

Pathophysiology of Psoriasis: Recent Advances on IL-23 and Th17 Cytokines

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T helper (Th) 17 cells, a novel T-cell subset, have been implicated in the pathogenesis of psoriasis and other autoimmune inflammatory diseases. Interleukin (IL)-23 stimulates survival and proliferation of Th17 cells, and thus serves as a key master cytokine regulator for these diseases. In psoriasis, IL-23 is overproduced by dendritic cells and keratinocytes, and this cytokine stimulates Th17 cells within dermis to make IL-17A and IL-22. IL-22, in particular, drives keratinocyte hyperproliferation in psoriasis. Future targeting of these key cytokines is likely to lead to dramatic clinical improvement in patients with psoriasis. This review focuses on the numerous recent studies on the roles of IL-23 and Th17 cells in the pathogenesis of psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin disease that affects 2% to 3% of the population worldwide and causes significant morbidity [1]. Its etiology is unknown, but it is generally believed to be a complex autoimmune inflammatory disease with a genetic basis [2]. Psoriasis shares immunologic and genetic features with other human autoimmune inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis. Novel CD4⁺ T-helper (Th) cells, called Th17 cells, are important in the pathogenesis of many of these diseases [3] including psoriasis [4•]. The primary immunologic driving force for psoriasis was previously thought to be interferon (IFN)- γ -producing Th1 cells. However,

the dependence of these diseases on Th17 cells rather than Th1 cells has led some to reclassify psoriasis and similar diseases as Th17 diseases. This review focuses on the emerging role of Th17 cells in psoriasis pathogenesis.

Transforming Growth Factor- β 1 and Interleukin-6: Required for Th17 Cell Development

Naïve T cells are induced to differentiate into Th1, Th2, Th17, or T-regulatory cells based on T-cell receptor stimulation and costimulation and the specific cytokines released by antigen-presenting cells [3]. For example, Th17 cells develop in peripheral tissue after exposure to extracellular transforming growth factor (TGF)- β 1 and interleukin (IL)-6 in an inflammatory milieu (Fig. 1) [5•,6•]. Tumor necrosis factor (TNF)- α and IL-1 β can amplify Th17 cell differentiation but cannot substitute for TGF- β 1 and IL-6. The intracellular transcription factors ROR γ t and Stat3 are also critical in the development of Th17 cells from naïve T-cell precursors (Fig. 1) [7•,8]. Mangan et al. [6•] found that mice deficient in TGF- β 1 have profoundly decreased or absent Th17 cells and high levels of IFN- γ . These mice can undergo Th17 development, however, if they are provided with exogenous TGF- β 1 and neutralizers of IFN- γ [6•]. In addition, mice overexpressing TGF- β 1 in T cells generated more Th17 cells, whereas mice with defective CD4⁺ T cell TGF- β 1 signaling lacked Th17 cells [5•]. By contrast, TGF- β 1 in the absence of IL-6 promotes development of anti-inflammatory T-regulatory cells. Recent data indicate that IL-1 and not TGF- β 1 is critical in the differentiation of naïve T cells into Th17 in humans [9].

In psoriasis, TGF- β 1 is elevated in plasma and in scales of lesions [10]. TGF- β 1 is also released by keratinocytes upon injury or infection [11]. This release combined with activation of dendritic cells through their pattern-recognition receptors, is likely sufficient to generate Th17 cells in skin-draining lymph nodes capable of inducing cutaneous inflammation. Indeed, transgenic mice with

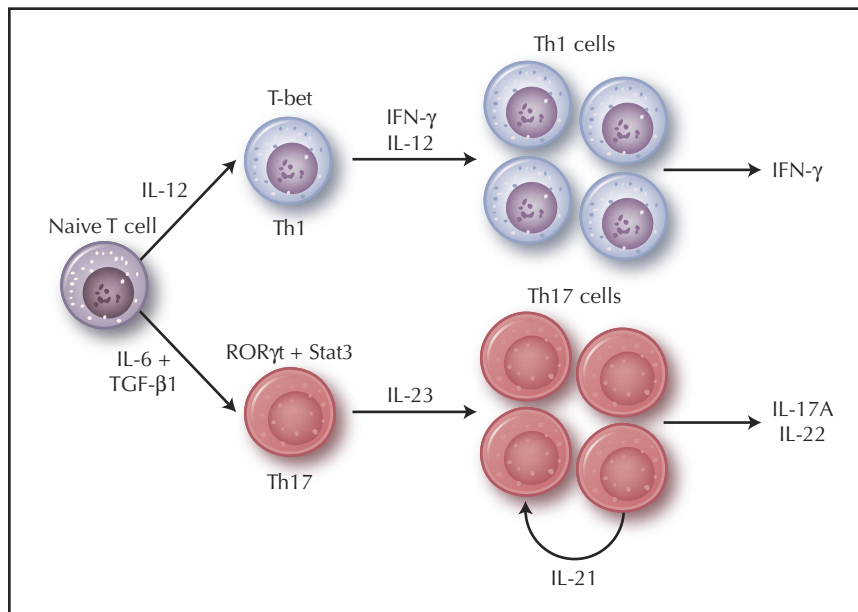


Figure 1. Schematic of the key cytokines and transcription factors involved in the differentiation, proliferation, and effector function of Th17 cells versus Th1 cells. Recent data indicate that IL-1 and not TGF- β 1 is critical in the differentiation of naive T cells into Th17 in humans [9]. IFN—interferon; IL—interleukin; TGF—transforming growth factor; Th—T helper.

basal keratinocytes that overproduce human TGF- β 1 exhibit classic signs of psoriasis, including thick, erythematous, and scaling plaques; the Köebner phenomenon; and histologic changes typical of psoriasis including hyperkeratosis, acanthosis, and infiltration by immune cells [12••]. Stat3 is also abundantly expressed in psoriasis, and transgenic mice that overexpress Stat3 in keratinocytes also exhibit a psoriasis-like phenotype [13••]. It is unclear, however, whether TGF- β 1 or Stat3 transgenic mice exhibit increased levels of IL-23 and increased numbers of Th17 cells, although we are currently studying the TGF- β 1 transgenic mice for this possibility.

IL-23 Promotes Th17 Cell Survival and Proliferation

Intracellular signaling through ROR γ t, Stat3, and extracellular TGF- β 1 is also capable of inducing expression of IL-23R on developing Th17 cells. IL-23R expression promotes responsiveness to IL-23, the key cytokine in the survival and proliferation of Th17 cells (Fig. 1) [3,14]. IL-23 is a heterodimeric protein consisting of a unique p19 subunit paired with a second subunit called p40. IL-12 is a related heterodimer consisting of p40 and a unique subunit called p35, and it promotes development of Th1 cells [3]. The IL-23 receptor is also a heterodimer consisting of IL-12R β 1 and IL-23R subunits, whereas the IL-12 receptor is composed of IL-12R β 1 and IL-12R β 2 subunits. IL-23 is produced by dendritic cells, other antigen-presenting cells [14], and keratinocytes [15••]. Interestingly, dendritic cells produce IL-23 when stimulated by infection with *Candida albicans*, and this event is mediated by dectin-1, a C-type lectin receptor [16••,17••]. In addition, activation through other innate receptors can trigger IL-23 production by dendritic cells, including Toll-like receptor (TLR) 4 signaling induced by lipopolysaccharide from *Bordetella*

pertussis and other sources [18,19]. It is unknown whether *C. albicans* and TLR ligands stimulate keratinocytes to make IL-23, but this is an intriguing possibility, because microorganisms have long been postulated to trigger some types of psoriasis.

IL-23 is clearly elevated in psoriasis lesions as indicated by increased levels of both *p19* and *p40* mRNA in lesional skin as compared to nonlesional skin, whereas mRNA levels of *p35* are not elevated [20,21••,22]. This finding implies that IL-23—but not IL-12—is increased in skin affected by psoriasis. Furthermore, immunohistochemical analyses have revealed p40 and p19 protein expression in dermal dendritic cells [23••] and keratinocytes [24] in psoriasis lesions. Importantly, IL-23 levels (assessed by either mRNA or protein) decrease with clinical improvement of psoriasis following effective treatment, providing a direct correlation between overproduction of IL-23 and active psoriasis [20,21••,22,23••,24–26].

The importance of IL-23 in psoriasis pathogenesis has also been strengthened by recent genetics studies. Tsunemi et al. [27] found that a single nucleotide polymorphism in *p40* was associated with psoriasis. This polymorphism was confirmed using genome-wide association studies and gene sequencing in additional independent cohorts [28••,29•]. The association was independent of *HLA-Cw*0602*, another gene linked to psoriasis [30]. A common risk haplotype was also identified for *IL-23R*, with proline at amino acid 310 and arginine at amino acid 381. In addition, a change in *IL-23R* at 381 from arginine to glutamine was found to be protective against psoriasis. This amino acid is located in the JAK2 kinase-binding domain of IL-23R, which transmits intracellular signals triggered following ligation of IL-23R. It is possible that the change to glutamine arrests the IL-23R signaling cascade and prevents inflammatory responses induced by Th17 cells, although this hypothesis has not been tested.

Of note, no polymorphisms in *p19*, *p35*, *IL-12Rβ1*, or *IL-12Rβ2* were associated with psoriasis susceptibility in these studies.

In transgenic mice, overexpression of individual subunits of IL-23 leads to inflammation. Ubiquitous expression of p19 causes severe multiorgan inflammation, runting, infertility, high circulating levels of TNF- α and IL-1, and premature death [31]. Overexpression of p40 in basal keratinocytes induces inflammatory skin disease [32]. These investigators also suggested that transgenic p40 combined with endogenous p19 that was produced in basal keratinocytes (rather than with endogenous p35) to form IL-23 and cause cutaneous inflammation. However, direct proof for this assertion is lacking. The simultaneous expression of both IL-23 subunits (p19 and p40) expressed in basal keratinocytes of transgenic mice has not been reported; we are in the process of creating and characterizing these mice (Fitch et al., unpublished data). Such mice will allow for detailed characterization of T-cell infiltrates and downstream proinflammatory cytokine expression triggered by cutaneous overexpression of IL-23. In other mouse studies, recombinant IL-23 injected into normal-appearing skin produced erythematous, thick, scaly skin, with histologic features reminiscent of psoriasis [21••,33••]. Interestingly, acanthosis induced by injection of IL-23 was dependent on the Th17 cytokine IL-22 (discussed in more detail later).

Th17 Effector Cytokines: IL-17A, IL-22, and IL-21

Th17 cells are defined at least in part by the specific set of proinflammatory cytokines they produce and secrete, including IL-6, IL-17A, IL-17F, IL-21, IL-22, and TNF- α (Fig. 1) [34]. This section focuses on IL-17A, IL-22, and IL-21, because recent studies highlighted the importance of these cytokines in Th17 cellular immune responses.

IL-17A (often referred to as IL-17), for which the Th17 cell lineage is named, is a homodimeric cytokine and is part of a family of six related cytokines (Fig. 1) [35]. IL-17A expression and secretion is restricted to memory T cells and natural killer cells, whereas the IL-17 receptor, IL-17RA, is expressed on epithelial cells, B and T cells, fibroblasts, monocytic cells, and bone marrow stroma. IL-17RA signaling activates both the nuclear factor- κ B and mitogen-activated protein kinase intracellular pathways [36]. IL-17A has pleiotropic effects, but its main effect is recruitment and activation of neutrophils. Subcutaneous injection of IL-17A into mice causes neutrophilia, which occurs by acceleration of neutrophil formation from committed progenitors and by enhanced chemotaxis [37,38]. In addition, IL-17A is able to directly inhibit apoptosis of neutrophils in inflamed tissues [39]. IL-17A also enhances angiogenesis [40] and mediates tissue remodeling by stimulating the production of angiogenic factors and matrix metalloproteases [41]. In addition, IL-17A synergizes with

TNF- α to enhance inflammation, causing the release of IL-6, TNF- α , and IL-1 β [42]. Finally, IL-17A can directly activate keratinocytes to express granulocyte macrophage colony-stimulating factor, IL-6, and a variety of chemokines and adhesion molecules [43,44].

IL-17A mRNA is elevated in psoriatic skin compared with nonlesional skin [21••]. Immunohistochemical staining for IL-17A-positive T cells has been reported as well [45], but these cells do not appear to be abundant in psoriatic skin. In part, this may be due to high levels of IFN- γ in psoriatic lesions, which can downregulate IL-17 production [33••]. Although IL-17A does not stimulate keratinocyte proliferation, it is interesting to speculate a role for this cytokine in subcorneal accumulation of neutrophils and marked angiogenesis—both tissue hallmarks of psoriasis.

IL-22 is a second important effector cytokine produced by Th17 cells (Fig. 1) [33••,46•]. In fact, activated Th17 cells produce higher levels of IL-22 than IL-17A [46•]. The receptor for IL-22 is a heterodimeric molecule composed of the shared IL-10R2 subunit and the unique IL-22R1 subunit, and it is expressed as a functional molecule at high levels in keratinocytes and cells in the pancreas, colon, liver, kidney, lung, and stomach. However, IL-22R1 is not expressed on any immune cells and therefore has no direct effect on their activity [47]. Signaling through the IL-22 receptor in keratinocytes occurs through activation and phosphorylation of Stat3 [47,48].

Unlike other Th17 cytokines, it is important to note that IL-22 induces keratinocyte hyperproliferation in vitro and in vivo; this effect is mediated through Stat3 signaling [33••,49••]. IL-22 also stimulates keratinocytes to secrete antimicrobial peptides [47,48,49••]. This is clinically relevant, because the overexpression of antimicrobial peptides in psoriatic plaques is believed to be the main reason lesional skin rarely becomes infected by viruses or bacteria [50]. In addition, IL-22 causes keratinocytes to produce matrix metalloproteinase 1, which is involved in tissue remodeling [49••].

Interestingly, levels of IL-22 are increased in psoriatic lesions and in plasma of psoriasis patients, and these levels correlate with disease severity [49••]. IL-22 amounts also correlated positively with production of β -defensins within skin [49••]. Levels of IL-22 mRNA as well as genes regulated by IL-22 normalized to basal levels in affected skin following effective treatment of psoriasis [49••]. These findings suggest several possible areas for future investigation. First, if found to be specific for psoriasis, IL-22 plasma levels could be used as a marker for psoriasis when diagnosis is in doubt. Second, if IL-22 was found to be the major circulating factor that induces keratinocyte proliferation, targeting this molecule would be an attractive therapeutic strategy for individuals with psoriasis. Third, if IL-22 was the main inducer of Stat3 in psoriatic keratinocytes, this cell-signaling molecule would also be an attractive target for therapeutic development.

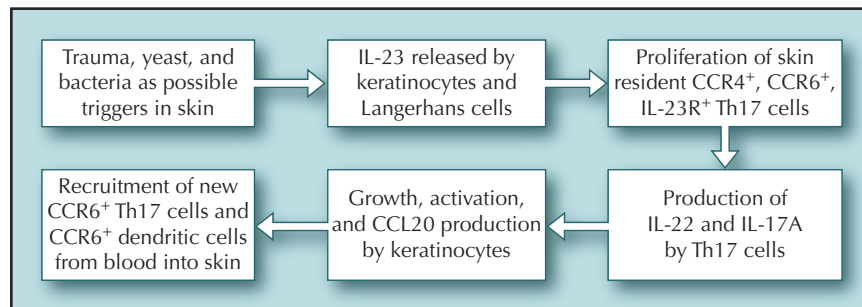


Figure 2. Sequence of events demonstrating the overall hypothesis that psoriasis is a Th17 disease. An initiating event such as trauma or skin surface microbes triggers IL-23 production by keratinocytes and resident dendritic cells, which in turn stimulates proliferation of CCR4⁺ and CCR6⁺ Th17 cells found within skin. These activated Th17 cells secrete Th17 cytokines including IL-22 and IL-17A, which cause keratinocyte growth and activation, respectively. Th17 cytokines also induce CCL20 production by keratinocytes, which fosters additional chemotaxis of CCR6⁺ Th17 cells and CCR6⁺ dendritic cells from blood into skin. Cytokines released by these newly recruited cells maintain psoriatic inflammation. IL—interleukin; Th—T helper.

In mouse studies, IL-22 has been directly linked as a key downstream mediator of IL-23–induced psoriasis-like inflammation in skin. That is, IL-23 injected into mouse ears caused psoriasis-like disease that was dependent upon Th17 cell infiltration into the skin and IL-22 production by the Th17 cells [33••]. Specifically, when IL-23 was injected into IL-22 knockout mice, researchers observed no keratinocyte hyperproliferation [33••]. Taken together, the current data suggests that IL-22—and not IL-17A—is the critical Th17 effector cytokine in psoriasis pathogenesis.

Recently, IL-21 was identified as a Th17 cytokine as well (Fig. 1) [8,51,52]. IL-21 belongs to the common γ chain family of cytokines [53]. When naïve T cells are stimulated with Th17-polarizing cytokines, IL-21 is highly expressed [8]. Both IL-6 and IL-21 drive expression of the IL-23R and Th17-specific transcription factor ROR γ t [51]. IL-21–deficient mice have decreased Th17 cells and a concomitant large increase in Foxp3⁺ T-regulatory cells [8]. Unlike IL-17A and IL-22, IL-21 is produced by Th17 cells and yet also acts in an autocrine manner to promote Th17 differentiation from naïve T-cell populations. Blocking IL-21 led to protection of mice from experimental autoimmune encephalitis [8], a model of multiple sclerosis and a disease known to be mediated by Th17 cells. Although data on IL-21 in psoriasis are lacking at this time, this finding suggests that IL-21 may also be a potential target for psoriasis or other autoimmune inflammatory diseases driven by Th17 cells.

Putting It All Together: How IL-23 and Th17 Cytokines May Create Psoriasis and How to Block this Pathway for Therapeutic Benefit

The central hypothesis put forth in this review is that the IL-23/Th17 inflammatory pathway is critically involved in psoriasis pathogenesis. Perturbation of resident keratinocytes and dendritic cells by trauma and/or stimulation of pattern recognition receptors (eg, dectin-1, TLR2, and TLR4) by microbes on the skin surface may trigger condi-

tions that promote IL-23 production [16••,17••] and thus lead to survival and proliferation of Th17 cells within skin (Fig. 2). As to how Th17 cells may migrate into the skin initially, chemokine receptor expression profiles, recently described for human Th17 cells, provide some clues [16••,54•]. CCR6, whose chemokine ligand CCL20 is secreted by keratinocytes, is found in abundance on Th17 cells; CCR4 is also expressed on Th17 cell surfaces [16••,54•]. Interestingly, these chemokine receptors are also characteristically found on resident skin T cells [55•]. Thus, it is possible that skin preferentially recruits Th17 cells in resting or noninflammatory states, and that perturbations that enhance local IL-23 production allow for expansion of these cells and thus produce inflammation.

Although a number of Th17 cell–derived cytokines may be playing important roles in psoriasis pathogenesis, IL-22 seems to be the key player involved in keratinocyte proliferation [33••,49••]. We have recently detected increased numbers of IL-22⁺ T cells in psoriasis lesions when compared with healthy skin from normal individuals (Harper et al., unpublished data). CCL20 is overexpressed in psoriasis [44], and we have also demonstrated recently that both IL-17A and IL-22 induce keratinocytes to produce CCL20 in vitro (Harper et al., unpublished data). This may be important in the maintenance of psoriasis lesions by stimulating ongoing chemotaxis of new CCR6⁺ Th17 cells and CCR6⁺ dendritic cells from blood.

In this new paradigm for psoriasis pathogenesis, IL-23 is a key master cytokine. Certain genetic alterations of the IL-23 subunit *p40* and the IL-23 receptor subunit *IL-23R* [27,28••,29•] are predicted to lead to enhanced IL-23 production and receptor-mediated signaling, and thus lead to psoriasis susceptibility. By contrast, other mutations that result in decreased IL-23 production and receptor-mediated signaling [28••,29•] will confer protection from psoriasis.

It is also predicted that inhibition of IL-23 will lead to Th17 cell death and abrogation of psoriasis. Indeed, monoclonal antibodies directed against *p40* have produced

Table 1. Potential new therapeutic targets for psoriasis based on the theory that psoriasis is a Th17 disease

Target	Functional role	Expected clinical result in psoriasis
p19	Key IL-23-specific subunit involved in promoting survival and proliferation of Th17 cells	Outstanding/dramatic: critical IL-23-specific subunit, an "upstream" regulator of inflammation, would be blocked
IL-23R	Induces cell signals after IL-23 binding and is expressed on Th17 cells but not on Th1 and Th2 cells	Excellent: pathogenic Th17 cells would be deleted
IL-22	Key effector cytokine secreted by Th17 cells; largely responsible for keratinocyte hyperproliferation	Good-to-excellent (similar to TNF- α inhibitors): key "downstream" effector cytokine would be blocked
Stat3	Key intracellular signaling molecule important in Th17 development and mediates IL-22-induced keratinocyte hyperproliferation	Good-to-excellent (similar to TNF- α inhibitors): major signaling pathway would be blocked

IL—interleukin; Th—T helper; TNF—tumor necrosis factor.

striking clinical results in psoriasis patients [56••,57]. These promising phase 2 studies have led to large-scale, ongoing phase 3 trials in patients with moderate-to-severe psoriasis. Although these drugs were initially developed to target IL-12, many scientists now believe that blocking the biologic activity of IL-23 is the main mechanism for the clinical activity of anti-p40 monoclonal antibody therapy in psoriasis. It will be interesting to directly test the hypothesis that blocking IL-23 alone—by using monoclonal antibodies directed against p19—is sufficient to improve psoriasis (Table 1). Initial safety results from short-term clinical trials of anti-p40 antibody are encouraging [56••,57], but long-term safety remains to be determined. It is postulated that specifically targeting IL-23 with anti-p19 monoclonal antibodies may confer the same efficacy as p40 targeting and perhaps increased safety by allowing normal IL-12-mediated Th1 responses to occur. In addition to p40 and p19, other attractive future targets for psoriasis include IL-23R, IL-22, and Stat3 (Table 1).

Conclusions

Several recent studies suggest that psoriasis is a Th17 cell-mediated disease driven by IL-23. However, more investigation is needed to substantiate this theory. A central issue will be the determination of triggers of IL-23 production by keratinocytes and dendritic cells. Is abnormal IL-23 production by these cells caused by dysregulation of signaling in the innate immune system of the skin? More specific questions related to dendritic cell biology require answers as well, including what causes dendritic cells in psoriasis to make IL-23 instead of IL-12, and thus skew T-cell responses from Th1 to Th17. Are external antigens, autoantigens, or a combination of both presented by dendritic cells to antigen-specific Th17 cells in psoriasis? The answers to many of these questions are now within reach of scientists involved in psoriasis research. This work in cellular immunology combined with advances in genetics offer the possibility of unraveling the remaining mysteries of this enigmatic disease.

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