36 inhibiting therapies may provide more complete clinical benefit in patients harboring *IL36RN* mutations [21–23]. In addition, data from the 12-week Effisayil-1 trial, which examined efficacy of spesolimab, a humanized monoclonal IgG1 anti-IL-36R antibody, demonstrated superiority (vs. placebo) in clearing flares in patients with generalized pustular psoriasis [24]. Efficacy of imsidolimab, another IL-36R monoclonal antibody, was examined in the GALLOP phase 2 open-label trial. Seventy-five percent of patients with generalized pustular psoriasis (6/8) receiving imsidolimab achieved improvement in Clinical Global Impression (CGI) based on the modified Japanese Dermatology Association Severity Index (mJDA-SI) both at week 4 and week 16 [25].

IL-6 has been reported to be highly elevated in active psoriatic plaques from 35 psoriasis patients compared to non-lesional biopsies. In addition, IL-6 levels were increased in plasma of these patients, which may also contribute to epidermal hyperplasia given that IL-6 stimulates keratinocyte proliferation [26]. While this might indicate that targeting IL-6 could be beneficial in psoriasis treatment, clinical data reveals the opposite. Tocilizumab, a monoclonal anti-IL-6R antibody indicated for

moderate-to-severe rheumatoid arthritis (RA), has been shown to induce psoriasis-like disease in a number of RA patients [27–29]. It is noteworthy that preclinical data originating from mouse studies have shown that genetic deletion of IL-6 can result in more severe psoriasis-like disease, potentially through a mechanism involving increased expression of proinflammatory cytokines that appear to compensate for IL-6 deletion [30, 31].

IL-8 levels are increased in psoriatic scale extracts as well as suction blister fluids in psoriatic skin lesions [32]. The major source of IL-8 in psoriatic tissue appears to be neutrophils located immediately under the parakeratotic stratum corneum (Munro's microabcess) [33]. Given that IL-8 induces chemotaxis in neutrophils, and that neutrophils can synthesize IL-8 upon activation, it is plausible that IL-8 acts in an autocrine fashion to maintain neutrophil infiltration in psoriatic tissue thereby contributing to inflammation [33].

Given the anti-inflammatory properties of IL-11, a phase I open-label clinical trial assessed the efficacy of daily recombinant human IL-11 (rhIL-11) subcutaneous injections in 12 psoriasis vulgaris patients [34]. 11/12 patients had a 20–80% improvement in Psoriasis Area and Severity Index (PASI) score after 8 weeks of treatment, which was associated with reduced

expression of proinflammatory cytokines such as IFN-γ, IL-8, IL-12, TNF-α, IL-1β. Large clinical trials remain necessary to confirm efficacy of rhIL-11 as an anti-inflammatory agent in psoriasis patients.

Ustekinumab acts by targeting the p40 subunit shared by IL-12 and IL-23, both of which are involved in inflammation and NK cell and CD4+ T-cell activation in psoriasis. Furthermore, both IL-23 and IL-23R are overexpressed in human psoriatic tissue [35]. The individual contribution of IL-12 and IL-23 in the imiquimod-induced psoriasis mouse model was recently examined [36]. As expected, mice deficient in the p40 subunit had a significant decrease in psoriatic plaque formation, however, mice that were engineered to be deficient of the IL-12 specific p35 subunit or the IL-12 receptor (i.e., intact IL-23 signaling) suffered from more severe inflammation and plaques compared to their wild type counterparts. This involved increased infiltration of IL-17A-producing Vγ4+ γδT cells. Importantly, this phenotype was alleviated by exposure to IL-12, suggesting that IL-12 has a protective effect and limits skin inflammation in this psoriasis mouse model. In human keratinocytes, IL-12 exposure also counteracted the psoriatic transcriptional signature, although the specific role of IL-12 in patients with psoriasis is still questionable as no monoclonal antibody targeting only IL-12 has been studied in humans. These data may suggest that concomitant targeting of IL-12 along
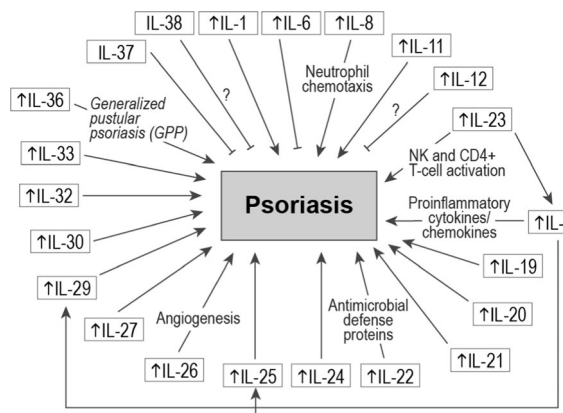
Fig. 1 Interleukins involved in pathogenesis of psoriasis. An upwards arrow (↑) indicates elevated expression. Many interleukins contribute to psoriasis pathogenesis whereas others may play a protective role through increased expression of antimicrobial defense proteins
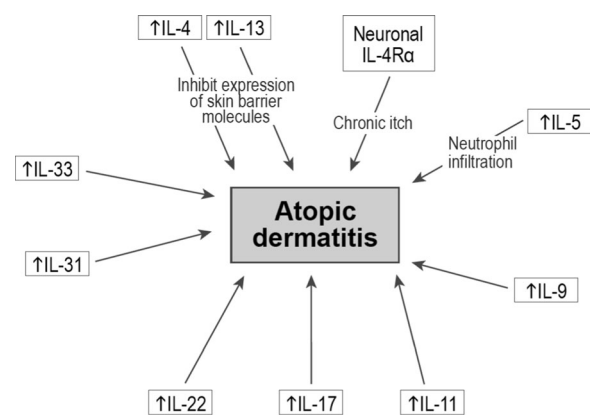
Fig. 2 Interleukins involved in pathogenesis of atopic dermatitis. An upwards arrow (↑) indicates elevated expression

Table 3 Interleukins involved in dermatological diseases, important associated comorbidities, and relevant experimental or approved therapeutics

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-1α/β IL-RA	Hereditary systemic autoinflammatory diseases[a] Systemic inflammatory diseases[b] Hidradenitis suppurativa Pustular psoriasis Neutrophilic dermatoses Urticarial vasculitis Kawasaki disease Erdheim–Chester disease	Diabetes Cardiac remodeling Gout RA Osteoarthritis GVHD Dry eye disease	Rilonacept is an interleukin-1 alpha (IL-1α) and interleukin-1 beta (IL-1β) cytokine trap indicated for cryopyrin-associated periodic syndromes, familial cold autoinflammatory syndrome and Muckle–Wells syndrome, deficiency of IL-1 receptor antagonist, and recurrent pericarditis Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody indicated for treatment of autoinflammatory periodic fever syndromes Anakinra is a recombinant, nonglycosylated form of IL-1RA indicated for rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS), and deficiency of interleukin-1 receptor antagonist (DIRA)	[113–118]
IL-2	Alopecia areata Malignant melanoma		Aldesleukin is a recombinant IL-2 protein therapy approved for use in patients with stage IV melanoma	[119, 120]
IL-4	Atopic dermatitis Scleroderma Bullous pemphigoid	Atopic comorbidities	Dupilumab, an FDA approved anti-IL-4Rα monoclonal antibody for treatment of patients with atopic dermatitis or asthma	[70, 121–124]
IL-5	Atopic dermatitis Hypereosinophilic syndrome	Asthma EoE Eosinophilic granulomatosis with polyangiitis Nasal polyposis	Benralizumab, mepolizumab, and reslizumab are 3 FDA-approved anti-IL-5 antibodies for treatment of adult patients with severe eosinophilic asthma	[125–127]

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-6	Psoriasis (−) Pustular psoriasis Hidradenitis suppurativa Wound Healing	RA Psoriatic Arthritis (−) Cardiovascular disease Depression Diabetes	Tocilizumab, monoclonal antibody against IL-6R, indicated for RA, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, cytokine release syndrome Siltuximab, monoclonal antibody against IL-6, indicated for multicentric Castleman's disease	[26, 31, 128–133]
IL-7	CTCL (elevated levels) Generalized verrucosis and HPV-3 susceptibility (inherited IL-7 deficiency)	T-cell acute lymphoblastic leukemia Sjögren's syndrome Multiple sclerosis	Safety of GSK2618960, an experimental anti-IL-7R antibody, has been assessed in healthy subjects (NCT02293161) RN168, an experimental anti-IL-7R antibody, is being assessed in patients with type I diabetes (NCT02038764)	[134–140]
IL-8	Psoriasis Pyoderma gangrenosum	IBD Ovarian cancer	BMS-986253 is an experimental anti-IL-8 monoclonal antibody being assessed in patients with incurable metastatic or unresectable solid tumors (NCT02536469)	[32, 33, 141–143]
IL-9	Atopic dermatitis Allergic contact dermatitis Mycosis fungoides Important defense mechanism against *Candida*			[75, 144–147]

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-10	SLE Pemphigus vulgaris Bullous pemphigoid Alopecia areata Psoriasis Atopic dermatitis Allergic contact dermatitis Melanoma BCC/SCC Cutaneous lymphomas Hypertrophic scarring	Important in viral diseases: HIV, EBV, Herpesviruses, CMV, Poxviruses Leishmaniasis Leprosy Systemic sclerosis	SCH708980, a monoclonal anti-IL-10 antibody being assessed as an anti-immunosuppressive agent in visceral leishmaniasis (NCT01437020)	[148, 149]
IL-11	Psoriasis Atopic dermatitis (skin remodeling)	Cardiovascular fibrosis		[34, 76, 150]
IL-12	Psoriasis Atopic dermatitis Photocarcinogenesis	Important in protection against infections and allergens	Ustekinumab, an anti-IL-12/23 antibody is indicated for moderate-to-severe plaque psoriasis, active psoriatic arthritis, moderate-to-severe Crohn's disease, and ulcerative colitis	[36, 151–154]

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-13	Atopic dermatitis Behçet's disease Systemic sclerosis Localized scleroderma		Dupilumab, see above Lebrikizumab, an experimental anti-IL-13 monoclonal antibody for treatment of atopic dermatitis (NCT03443024) or asthma (NCT02104674) Tralokinumab, anti-IL-13 antibody for treatment of patients with atopic dermatitis (NCT03131648 and NCT03160885) or asthma (NCT02161757 and NCT02194699). It has received regulatory approval by Health Canada	[83, 155–162]
IL-14	Sjögren's syndrome SLE			[163, 164]
IL-15	Vitiligo Mycosis fungoides	RA Sarcoidosis IBD Transplant rejection Hematologic malignancies Infections	IL-15 superagonist complex N-803 is an experimental treatment being assessed in BCG-unresponsive non-muscle invasive bladder cancer patients (NCT03022825)	[165–168]
IL-16	Cutaneous T-cell lymphoma Systemic sclerosis SLE Bullous pemphigoid	HIV/immune reconstitution syndrome		[169–173]

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-17	Psoriasis	Asthma	Secukinumab and ixekizumab (IL-17A antibodies) and brodalumab (IL-17RA antibody)	[39, 40, 43, 174–178]
	Psoriatic arthritis	IBD	Bimekizumab, a monoclonal antibody that targets both IL-17A and IL-17F that was assessed in clinical trials in patients with plaque psoriasis (NCT03536884). It is approved by the EMA, and pending approval by the FDA and Health Canada	
	Ankylosing spondylitis			
	Tumor progression		Sonelokimab is an IL-17A/17F nanobody which neutralizes both IL-17A and IL-17F, and is currently being assessed in patients with plaque psoriasis (NCT03384745)	
IL-18	Lupus	IBD	GSK1070806, an experimental monoclonal antibody against IL-18 (NCT03522662)	[179–183]
	Hemophagocytic syndrome	CVD		
IL-19	Psoriasis			[46, 184]
	Atopic dermatitis			
IL-20	Psoriasis	RA		[47, 49]
		PsA		
IL-21	SLE	RA		[50, 185–192]
	Psoriasis	IBD		
	Atopic dermatitis	Colon cancer		
	Alopecia areata			
	Melanoma (anti-tumorigenic role)			

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-22	Psoriasis Atopic dermatitis Contact dermatitis Scleroderma CTCL Squamous cell carcinoma	Multiple sclerosis RA	Fezakinumab, a monoclonal anti-IL-22 antibody being assessed in atopic dermatitis (NCT01941537)	[51, 52, 77, 193–200]
IL-23	Psoriasis	Crohn's disease RA PsA	Ustekinumab, see above Guselkumab, risankizumab, tildrakizumab	[35, 90, 201–203]
IL-24	Psoriasis Contact dermatitis Atopic dermatitis	IBD (suppresses mucosal inflammation)		[48, 54, 204–206]
IL-25	Psoriasis	Asthma		[55, 207, 208]
IL-26	Hidradenitis suppurativa Psoriasis Behçet's disease	RA Crohn's disease Asthma COPD		[56, 209–215]
IL-27	Psoriasis Systemic sclerosis	COPD Breast cancer Sjögren's syndrome Rheumatoid Arthritis		[58, 216–220]

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-28	SLE	Sepsis		[221–224]
		HCV clearance		
		Hashimoto's thyroiditis		
IL-29	SLE	RA	Peginterferon Lambda-1A or IL-29 is being assessed in clinical trials for treatment of patients with COVID-19 (NCT04354259) or hepatitis C (NCT01866930)	[62, 224–231]
	Psoriasis	Osteoarthritis		
	Atopic dermatitis	Uveitis		
	Systemic sclerosis	Sjögren's syndrome		
		Hashimoto's thyroiditis		
IL-30	Psoriasis	Breast cancer		[59, 232, 233]
		Prostate cancer		
IL-31	Chronic pruritic skin disorders	Allergic asthma and rhinitis		[234]
		IBD		
		Osteoporosis		
IL-32	Psoriasis	Grave's disease		[64, 235–239]
	Atopic dermatitis	RA		
		Pulmonary arterial hypertension		
		COPD		

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-33	Psoriasis	Allergic rhinitis	Itepekimab, experimental monoclonal antibody against IL-33 in COPD (NCT04751487)	[60, 240–247]
	Atopic dermatitis	Asthma		
	Allergic contact dermatitis	RA		
	Vitiligo	Ulcerative colitis		
	Chronic spontaneous urticaria			
IL-34	SLE	RA		[65, 248–253]
	Psoriasis	Sjögren's syndrome		
		IBD		
		Nonalcoholic fatty liver disease		
		Lung cancer		
		PsA		
IL-35	Systemic sclerosis	Sjögren's syndrome		[254–256]
		MS		
IL-36	Psoriasis	RA	Imsidolimab, a monoclonal antibody against IL-36R; hidradenitis suppurativa (NCT04856930), acneiform eruptions (NCT04697069), ichthyosis (NCT04697056)	[16, 17, 23, 257–261]
	SLE	PsA		
	AD	UC		
		Sjögren's syndrome		
IL-37	Psoriasis	Ankylosing spondylitis		[66, 262–266]
	SLE	Graves' disease		
		Guillain-Barré syndrome		
		RA		

Table 3 continued

Interleukin	Important dermatological conditions	Important co-morbidities	Relevant therapeutics	References
IL-38	Psoriasis	RA		[18, 65, 67, 267, 268]
		Idiopathic pulmonary lung fibrosis		
IL-39		Neuromyelitis optica spectrum disorders		[269, 270]
		ST-segment elevation myocardial infarction		

AD, atopic dermatitis; BCC, basal cell carcinoma; COPD, chronic obstructive pulmonary disease; CTCL, cutaneous T-cell lymphoma; CVD, cardiovascular disease; GVHD, graft-versus-host-disease; IBD, irritable bowel syndrome; MS, multiple sclerosis; NTK, natural killer T; PsA, psoriatic arthritis; SCC, squamous cell carcinoma; SLE, systemic lupus erythematosus; UC, ulcerative colitis

[a]Hereditary systemic autoinflammatory diseases: familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), TNF receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome (HIDS), periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA), deficiency of interleukin-1 (IL-1) receptor antagonist (DIRA)

[b]Systemic inflammatory diseases: Systemic juvenile idiopathic arthritis, Adult-onset Still's disease, Schnitzler syndrome, Behçet's disease, PFAPA, synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, macrophage activation syndrome

ith IL-23 may be counterproductive. Indeed, it has been reported that guselkumab and risankizumab, which target the p19 subunit of IL-23, were both associated with superior clinical responses in patients with moderate-to-severe plaque psoriasis, compared to ustekinumab [37, 38].

While the general consensus is that Th17 cells are a major source of IL-17 in psoriatic lesions, other cell types such as mast cells and γδ T cells are also important cellular players [39, 40]. IL-17 production by Th17 cells is stimulated by IL-23, which also promotes survival of these cells [41]. IL-17 stimulates keratinocytes to produce antimicrobial peptides as well as various proinflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines (CXCL1/3/5). The role of the IL-17/IL-23 axis in psoriasis pathogenesis has been examined in IL-17 deficient mice [42]. IL-23 exposure was sufficient to induce epidermal hyperplasia in wild-type mice but not in IL-17-deficient mice. In addition, preexposure to anti-IL-17A antibodies prevented IL-23-mediated epidermal hyperplasia. These data suggest that IL-17A plays a critical role in IL-23-mediated psoriatic pathology. However, it remains unclear whether IL-17 upregulation alone is sufficient to initiate psoriatic disease, and whether it can be counteracted by IL-23 targeting antibodies or in an IL-23 −/− genetic background. Finally, it's noteworthy that inhibition of IL-17F in addition to IL-17A has been shown to provide more effective clinical responses compared to sole inhibition of IL-17A. Indeed, the BE RADIANT trial showed that 61.7% of patients who received bimekizumab (230/373), anti-IL17A/17F antibody, achieved a PASI100 response at week 16, compared to 48.9% in the secukinumab arm (181/370) [43]. Similar results were also seen with sonelokimab, a novel trivalent nanobody that comprises three monovalent camelid-derived (i.e., from the Camelidae family of mammals) monovalent nanobodies against IL-17A, IL-17F, and human serum albumin. Indeed, 76.5% of patients receiving sonelokimab achieved a PASI90 response (39/51) at week 12, compared to 64.2% in the secukinumab arm (34/53) [44].

The IL-10 family of cytokines is comprised of IL-10, IL-28, IL-29 and the IL-20 subfamily (IL-19, IL-20, IL-22, IL-24, and IL-26) [45]. These cytokines are implicated in psoriasis. Expression of IL-19 and IL-20 is elevated in basal and suprabasal psoriatic keratinocytes, although their expression was lower in the sera of psoriasis patients compared to healthy volunteers [46, 47]. Given that IL-19 is one of the main cytokines induced by IL-1β, its elevated expression may be a consequence of elevated expression of IL-1β in psoriatic tissue as mentioned earlier [48]. Both IL-19 and IL-20 can induce expression of keratinocyte growth factor (KGF) in CD8+ T cells. In a study of paired synovial tissue and psoriatic skin lesions of patients with psoriatic arthritis (PsA) and plaque psoriasis, IL-20 expression positively correlated with disease activity at baseline (PASI) and after treatment with alefacept [49]. Interestingly, alefacept treatment resulted in a significant reduction in IL-20 expression in skin lesions whereas its expression remained unchanged in synovial tissue, suggesting a role of CD4+ and CD8+ T cells in regulating its expression in psoriatic lesions.

IL-21 expression is also elevated in human psoriasis skin lesions, and intradermal exposure of mice to this interleukin results in keratinocyte hyperplasia [50]. Importantly, IL-21 antibody treatment was able to resolve inflammation and epidermal hyperplasia in a human psoriasis xenograft mouse model, suggesting that IL-21 targeting therapy may be a potential treatment avenue for psoriasis in the future.

IL-22 expression is increased in psoriatic skin lesions and sera of psoriasis patients compared to healthy volunteers [51]. It appears that IL-22 is responsible for expression of antimicrobial defense proteins such as psoriasin, calgranulin A, and calgranulin B, and keratinocyte mobility proteins such as matrix metalloproteinases (MMP1 and MMP3). In addition, IL-22 plasma levels positively correlated with disease severity as defined by PASI score, suggesting this interleukin may be involved in psoriasis pathogenesis, although a monoclonal antibody targeting IL-22, fezakinumab, was not effective in a phase 1 trial [52, 53].

One of the main target tissues of IL-24 is the skin, where its receptors IL-22R1/IL-20R2 or IL20R1/IL-20R2 are highly expressed. In addition, IL-24 expression is elevated in psoriatic lesions, and it is synthesized by both peripheral blood mononuclear cells (PBMCs) and keratinocytes [48]. Expression of IL-19, IL-20, and IL-24, all of which are of epidermal origin, was drastically reduced by etanercept treatment in psoriasis patients after 1 week [54]. In addition, expression of various keratinocyte-derived chemokines and proinflammatory interleukins was suppressed by etanercept. These changes took place concomitantly or prior to reduction in epidermal hyperplasia. Interestingly, expression of the IL-17/IL-23 interleukins IL-23p19, IL-12p40, IL-17A was also reduced although only after 3–4 weeks of treatment. These data highlight the complex regulation of various interleukins by TNF-α in the pathogenesis of psoriasis.

IL-25 or IL-17E is highly expressed in human psoriatic lesions, and is sufficient to cause psoriasis-like pathological features in mice such as acanthosis, parakeratosis, and immune cell infiltration [55]. Importantly, IL-25 (IL-17E) is induced by IL-17 and also positively autoregulates itself in keratinocytes via IL-17RB receptors leading to increased expression of proinflammatory cytokines and chemokines. This autoregulatory IL-25 circuit may therefore present a novel target in psoriasis, with potentially less adverse effects in patients particularly as its inhibition does not affect IL-17-dependent host defense mechanisms against infections [55].

IL-26 is increased in psoriatic tissue, and is implicated in vascularization and immune cell infiltration [56]. IL-26 can stimulate human keratinocytes to produce high levels of fibroblast growth factors that are involved in angiogenesis [56]. Not only are these factors known to be elevated in plasma of psoriasis patients, but they also correlate positively with disease severity [57]. IL-27, IL-30 and IL-33 serum levels were increased in psoriasis patients and correlated with disease PASI scores [58–60]. IL-29, which is mainly produced by Th17 cells, is also highly expressed in human psoriatic lesions [61]. Exposure of human keratinocytes to IL-27 or IL-29 results in enhanced expression of various chemokines such as CXCL9 and CXCL10 known to be induced in human psoriatic lesions [58, 62, 63]. IL-32, IL-33, and IL-36α are all elevated in the plasma of psoriasis patients or psoriatic lesions with less characterized roles in pathogenesis of the disease [64, 65].

IL-37 and IL-38 follow a distinct mechanism of action in psoriasis pathogenesis compared to previous interleukins. IL-37 is an inhibitor of innate immunity and has potent anti-inflammatory activity whereby it suppresses expression of proinflammatory genes CXCL8, IL-6, and S100A7 in human keratinocytes [66]. IL-37 exposure was also able to diminish psoriasis symptoms in the K14-VEGF-Tg human psoriasis mouse model [66]. Additional studies remain necessary to understand the anti-inflammatory properties of IL-37 and whether these can be harnessed for treatment of human psoriasis. Expression of IL-38, also known as a receptor antagonist for IL-36, is reduced in serum and psoriatic lesions in psoriasis patients [67]. Interestingly, IL-38 expression is enhanced by secukinumab (anti-IL-17A) treatment and is correlated with its therapeutic efficacy [67]. It remains important to investigate any potential clinical efficacy of IL-36 pathway inhibitors such as imsidolimab and spesolimab, or recombinant IL-38 in treatment of psoriasis.

Atopic Dermatitis

Atopic dermatitis (AD) is a common inflammatory disease that usually begins in childhood and continues into adulthood, although it may less often also start later in life [68]. AD is characterized by pruritus and disease flares, and its pathogenesis primarily involves skin barrier dysfunction together with immune cell dysregulation [68, 69]. Disruption of the epidermal layer along with environmental triggers activates keratinocytes to begin production of various proinflammatory cytokines, which in turn can activate dendritic cells. Dendritic cells subsequently stimulate production of Th2 cell cytokines IL-4, IL-5, IL-13, IL-31, and IL-33, which lead to barrier dysfunction, inhibition of keratinocyte differentiation and pruritus. The chronic phase of the disease is characterized by

activation of additional Th cells such as Th17, Th1, and Th22 cells that produce IL-17, IFN-γ, and IL-22, respectively, leading to T-cell chemotaxis, abnormal keratinocyte proliferation, and thickening of the epidermal layer [69].

Consistent with a pathogenic role of IL-4 and IL-13 in AD pathogenesis, dupilumab, which is an approved anti-IL-4Rα monoclonal antibody, improved AD signs and symptoms, including pruritus, and quality of life, compared to placebo in the SOLO 1 and SOLO 2 trials [70]. As mentioned above, Th2 cytokines are the main hallmark of AD disease. Both IL-4 and IL-13 can inhibit expression of skin barrier molecules such as filaggrin, loricrin, and involucrin, which in turn further disrupts tight cell junctions, and may increase susceptibility to infections [71, 72]. In addition, neuronal IL-4Rα signaling has been shown to be a crucial component of chronic itch, given that Th2 cytokines can sensitize sensory neurons to a number of pruritogens [73]. IL-5, which plays an important role in eosinophil development, survival and proliferation, leads to increased infiltration of eosinophils in the epidermis in AD together with increased neuronal branching [74]. Th9 cell numbers, IL-9 expression in AD lesions, and IL-9 serum concentration were all elevated in AD patients compared to psoriasis patients and healthy volunteers [75]. IL-11 and type I collagen deposition consistent with papillary dermal fibrosis were found to be increased in chronic AD lesions [76]. IL-22 producing CD4+ and CD8+ T cells were significantly increased in AD skin lesions compared to psoriatic lesions, and correlated with AD disease severity [77]. IL-31, also known as the pruritic interleukin, was highly expressed in pruritic AD skin tissue compared to nonpruritic psoriatic skin lesions [78]. Mice treated with IL-31 had itch-associated scratching behavior similar to that observed in human AD [79]. IL-33 serum levels were elevated in AD patients compared to patients with urticaria and psoriasis or healthy volunteers, and correlated with disease severity [80]. Interestingly, transgenic mice that overexpress IL-33 develop itchy dermatitis with epidermal thickening and eosinophil infiltration, which are disease hallmarks reminiscent of human AD [81].

With regards to emerging therapies for treatment of AD, IL-13 inhibitors and IL-31 inhibitors have all demonstrated efficacy to reduce signs and symptoms of AD. Lebrikizumab is a monoclonal antibody against soluble IL-13 that is currently being assessed in the ADvocate 1 and ADvocate 2 phase 3 trials for treatment of patients with moderate-to-severe AD. It was recently announced that the trials met their primary endpoints, with EASI 75 achieved in > 50% of patients, and this was associated with significant itch improvement [82]. Tralokinumab, which has received regulatory approval by Health Canada, is a humanized IgG4 monoclonal antibody that binds with high affinity to IL-13, and prevents its interaction with IL-13R. Data from the ECZTRA 1 and ECZTRA 2 trials in patients with moderate-to-severe AD revealed that compared to placebo, significantly more patients who received tralokinumab achieved an IGA score of 0 or 1 (ECZTRA 1: 15.8% vs. 7.1%; ECZTRA 2: 22.2% vs. 10.9%) or EASI 75 (ECZTRA 1: 25% vs. 12.7%; ECZTRA 2: 33.2% vs. 11.4%) [83]. Nemolizumab is a humanized monoclonal antibody against IL-31 receptor A whose efficacy was examined in a double-blind phase 3 trial in Japan in patients with AD and moderate-to-severe pruritus. The mean % change in the visual-analogue scale (VAS) score at week 16 was − 42.8% in the nemolizumab group compared to − 21.4% with placebo ($p < 0.001$) [84].

INTERLEUKINS IN METABOLIC AND PSYCHIATRIC COMORBIDITIES ASSOCIATED WITH DERMATOLOGICAL DISEASES

Metabolic, cardiovascular, gastrointestinal, and psychiatric conditions are amongst the most common comorbidities known to be associated with dermatologic diseases. IL-1β has been linked to etiology of type 2 diabetes mellitus, which is characterized by β cell destruction. Activation of nod-like receptor protein 3 inflammasomes in macrophages and dendritic cells via islet amyloid polypeptides (IAPP) leads to enhanced production of IL-1β that acts on IL-

1β receptors on β cells and causes β cell death, and defective insulin production [85]. Obesity can also lead to enhanced inflammasome activation in adipose tissue and increased IL-1β synthesis, which induces adipocyte differentiation and decreases fat oxidation [85]. Importantly, anakinra, a recombinant human IL-1-receptor antagonist, has been shown to improve glycemia and beta-cell secretory function in patients with type 2 diabetes [86]. IL-1β through activation of IL-6 signaling also plays a role in cardiovascular disease. Canakinumab, an anti-IL-1β antibody, results in reduction of plasma levels of IL-6 and high-sensitivity C-reactive protein, which are inflammatory biomarkers associated with increased risk of cardiovascular disease [87]. In addition, the CANTOS trial showed that canakinumab resulted in a significantly lower rate of recurrent cardiovascular events in patients with previous myocardial infarction, although it did not reduce incident diabetes [88, 89].

IL-23 plays an important role in inflammatory bowel disease (IBD). Genome-wide association studies have identified a strong association between *IL23R* and ulcerative colitis [90]. Furthermore, Th17 interleukins are increased in intestinal tissue of patients with IBD [91, 92]. This is consistent with increased activation and expression of IL-23, which as mentioned earlier, is a robust activator of Th17 signaling [93]. Indeed, ustekinumab resulted in significantly higher clinical response rates and remission rates compared to placebo in patients with Crohn's disease or ulcerative colitis in the UNITI-1, UNITI-2, and IM-UNITI trials [94].

Psychosocial stress and some dermatologic conditions exist in a positive feedback loop where each condition exacerbates the other. Patients with psoriasis may develop anxiety because of associated chronic pruritus and skin disfiguration [95, 96]. Pruritus intensity positively correlates with patients' quality of life, and feelings of stigmatization [97]. In addition, perceived poor social support has been associated with exacerbation of psoriasis [98]. Also, patients with moderate or severe depression had a significantly higher risk of developing psoriasis [99]. Early maladaptive schemas such as emotional deprivation, social isolation, failure, and vulnerability to harm were all more prevalent in patients with psoriasis [100]. On the other hand, there are several mechanisms by which psoriasis can trigger or exacerbate anxiety. Psychological stress can perturb homeostasis of epidermal permeability barrier [101]. Activation of the hypothalamus–pituitary–adrenal (HPA) axis and sympathetic adrenomedullary (SAM) axis is a response to stress. These processes are deregulated in psoriasis patients, which results in reduced secretion of cortisol and elevated epinephrine and norepinephrine [102, 103]. This in turn may trigger activation of mast cells and upregulation of proinflammatory cytokines, which creates a self-maintaining cycle [96].

A comprehensive literature review conducted by Gananḉa et al. to assess cytokine roles in suicidal behavior identified IL-6 elevations as the most robust association with suicidal ideation, trait aggression, impulsivity, and hopelessness [104]. Patients who have major depressive disorder have also been shown to have higher levels of IL-6, and other proinflammatory cytokines such as IL-1β, TNF-α, all of which may contribute to psoriatic pathogenesis [105–107]. In addition, several reports point to involvement of the nervous system in the development of psoriasis skin lesions, and as such IL-12 can also serve as a potential link between the skin immune system and the nervous system as it is produced by peripheral nerve cells [108, 109]. Cytokines are also known to stimulate activity of indoleamine 2,3-dioxygenase, which catalyzes conversion of tryptophan to kynurenine [110]. Kynurenine metabolism alterations are strongly associated with progression of various neurological diseases [111]. In addition, plasma kynurenine levels are increased in individuals who attempted suicide [112]. It remains unclear whether increased production of proinflammatory cytokines in dermatologic diseases influences kynurenine metabolism.

With increased prevalence of mental health disorders such as depression and suicidal ideation in psoriasis patients, it becomes important to utilize tools to measure quality of life and psychiatric comorbidities in the clinic. Some of these validated tools include the patient health

questionnaire (PHQ), psoriasis quality of life questionnaire (PQOL-12), psychological general well-being (PGWB) index, Columbia suicide severity rating scale (C-SSRS), and Columbia classification algorithm for suicide assessment (C-CASA) [110].

FUTURE DIRECTIONS

Pathogenesis of psoriasis and AD is largely driven by a complex cross-regulatory network of interleukins (Figs. 1, 2). As previously discussed, expression of many interleukins is elevated in psoriatic and AD affected areas as well as in patient sera. Targeting these pathogenic interleukins for treatment of psoriasis and AD patients has proven successful in the clinic, although some patients may require dose adjustment, combination therapy, or switching to other biologic or nonbiologic agents due to intrinsic or acquired resistance. Trivalent antibodies that can target more than one interleukin may prove beneficial, although combined inhibition of several interleukins may be a concern from a safety standpoint. Continued discovery of interleukins and cytokines, elucidation of their structure and immune functions, along with next-generation sequencing of pathogenic tissues is critical in identifying new targets in pathogenesis of inflammatory skin diseases. In addition, identifying immune biomarkers that can predict patient response to therapy will be important in improving patient outcomes.

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