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The Immunologic Role of IL-17 in Psoriasis and Psoriatic Arthritis Pathogenesis

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Abstract
Psoriasis is a chronic, immune-mediated, inflammatory disease that is pathogenically driven by proinflammatory cytokines. This article reviews the immunologic role of interleukin (IL)-17, the major effector cytokine in the pathogenesis of psoriatic disease, along with the rationale for targeting the IL-17 cytokine family (IL-17A, IL-17F, and IL-17 receptor A) in the treatment of psoriasis and psoriatic arthritis. Emerging evidence indicates that major sources of IL-17A in patients with psoriatic disease are mast cells, γδ T cells, αβ T cells, and innate lymphoid cells in lesional skin and synovial fluid. Within the skin and joints, IL-17A acts on cellular targets, including keratinocytes, neutrophils, endothelial cells, fibroblasts, osteoclasts, chondrocytes, and osteoblasts, to stimulate production of various antimicrobial peptides, chemokines, and proinflammatory and proliferative cytokines, which, in turn, promote tissue inflammation and bone remodeling. The critical importance of the IL-23/IL-17A axis to the pathogenesis of psoriatic disease has resulted in many new biologic treatments targeting these cytokines. These biologics dramatically improve skin and joint symptoms in patients with moderate-to-severe psoriasis and psoriatic arthritis.

Keywords Psoriasis · IL-17A · IL-17F · IL-17 receptor A · Innate immunity · Adaptive immunity

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory disease in which genetic and epigenetic changes result in a disease phenotype characterized by altered immune function, keratinocyte activation and hyperproliferation, and the development of erythematous, indurated, scaly plaques [1–4]. Psoriasis is driven by T cell activation associated with the secretion of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-17A, IL-22, and interferon IFN-γ [1, 5]. The IL-23/IL-17 immunologic pathway plays an especially important role in promoting disease onset and perpetuation. Data from in vitro and clinical studies indicate that IL-17A, a critical effector cytokine in this pathway, principally drives changes within affected tissues [6–11].

Direct evidence supporting the central role of IL-17A in psoriasis includes upregulation of *IL-17A* and related genes in lesional and non-lesional skin of patients with psoriasis and production of IL-17A by cells associated with psoriasis [6, 8, 12]. In an in vitro study using reconstituted human epidermal sheets, IL-17A stimulated greater transcriptional activation than IL-22 or IFN-γ, correlating with the psoriasis transcriptome [13]. IL-17 also increases expression of the antimicrobial peptide LL37, a psoriasis autoantigen that promotes production of proinflammatory cytokines, and C-X-C motif chemokine ligand 1 (CXCL1) [14, 15]. This, in turn, drives expansion of ADAMTS-like protein 5 (ADAMTSLP5), another psoriasis autoantigen, causing additional expression of IL-17A and IFN-γ [15, 16].

In addition to IL-17A, the IL-17 family consists of five other members (IL-17B-F) [17–23]. Within this family, IL-17A, IL-17C, and IL-17F are implicated in psoriasis pathogenesis as their expression is increased up to eightfold in psoriatic lesions [6, 24, 25]. Although there is more IL-17C and IL-17F in psoriatic lesions, IL-17A is the most biologically active (up to 30-fold more active than IL-17F) [10, 24]. While these three cytokines act on keratinocytes to stimulate production of proinflammatory cytokines and chemokines, the exact role of IL-17C in psoriasis pathogenesis is poorly understood [6,

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25]. Despite high levels of IL-17C in psoriatic lesions, IL-17C has less impact on keratinocyte gene expression than IL-17A, IFN-γ, and TNF-α, suggesting that IL-17A is more important than IL-17C in promoting cutaneous inflammation [26].

Therapies targeting IL-17A alone are known to modulate gene expression of various cytokines and chemokines, and effectively clear psoriatic lesions [6, 27–29]. More specifically, 2 weeks of IL-17A inhibition resulted in normalization of 765 genes, whereas TNF-α inhibition resulted in the normalization of far fewer genes (< 200) [30, 31]. In this article, the immunologic role of IL-17 in psoriasis and psoriatic arthritis (PsA) pathogenesis, including its role in innate and adaptive immunity, and the rationale for targeting IL-17A, IL-17F, and IL-17 receptor A in the treatment of psoriasis and PsA, are reviewed.

Cellular Sources of Interleukin-17 in Innate and Adaptive Immunity

For several years, it was hypothesized that the primary source of IL-17A in psoriasis was T helper 17 (Th17) cells. Specifically, human Th17 cells differentiate from naïve T cells under the influence of TGF-β1 and proinflammatory cytokines (IL-1β, IL-6, and/or IL-21) [32, 33]. Differentiated human Th17 cells are stimulated to produce cytokines by IL-23, which also promotes the survival of Th17 cells [34, 35]. Th17 cells produce a wide variety of cytokines in addition to IL-17A, including IL-17F, IL-21, IL-22, IL-26, and TNF-α [34, 36]. Additionally, increased numbers of Th17 cells are found in the blood and affected skin of patients with psoriasis and in the blood and synovial fluid of patients with PsA [11, 37]. Recently, however, there has been a paradigm shift in the understanding of cellular sources of IL-17A in psoriasis and PsA. Increasingly, data indicate that additional important cellular sources of IL-17A are mast cells, γδ T cells, αβ T cells, and innate lymphoid cells (ILCs; Table 1) [38, 39, 47].

It was long thought that neutrophils were an abundant source of IL-17A in psoriasis; however, emerging data indicate that highly purified human neutrophils are not capable of expressing IL-17A or other IL-17 family cytokines in vitro [40, 48–51]. Rather, IL-17A may be released from extracellular neutrophil traps, which are a central function of neutrophil host defense and inflammatory function [40, 41, 52]. Studies on this topic have yielded differing results: (1) retinoic orphan

Table 1 Cellular sources of IL-17 [38–46]

Cell type	Description
γδ T cells	• Potent source of innate IL-17 produced independently of IL-6 • Properties are similar to Th17 cells (e.g., expression of CCR6, IL-23R, and RORγt); these cells also express TLR1, TLR2, and dectin-1 • Levels of IL-17-producing γδ T cells increase during some types of bacterial infections • Different subsets of γδ T cells in the thymus produce either IL-17 or IFN-γ • Major source of gut-protective IL-17, which acts independently from IL-23
αβ T cells	• Recent data indicate CD4/CD8 double-negative αβ T cells produce IL-17 in psoriatic inflammation • These cells respond to IL-23 to produce IL-17 • These cells likely express RORγt and CCR6
Neutrophils	• Rich source of IL-17 in psoriasis • IL-17 is held and released by neutrophils via extracellular trap formation • Conflicting data have been reported on whether IL-17 mRNA is present in neutrophils
Mast cells	• In response to trauma or infection, preformed inflammatory mediators, including IL-17, are released from mast cells via granulation or mast cell extracellular trap cell death • Mast cells also express IL-17 mRNA and produce IL-17A and IL-17 receptor A
ILC3s	• Subset of ILCs defined by their capacity to produce IL-17A and/or IL-22 • Found in lesional and non-lesional skin, and in peripheral blood in patients with psoriasis, and in synovial fluid in patients with PsA
iNKT cells	• Cells that express a restricted TCR that recognizes glycolipid antigens • May provide an alternative source of IL-17 when IL-6 is not present to stimulate Th17 cells • IL-17$^+$ cells express IL-23R and IL-1R1
Adaptive Th17 cells	• A subset of activated CD4$^+$ T helper cells that produce high levels of IL-17A, IL-17F, IL-22, and IFN-γ, and express IL-23R • CD4$^+$ TCRα/β$^+$ Th17 cells are a well-characterized source of IL-17 that play a key role in immune inflammatory responses
Natural Th17 cells	• Subset of thymic Th17 cells that acquire effector function prior to peripheral antigen exposure • These cells have different TCR gene usage and signaling properties compared with conventional Th17 cells
Tc17 cells	• Subset of CD8$^+$ cells that produces IL-17 • May play a role in pathogenic skin and joint inflammation in psoriasis and PsA, respectively

CCR6, C-C chemokine receptor type 6; *CD*, cluster of cell differentiation; *IFN*, interferon; *IL*, interleukin; *IL-1R1*, interleukin-1 receptor, type 1; *IL-23R*, interleukin-23 receptor; *ILC*, innate lymphoid cell; *iNKT*, invariant natural killer T; *PsA*, psoriatic arthritis; *ROR*, retinoic orphan receptor; *Tc17*, IL-17-expressing CD8+ T cells; *TCR*, T cell receptor; *Th17*, T helper 17; *TLR*, toll-like receptor

receptor (ROR)γt$^+$ neutrophils expressed IL-17 mRNA, and were capable of producing IL-17 [41, 47]; (2) certain populations of bone marrow neutrophils exhibited autocrine IL-17 activity, which was driven by interactions between IL-17A and IL-17RC [53]; and (3) neutrophils in psoriatic lesions produce IL-17 [54]. Regardless of its source, neutrophil-derived IL-17 may be an early target of IL-17A inhibitors as these drugs interrupt neutrophil-keratinocyte crosstalk and disrupt the influx of neutrophils into psoriatic lesions [48].

Similarly, mast cell extracellular trap formation, induced by IL-23 and IL-1β, is associated with the release of IL-17 [40, 47]. When mast cells in healthy skin respond to trauma or microbial infection, preformed inflammatory mediators, including TNF-α, IL-17, and CXCL2, are released via degranulation or mast cell extracellular trap cell death [40]. Mast cells may also express IL-17 mRNA, produce small amounts of IL-17A, and express IL-17 receptor A [42]. Additionally, mast cells can capture, store, and release exogenous IL-17A and trigger the release of IL-17 and IFN-γ from Th1 and Th17 cells by modulating dendritic cell maturation and function [55, 56].

Neutrophils, mast cells, and other innate immune cells are also important in the pathogenesis of PsA [57]. In patients with PsA, high levels of IL-23, IL-17A, and IL-17 receptor A are present in synovial membranes, and resident Th17 cells located in entheses overexpress IL-17 and IL-22, contributing to inflammation and bone remodeling [58, 59]. Additionally, activation of the IL-23/IL-17 axis promotes production of granulocyte-colony stimulating factor, granulocyte-macrophage stimulating factor, and chemokines, including CXCL1, CXCL2, CXCL5, and CXCL8/IL-8, which promote neutrophil recruitment and migration into joint spaces [60]. Mast cell infiltration and IL-17A expression are also observed in spondyloarthritis synovial inflammation, and both mast cells and neutrophils (as opposed to T cells) are major cellular sources of IL-17 in atherosclerosis [40, 61, 62].

Elevated levels of γδ T cells, which can express RORγt, IL-23R, and C-C chemokine receptor type 6 (CCR6), are found in the dermis of psoriatic plaques as well as in the peripheral blood and synovial fluid of patients with PsA; of note, IL-17 signaling was higher in psoriatic lesional skin than in synovial tissue of patients having both skin and joint involvement [12, 63]. Stimulation of these cells with IL-23 results in production of IL-17 and IL-17 expression is observed in synovial tissue of patients with PsA [64–66]. Dermal γδ T cell production of IL-17 is likely independent of αβ T cells; however, a CD4 and CD8 double-negative subset of αβ T cells can produce IL-17 and contribute to psoriatic skin inflammation [39]. In a murine model of psoriasis, a subset of RORγt$^+$ γδ T cells form resident-memory cells in skin that rapidly produce large amounts of IL-17A/F [67]. Additionally, CCR6 is a cell surface marker of peripheral IL-17A-expressing γδ T cells [68]. IL-17A in the epidermis can induce keratinocyte expression of chemokine ligand 20 (CCL20), which, in turn, recruits IL-17A-producing CD8+ T cells (Tc17) and CCR6$^+$ CD4+ T cells into skin [1, 69–73]. CCR6$^+$ cells also migrate to the epidermis or dermal-epidermal junction in response to psoriasis-triggering stimuli in murine models of psoriasis [68, 74]. In human psoriatic lesions, expression of CCR6 and its ligand CCL20 by dendritic cells and T cells has led to a hypothesis that interactions between CCR6 and CCL20 play an important role in crosstalk between dendritic cells and T cells, which ultimately causes T cell activation [75, 76]. Furthermore, synovial fluid of patients with PsA is enriched with CCR6$^+$ ILCs [37, 43]. CCR6 is, therefore, being investigated as a possible new target in the treatment of both psoriasis and PsA [68, 75–77].

ILC3s produce IL-17A and are implicated in psoriasis and PsA pathogenesis [43, 78]. Elevated numbers of ILC3s are found in lesional and non-lesional skin of patients with psoriasis, in peripheral blood of patients with psoriasis, and in synovial fluid of patients with PsA [43–45, 78]. ILC3s express high levels of IL-17A, IL-22, CCR6, and natural cytotoxicity receptors, which are all upregulated in psoriatic lesions [43–45, 79]. Expression of IL-17 and IL-22 in ILC3s is specifically dependent on expression and stimulation of RORγt [79, 80]. IL-23 and TNF-α also promote ILC3 differentiation [45, 79]. Interestingly, natural cytotoxicity receptor positive ILC3 levels correlate with psoriasis severity in untreated patients and decrease with anti-TNF-α therapy [45, 79]. Additionally, murine models of psoriasis indicate that ILC3s may be a rich source of non-T cell-derived IL-22 [77, 78].

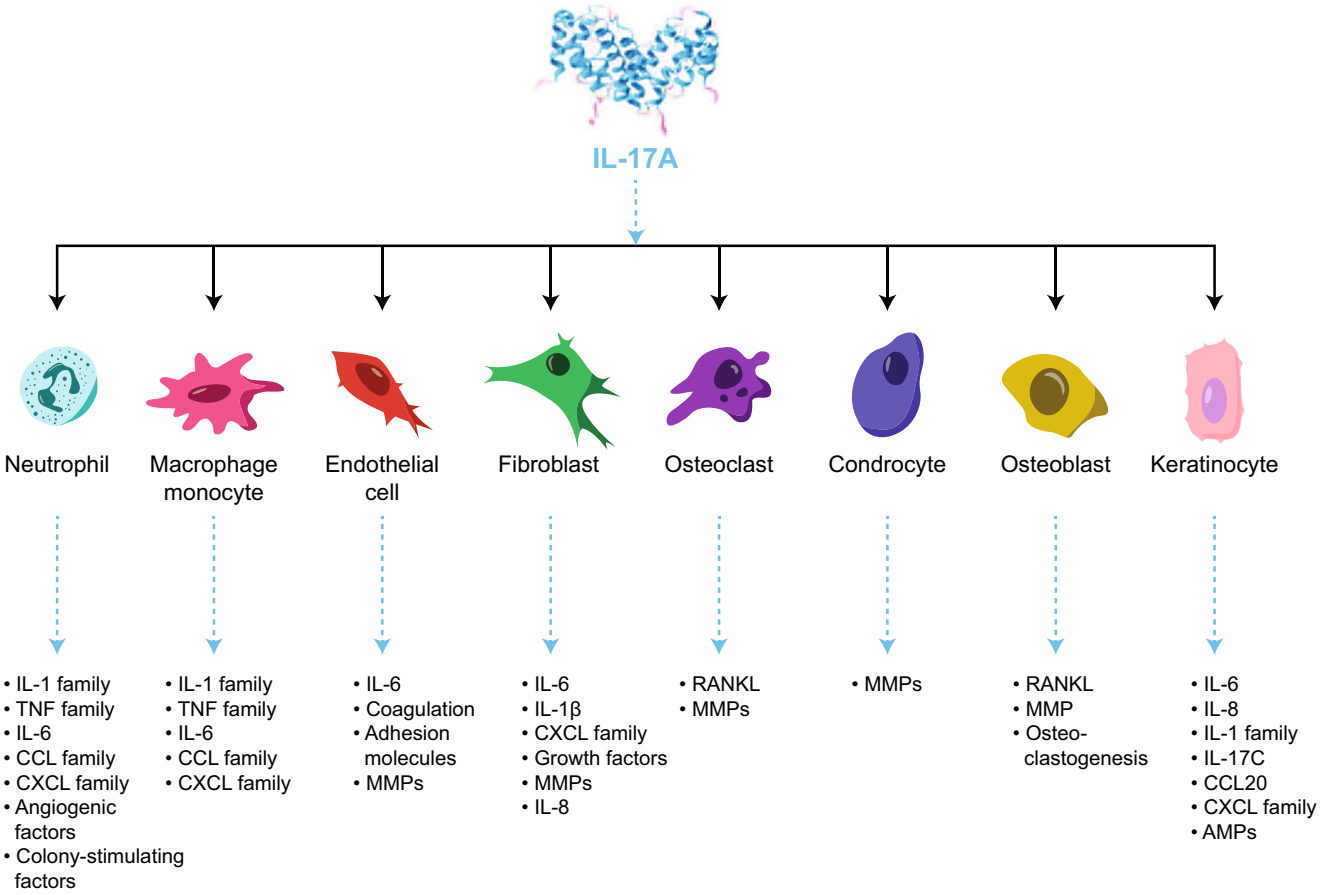
Role of Interleukin-17 in the Pathogenesis of Psoriasis and Psoriatic Arthritis

Early studies on the pathogenesis of chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease, led to identification of TNF-α as a key trigger of innate inflammatory pathways [31]. Although TNF-α blockers first successfully treated rheumatoid arthritis, they were quickly extended to psoriasis and PsA. Effects of TNF-α inhibition in psoriasis and PsA are complex, because therapeutic benefits likely result from indirect adaptive immune effects on the IL-23/IL-17A axis [31]. Evidence of this indirect effect was observed in clinical trials of etanercept, in which genomic data indicated that etanercept efficacy was dependent on downregulation of IL-17A or IL-17A signaling [31, 81]. The relationship between IL-17 and TNF-α is further complicated as they act synergistically to co-regulate many keratinocyte genes that are highly expressed in psoriatic skin lesions [5]. Together, these findings suggest that IL-17A and TNF-α act through distinct mechanisms to regulate downstream gene expression, with the IL-23/IL-17A axis at the core of psoriasis pathogenesis, and TNF-α playing a more ancillary role in promoting inflammation through synergism with

IL-17A and through development and maturation of myeloid dendritic cells [6, 31]. This hypothesis is further supported by evidence that IL-17A inhibition alone is highly effective in psoriasis and PsA in the absence of TNF-α inhibition [7].

IL-23 and IL-17A are key inflammatory cytokines in psoriasis pathogenesis [82, 83]. IL-23 stimulates differentiation, activation, proliferation, and survival of Th17 cells that promote production of effector cytokines such as IL-17A and IL-22, but IL-17 is also produced independently of IL-23 [13, 82, 84–86]. IL-23 injection produces psoriasis-like disease in wild-type mice, but not in *IL17* knockout mice, and IL-23-mediated disease could be blocked in wild-type mice by pretreatment with anti-IL-17A antibodies [82]. This and similar evidence in other IL-23/IL-17-mediated murine disease models indicate that IL-23 is "upstream" of IL-17A, whereas IL-17A, acting "downstream," directly affects tissue. IL-17A has a range of effects on different cellular targets within the skin and joints by promoting inflammation, coagulation, and bone/joint damage (Fig. 1) [87–89].

Major targets of IL-17 in psoriasis include keratinocytes, endothelial cells, and innate immune cells [89]. In keratinocytes, IL-17 stimulates production of antimicrobial peptides (lipocalin 2, S100A proteins (S100A7, psoriasin), and beta defensins), proinflammatory cytokines and chemokines (IL-1β, TNF-α, IL-6, IL-17C, CXCL1, CXCL3, CXCL5, CXCL8 (IL-8), and CCL20), and proproliferative cytokines (IL-19) [5, 73, 89]. In endothelial cells, IL-17 interacts to promote tissue inflammation and procoagulant activity through upregulation of IL-6, IL-8, and intracellular adhesion molecule-1 [87, 89]. Moreover, IL-17-mediated endothelial dysfunction may contribute to development of cardiovascular comorbidities in psoriasis [89]. Although fibroblasts are not considered disease-relevant/critical target cells, they are capable of sustaining inflammation; an in vitro study showed they produce proinflammatory mediators, including IL-8, IL-1β, and IL-6 and CXCL1, CXCL2, CXCL3, CXCL5, and CXCL6, in response to IL-17 [13]. Lastly, IL-17A has



Abbreviations
AMP, antimicrobial peptide; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF, tumor necrosis factor.

Fig. 1 Effects of IL-17 on different cellular targets

proinflammatory effects on antigen-presenting cells, including macrophages [90].

The centrality of IL-23 and IL-17A to psoriasis and PsA pathogenesis has resulted in many new biologic therapies targeting these cytokines (Table 2) [98, 99]. These drugs, however, can have notable clinical differences related to dosing and safety profiles. Therapies targeting cytokines further upstream in this pathway require less-frequent dosing to maintain efficacy than drugs targeting more downstream cytokines and receptors [100]. IL-23 and IL-12/23 inhibitors (furthest upstream) require maintenance dosing every 8–12 weeks, whereas maintenance dosing with approved IL-17A inhibitors (midstream) is required every 4 weeks, and the IL-17 receptor A antagonist brodalumab (furthest downstream) is administered every 2 weeks [98, 101]. Mechanistic studies indicate that IL-17A has both protective and proinflammatory effects in the gut. There is strong evidence to support the role of γδ T cell-derived IL-17A in the protection of epithelial barriers in the intestinal mucosa; as such, IL-17A blockade may exacerbate inflammatory bowel disease [102–106]. Additionally, IL-17A production has been observed in subpopulations of T regulatory cells, and it is hypothesized that these cells may be protective against inflammatory bowel disease [107, 108]. Pooled safety data from clinical trials of ixekizumab and secukinumab, however, show that exacerbation of inflammatory bowel disease rarely occurs with IL-17A inhibition [109–111]. Nonetheless, IL-17A inhibitors should be used with caution in patients with a history of inflammatory bowel disease [112]. IL-17A blockers are also associated with increased risk for mucocutaneous candidiasis (< 5% of treated patients) because IL-17 is important in the control of *Candida albicans* infections within skin and mucosa [99, 113]. Thus, patients being treated with IL-17A blockers should be screened regularly for signs of mucocutaneous candidiasis; in the small percentage of patients who develop these types of infections, treatment with topical or oral antifungal therapy is generally effective and discontinuation of anti-IL-17A therapy is not necessary [113]. In phase 3 psoriasis trials of brodalumab, psychiatric adverse events, including depression, anxiety, and suicidal ideation and behavior, were observed, suggesting a possible safety concern [114]. However, analysis of data across five clinical trials did not find a causal relationship between treatment with brodalumab and suicidality; rates of adverse events of suicidal ideation and behavior were similar with brodalumab, placebo, and ustekinumab [114]. Patients with psoriasis are known to be at increased risk for psychiatric comorbidities, and all patients with suicidal ideation who received brodalumab had underlying psychiatric disorders or stresses [115]. Of note, similar safety signals have not been observed with either secukinumab or ixekizumab [116].

Expanding Our Understanding of the Immunologic Role of IL-17

An important issue in managing psoriasis is recurrence of lesions after treatment discontinuation, which is linked with a residual disease genomic profile [117–119]. Relapses may be caused by residual tissue-resident memory T cells not being fully eradicated with anti-TNF therapy. In an etanercept trial, a subset of inflammatory genes that contribute to psoriasis pathogenesis, including IL-12p35, IL-22, IL-17, and IFN-γ, did not return to non-lesional levels [117, 118]. Particularly, clinical recurrences at the same body areas may be determined by the marked presence of IL-17A-producing αβ T cell clones in post-treatment-resolved psoriatic lesional skin, which produce eightfold more IL-17A than αβ T cell clones in healthy skin [120].

Given the critical role of IL-17A in psoriasis pathogenesis, it is not surprising that the IL-17A inhibitors secukinumab and ixekizumab are associated with complete or near complete skin clearance in many patients and have demonstrated efficacy that is superior to many other agents (i.e., TNF-α inhibitors and ustekinumab) [27, 95, 121]. In patients with psoriasis, IL-17A inhibition by secukinumab normalizes levels of dysregulated proteins, including IL-1β, IL-8, IL-1 receptor antagonist, myeloperoxidase, antimicrobial peptides (β-defensin 2 and lipocalin 2), matrix metalloproteinase-1,

Table 2 Drugs that inhibit IL-23 or IL-17 function

Drug name	Target	FDA approval date and indication
Ustekinumab [91]	p40 subunit (IL-12 and IL-23)	2009 psoriasis, 2013 PsA
Guselkumab [92]	p19 subunit (IL-23)	2017 psoriasis
Tildrakizumab [93]	p19 subunit (IL-23)	2018 psoriasis
Risankizumab [94]	p19 subunit (IL-23)	Not approved
Mirikizumab (NCT03482011)	p19 subunit (IL-23)	Not approved
Secukinumab [27]	IL-17A	2015 psoriasis, 2016 PsA
Ixekizumab [95]	IL-17A	2016 psoriasis, 2017 PsA
Bimekizumab [96]	IL-17A and IL-17F	Not approved
Brodalumab [97]	IL-17RA (IL-17A, IL-17E, IL-17F)	2017 psoriasis

FDA, Food and Drug Administration; *IL*, interleukin; *IL-17RA*, IL-17 receptor A; *PsA*, psoriatic arthritis

matrix metalloproteinase-8, matrix metalloproteinase-9, and the chemokines CXCL1, CXCL5, and CCL20 [122, 123]. Secukinumab also decreases mRNA levels of antimicrobial peptides, chemokines, IL-36α, IL-36β, IL-36γ, IL-36RN, IL-17A, and IL-17F [122]. Additionally, ixekizumab normalizes >3 times more genes than etanercept after 2 weeks [30, 31]. Targeting IL-17 receptor A with brodalumab is also highly effective and inhibits signaling induced by IL-17A, IL-17F, IL-17E (IL-25), and IL-17A/F [97, 124, 125]. Brodalumab also normalizes psoriatic lesional skin transcriptome, the gene expression profile associated with IL-17A, IL-17C, and IL-17F, and reduces IL-23 levels along with keratinocyte-derived mediators of inflammation, including chemokines, IL-36A, and S100s [125]. More recently, bimekizumab, a monoclonal antibody targeting IL-17A and IL-17F, demonstrated high efficacy in psoriasis [96]. Whether this is due to the highly effective blockade of IL-17A or combined effects of blocking 2 IL-17 isoforms is unclear. Interestingly, studies indicate the blockade of both IL-17A and IL-17F decreases inflammation more than the inhibition of IL-17A alone [126–128].

Although the IL-17A gene signature is higher in skin from patients with PsA compared with joints, IL-17A is thought to play a key role in PsA pathogenesis, acting on synovial-like joint fibroblasts, osteoblasts, and osteoclast precursors to promote inflammation and joint damage [12, 129]. Specifically, IL-17A, TNF-α, IL-23, and other inflammatory cytokines activate the innate immune regulators, nuclear factor κB (NFκB), and its receptor activator/ligand (RANK/RANKL). NFκB and RANKL upregulation triggers transcription of genes that promote secretion of bone matrix-degrading enzymes, including matrix metalloproteinase-9, tartrate-resistant acid phosphatase, and cathepsin K [60, 130, 131]. The IL-17A inhibitors secukinumab and ixekizumab are approved for PsA based on phase 3 data (FUTURE 1 and FUTURE 2 for secukinumab, SPIRIT-P1 and SPIRIT-P2 for ixekizumab) [132–135]. These studies demonstrated that treatment with IL-17A blockers improved joint and skin signs and symptoms of PsA, along with physical functioning and quality of life, compared with placebo [132–135]. Finally, a phase 2 study of brodalumab in PsA provided improvements in joint and skin symptoms and physical functioning (with higher doses) compared with placebo [136].

IL-17 also promotes vascular inflammation, endothelial dysfunction, coagulation, thrombosis, and arterial hypertension. Correspondingly, elevated serum IL-17 has been observed in patients with acute myocardial infarction, and monoclonal antibodies that neutralize IL-17 may improve outcomes in patients with psoriasis and/or PsA and comorbid cardiovascular disease [137, 138]. This hypothesis is further supported by a murine model of atherosclerosis; inhibition of IL-17A led to prevention of lesion progression and induction of plaque stabilization in advanced lesions [90]. In a murine model of IL-17A overexpression, neutralization of cytokines downstream of IL-17A improved vascular health [139]. Additionally, anti-IL-17A monoclonal antibodies prevented vascular disease in a murine model of psoriasis [140]. In humans, an acute myocardial infarction registry demonstrated that serum IL-17A below a median of 6.26 pg/mL was associated with higher risk for all-cause mortality and recurrent myocardial infarction, but many patients had IL-17A levels below the assay's detection limit of 2.5 pg/mL [141]. To more directly study this issue in moderate-to-severe psoriasis, Gelfand and colleagues are assessing whether treatment with secukinumab can lead to improvements in aortic inflammation (VIP-S, NCT02690701), a well-established biomarker of atherosclerotic cardiovascular disease.

Conclusions

Many cytokines are involved in psoriasis development; however, data identify IL-17A as the major effector cytokine driving pathogenesis. IL-17 is produced by many cell types, acts on a range of cellular targets in tissue and immune cells, and plays important roles in innate and adaptive immunity. Inhibition of IL-17A, IL-17 receptor A, or simultaneous inhibition of IL-17A and IL-17F leads to disruption of signaling pathways critical to the development and maintenance of psoriasis. Accordingly, biologics that target IL-17A function lead to rapid and dramatic improvement of skin and joint symptoms in psoriasis and PsA.

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Compliance with Ethical Standards

Conflict of Interest A Blauvelt has been a scientific adviser and clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Inc., Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Leo Pharma, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac, and a paid speaker for Janssen, Regeneron, and Sanofi Genzyme. A Chiricozzi has been a scientific consultant and/or clinical study investigator for AbbVie, Biogen, Eli Lilly and Company, Janssen, Leo Pharma, Novartis, Sanofi Genzyme, and a speaker for Eli Lilly and Company, Janssen, AbbVie, and Novartis.

Ethical Approval This article does not contain any studies with human participants or animals performed by either author.

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