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The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses

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Abstract

Psoriasis is a complex inflammatory process resulting from activation of the well-defined IL-23/T17 cytokine axis. We review the role of key cytokines interleukin (IL)-17 and IL-23 in psoriasis, as well as tumor necrosis factor alpha (TNα), focusing on therapeutic cytokine interventions and what they reveal about psoriatic inflammation. The potential role of recently described epidermal *IL-36RN* and *CARD14* genetic mutations in psoriasis pathogenesis will also be explored, as they augment keratinocyte responses to pro-inflammatory cytokines. The discovery of these genetic mutations in familial and pustular psoriasis suggest new links between cytokine-induced gene products and IL-1 family members from keratinocytes, which may regulate features of the disease, including epidermal hyperplasia and neutrophil infiltrating responses.

Introduction

In 2004, we presented a review of psoriasis that focused on the “Th1 pathway” as the dominant pathogenic model for psoriasis [1]. At that time, it was appreciated that there was a strong interferon gamma (IFNγ) signature in psoriasis lesions: IFNγ-producing T helper (Th)1 cells were abundant in psoriasis lesions and blood, and these Th1 cells were reduced with successful therapy. Recently, clinical studies have been conducted with individual cytokine antagonists that suggest a central role for IL-23 and IL-17, along with TNFα, in driving disease pathology (Table 1). Furthermore, the feedback interactions between cytokines and triggering events (such as infection or trauma) will be discussed. Although a great deal of complexity exists in gene circuits activated in psoriasis [2–4], we have focused this review on a set of pathways and molecules that are now established as key regulators of skin inflammation through therapeutic antagonists or from recent genetic studies.

Fully established psoriasis lesions have a classic clinical appearance of well-demarcated, erythematous scaly plaques on elbows, knees and scalp that typically are quite stable. Lesions are not often biopsied in clinical practice as the diagnosis can usually be made

CONFLICT OF INTEREST CBR, DAM, and JET are employed by Amgen, which developed brodalumab. JGK has consulted for many pharmaceutical companies, including those mentioned above. MAL does not have any conflict of interest.

clinically, but on hematoxylin and eosin (H&E) staining of a lesional skin biopsy, there are several important features of “psoriasiform” histology, including acanthosis (an increase in epidermal thickness), hyperkeratosis, parakeratosis, dilated blood vessels, and a dense dermal immune cell infiltrate. Acanthosis is caused by keratinocyte hyperplasia; hyperkeratosis is an increase in the outer stratum corneum; parakeratosis is retention of nuclei in the cornified layer as the keratinocytes move through the epidermis over days rather than weeks; blood vessel dilatation gives the lesions their erythematous color; and there is a dense dermal mononuclear infiltrate. Collections of neutrophils can be seen in the epidermis, and have been given eponymous names (i.e. Munro's microabscesses and Kogoj pustules). This epidermal response is actually not diagnostic but may represent a characteristic cutaneous response pattern. Other non-psoriasis skin disorders may have a psoriasiform presentation, such as chronic dermatitis, which may reflect the response of the skin to the underlying cytokine milieu [5]. Further immunohistochemical stains for specific leukocyte markers or molecular tests for cytokines may yield patterns that are more diagnostic of psoriasis and enable exclusion of these other differential diagnoses.

The current pathogenic model of psoriasis emphasizes the *IL-23/T17 axis* (Figure 1), but also contains other T cell subsets. For our review, IL-17-producing T cells will be denoted as T17. While current convention is that Th17 are $CD4^+IL\text{-}17^+$ cells, and Tc17 are $CD8^+IL\text{-}17^+$ cells, recent data indicate that both αβ and γδ T cells can produce IL-17. This will be discussed further below. Activated dendritic cells (DCs) produce IL-23 and IL-12 [6], which stimulates the three populations of resident T cells, T17, Th22 and Th1. IL-23 from inflammatory DCs activates T17 cells to produce IL-17A and IL-17F, which drive keratinocyte responses. Once activated, the epidermis can produce abundant cytokines and inflammatory mediators, including IL-8/chemokine CXCL8, MCP-1/CCL2, CXCL1, CXCL2, and CXCL3, and CCL20 [7–9]. These chemokines attract leukocytes such as neutrophils, DCs, and $CCR6^+$ T17 cells. CXCL9, CXCL10, and CXCL11 are also produced which recruit additional circulating $CXCR3^+$ Th1 cells into the dermis and epidermis [8]. T cell derived cytokines act on epidermal keratinocytes as proximal inducers of these inflammatory circuits.

Cutaneous chemokine induction and leukocyte recruitment can occur within hours. In a recent study with a single injection of IFNγ into healthy skin, abundant leukocytes accumulated within 24 hours in the dermis, even when there were no visible changes in the skin appearance [10]. IFNγ is released by Th1 cells, and a subset of T17 cells may play an important role in the maintenance phase of psoriasis, further activating myeloid DCs and amplifying response circuits. Additional soluble factors, including IL-22 (from Th22 cells), IL-19, IL-20, and keratinocyte-derived IL-36, induce epidermal proliferation. Vascular endothelial growth factor (VEGF) induces vascular dilation and hyperplasia. Stimulation of keratinocytes also induces IL-17C [11]. Once the cycle of psoriatic inflammation is underway, it is self-perpetuating.

Current therapeutic options for psoriasis include various topical agents for limited disease (corticosteroids and vitamin D analogues), oral systemic immunosuppressive agents (such as methotrexate, retinoids and cyclosporine), and phototherapy. More recently, biologics such as anti-TNF and anti-IL-12/23 antibodies have been FDA-approved, and there are evolving agents such as anti-IL-23p19 and anti-IL-17 currently in clinical trials. Therapeutic effectiveness of various agents may be related to how well this cycle of inflammation is broken. In general, the effectiveness increases as one ascends this “therapeutic ladder”, with the anti-cytokine therapies being the most effective agents currently available for extensive psoriasis. There is still a need to develop even better and more specific treatments, with safer side-effect profiles.

TNFα

TNFα blockade was the first widely used anti-cytokine therapy for psoriasis, although TNFα inhibitors were available for rheumatoid arthritis long before their use to treat skin disease. TNFα can be produced by many cell types including keratinocytes and T cells, and in psoriasis, it is produced by TNFα- and iNOS-producing DCs (Tip-DCs), a subset of myeloid inflammatory DCs [6, 12, 13]. Blockade of TNFα is very efficacious, with over 50% of subjects achieving a *PASI75* by 3 months. There are three FDA-approved anti-TNFα agents approved to treat psoriasis (Table 1): Infliximab is a chimeric monoclonal antibody that binds soluble and membrane TNF, Etanercept is a soluble TNFα receptor-IgG fusion protein, and adalimumab is a fully human anti-TNFα IgG1 monoclonal antibody.

The mechanism of action of TNFα in disease is multifaceted, but a key effect appears to be regulation of antigen-presenting cells [14]. Our group showed that lesional DCs had lower levels of co-stimulatory molecules when psoriasis subjects were on etanercept [15]. Furthermore, DCs generated *in vitro* in the presence of etanercept down-regulated maturation markers and co-stimulatory molecules (CD86, HLA-DR, CD11c), and were less able to stimulate allogeneic T cell proliferation. This suggests that a key mechanism of action of TNFα inhibitors is by impairing DC-T cell interactions, resulting in decreased epidermal stimulation by T cell cytokines. TNFα is thus an activator of IL-23 synthesis in DCs (Figure 1), and clinical benefit seen with TNFα blockade may be linked to suppression of the IL-23/T17 axis [15].

Cellular sources of IL-17

Both $CD4^+$ and $CD8^+$ T cells in psoriasis lesions produce IL-17A and IL-17F on *ex vivo* stimulation, and the populations have been termed Th17 and Tc17, respectively. It has been assumed that most T cells in the skin are αβ TCR^+, but recent studies have identified a group of dermal γδ T cells that produce IL-17 [16–21]. Psoriasis dermal suspensions and lesions showed abundant $CD3^+$ T cells expressing γδ TCR (40% dermal $CD3^+$ cells were γδ T cells), significantly more than healthy control skin [19]. When stimulated *ex vivo* with IL-23, these γδ T cells increased their expression of IL-17 many fold more than αβ T cells. The recently developed murine model of daily imiquimod (TLR7/8 agonist) treatment of skin demonstrated the critical role of the IL-23/IL-17/IL-22 axis for the psoriatic phenotype [22, 23]. Furthermore, IL-17 production by γδ T cells was demonstrated in this setting [24, 25].

Although both αβ and γδ T cells may be stimulated by IL-23 to synthesize IL-17, some γδ T cells show less-specific antigen-responses than conventional αβ T cells. Clearly, further studies need to examine the antigen-responsiveness of IL-17-producing cells in psoriasis, clonality of this subset, and whether any innate-inducer lymphocytes, such as those seen in the gut [26], are present. Lin *et al* recently showed that neutrophils and mast cells may be a major source of IL-17 [27], which could place the IL-17 response early in the pathogenic pathway. However, care needs to be exercised in attributing IL-17 ligand production to other leukocytes, because IL-17 receptors are abundant on many lymphocytes, and so staining for IL-17A may only identify cells with high levels of IL-17 receptors occupied with ligand [28].

IL-17 is an ancient cytokine that appears to have been adopted by the adaptive immune system [18]. The main mechanisms by which IL-17 induces psoriasis are by pleiotropic effects on immune cells, keratinocytes, and fibroblasts, inducing many inflammatory mediators including cytokines (IL-6, IL-1β, TNF, GM-CSF), chemokines (CXCL1, CXCL2, CCL20, CXCL8), MMPs, antimicrobial peptides (LL37, S100s, β-defensin), and complement. Hence there is recruitment and activation of neutrophils, lymphocytes, and

myeloid cells, leading to local cutaneous inflammation [29, 30]. This occurs in synergy with other cytokines such as IL-23 and possibly IL-36, as discussed further below.

IL-17 as key pathogenic psoriatic cytokine

To date, direct blockade of IL-17 appears to be the anti-psoriatic therapeutic strategy with the most rapid efficacy, although these agents are not yet FDA-approved for use to treat psoriasis (Table 1). The studies presented below suggest that IL-17 ligands are the "key" pathogenic psoriatic cytokines, and that inhibiting this axis is essential for disease resolution. IL-17 and its downstream genes are turned off by many other psoriasis treatments we have studied, including cyclosporine [31], and NB-UVB [32]. At the time T17 cells were being appreciated as critical mediators of autoimmunity, our group showed that TNFα blockade with etanercept reduced T cells, T17 cell products, and IL-17-induced genes (including IL-22, CCL20, β-*defensin 4*/HBD2), and that efficacy was associated with the reduction in the IL-17 gene expression signature [15, 33]. Hence, for disease resolution IL-17 must be switched off, implying that IL-17 signaling is required for disease presence.

Proof of principle that IL-17 blockade could be effective in autoimmune diseases was first shown in 2010 (Table 1) [34]. Three of the six known IL-17 ligands are over-expressed in psoriasis: IL-17A, IL-17F and IL-17C. IL-17A and IL-17F bind to a heteromeric IL-17 receptor composed of IL-17 Receptor (IL-17R) A and IL-17RC, whereas IL-17C binds to an IL17RA/IL17RE complex [35]. There have been three anti-IL-17 agents tested in psoriasis, with slightly different targets. Secukinumab and ixekizumab selectively bind IL-17A [34, 36–38], while brodalumab inhibits the IL-17 Receptor A subunit [39, 40].

Hueber *et al.* first presented clinical improvement in psoriasis with the anti-IL-17A monoclonal antibody secukinumab [34]. Studies with the IL-17RA antibody brodalumab, in subjects with "moderate-to-severe" psoriasis (defined as psoriasis covering more than 10% of the body with a psoriasis areas and severity index [PASI] score of greater than 12), showed rapid cellular and molecular responses to IL-17 blockade (Figure 2a) [39, 40]. Similar responses were seen with ixekizumab for subjects with moderate-to-severe psoriasis (Figure 2b) [37, 38]. Both brodalumab and ixekizumab appear to work quickly as there were significant improvements by 1–2 weeks. In the high dose groups across these studies, ~75–85% of subjects had a PASI75 response (i.e. 75% improvement in clinical symptoms from baseline) by 12 weeks. Furthermore, a large proportion of subjects achieved PASI90 and PASI100 responses (75% and 62%, respectively, with brodalumab), indicating IL-17 pathway blockade eliminates an essential component of psoriasis.

The extent to which IL-17 inhibitors reverse cellular, molecular and clinical phenotypes of psoriasis was a surprise, because multiple T cell subtypes are co-activated in psoriasis (Figure 1). Thus, one of the biggest remaining questions is to determine exactly how IL-17 signaling drives a complex inflammatory phenotype in skin. In this regard, IL-17A-treament of keratinocytes *in vitro* induces only 40 genes [28]. However, there are a number of genes (approximately 160 genes), that are synergistically regulated by IL-17 and TNFα, [i.e. their expression was greater than either IL-17 and TNFα could induce alone, and more than simply adding together their effects (196 genes were additive)] [41]. At two weeks, anti-IL-17A treatment of psoriasis reduced a six-fold greater number of genes than anti-TNFα treatment (as defined by >75% change from baseline) [38], and genes synergistically regulated by IL-17 and TNFα were blocked to a higher magnitude by anti-IL-17A than anti-TNF treatment. Synergism between IL-17 and IL-22 has also been shown [42], but may also exist with other IL-20 family cytokines (IL-19, IL-20, IL-24) that bind a common receptor. Overall, this supports the crucial role of IL-17 in driving psoriasis pathogenesis and the complex synergistic effects of these pro-inflammatory cytokines.

IL-23

IL-23 appears to be the critical driver behind T17 activation, as well production of IL-17. IL-23 is a heterodimer of a unique IL-23p19 and shared IL-12/23p40 chains. IL-23 is produced by both resident (BDCA-1/CD1c^{+}) and inflammatory myeloid DCs (CD11c^{+} BDCA-1/CD1c^{-}), as well as macrophages (CD163^{+}) in psoriasis [6, 43, 44]. IL-12, a heterodimer of IL-12/23p40 and IL-12p35, is produced by the same cells and is more important in activating Th1 cells. Both IL-12/23p40 and IL-23p19 are elevated in psoriasis, while IL-12p35 is not [45]. Among a large set of psoriasis-associated genes (reviewed in [46]), recent genetic studies have identified single nucleotide polymorphisms (SNPs) in several IL-23 axis genes [47–49]. In one example, an IL-23R allele associated with decreased T17 response was also associated with reduced susceptibility to developing psoriasis [50].

Ustekinumab, an FDA-approved monoclonal antibody to IL-12/23p40, has been very successful for psoriasis subjects; more than 60% of patients achieve a PASI75 response (Table 1) [51, 52]. Briakinumab, a second IL-12/23p40 inhibitor, shows similar efficacy [53–55]. Apilimod is an oral, small molecule inhibitor of IL-12/IL-23p40 synthesis, which induced substantial improvements in psoriatic clinical and histological features in a small open-label dose-escalation study [56]. Studies are underway to block the unique p19 chain of IL-23, which targets IL-23 specifically and spares IL-12 (Table 1). A phase I study of a single dose of anti-IL-23p19 (CNTO 1959) was reported at the Psoriasis: from Gene to Clinic 6th International Congress meeting in November 2011. *PASI75* was seen in all subjects at the highest dose (300mg) [57]. Head-to-head comparison of IL-23 specific inhibition and IL-12/23p40 inhibition will help determine how these agents differ in the clinical setting, and the specific role, either positive or negative, of IL-12 in psoriasis. Overall, disease improvements mediated by TNFα, p40 and IL-17 antagonists support the concept that inflammatory loops in psoriasis can be targeted at different points in the pathogenic cycle (Figure 1).

IFNγ

The role of IFNγ in psoriasis pathogenesis is now less clear, although approximately 400 of the genes upregulated in psoriasis lesions can be traced to STAT1 activation, a key IFNγ transcription factor [10]. Initially, before the discovery of IL-17, it was considered that psoriasis was primarily an IFNγ-mediated disease [58, 59]. Kryczeck *et al*. suggested that one of the main effects of IFNγ was activating antigen-presenting cells early in the psoriatic cascade [60]. Admittedly, assignment of IFN-regulated genes to IFNγ is complicated by strong up-regulation of IFNα in psoriasis lesions [61].

To dissect the contribution of IL-17, TNFα, IFNγ, and IL-22 to psoriasis pathogenesis, we treated keratinocytes with these different cytokines, and profiled the effects by microarray to generate cytokine-keratinocyte “gene sets” or “pathways” [28]. Many of these up-regulated cytokine-derived pathways were highly represented in the psoriasis transcriptome [62]. Analysis of the cutaneous transcriptome during blockade of TNFα in psoriasis patients revealed the specific and relative contributions of IL-17 and IFNγ. In psoriasis subjects responding to etanercept, there was decreased expression of IL-17-and TNFα-induced genes at 3 months, whereas non-responders still showed expression of these pathways. The relative kinetics were such that IL-17 down-stream products were reduced more quickly than IFNγ-induced mediators, although down-regulation of IFNγ genes was consistently observed with response to treatment [33].

Keratinocyte-derived factors that synergize with IL-23/T17 axis

Psoriasis can be considered to have an initiation phase that starts the inflammation, and a maintenance phase that perpetuates this inflammatory state. Triggers that start psoriasis lesion initiation are not fully understood, but include infections (particularly streptococcal infections); trauma, often seen as the Koebner phenomenon (psoriasis in areas of injury); and medications [63]. The classic location of psoriasis plaques on elbows and knees still defies a full scientific explanation, but could be due to constant trauma in these areas. The role of keratinocytes in the initiation phase of psoriasis lesions is not completely understood. However, there are new findings that support a role for keratinocytes in both psoriatic initiation, as well as amplifiers of psoriatic inflammation during maintenance of lesions. Specifically, mutations in *IL36RN*, the gene encoding the IL-36 receptor antagonist (IL-36Ra, formerly IL-1F5), and in the caspase recruitment domain-containing protein 14 (*CARD14*) gene, have been linked to specific psoriatic phenotypes.

Mutations in the *IL-36RN* gene (which encodes IL-36Ra protein) in familial systemic pustular psoriasis were first described in 2011 [64–66]. IL-36 family members are strongly upregulated in psoriasis and with IL-17A stimulation of keratinocytes, and they have been localized to the epidermis in psoriasis [67, 68]. The three IL-36 stimulatory cytokines (IL-36α, IL-36β, IL-36γ formerly IL-1F6, IL-1F8, and IL-1F9 respectively) belong to the IL-1 family, and all bind to the IL-36R (IL-1RL2), activating nuclear factor kappa B (NFκB). IL-36Ra is a natural antagonist of this interaction and homozygous mutations leading to the loss of active IL-36Ra protein result in unopposed pro-inflammatory effects of the IL-36α/β/γ cytokines. Strong IL-36 activity in the absence of the antagonist may therefore lead to excessive neutrophil accumulation seen in pustular psoriasis. As IL-36Ra is abundant in psoriasis vulgaris (non-familial cases) [67], it could function to attenuate agonist activity in this disease.

Overexpression of IL-36α in keratinocytes under the K14 promoter in mice results in transient acanthosis, hyperkeratosis, a mixed inflammatory cell infiltrate, and increased expression of cytokines and chemokines [69]. The importance of IL-36Ra to this phenotype became clear when the IL-36α transgenic mice were crossed onto the *IL-36RN* null background and the majority of mice did not survive. IL-36α transgenics on the *IL-36RN*$^{+/-}$ background had a persistent phenotype that resembled psoriasis although it was T cell independent. Similarly, if adolescent IL-36α transgenic mice with histologically normal skin were exposed to 12-O-tetradecanoylphorbol-13-acetate (TPA) painted on the skin, they developed a psoriatic phenotype [69, 70]. Indeed, anti-IL1R2 antibodies decreased epidermal thickness and psoriatic pathology in this xenotransplant model, to a similar degree as etanercept [70]. This suggests a two-step process is required for the psoriatic phenotype in this mouse model: IL-36 overexpression along with either IL-36Ra deficiency or an independent activating agent such as TPA [69]. Similar two-step activation in humans could involve IL-36. All three IL-36 ligands are orders of magnitude more active upon truncation [71], and therefore, a second step could involve activation of an IL-36-cleaving protease as a result of injury or infection. The IL-36 family may be significant contributors to the positive feedback loop of inflammation in psoriasis. IL-36 cytokines induce IL-23 gene expression from DCs and keratinocytes [72]. They therefore fill a role for completing an amplifying loop from IL-23 to IL-17 to IL-36 and back again to IL-23, thus sustaining the chronic inflammatory state.

CARD14 mutations and rare variants were described very recently [73, 74]. Different *CARD14* mutations resulted in psoriatic phenotypes of varying severity, from typical large plaque psoriasis to severe psoriasis in a young child. The *CARD14* gain-of-function mutations lead to unopposed NFκB activation, and induction of inflammatory mediators

from keratinocytes. CARD14 protein is found in keratinocytes of patients, and the keratinocyte response to physical injury or to cytokines could initiate cascades that include CARD14. Transfection of keratinocytes with the CARD14 mutation, as well as keratinocytes from the patient with the most severe phenotype, lead to the production of inflammatory cytokines such as IL-8, CCL20, and IL-36γ. Hence, the presence of the CARD14 mutation may result in a greater amplitude of inflammatory response upon epidermal activation, and lead more readily to lesion development. CARD14 may be acting in a synergistic manner with IL-17, activating the NFκB and c-EBPβ transcription factors, respectively [35].

LL37 and other antimicrobial peptides

In addition to the classic cytokine network, other signals may be carried by a set of small proteins known as antimicrobial peptides (AMPs), which may also activate innate immune receptors. The AMPs are expressed in the epidermis, and may play an important role in psoriasis pathogenesis, because they are strongly induced by the IL-17 family and may create feed-forward pathways of immune activation [75]. When plasmacytoid dendritic cells (PDCs) are activated by cathelicidin antimicrobial peptide (CAMP)/LL37 complexed to self-DNA or -RNA, they release abundant IFNα [76, 77]. IFNα along with LL37-self-RNA complexes, activate dermal myeloid DCs, leading to DC maturation, TNFα and IL-6 production [77]. In psoriasis sections, extruded DNA and RNA can be demonstrated [27, 77]. In contrast, LL37 was shown to independently inhibit activation of the *AIM2* inflammasome in keratinocytes [78, 79] suggesting an additional early regulatory role for this AMP in psoriasis. S100 proteins may also have a major inflammatory role. S100A12 (also known as EN-RAGE or Calgranulin C), S100A7 (psoriasin), and S100A7A (S100A15 or koebnerisin) are abundant in psoriasis and can activate RAGE receptors [80, 81], or TLR receptors [80]. S100 proteins and β-defensins can also be chemotactic for multiple inflammatory cell types [81, 82], further amplifying inflammation.

Concluding remarks

In this review we have highlighted the central role of the IL-17 cytokines in psoriasis, and their position in a positive feedback loop that maintains the inflammatory psoriatic state. Other important signaling proteins in this loop include IL-23, immediately upstream of IL-17A and IL-17F, and IL-36 and the AMPs immediately downstream of IL-17 activity on the keratinocytes. TNFα has activities independent of IL-17, but also can synergize with it, whereas IFNγ has complex interactions. The roles of IL-17C, IL-19, and IL-20 are just beginning to be understood. It has also become clear that the inflammatory state in psoriasis may be better thought of as a complex network of cytokines interacting in positive and negative feedback loops rather than as a linear pathway or signaling cascade. Therapies targeted against IL-17 signaling, TNFα, or the IL-23 subunits have all shown varying levels of efficacy. In all investigated cases, efficacy has been associated with reductions in the expression of the other network cytokines.

Although our understanding of the network involved in maintaining the inflamed state within the skin has advanced considerably, we are at an early stage in defining the molecular triggers that may initiate psoriasis, and systemic inflammation syndromes associated with psoriasis (Text Box). Rare mutations with potent effects in *IL36RN* and *CARD14* identify some potential actors, but it is not yet clear what role these pathways play in the presence of a normal genetic background. Investigations into the molecular mechanisms activated by the known environmental triggers may shed light on how the inflammatory cytokine network arises from previously non-lesional skin.

TEXT BOX Inflammation beyond the skin

Although this review has focused on the interaction of cytokines in the skin, a new area of great interest is the recently appreciated association between psoriasis and co-morbid conditions. Psoriasis patients have an increased incidence of arthritis, cardiovascular disease, diabetes mellitus, metabolic syndrome, obesity, impaired quality of life, and depression [83–89]. A recent study has identified an abundance of inflammatory products in the blood that are also over-produced in skin lesions [3], leading to a hypothesis that some systemic co-morbidities could result directly from immune circuits activated in skin lesions. An important future endeavor will be to increase our understanding of mechanistic links between skin inflammation and the range of immune-related co-morbidities that are seen in psoriasis with the view of translating this important information to health improvements in a disease that shortens life

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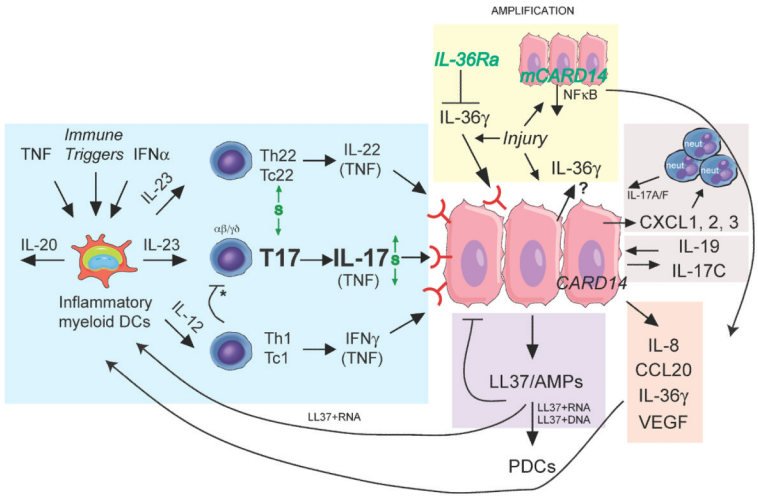

Figure 1. Essential cells and molecules in the pathogenesis of psoriasis lesions

The IL-23-IL-17 axis is well understood in psoriasis. Inflammatory and resident myeloid DCs become activated to produce IL-23. This drives production of IL-17 ligands (IL-17A, IL-17F) from αβ and γδ T cells (T17), and IL-22 by subsets of $CD4^+$ (Th22) and $CD8^+$ (Tc22) cells, while IL-12 drives production of IFNγ. These T-cell derived cytokines can then activate the epidermis to produce further inflammatory chemokines and cytokines. Some will recruit cells into the skin: IL-8, CXCL1, 2 & 3 are all neutrophil chemotaxins; CCL20 attracts $CCR6^+$ DCs and T17 cells; and VEGF is important in inducing the vascular hyperplasia seen in psoriasis. Others such as IL-19, IL-20, and IL-22 induce epidermal hyperplasia, while IL-17C is a keratinocyte produced IL-17 ligand. There is synergy (green S) between IL-17 and TNFα, as well as between IL-17 and IL-22. Chemokines for inflammatory DCs (immune triggers) such as CCL20 may help initiate lesions. There are abundant IL-36 cytokines in psoriasis, which are also involved in neutrophil chemotaxis, and IL-36Ra is the natural antagonist for this effect. Mutations in the *IL-36Ra* gene lead to the runaway inflammation seen in familial pustular psoriasis. Mutations in epidermal *CARD14* (*mCARD14*) in familial psoriasis may increase endogenous activation in response to a trigger, inducing abundant cytokine and chemokine production (such as IL-8, CCL20, IL-36). Wild-type CARD14 may also play a role in initiating and amplifying the psoriatic process. LL37 complexed with nucleic acids can activate DCs. When established, over 4000 transcripts are dysregulated in psoriasis, undoubtedly with other interactive circuits that are not diagramed here. * T cells bearing γδ TCR may be less inhibited by IFNγ [90].

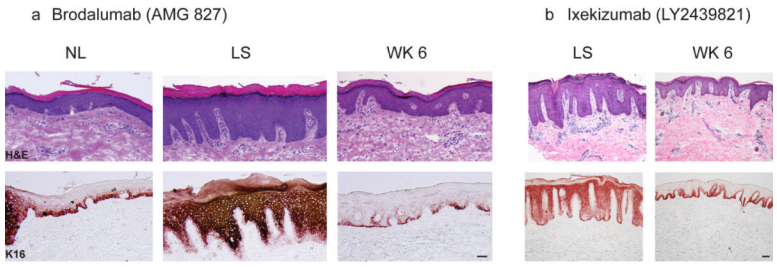

Figure 2. Histological responses of psoriasis lesions to IL-17 blockade

Hematoxylin and eosin sections (upper panel) and keratin 16 (K16, lower panel) during early phase clinical trials with (a) brodalumab (AMG 827), and (b) Ixekizumab (LY2439821) at baseline non-leisonal (NL), lesional (LS), and week 6 (WK 6). NL skin showed some K16 staining around a hair follicule (left) There was resolution of the histological changes of psoriasis as well as decreased keratin 16 (K16) staining. Size bar is 100μm. Reprinted with permission from the original publications ([references 40] and [38]).

Table 1

Anti-cytokine therapies currently tested in psoriasis

Drug *(Trade name)*	Drug target	Drug Type	Company	References
Secukinumab AIN457	IL-17A	human MoAb	Novartis	[34]
Ixekizumab LY2439821	IL-17A	humanized IgG4 MoAb	Eli Lilly and Co	[37, 38]
Brodalumab AMG 827	IL-17 Receptor A	human IgG2 MoAb	Amgen	[39, 40]
Ustekinumab (*Stelara*®)	IL-12/23p40	human anti-p40 moAb	Janssen	[51, 52]
Briakinumab ABT 874	IL-12/23p40	human anti-p40 moAb	Abbott	[53–55]
Apilimod	IL-12/IL-23 p40	Small molecule inhibitor	Synta Pharmaceuticals	[56]
LY2525623	IL-23p19	humanized anti-p19 moAb	Eli Lilly and Co	NCT 01018810
SCH 900222	IL-23p19	humanized anti-p19 moAb	Schering Plough/Merck	NCT 01225731
CNTO 1959	IL-23p19	Human anti-p19 Ab	Janssen	[57]
Infliximab (*Remicade*®)	TNF	chimeric anti-TNF moAb	Janssen	[91–93]
Adalimumab (*Humira*®)	TNF	human anti-TNF moAb	Abbott	[94–96]
Etanercept (*Enbrel*®)	TNF	soluble TNF-α receptor-IgG fusion protein	Amgen/Pfizer	[97–99]