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IL-23 Versus IL-17 in the Pathogenesis of Psoriasis: There Is More to the Story Than IL-17A

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ABSTRACT

Our understanding of psoriasis pathogenesis has evolved considerably. Cytokines within the TH1 and TH17 pathways have been found to be critical in psoriasis immunopathology. The TH17 pathway, which is centered around the interplay between IL-23 and IL-17, is now known to be at the core of psoriasis immune dysregulation. IL-23 acts as a key regulator of the TH17 pathway. Therapies targeting either IL-23 or IL-17 have shown great efficacy in psoriasis and have helped augment our understanding of psoriasis pathogenesis. Therapies such as ustekinumab and guselkumab inhibit IL-23. Ustekinumab targets the p40 subunit common to both IL-23 and IL-12 while guselkumab targets the p19 subunit found in IL-23. IL-17 subtypes trigger downstream inflammation in psoriasis. In particular, IL-17A, IL-17F, and IL-17C are elevated in psoriatic lesions; with IL-17F and IL-17C more elevated than IL-17A. Therapies such as secukinumab, ixekizumab, and brodalumab inhibit IL-17 subtypes. For example, brodalumab inhibits the downstream effects of all five IL-17 subtypes (IL-17A, IL-17AF, IL-17F, IL-17C, and IL-17E) via IL-17 receptor blockade; brodalumab can also normalize the levels of IL-23. Therefore, using a receptor-blocking therapy, such as brodalumab, that can act on multiple inflammatory cytokines, both IL-17 and IL-23 can be suppressed.

In this paper, we describe the importance of the TH17 pathway in psoriasis pathogenesis with a focus on the roles of IL-23 and IL-17 within this pathway. We also discuss the different IL-17 subtypes involved in psoriasis immunopathology and the multitude of cells that can produce these subtypes. Finally, we examine treatments that inhibit IL-23 and IL-17.

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INTRODUCTION

Our understanding of psoriasis pathogenesis has evolved over time. Before the 1980s, psoriasis was viewed as a skin-limited disease and the therapeutic mechanisms of commonly used treatments were not well understood.[1,2] When cyclosporine was found to improve psoriasis in transplant patients, researchers and clinicians began to appreciate the importance of the immune system in psoriasis pathogenesis.[1–3] In the 1980s, researchers discovered that inhibition of tumor necrosis factor alpha (TNF-α) led to significant improvements in psoriasis.[4] This initiated the development of multiple medications that target TNF-α. By the early 2000s, interleukin (IL)-17 was believed to play an essential role in psoriasis pathogenesis after IL-17 inhibition resulted in complete or near complete psoriasis clearance.[5–8] Additionally, the efficacy of ustekinumab and other IL-23-specific therapies led to our appreciation that IL-23 has a critical role as a key regulator in psoriasis pathogenesis.

Thus, three cytokines, TNF-α, IL-23, and IL-17, have been instrumental in expanding our understanding of psoriasis pathogenesis and in developing efficacious psoriasis therapies. Below, we discuss in detail psoriasis pathogenesis, with a focus on the roles of IL-23 and IL-17 and therapies that target these two cytokines.

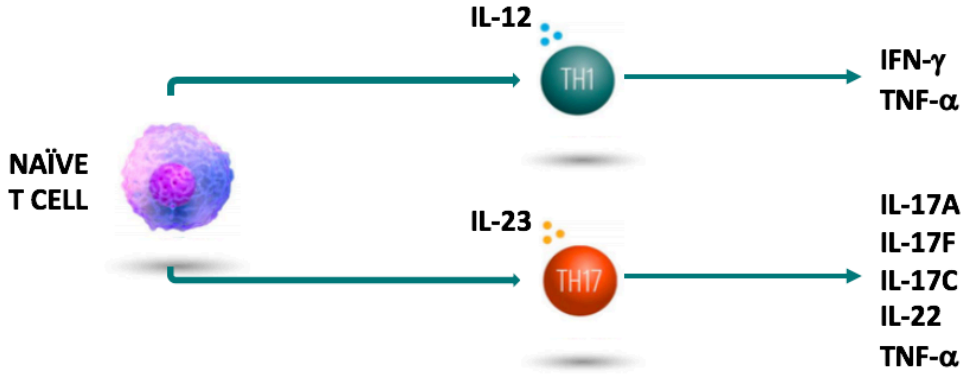
Overview of Pathogenesis of Psoriasis: TH1 and TH17 Pathways

Psoriasis occurs secondary to a complex interplay between the innate and adaptive immune systems, with the adaptive immune system performing a critical role.[9] In psoriasis, dendritic cells secrete IL-12 and IL-23 cytokines.[2,9] IL-12 stimulates naive T cells to differentiate into TH1 cells (Figure 1).[2]

The key cytokines of the TH1 pathway include interferon gamma (IFN-γ) and TNF-α (Figure 1).[2] TNF-α plays several roles in the inflammatory cascade of psoriasis, including stimulating the infiltration of inflammatory cells into lesional skin, augmenting keratinocyte proliferation, and activating dendritic cells and TH17 cells.[10–12]

The TH17 pathway is central to psoriasis pathogenesis. Following IL-23 stimulation of naive T cells, TH17 cells secrete a number of inflammatory cytokines including IL-17, a key cytokine in psoriasis pathogenesis. A complex network of interactions between IL-23, IL-17, and other TH17 cell secreted molecules characterizes the TH17 pathway in what is known as the "IL-23/IL-17 axis".[13–18] This axis plays a critical role in psoriasis disease initiation and perpetuation, triggering a cascade of inflammatory molecules that lead to vasodilatation and angiogenesis.[19,20] These vascular changes result in the skin thickening and erythema characteristic of plaque psoriasis.[1]

FIGURE 1.[14,5,23] The TH1/TH17 Pathways.



Abbreviations: IFN-γ: interferon gamma; IL: interleukin; Th: T helper; TNF-α: tumor necrosis factor alpha.

Before we understood the importance of the TH17 pathway, the TH1 pathway was thought to be the canonical pathway for psoriasis. We now appreciate that the TH17 pathway is the dominant pathogenic pathway in psoriasis and that this pathway interacts synergistically with the TH1 pathway.[21–27] For example, inhibition of IL-17A has been shown to be highly effective in psoriasis.[26–28] Evidence also suggests that the benefits of TNF-α inhibition may be primarily mediated through indirect downregulation of the TH17 pathway rather than direct inhibition of the TH1 pathway.[26–28] To explain this TH17 pathway downregulation, TNF-α blockade is thought to suppress TNF-α activation of dendritic cells and, as a consequence, decreases IL-23 production.[18] TNF-α inhibition also reduces the full effect of IL-17 on its targets.[28]

IL-23 in Psoriasis Pathogenesis and Therapies That Target IL-23

In psoriasis, IL-23 acts as a key regulator of the TH17 pathway. IL-23 promotes TH17 cell phenotype maintenance and survival and, therefore, the production of proinflammatory cytokines secreted by TH17 cells such as IL-17A and IL-17F.[2,9,29–35] Furthermore, IL-23 promotes T-regulatory (Treg) cell differentiation into TH17 cells.[36]

IL-23 consists of a p19 subunit and a p40 subunit; the p40 subunit is also common to IL-12. IL-23 is secreted by innate immune cells (Langerhans cells, dendritic cells, and monocytes/macrophages) following an inflammatory or biochemical insult to the skin.[37–39]

Three FDA-approved biologic therapies target IL-23 in psoriasis. Ustekinumab inhibits both IL-12 and IL-23 by inhibiting the common p40 subunit. Guselkumab and tildrakizumab both target IL-23 specifically by inhibiting the p19 subunit. Two IL-23 inhibitors in late phase development, risankizumab and mirikizumab, also target the p19 subunit.

Interestingly, the pharmacodynamic properties of therapeutic IL-23 antibodies appear to exceed their pharmacokinetics. In other words, the clinical effect of IL-23 inhibition is much longer than the functional half-life of IL-23 antagonists; therefore, reduced dosing frequencies up to every 12 weeks are possible.[40–42] It is postulated that these effects may be secondary to the reversal of IL-23 effector functions in psoriasis. That is, IL-23 inhibition may bring about prolonged efficacy through improved Treg cell functioning, decreased production and survival of TH17 cells, and/or a phenotypic change of TH17 cells, resulting in reduced proinflammatory cytokines.[20,43–46] Impaired survival of TH17 cells has important implications in psoriasis as TH17 cells are usually long-lasting and active as resident effector T-memory cells even after skin repair.[44,45] A survey of psoriasis patients showed that, when considering treatment options, the medication's ability to achieve clear or almost clear skin was more important than dosing frequency.[47]

Furthermore, IL-23 inhibition incompletely blocks IL-17. That is, when IL-23 is blocked, only TH17 cell derived IL-17 subtypes are at risk of being inhibited. However, IL-17 subtypes produced by cells independent of TH17 cells can still be expressed (Table 1).[48–50] In the treatment of psoriasis, inhibiting only the pathogenically elevated amounts of IL-17 is important because appropriate amounts of IL-17 are necessary for protection against fungal infections including mucocutaneous infections such as candida albicans.[51,52] The challenge lies in inhibiting just the appropriate amount. That is, while inhibiting too much IL-17 may be associated with emergence of fungal infections, inhibiting too little can be associated with residual psoriatic disease.

The IL-17 Family

The IL-17 family comprises five IL-17 isoforms based on subunits A, F, C, and E: AA homodimer, AF heterodimer, FF homodimer, CC homodimer, and EE homodimer.[16,53] The most important IL-17 family members or subtypes in psoriasis pathology are IL-17A, IL-17F, IL-17C, and IL-17E.[54–57]

There are four relevant IL-17 receptor (R) isoforms in psoriasis: IL-17RA, IL-17RB, IL-17RC, and IL-17RE. All IL-17 family isoforms share the IL-17RA subunit.[58]

TABLE 1.[16–18,53]

Relevant IL-17 Subtypes in Psoriasis				
IL-17 Subtype	**Elevation in Psoriasis**	**Receptor**	**Downstream Effects**	**IL-17-Producing Cell Types**
IL-17A	28x	IL-17RA, IL-17RC	Neutrophil recruitment and immunity to extracellular pathogens.[16] Activation of keratinocytes.[18]	Th17 cells, ILCs, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, NKT cells, and LTi cells
IL-17F	33x	IL-17RA, IL-17RC	Thought to be proinflammatory.[16] Involved in neutrophil recruitment.[16] Provides immunity to extracellular pathogens.[16]	Th17 cells, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, NKT cells, and LTi cells
IL-17C	30x	IL-17RA, IL-17RE	Thought to be proinflammatory and may be involved in epidermal thickening and joint inflammation.[16,54,57,76,78,79]	Prostate and fetal kidney cells, keratinocytes, colonic epithelial cells, and lung epithelial cells
IL-17E	Unknown	IL-17RA, IL-17RB	May be anti-inflammatory or proinflammatory.[16,54,57,64] Involved in neutrophil recruitment.[16] Provides immunity to extracellular pathogens.[16]	Intraepithelial lymphocytes, lung epithelial cells, alveolar macrophages, eosinophils, basophils, NKT cells, Th2 cells, mast cells, and cells of the gastrointestinal tract and uterus

Abbreviations: IL: interleukin; ILCs: innate lymphoid cells; LTi: lymphoid tissue inducer; NK: natural killer; NKT: natural killer T; Th: T helper; RA: receptor A; RB: receptor B; RC: receptor C; RE: receptor E.

The IL-17 subtypes can be produced by a number of different cell types including TH17 cells (Table 1).[32,59] Importantly, while TH17 cells are highly noted in psoriasis pathogenesis, many other immune cells as well as epithelial cells can also potentially produce excess IL-17.

Various therapies have been used to target IL-17. Some of these therapies target the IL-17A subtype while others target the IL-17 receptor. Receptor antagonism, in agents such as brodalumab, has different implications to cytokine antagonism in that more than one IL-17 subtype will be inhibited. In this section, we discuss not only cytokines IL-17A and IL-17F but also other cytokines such as IL-17C that are being studied in psoriasis pathogenesis.

IL-17A in Psoriasis Pathogenesis and Therapies That Target IL-17A

In psoriasis, IL-17A is elevated 28-fold compared to non-lesional skin.[54] The primary function of IL-17A is in the recruitment of neutrophils, providing immunity to extracellular pathogens, and the activation of keratinocytes.[16,56] IL-17A primarily induces these functions through keratinocytes, endothelial cells, and innate immune cells.[18] In keratinocytes, IL-17A induces the production of antimicrobial peptides, proinflammatory cytokines and chemokines, and pro-proliferative cytokines.[16,18,24,56,60] Activation of keratinocytes is crucial in the pathology of psoriasis as this propagates the cytokine cascade and leads to the formation of plaque psoriasis.[18] In endothelial cells, IL-17A induces tissue inflammation and procoagulant activity via increased IL-6, IL-8, and intracellular adhesion molecule-1, which may attribute to cardiovascular comorbidities associated with psoriasis.[18,61] In innate immune cells, IL-17A acts to recruit neutrophils and has proinflammatory effects on antigen-presenting cells.[16,56,62]

IL-17A binds to IL-17RA and IL-17RC, with a 50% homology to IL-17F.[16,63] Compared to IL-17F, IL-17A has a stronger binding affinity to these receptors and, therefore, has a greater transductional power. IL-17A can also present as a homo- or heterodimer.[16,63]

IL-17A is produced by many immune cells other than TH17 cells.[16] These immune cells include innate lymphoid cells (ILCs), mast cells, neutrophils, CD8+ T cells, natural killer (NK) cells, natural killer T (NKT) cells, and lymphoid tissue inducer (LTi) cells.[16] In fact, histological examination of lesional psoriatic skin shows that most IL-17A is expressed by neutrophils and mast cells; and IL-17A positive T cells such as TH17 are scarce.[17,55,64]

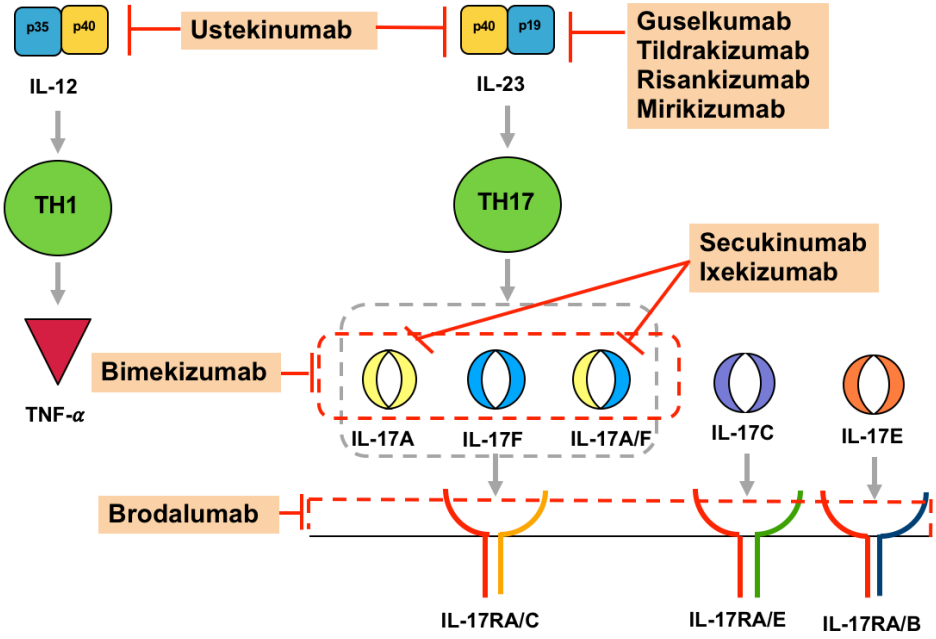
Two FDA-approved biologic therapies, secukinumab and ixekizumab, bind to the IL-17A subunit, thereby blocking two of the five IL-17 isoforms (AA and AF) (Figure 2). These agents offer therapeutic benefit through the normalization of dysregulated immune mediators and their genetic expression.[26,65–68]

IL-17F in Psoriasis Pathogenesis and Therapies That Target IL-17F

In psoriatic lesions, IL-17F is elevated by 33-fold compared to non-lesional skin and is, therefore, more elevated than IL-17A.[54] Similar to IL-17A, the primary function of IL-17F in psoriasis is in the recruitment of neutrophils and providing immunity to extracellular pathogens.[16,56] Additionally, IL-17F can act synergistically with TNF-α and IL-17A.[69–71]

IL-17F binds to the same receptors as IL-17A, IL-17RA, and IL-17RC, with a 50% homology.[16,63] IL-17F can also present as a homo- or heterodimer.[16,63] IL-17F is produced by many of the same cells as IL-17A (Table 1).[16]

FIGURE 2.[6–8,72,73,83] TH17 pathway treatment targets.



Abbreviations: IL: interleukin; R: Receptor; Th: T helper; TNF-α: tumor necrosis factor alpha.

Currently, the only FDA-approved biologic therapy that can inhibit the effects of IL-17F is brodalumab, as discussed below. One molecule in late phase development that targets IL-17F is bimekizumab. Bimekizumab binds to both the IL-17A and F subunits, thereby blocking three of the five IL-17 isoforms (AA, FF, and AF) (Figure 2).[72,73] It is unclear whether preliminary successes observed in psoriasis and psoriatic arthritis are secondary to effective inhibition of IL-17A or the combined effect of blocking IL-17A and IL-17F.[71,72] Some studies suggest that combined blockade of IL-17A and IL-17F may be more effective at lowering inflammation than IL-17A alone.[74,75]

IL-17C in Psoriasis Pathogenesis and Therapies That Target IL-17C

IL-17C is the most abundant IL-17 cytokine in psoriatic skin lesions.[57] In psoriasis, the role of IL-17C is not well understood but it is believed to be crucial in the pathogenesis. The primary function of IL-17C is to promote inflammation through the induction of inflammatory cytokines, chemokines, and antimicrobial peptides.[57,76,77] In vitro and in vivo studies suggest that IL-17C is upregulated in psoriasis skin inflammation and is involved in epidermal thickening.[54,57,76,78] Preliminary studies also show that IL-17C may be involved in joint inflammation.[79] Of note, IL-17C acts synergistically with TNF-α.[57]

IL-17C binds to IL-17RA and has a 23% homology with IL-17A.[16] IL-17C also mediates further signaling by binding to a IL-17RA/IL-17RE complex.[80] IL-17C is expressed by many epithelial cells such as prostate and fetal kidney cells and keratinocytes rather than immune cells (Table 1).[16]

Brodalumab is a monoclonal antibody that binds to IL-17RA. IL-17RA mediates the signaling for IL-17A, IL-17F, IL-17C, and IL-17E. Therefore, brodalumab blocks the function of all five IL-17 isoforms (AA, AF, FF, CC, and EE) by binding to IL-17RA (Figure 2).[81] Importantly, brodalumab is the only therapeutic antibody that binds to all five IL-17 isoforms and that can bind to the IL-17C and E subunits. Data suggest that brodalumab also leads to a reduction in IL-23.[82] Therefore, targeting IL-17RA by brodalumab appears to normalize the levels of IL-17 subtypes (IL-17A, IL-17F, IL-17C, and IL-17E) as well as IL-23. A recent network meta-analysis showed that brodalumab has superior efficacy compared to TNF-a inhibitors (adalimumab, etanercept, and infliximab), ustekinumab, and secukinumab.[83–86] Although a direct comparison study has not been conducted, these findings suggest that targeting IL-17RA may be more efficacious than targeting IL-17A alone.[83] Additionally, a comparison study showed that, compared to ustekinumab, almost twice as many patients treated with brodalumab achieved psoriasis area severity index (PASI)-100; and in patients who had failed previous therapies, three times as many patients treated with brodalumab achieved PASI-100 (32.0% vs 11.3%).

Furthermore, recent studies have shown that patients who failed treatment with an IL-17A inhibitor (secukinumab and ixekizumab) or a IL-23/IL-23 inhibitor (ustekinumab), responded to brodalumab.[86–89] Following failed treatment with secukinumab or ixekizumab, subsequent treatment with brodalumab, by week 16, led to PASI-75 in the majority of patients (67-69%), PASI-90 in 44% of patients, and PASI-100 in 28% of patients.[87]

These novel findings suggest that targeting IL-17A alone may be inadequate to control psoriasis, particularly in patients with severe and recalcitrant disease. Additionally, compared to patients who continued treatment with ustekinumab, patients who received brodalumab had superior rates of PASI-75 (72.6% vs 61.7%), PASI-90 (58.1% vs 25.2%), and PASI-100 (36.3% vs 5.4%).[90] Proposed mechanisms to explain these findings of superiority of IL-17RA blockade (brodalumab) over IL12/23 blockade (ustekinumab) in psoriasis include incomplete suppression of IL-17 because IL-17 subtypes may still be expressed independent of TH17 cells.

IL-17E in Psoriasis Pathogenesis and Therapies That Target IL-17E

In psoriasis, the role of IL-17E is not understood. While some investigators have found IL-17E to have anti-inflammatory effects, others found IL-17E to have proinflammatory effects.[16,57] The inflammatory effects of IL-17E may occur by activating macrophages to release inflammatory cytokines such as TNF-α and neutrophil chemokines.[57] Evidence also suggests that IL-17E may be involved in the recruitment of innate immune cells.[55,64]

IL-17E signals via a heterodimeric receptor complex consisting of IL-17RA and IL-17RB and has a 16% homology with IL-17A.[58,64] IL-17E is produced by both epithelial and immune cells.[16] Epithelial cells that produce IL-17E derive from the lung, gastrointestinal tract, and uterus.[16] Immune cells that produce IL-17E include intraepithelial lymphocytes, alveolar macrophages, eosinophils, NKT, and TH2 cells.[16] Brodalumab is the only FDA-approved psoriasis therapy that targets IL-17E via IL-17RA inhibition (Figure 2).[81]

CONCLUSION

In conclusion, psoriasis pathogenesis involves a complex interplay between IL-23 and IL-17, and both cytokines play crucial roles in psoriasis. IL-17 subtypes such as IL-17A, IL-17C, and IL-17F are abundant in psoriatic lesions. Furthermore, IL-17 subtypes can be produced by other non-TH17 cells. Thus, IL-17 produced by non-TH17 cells may contribute to pathogenesis of psoriasis and psoriatic arthritis. Therapies that target IL-23 and IL-17 have been shown to be effective in psoriasis. Importantly, aside from the therapeutic target, other factors such as binding affinity, dosing, and low immunogenicity profile may also play a key role in the efficacy of these psoriasis therapies.

DISCLOSURE

AWA has served as investigator or consultant to AbbVie, Janssen, Lilly, Leo, Novartis, UCB, Ortho Dermatologics, Dermira, Sanofi Genzyme, Regeneron, BMS, Dermavant, and Modernizing Medicine.

CLL served as a consultant/advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Dermira, Eli Lilly and Company, Janssen Pharmaceuticals, Inc., Leo Pharma A/S, Ortho Dermatologics, Pfizer, Inc., Sandoz (a Novartis Company), UCB, and Vitae; as a speaker for AbbVie, Amgen, Celgene Corporation, Eli Lilly and Company, Novartis, Sun Pharmaceuticals, Ltd., and UCB; as a principal investigator for Actavis, Amgen, Boehringer Ingelheim, Celgene Corporation, Cellceutix, Coherus Biosciences, Corrona, Dermira, Eli Lilly and Company, Galderma Laboratories, L.P., Glenmark Generics, Inc., Janssen Pharmaceuticals, Inc., Leo Pharma, Inc., Merck, Novartis, Novella, Pfizer, Inc., Sandoz (a Novartis Company), Sienna Biopharmaceuticals, Stiefel a GSK company, UCB, and Warner Chillcott.

LHK has been either an investigator, consultant, advisory board member, or a speaker for Amgen, Celgene, Ely Lilly, Novartis, OrthoDermatologics, Pfizer, SunPharma, and UCB.

CR has no conflicts to disclose.

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