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

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 naive 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].
| 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 |
| 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)    |               | Dendritic cells, PBMCs, T reg cells, virus-infected cells, monocytes | IL-28R1/IL-10R2 | Have antiviral activities against various viruses |
| IL-28B (IFN-λ3)    |               |                     |             |                           |
| IL-29 (IFN-λ1)     |               |                     |             |                           |
| 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 |
| 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 |
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 underlying 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 microabscess) [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 with other therapies could provide additional therapeutic benefits in psoriasis.

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.
| Interleukin | Important dermatological conditions | Important co-morbidities | Relevant therapeutics | References |
|------------|------------------------------------|--------------------------|----------------------|------------|
| IL-1α/β   | Hereditary systemic autoinflammatory diseases<sup>a</sup> | Diabetes | 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 | [113–118] |
| IL-RA      | Systemic inflammatory diseases<sup>b</sup> | Cardiac remodeling | Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody indicated for treatment of autoinflammatory periodic fever syndromes | |
|           | Hidradenitis suppurativa | Gout | 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) | |
|           | Pustular psoriasis | RA | | |
|           | Neutrophilic dermatoses | Ostearthritis | | |
|           | Urticarial vasculitis | GVHD | | |
|           | Kawasaki disease | Dry eye disease | | |
|           | Erdheim–Chester disease | | | |
| IL-2       | Alopecia areata | | Aldesleukin is a recombinant IL-2 protein therapy approved for use in patients with stage IV melanoma | [119, 120] |
|           | Malignant melanoma | | | |
| IL-4       | Atopic dermatitis | Atopic comorbidities | Dupilumab, an FDA approved anti-IL-4Rα monoclonal antibody for treatment of patients with atopic dermatitis or asthma | [70, 121–124] |
|           | Scleroderma | | | |
|           | Bullous pemphigoid | | | |
| IL-5       | Atopic dermatitis | Asthma | Benralizumab, mepolizumab, and reslizumab are 3 FDA-approved anti-IL-5 antibodies for treatment of adult patients with severe eosinophilic asthma | [125–127] |
|           | Hypereosinophilic syndrome | EoE | | |
|           | | Eosinophilic granulomatosis with polyangitis | | |
|           | | Nasal polyposis | | |
| Interleukin | Important dermatological conditions | Important co-morbidities | Relevant therapeutics | References |
|------------|-----------------------------------|-------------------------|----------------------|------------|
| IL-6       | Psoriasis (–)                      | RA                      | 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 | [26, 31, 128–133]|
|            | Pustular psoriasis                 | Psoriatic Arthritis (–) |                      |            |
|            | Hidradenitis suppurativa           | Cardiovascular disease  |                      |            |
|            | Wound Healing                      | Depression              |                      |            |
|            |                                   | Diabetes                |                      |            |
| IL-7       | CTCL (elevated levels)             | T-cell acute lymphoblastic leukemia | Safety of GSK2618960, an experimental anti-IL-7R antibody, has been assessed in healthy subjects (NCT02293161) | [134–140]|
|            | Generalized verrucosis and HPV-3 susceptibility (inherited IL-7 deficiency) | Sjögren’s syndrome | RN168, an experimental anti-IL-7R antibody, is being assessed in patients with type I diabetes (NCT02038764) |            |
| IL-8       | Psoriasis                          | IBD                     | 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]|
|            | Pyoderma gangrenosum               | Ovarian cancer          |                      |            |
| IL-9       | Atopic dermatitis                  |                         |                      | [75, 144–147]|
|            | Allergic contact dermatitis        |                         |                      |            |
|            | Mycosis fungoides                  |                         |                      |            |
|            | Important defense mechanism against |                        |                      |            |
|            | *Candida*                          |                         |                      |            |
| Interleukin | Important dermatological conditions | Important co-morbidities | Relevant therapeutics | References |
|------------|-----------------------------------|--------------------------|-----------------------|------------|
| IL-10      | SLE                               | Important in viral diseases: HIV, EBV, Herpesviruses, CMV, Poxviruses | SCH708980, a monoclonal anti-IL-10 antibody being assessed as an anti-immunosuppressive agent in visceral leishmaniasis (NCT01437020) | [148, 149] |
|            | Pemphigus vulgaris                |                          |                       |            |
|            | Bullous pemphigoid                |                          |                       |            |
|            | Alopecia areata                   |                          |                       |            |
|            | Psoriasis                         |                          |                       |            |
|            | Atopic dermatitis                 |                          |                       |            |
|            | Allergic contact dermatitis       |                          |                       |            |
|            | Melanoma                          |                          |                       |            |
|            | BCC/SCC                           |                          |                       |            |
|            | Cutaneous lymphomas               |                          |                       |            |
|            | Hypertrophic scarring             |                          |                       |            |
| IL-11      | Psoriasis                         | Cardiovascular fibrosis  |                       | [34, 76, 150] |
|            | Atopic dermatitis (skin remodeling)|                          |                       |            |
| IL-12      | Psoriasis                         | 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] |
|            | Atopic dermatitis                 |                          |                       |            |
|            | Photocarcinogenesis               |                          |                       |            |
| Interleukin | Important dermatological conditions | Important co-morbidities | Relevant therapeutics | References |
|------------|------------------------------------|--------------------------|----------------------|------------|
| IL-13      | Atopic dermatitis                  | Behçet’s disease         | Dupilumab, see above  | [83, 155–162] |
|            |                                    | Systemic sclerosis       | Lebrikizumab, an experimental anti-IL-13 monoclonal antibody for treatment of atopic dermatitis (NCT03443024) or asthma (NCT02104674) | |
|            |                                    | Localized scleroderma    | 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 | |
| IL-14      | Sjögren’s syndrome                 | SLE                      |                      | [163, 164] |
| IL-15      | Vitiligo                           | RA                       | IL-15 superagonist complex N-803 is an experimental treatment being assessed in BCG-unresponsive non-muscle invasive bladder cancer patients (NCT03022825) | [165–168] |
|            | Mycosis fungoides                  | Sarcoidosis              |                      |            |
|            |                                    | IBD                      |                      |            |
|            |                                    | Transplant rejection     |                      |            |
|            |                                    | Hematologic malignancies |                      |            |
|            |                                    | Infections               |                      |            |
| IL-16      | Cutaneous T-cell lymphoma          | HIV/immune reconstitution syndrome |                      | [169–173] |
|            | Systemic sclerosis                 |                          |                      |            |
|            | SLE                                |                          |                      |            |
|            | Bullous pemphigoid                 |                          |                      |            |
| 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             |                         | 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) | |
|            | Tumor progression                  |                         |                      |            |
| 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                  |                         |                      |            |
|            | Alopecia areata                    |                         |                      |            |
|            | Melanoma (anti-tumorigenic role)   |                         |                      |            |
Table 3 continued

| Interleukin | Important dermatological conditions | Important co-morbidities | Relevant therapeutics | References |
|-------------|-------------------------------------|--------------------------|-----------------------|------------|
| IL-22       | Psoriasis                           | Multiple sclerosis       | Fezakinumab, a monoclonal anti-IL-22 antibody being assessed in atopic dermatitis (NCT01941537) | [51, 52, 77, 193–200] |
|             | Atopic dermatitis                   | RA                       |                       |            |
|             | Contact dermatitis                  |                          |                       |            |
|             | Scleroderma                         |                          |                       |            |
|             | CTCL                                 |                          |                       |            |
|             | Squamous cell carcinoma             |                          |                       |            |
| IL-23       | Psoriasis                           | Crohn’s disease          | Ustekinumab, see above | [35, 90, 201–203] |
|             | RA                                   |                          | Guselkumab, risankizumab, tildrakizumab |            |
|             | PsA                                  |                          |                       |            |
| IL-24       | Psoriasis                           | IBD (suppresses mucosal  |                       | [48, 54, 204–206] |
|             | Contact dermatitis                  | inflammation)            |                       |            |
|             | Atopic dermatitis                   |                          |                       |            |
| IL-25       | Psoriasis                           | Asthma                   |                       | [55, 207, 208] |
| IL-26       | Hidradenitis suppurativa            | RA                       |                       | [56, 209–215] |
|             | Psoriasis                           | Crohn’s disease          |                       |            |
|             | Behçet’s disease                    | Asthma                   |                       |            |
|             |                                      | COPD                     |                       |            |
| IL-27       | Psoriasis                           | COPD                     | Breast cancer         | [58, 216–220] |
|             | Systemic sclerosis                  |                          | Sjögren’s syndrome    |            |
|             |                                      |                          | Rheumatoid Arthritis  |            |
| 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                           | RA                       |                      |            |
|            | Atopic dermatitis                   | Osteoarthritis           |                      |            |
|            | Systemic sclerosis                  | Uveitis                  |                      |            |
|            |                                     | 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                     |                      |            |
| 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                     |                     |            |
| 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 | ST-segment elevation myocardial infarction |                      | [269, 270] |

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

*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)

*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 Gananc¸a 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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