

REVIEW

Cytokines Focus

Interleukin-17 cytokines: Effectors and targets in psoriasis—A breakthrough in understanding and treatment

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The IL-17 cytokine family comprising IL-17A to IL-17F and receptor subunits IL-17RA to IL-17RE represents a genetically ancient intercellular network regulating local tissue homeostasis. Its pivotal role in antifungal defense and its central position in the pathogenesis of inflammatory diseases including psoriasis were discovered only relatively late in the early 2000s. Since the connection of dysregulated IL-17 and psoriasis pathogenesis turned out to be particularly evident, a number of monoclonal antibodies targeting IL-17 pathways have been approved and are used as first line treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis, and further agents are currently in clinical development.

IL-17 and its pivotal role in psoriasis

Over the last few years, we have witnessed a remarkably fast and very successful translation of basic IL-17 biology research to the development of efficient drugs targeting IL-17. Most prominently, mAb designed to neutralize IL-17A, IL-17F, or IL-17RA are either already approved or in clinical trials to treat psoriasis, psoriatic arthritis (PsA), and other chronic inflammatory diseases (Kurschus and Moos, 2017; McGeachy et al., 2019), as summarized in Table 1 and Table 2. In this review, we will focus on the role of IL-17 cytokines as effectors and targets in psoriasis, where dysregulated local IL-17 levels are clearly the key effector mechanism driving the pathophysiology of psoriasis, i.e., neutrophil influx and keratinocyte hyperproliferation. Accordingly, novel biologics targeting IL-17 pathways have been shown to be highly efficacious in moderate-to-severe plaque psoriasis and PsA. As compared with other inflammatory cytokines such as IL-6 or TNF- α , IL-17 cytokines are rather acting locally, particularly at mucosal surfaces and in the skin.

Before we summarize the present clinical data and therapies targeting IL-17 cytokines and its upstream “master cytokine” IL-23, we will review the current understanding of IL-17’s physiological role in establishing local homeostasis with skin microbiota and subsequently discuss the mechanisms that can lead to a pathogenic dysregulation of the IL-23/IL-17 axis.

IL-17 immunity

In the search for cytotoxic lymphocyte-specific genes in mice, Pierre Golstein found the gene *Ctla-8* that was 57% homologous to the putative protein encoded by the ORF13 gene of T lymphotropic herpesvirus Saimiri (Rouvier et al., 1993). In the meantime, CTLA-8 is known as IL-17A, the prototype of the IL-17 cytokine family comprising six related proteins from IL-17A to IL-17F (Gaffen, 2009; Moseley et al., 2003; Weaver et al., 2007), recently reviewed in Monin and Gaffen (2018). Members of the IL-17 family are relatively “local cytokines,” acting mainly on nonclassical immune cells such as epithelial, endothelial, and fibroblastic cells (Fossiez et al., 1996; Moseley et al., 2003; Yao et al., 1995). Those cells express IL-17 receptors that are heterodimers composed of the subunit IL-17RA associated with either IL-17RC, IL-17RE, or IL-17RB, giving combinations specific for IL-17A and F, IL-17C, and IL-17E (IL-25), respectively. Cytokine binding to IL-17 receptors recruits and activates the kinase Akt1 (Chang et al., 2006; Qian et al., 2007), which transduces signals via TNF receptor-associated factor 6-mediated pathways (Schwandner et al., 2000) and ultimately leads to activation of canonical NF- κ B as well as the ERK pathway in a cell context-dependent manner (Gaffen et al., 2014). While these transcriptional activations are key components of the IL-17 pathway, more recent studies collectively point to a crucial aspect of IL-17

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Table 1. **Biological drugs targeting IL-17 or IL-23 approved for psoriasis, PsA, and/or AS**

INN	Target	Construct	Labeled indication
Brodalumab	IL-17RA	Fully human mAb	Pso, PsA (Japan only)
Ixekizumab	IL-17A	Humanized mAb	Pso, PsA, AS
Secukinumab	IL-17A	Fully human mAb	Pso, PsA, AS
Guselkumab	IL-23p19	Fully human mAb	Pso
Risankizumab	IL-23p19	Humanized mAb	Pso
Tildrakizumab	IL-23p19	Humanized mAb	Pso
Ustekinumab	IL-12/23p40	Fully human mAb	Pso, PsA

INN, international nonproprietary names; Pso, psoriasis.

signaling, namely its ability to stabilize transcripts of cytokines and chemokines (Amatya et al., 2018; Herjan et al., 2018; Tanaka et al., 2019). In fact, in most cell culture models, IL-17 is a weak transcriptional activator. Thus, the impact of IL-17 on post-transcriptional regulation of gene expression is fundamental to its pro-inflammatory activity. In response to IL-17 signaling, keratinocytes produce antimicrobial peptides (AMP) and chemokines, which together induce local inflammation and neutrophil influx (Ivanov and Lindén, 2009). In line with the prominent local action of IL-17, it has been shown that IL-17 rather sticks with the extracellular matrix and can be detected even on the producing cells themselves (Brucklacher-Waldert et al., 2009). IL-17 signaling induces different outcomes in different target cells ranging from receptor activator of NF- κ B ligand production in osteoclasts leading to bone remodeling (Noack et al., 2019) to production of IL-6 and IL-8 (CXCL8) in fibroblasts, leading to local inflammation and neutrophil influx (Noack et al., 2019). In experimental psoriasis, current data suggest that keratinocytes are the cells that are primarily involved in IL-17-driven pathogenesis of psoriasis (Garzorz-Stark and Eyerich, 2019). In the Aldara model of psoriasis-like skin inflammation, Moos et al. (2019) showed that epidermal hyperplasia was only seen in mice expressing IL-17RA in keratinocytes. As demonstrated by Ha et al. (2014), IL-17A can increase the number of human keratinocytes in S-phase dependent on calcium concentration. A very recent study found that IL-17 and IL-22 promote keratinocyte stemness (Ekman et al., 2019). In two studies, it was shown that mice with a gain-of-function mutation of the *card14* gene, a known risk locus for human psoriasis, developed spontaneous psoriasis-like skin inflammation triggered by IL-17 mostly derived from $\alpha\beta$ T cells acting on keratinocytes (Mellett et al., 2018; Wang et al., 2018). This was mediated by intracellular CARMA2 accumulation and activation. Anti-IL-23p19 antibodies could significantly reduce inflammation by blocking IL-17-mediated effects on keratinocytes. These findings argue for a direct effect of IL-17 on keratinocyte proliferation and activation that contributes to the increased epidermal turnover, and AMP and chemokine overexpression in psoriasis.

Within the IL-17 family, the leading member in tissue inflammation, autoimmunity, and host defense is IL-17A. Its relative IL-17F shares the highest homology with IL-17A

Table 2. **Investigational drugs targeting IL-17 in indications of interest**

INN/Code	Target	Construct	Indication ^a
Bimekizumab	IL-17A/F	Humanized mAb	Pso, PsA, AS
M1095	IL-17A/F	Nanobody	Pso, PsA
ALX-0761	IL-17A/F	Nanobody	Pso, PsA
BCD-085	IL-17A	mAb	Pso, PsA
COVA322	IL-17A/TNF	Bispecific mAb	Pso, PsA

INN, international nonproprietary names; Pso, psoriasis.

^aIn clinical trials/planned.

(Kawaguchi et al., 2001; Starnes et al., 2001), and the genes encoding IL-17F and IL-17A are actually syntenic, located on chromosome 6 in humans and on chromosome 1 in mice. Mouse studies of either single or double knockout mice suggested an important contribution of both cytokines to the defense against mucocutaneous infection, while only IL-17A- but not IL-17F-deficient mice were protected in inflammatory disease models (Ishigame et al., 2009). IL-17A and IL-17F can act as homo- or heterodimers (Liang et al., 2007), binding and signaling through the IL-17RA/IL-17RC receptor expressed on a variety of stroma and tissue cells including keratinocytes.

The finding that retinoic acid receptor-related orphan receptor γ isoform t was promoting differentiation of naive CD4⁺ T cells into IL-17-producing pro-inflammatory T helper 17 (Th17) cells initiated a bonanza of studies elucidating Th17 differentiation (Harrington et al., 2005; Ivanov et al., 2006), Th17 plasticity (Lee et al., 2009), and Th17 balance with Foxp3⁺ regulatory T cells (Bettelli et al., 2006). However, as suggested by its original name, *Ctla-8*, the *Ili7a* gene was originally cloned from activated cytotoxic lymphocytes, and therefore it is not surprising that CD8⁺ T cells can also be an important source of IL-17 in mice (He et al., 2006) and humans (Singh et al., 2008). At the same time, it emerged that not Th17 cells, but rather $\gamma\delta$ T cells, innate T cells, and innate lymphoid cells (ILCs), are the main sources of IL-17 in tissues (Awasthi et al., 2009; Roark et al., 2008). In mouse skin, a self-renewing population of dermal $\gamma\delta$ T cells was identified as the major source of IL-17 in steady state (Gray et al., 2011; Sumaria et al., 2011). These IL-17-producing $\gamma\delta$ T cells ($\gamma\delta$ 17 cells) in the dermis are chronically activated by local signals and fairly tissue-resident (Laidlaw et al., 2019; Tan et al., 2019). In human skin, the contribution of $\gamma\delta$ 17 cells and other innate lymphocytes to steady state IL-17 production is currently less clear (Brüggen et al., 2016).

IL-17 balancing microbiota and pathogens

The skin is the body's most exposed barrier. It maintains and tolerates its own commensal microbiome, which is layered according to anatomical site and age to the environment (Belkaid and Segre, 2014; Gerstel et al., 2018; Sanford and Gallo, 2013). Interestingly, a number of recent experimental studies revealed how specific members of the skin microbiota, e.g., *Staphylococcus epidermidis* and *Corynebacterium accolens*, train and support the immune response to pathogens such as *Staphylococcus aureus*, the parasite *Leishmania major*, and invasive fungi (Naik et al., 2015; Ridaura et al., 2018). In those and other examples, the protective

role of commensal colonization relied on the induction of local IL-17-mediated immunity in the skin (Linehan et al., 2018).

Likewise, absence or impaired IL-17 immunity predisposes patients to chronic mucocutaneous candidiasis disease caused by *Candida albicans* and, to a lesser extent, *S. aureus* (Boisson et al., 2013; Eyerich et al., 2008; Ling et al., 2015; Puel et al., 2011). Importantly, a single human null mutation of the *IL17F* gene was sufficient to cause an inherited susceptibility to mucocutaneous infections (Puel et al., 2011). Those findings highlight the central role of the cytokines IL-17A and IL-17F in establishing skin-commensal homeostasis and in protective immune responses to pathogens and opportunistic infections, in particular to fungi. Along these lines, the single or double knockout mice for *Il17a* and/or *Il17f* can be kept with no signs of pathology under specific pathogen-free conditions (Haas et al., 2012; Ishigame et al., 2009), but otherwise mouse lines with defective IL-17 signaling collectively show profoundly increased susceptibility to chronic infection with *C. albicans* and to a lesser extent *S. aureus* (Cho et al., 2010; Conti et al., 2009; Saijo et al., 2010). Experimental models indicated that IL-17 contributes to protection from fungi other than *C. albicans* (Burstein et al., 2018; Hernández-Santos et al., 2019; Sparber et al., 2019; Sparber and LeibundGut-Landmann, 2019; Wüthrich et al., 2011). A recent human study showed that Th17 cells directed against other fungi are induced by cross-reactivity to *C. albicans* (Bacher et al., 2019).

Dysregulation of IL-17

Experimental models of IL-17-driven psoriasis

In skin, invasive infections and disturbances in barrier function induce profound effects. Subsequent activation of keratinocytes and dendritic cells (DCs) as sentinels of danger signals due to barrier disruption leads to the activation of innate and adaptive immunity. Recruitment of neutrophils and increased production of AMP in psoriasis are induced at least in a major part through the activity of IL-17 cytokine family members. It follows that mouse models for human psoriasiform skin inflammation depend on the overabundance of IL-17 in the skin (Fig. 1). However, as discussed previously, none of the current models is perfectly representing human psoriasis (Bocheńska et al., 2017; Chuang et al., 2018; Hawkes et al., 2018; Swindell et al., 2011). In steady state, direct and indirect sensing (via nociceptive sensory fibers; Cohen et al., 2019; Kashem et al., 2015; Riol-Blanco et al., 2014) of skin microbiota induce dermal DCs to produce basal levels of IL-23, which activates IL-17A and IL-17F secretion of tissue-resident lymphocytes. IL-17A and IL-17F in turn are essential to limit microbial invasion and to ensure skin integrity. Direct overexpression of IL-17A under the control of a keratinocyte-specific K14 Cre recombinase in mice induced a pathology resembling human psoriasis including dermal infiltration of effector T cells, formation of neutrophil microabscesses, and hyperkeratosis (Croxford et al., 2014). Similarly, keratinocyte-specific overexpression of IL-17C also promoted psoriasiform skin inflammation (Johnston et al., 2013). Other experimental models function via induction of elevated levels of dermal IL-23, which in turn activates IL-23R-expressing dermal lymphocytes including $\gamma\delta 17$ cells, $\alpha\beta$ T cells, and ILCs. This may be achieved directly by intradermal injection of IL-23 (Gauld et al., 2018;

Rizzo et al., 2011), or via increased systemic levels of IL-23 (Leys et al., 2019), although human psoriasis is not usually accompanied by increased serum levels of IL-23 (Bai et al., 2017). The most widely used experimental model is topical application of the TLR7/8 agonist imiquimod (Aldara; Gilliet et al., 2004; van der Fits et al., 2009), which induces the innate activation of dermal DCs (van der Fits et al., 2009). This leads to locally increased IL-23 production, activating downstream IL-23R-expressing dermal lymphocytes that in turn respond by augmented IL-17 secretion (Gladiator et al., 2013; Pantelyushin et al., 2012). Among those IL-23-responsive skin-resident effector lymphocytes, $\gamma\delta 17$ cells seem to be the most important population, because their conditional depletion protected from imiquimod-induced psoriasis-like inflammation (Sandrock et al., 2018). Together, all IL-23/IL-17-dependent models ultimately induce skin inflammation characterized by keratinocyte hyperproliferation and neutrophil influx resembling human psoriasis.

IL-17 in the pathogenesis of human psoriasis

Accumulating evidence suggests that a dysregulated IL-23/IL-17 cytokine axis is at the heart of the pathogenesis of human psoriasis, further supported by the high efficacy of drugs targeting this pathway (see below). The data that initially pointed toward these cytokines as pathogenic suspects and thus prime targets for therapy were describing their increased expression in psoriatic lesions (Lee et al., 2004; Teunissen et al., 1998), as well as accumulations of IL-17-producing T cells (Lowe et al., 2008), suggesting key roles for IL-17A and IL-23 in the treatment of psoriasis (Lowe et al., 2007; Nickoloff, 2007). Accordingly, human psoriasis and related mouse models are considerably similar, i.e., dermal DCs produce IL-23, which activates tissue-resident lymphocytes to secrete IL-17A and IL-17F leading to recruitment of neutrophils, increased production of AMP and chemokines, and epidermal changes (Fig. 2). However, the factors that drive human psoriasis are certainly different and depend on genetic susceptibility and environmental factors.

In humans, the observation that topical imiquimod (Aldara) application led to exacerbation of psoriasis together with further investigations contributed to the elucidation of the role of IL-17 cytokines in psoriasis (Gilliet et al., 2004). However, there is considerable difference between natural psoriasis and Aldara-induced lesions in humans (Vinter et al., 2015). Along these lines, what drives the initial activation of the IL-23/IL-17 axis? Initial events might be the TLR9-dependent recognition of self-DNA complexed with the cationic AMP LL37 by plasmacytoid DCs, which subsequently activate dermal DCs via type I interferons (Lande et al., 2007). Self-RNA-LL37 complexes might in addition trigger IL-23 production by dermal myeloid DCs directly via TLR8 (Ganguly et al., 2009). This may induce a vicious circle, as IL-23 drives proliferation and accumulation of IL-23R-expressing innate lymphocytes; however, in human dermis, the majority of these may be ILC3s instead of $\gamma\delta 17$ cells (Dyring-Andersen et al., 2014; Villanova et al., 2014). Their augmented secretion of IL-17A and IL-17F next acts on nearby keratinocytes, which in turn produce more AMP and chemokines and thereby perpetuate the dysregulated IL-23/IL-17 axis.

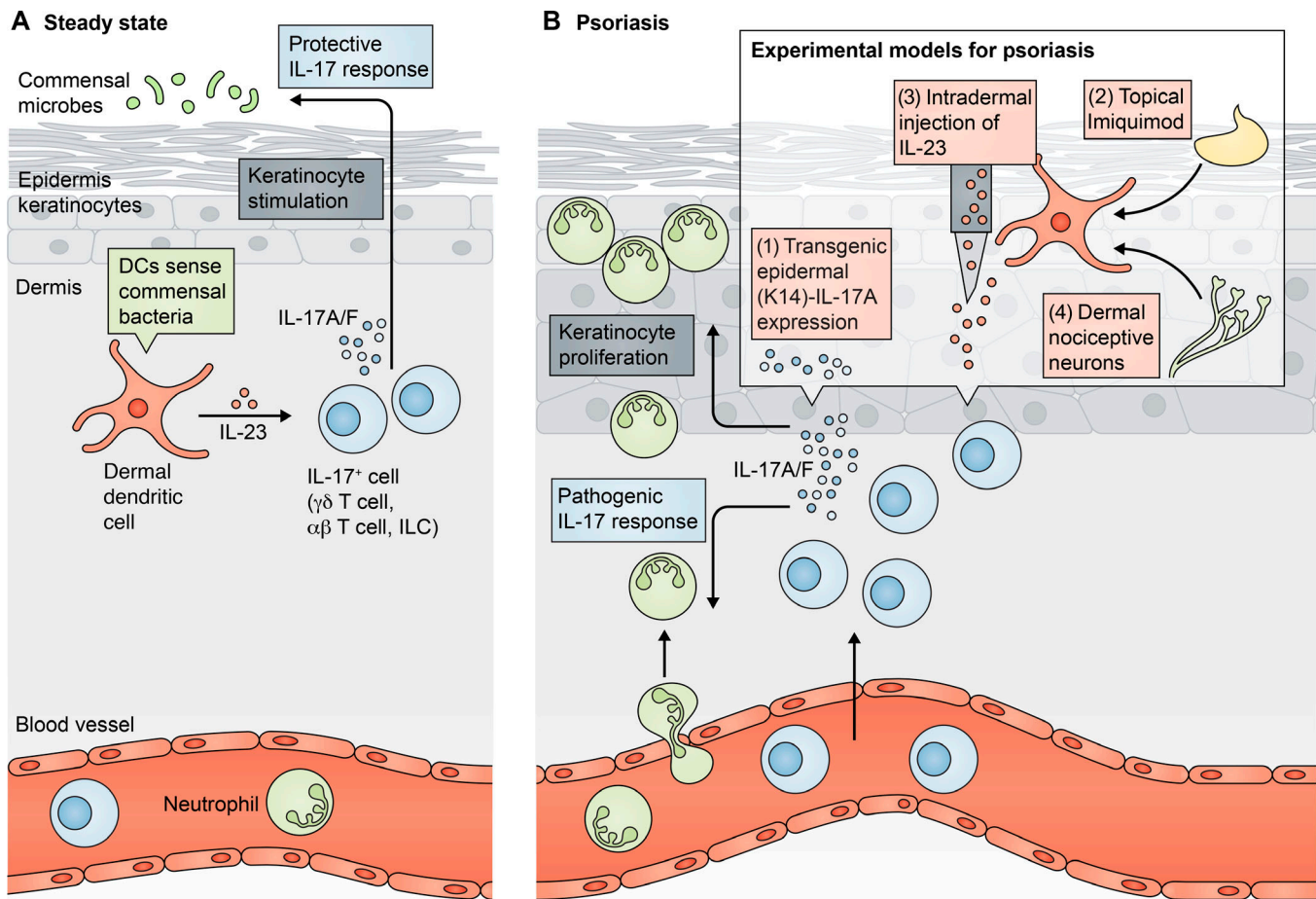


Figure 1. IL-17 immunity and experimental psoriasis in mouse skin. (A) Healthy mouse skin is composed of a thin epidermal layer and the subjacent dermis. At steady state, dermal DCs sense the presence of commensal bacteria and secrete basal levels of IL-23 acting on local IL-17 producing lymphocytes including $\gamma\delta$ T cells, $\alpha\beta$ T cells, and ILC3s. In turn, dermal lymphocyte-derived IL-17 induces a protective IL-17 response that stimulates keratinocytes and ensures epithelial barrier integrity and homeostasis with commensal microbes. **(B)** Different experimental models for psoriasis induce a pathogenic IL-17 response that results in release of chemokines and cytokines attracting neutrophils from the circulation and aberrant proliferation of keratinocytes leading to acanthosis with hyper- and parakeratosis. (1) Genetic overexpression of IL-17A by K14+ keratinocytes, (2) topical application of imiquimod resulting in local secretion of IL-23 by dermal DC, and (3) intradermal injection of IL-23. Further, (4) activation of dermal nociceptive neurons results in pathogenic IL-17 response and proliferation of keratinocytes.

Further support for an autoimmune cause of psoriatic skin inflammation comes from two reports identifying (1) LL37 peptides as direct targets of CD4+ and CD8+ T cells (Lande et al., 2014) and (2) a strong linkage of many clinical forms of psoriasis with HLA-C*06:02 mediating antigen-specific responses to melanocyte antigen ADAMTS-like protein 5 (Arakawa et al., 2015).

There is good evidence that the IL-23/IL-17 axis is at least in part responsible for the inflammation at the entheses, the hallmark of PsA that develops in ~20% of patients with plaque psoriasis (Ritchlin et al., 2017). Biomechanical stress and microbiome alterations are discussed as trigger factors for PsA leading to an IL-17-mediated bone and joint inflammation (McGonagle et al., 2019). A link between inflammation of skin, joints, and blood vessels related to IL-17 was provided by using the model of keratinocyte-specific K14 Cre recombinase (see above). The phenotype of mice showed psoriasis-like flaky skin and histological features of psoriasis-like inflammation,

thinning of bone cortex and trabecular structure, and endothelial cell dysfunction (Karbach et al., 2014; Uluçkan et al., 2016).

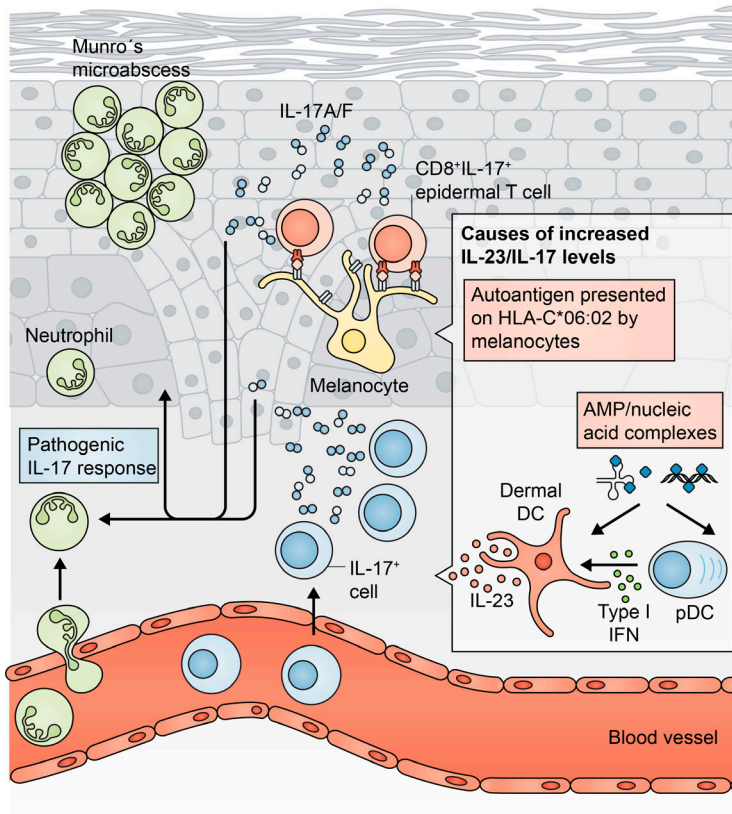
Together, although the final common pathways of experimental psoriasis-like dermatitis and human psoriasis are sharing features such as increased numbers of dermal IL-23R-positive lymphocytes, keratinocyte hyperproliferation, and formation of neutrophil microabscesses, a number of autoimmune or cross-recognition events accidentally trigger and propagate the local production of IL-17 in the pathogenesis of the human disease, which are not covered by the experimental models.

Current therapies targeting IL-17 cytokines

Targeting IL-17 in psoriasis—A perfect match?

Excitement about the potential of anti-IL-17-based therapies for pathologies with an IL-17 signature was first generated by the work of Hueber et al. (2010), investigating the effect of secukinumab/AIN457, a fully human mAb against IL-17A, in a

A Psoriasis untreated



B Psoriasis treated

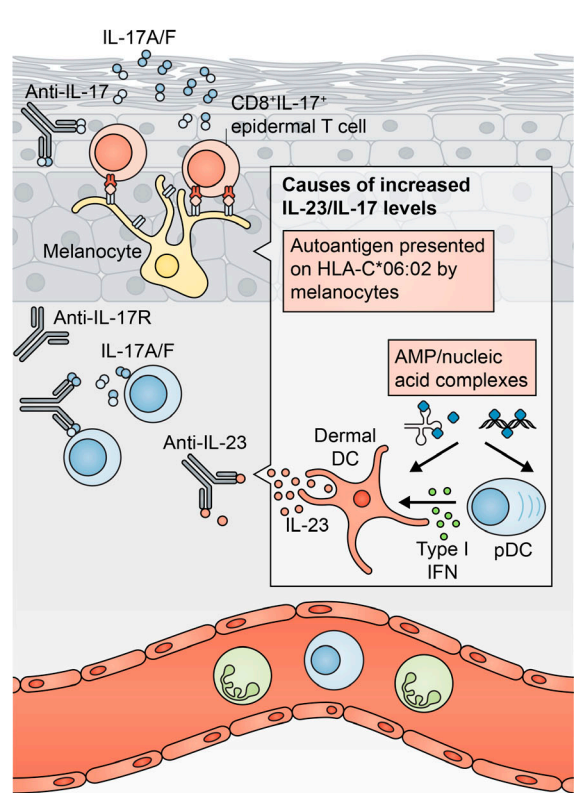


Figure 2. IL-17 immunity in human psoriasis. (A) Psoriasis pathogenesis is induced by increased levels of IL-17 that stimulate keratinocyte proliferation resulting in acanthosis, para- and hyperkeratosis, and release of AMP and chemokines that recruit neutrophils from the circulation, leading to formation of Munro’s microabscesses within the stratum corneum. Increased IL-23/IL-17 levels can be caused by presentation of autoantigens by melanocytes to autoreactive epidermal CD8⁺ T cells resulting in IL-17 secretion and by plasmacytoid DCs (pDCs) activated by antimicrobial peptide (AMP)–nucleic acid complexes to secrete type I interferons that in turn induce secretion of IL-23 by dermal DCs subsequently stimulating and recruiting IL-17 producing lymphoid cells. **(B)** Targeting IL-23, IL-17, and/or IL-17R by specific mAb leads to less stimulation of keratinocytes and IL-17-secreting cells. This results in reduced acanthosis, inhibits infiltration of neutrophils, and thus ameliorates psoriasis pathology.

proof-of-concept setting in plaque psoriasis, rheumatoid arthritis, and uveitis. In patients with plaque psoriasis, secukinumab was given as single intravenous infusion (3 mg/kg), and disease severity was assessed in short intervals until week 12 using the psoriasis area and severity index (PASI). In >40% of patients, a reduction of PASI of >75% (PASI75) was achieved at week 12 in comparison to placebo (4%). Secukinumab was fast-acting and already achieved the maximum efficacy at week 6. Efficacy was also shown in rheumatoid arthritis and uveitis. Subsequently, a large clinical trial program was started, leading to the registration of secukinumab for plaque psoriasis in 2015 with a dose of 300 mg subcutaneously given every 4 wk in maintenance therapy after an up dosing in weekly intervals in the initial 4 wk of therapy (Langley et al., 2014). Because of efficacy, speed of onset of activity, and a favorable benefit–risk profile, secukinumab was the first biological given a first-line label for plaque psoriasis.

Subsequently the anti-IL-17A humanized mAb ixekizumab (Griffiths et al., 2015) and a mAb against the IL-17 receptor A, brodalumab (Lebwohl et al., 2015), have been registered first-line for plaque psoriasis. The efficacy of anti-IL-17RA brodalumab is very high, possibly because IL-17RA neutralization blocks

binding to all known heterodimeric receptors for IL-17A/F, but also IL-17C and IL-17E. However, because of the continued presence of active IL-17 cytokines, there is a rather quick relapse after stopping treatment with brodalumab (Masson Regnault et al., 2017). Three individual cases of suicide occurred connected to a brodalumab trial, and therefore the US Food and Drug Administration and Health Canada approval of this drug carries a suicide warning (Mullard, 2017). Although there are some recent data connecting deficient IL-17 signaling to impaired short-term memory (Ribeiro et al., 2019) a potential causal connection of psychiatric disease and blocking IL-17RA is regarded as controversial (Beck and Koo, 2019; Rodriguez-Bolanos et al., 2019).

A puzzling clinical observation is that there is primary and secondary nonresponse to anti-IL-17 drugs in a subgroup of patients. It cannot be explained today why a patient showing secondary nonresponse to secukinumab can successfully be switched to ixekizumab and vice versa (Gasslitter et al., 2019).

In a first randomized trial in palmoplantar pustulosis characterized by a prominent infiltrate of neutrophils, secukinumab showed improvement over placebo. However, given the hypothesis that IL-17A is an important cytokine mediating

neutrophil recruitment, the estimate of a high efficacy was not met (Mrowietz et al., 2019).

Based on data about a pathophysiological role of IL-17 family members in PsA, clinical trial programs were launched leading to registration of ixekizumab (Mease et al., 2017; Nash et al., 2017) and secukinumab (McInnes et al., 2015) for this indication (brodalumab got a PsA indication only in Japan). As the pathophysiology of axial PsA has a number of similarities to ankylosing spondylitis (AS), anti-IL-17 drugs have been investigated for that indication. Because of the high efficacy, ixekizumab (van der Heijde et al., 2018) and secukinumab (Baeten et al., 2015) were further registered for treatment of AS. In clinical practice, anti-IL-17 drugs are now preferred over anti-TNF-targeted therapies for plaque psoriasis and for patients with concomitant PsA.

Related to their mode of action, two main safety signals became known when using anti-IL-17 drugs: candidiasis including rare cases of chronic mucocutaneous candidiasis disease and induction or exacerbation of Crohn's disease. As mentioned above, IL-17 is a key cytokine required for antifungal defense, and known genetic deficiencies in IL-17 signaling or function lead to severe *Candida* infections (Lévy et al., 2016; Puel et al., 2011). In patients treated with anti-IL-17 drugs, candidiasis develops in up to 4% of patients (Saunte et al., 2017). Clinical trials to treat Crohn's disease or other forms of inflammatory bowel disease with anti-IL-17A drugs turned out to be ineffective, and higher rates of adverse events were noted compared with placebo (Hueber et al., 2012). Although there is a low rate of anti-IL-17-induced Crohn's disease according to a recent analysis using all clinical data of the secukinumab trial program, there are individual cases of new-onset Crohn's or exacerbation of known disease (Schreiber et al., 2019). This suggests that IL-17 plays a different pathophysiological role in psoriasis and PsA versus inflammatory bowel disease, where the function in intestinal tissue repair and epithelial barrier function is pivotal (Lee et al., 2015; Maxwell et al., 2015; O'Connor et al., 2009; Zapp et al., 2017).

New data provided evidence that apart from IL-17A, other family members such as IL-17F and E may play an equally important role in plaque psoriasis and even in PsA (Bertelsen et al., 2018; Senra et al., 2016). A new dual antagonist antibody in phase 3 clinical trial development, bimekizumab (UCB4940), targeting IL-17A and F, showed PASI90 improvement in 79% of plaque psoriasis patients after 12 wk (Papp et al., 2018b). In a proof-of-concept trial in PsA, bimekizumab showed an ARC50 response (American College of Rheumatology 50% response criteria) in 57% of patients at week 12, suggesting a very high efficacy and a very fast onset of activity (Glatt et al., 2018). In a recent proof-of-concept trial, a new anti-IL-17A/F nanobody (M1095) given subcutaneously showed a PASI90 response at day 85 in up to 100% of patients, representing a level of efficacy among the highest known so far (Svecova et al., 2019).

Apart from therapeutics with a direct effect on IL-17 family members, there is accumulating evidence for a reduction of lesional IL-17 levels with known systemic drugs for plaque psoriasis including methotrexate (Furiati et al., 2019; Reich et al., 2019a).

Plaque psoriasis is associated with vascular inflammation and among key cytokines involved IL-17A plays a pivotal role. In the KC-Tie2 mouse model, animals develop psoriasis-like skin inflammation along with increased IL-17, IL-23, and increased occlusive thrombus formation. Treatment with mAbs against IL-17A or IL-17RA was able to lengthen the time to thrombus formation (Li et al., 2018). In recent studies in mice presenting either with IL-17RA or IL-17A deficiency, a clear link between the promotion of endothelial cell activation, vascular inflammation, and leukocyte infiltration mediated by IL-17 was demonstrated that could be inhibited by using an anti-IL-17A antibody (Nordlohne et al., 2018). The circulating IL-17 level correlates positively with the severity and progression of carotid artery plaques in patients with atherosclerosis, and there is a correlation of peripheral Th17 cells and Th17 cell-associated cytokines to the severity of carotid artery plaque (Liu et al., 2012). In a 52-wk randomized, placebo-controlled trial with secukinumab in plaque psoriasis, flow-mediated dilation was continuously measured as a surrogate marker for vascular inflammation (von Stebut et al., 2019). In the secukinumab group, flow-mediated dilation was higher but did not reach significance against placebo at the primary endpoint at week 12 but after 52 wk in the open phase.

Periodontitis, an inflammation of the gingival tissue surrounding the gingival crevice, is characterized by a prominent infiltration of neutrophils and excessive levels of IL-17 cytokines, namely IL-17A and F (Apatzidou et al., 2018; Hajishengallis, 2014). There is a significant association between periodontitis and plaque psoriasis and an even stronger link to PsA (Egeberg et al., 2017). Experimental models pointed toward a contribution of mechanical stress, i.e., mastication, as well as involvement of dysbiotic oral microbiota to the activation of inflammatory gingival Th17 cells and $\gamma\delta 17$ cells (Dutzan et al., 2017, 2018; Krishnan et al., 2018; Wilharm et al., 2019). The concept that mechanical signals can trigger innate IL-17 production, while shown in periodontal inflammation, have also been discussed for AS (Reinhardt et al., 2016; Sherlock et al., 2012) and may also be applicable to psoriasis.

Psoriasis as a systemic disorder comprises a complex pathology that affects not only the skin. Comorbidity including joint and vascular manifestations varies among patients, respective triggers, and risk factors. Thus, the aim of disease management is to improve the main symptoms and comorbidity at the same time (Mrowietz et al., 2014). With therapeutics targeting IL-17-dependent pathways/events, this strategy seems to work well.

Targeting the master cytokine IL-23

A pivotal question about the pathophysiological relevance of IL-17 and its role as therapeutic target in psoriasis still remains open: Is the master cytokine IL-23 a better choice for treatment? It has long been known that IL-23 stimulates the differentiation of Th17 cells and subsequently the production of IL-17 (McGeachy et al., 2009). Very recently a group 2 ILC subpopulation was described that can convert into IL-17-producing NKp44⁺ ILC3-like cells under the control of IL-1 β and IL-23 and that can home into skin through CCR6 expression (Bernink

et al., 2019; Bielecki et al., 2018 Preprint). These studies are reminiscent of earlier reports describing the innate activation of $\gamma\delta$ T cells by IL-1 β and IL-23 (Haas et al., 2009; Martin et al., 2009; Sutton et al., 2009).

The latest registered IL-23p19 therapeutic antibody risankizumab is able to improve psoriasis to clear or almost clear skin in >80% of patients after a year of therapy (Gordon et al., 2018). Even more intriguing data were generated in the early development program of risankizumab. After having received a single subcutaneous dose of risankizumab (0.25 mg/kg and 1 mg/kg), six of eight patients (of a total of 13 enrolled) with moderate to severe psoriasis maintained clear skin for at least 41–66 wk (Krueger et al., 2015). Data from a randomized withdrawal setting with the IL-23p19 inhibitor guselkumab shows maintenance of clear or almost clear skin in >40% of patients after 20 wk following the last dose (Reich et al., 2017). In this group of patients, serum levels of IL-17A and F remained low as compared with those not maintaining this level of efficacy (Gordon et al., 2019). As the pharmacological half-life of therapeutic IgG antibodies is about 3 wk, the very long disease-free time after IL-23p19 inhibition must be caused by lasting immunomodulatory effects. So far, known the high efficacy of IL-23 inhibitors is not associated with adverse events such as *Candida* infections seen when using IL-17A/IL-17RA antagonists, as exemplified by first long-term data on the IL-23p19 antagonist tildrakizumab (Reich et al., 2019b).

Concluding remarks

A balanced signaling along the IL-23/IL-17 cytokine axis is an important mechanism to ensure skin-microbial homeostasis. Experimental and clinical evidence suggest that its dysregulation induces psoriasis. Thus, targeting the IL-23/IL-17 cytokine axis is a straightforward approach to treat psoriasis, as demonstrated in clinical trials as well as in real-world data (Rompoti et al., 2019). Nevertheless, the universe of treatment options in psoriasis is expanding, and manifold new targets are evolving. JAK inhibitors were effective for moderate to severe plaque psoriasis in randomized trials (Bachelez et al., 2015; Papp et al., 2016). Specific inhibitors for tyrosine kinase 2 downstream of the IL-23 receptor resulted in improvement of psoriasis in clinical trials (Papp et al., 2018a). Furthermore, psoriasis is the lead indication for small molecule inhibitors antagonizing the activity of Th17 cell differentiation determining transcription factor retinoic acid receptor-related orphan receptor γ isoform t (Bronner et al., 2017; Ecoeur et al., 2019). However, IL-17A and IL-17F are the central effector cytokines, and their neutralization or blocking of their interaction with specific cytokine receptors turned out to be a game changer for patients suffering from psoriasis or PsA.

Some caution is necessary because rare congenital defects in the IL-17 pathway exemplify the relevance of IL-17 in protective immunity (Sparber and LeibundGut-Landmann, 2019) as genetic defects in IL-17 signaling displayed strong phenotypes characterized by susceptibility to fungal infection (Lévy et al., 2016; Okada et al., 2016; Puel et al., 2011). Therefore, it is somewhat surprising that the side effects of anti-IL-17 therapies are relatively mild. One theory is that targeting IL-17A inhibits

IL-17A homodimers and A/F heterodimers but spares IL-17F homodimers (Kurschus and Moos, 2017). In addition, neutralizing cytokines with mAb depends on dosage, timing, and tissue penetration. A nonquantitative antagonism of IL-17 in the epidermis probably spares sufficient cytokine molecules required for antimicrobial defense. Neutralizing the upstream master cytokine IL-23 and not IL-17 cytokines directly spares IL-23-independent IL-17 production and thus should leave the required amount for local antimicrobial responses. In this context, targeting IL-23 still seems to be able to induce long-term remissions of the disease severity in psoriasis. Such long-lasting effects may be explained by a negative impact on the homeostasis and survival of IL-23R-dependent skin-resident lymphocytes, i.e., $\gamma\delta$ T cells, $\alpha\beta$ T cells, and ILCs, all of which may take some considerable time to recover in numbers once IL-23 blockade is discontinued. Monitoring the major cellular sources of IL-17 in a large number of patients treated with anti-IL-17 versus anti-IL-23 mAb will in turn be very instructive for understanding human IL-17 biology.

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