Cytokines of the IL-17 family in psoriasis

Felix Lauffer¹, Kilian Eyerich¹, Wolf-Henning Boehncke², Khusru Asadullah³, Stefan Beissert⁴, Kamran Ghoreschi⁵, Michael P. Schön⁶-⁷

(1) Department of Dermatology and Allergy Biederstein, University hospital of the Technical University Munich (TUM), Munich, Germany
(2) Division of Dermatology and Venereology and Department of Pathology and Immunology, University Hospital of Geneva, University of Geneva, Geneva, Switzerland
(3) Dermatology practice Potsdam, Potsdam, Germany
(4) Department of Dermatology, Carl Gustav Carus University Medical Center, Dresden Technical University, Dresden, Germany
(5) Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
(6) Department of Dermatology, Venereology and Allergology, University Medical Center, Göttingen University, Göttingen, Germany
(7) Lower Saxony Institute of Occupational Dermatology, Göttingen, Germany

Summary
Various immune cells and their messenger substances influence the development of psoriasis. Cytokines of the IL-17 family are of particular importance. In addition to IL-17A, which plays a central role in the pathogenesis of psoriasis, other subtypes of the IL-17 family also have a proinflammatory effect. This review provides an up-to-date overview of the immunopathogenesis of psoriasis with regard to the six IL-17 subtypes, in particular their physiological and pathogenic properties, as well as their significance for psoriasis therapy.

Cytokines of the IL-17 family in the immunopathogenesis of psoriasis

The IL-17 family has six subtypes: IL-17A, IL-17B, IL-17C, IL-17 D, IL-17E (also known as IL-25) and IL-17F. The
subtypes IL-17A and IL-17F have the highest homology (55%) and are most often expressed together (co-expression). The sequences of IL-17B, IL-17D, and IL-17C overlap with IL-17A by about 23% to 29%, but the overlap with IL17-E is only 16% [2]. IL-17 subtypes produce organ-specific pro- or anti-inflammatory responses via a total of six receptors [9] (Figure 1). Table 1 shows the IL-17 subtypes, their receptors, producing cells and effects on other cells, as well as their associations with various diseases [2].

**IL-17A**

IL-17A plays a central role in the pathogenesis of psoriasis. This was shown in several studies with the successful use of inhibiting antibodies [11]. It acts on non-hematopoietic cells, particularly epithelial cells, and plays an essential role in the immune response in neighboring organs. In the skin, IL-17A leads to increased proliferation and changed differentiation of keratinocytes, and induces antimicrobial peptides and chemokines. IL-17A also has a role in other inflammatory diseases. Elevated IL-17A concentrations have been measured in patients with multiple sclerosis (MS), rheumatoid arthritis and acute coronary syndrome that correlated with parameters of systemic inflammation [2, 7].

**IL-17F**

IL-17F and IL-17A are coded at the same gene locus (6p12) and are regulated in a similar way. IL-17F can create heterodimers together with IL-17A. In psoriasis patients, IL-17F can be found in plaques at higher levels than in unaffected parts of the skin.

Studies have shown synergistic effects of IL-17F and IL-17A: unlike the inhibition of IL-17A alone, simultaneous inhibition of both cytokines leads to a significant increase in downregulation of inflammatory mediators in skin and joint fibroblasts [2, 12]. IL-17F and IL-17A perform similar functions in bacterial or fungal infections [2, 13, 14].
### Table 1 Overview of IL-17 subtypes with associated receptors, producing cells, effects on other cells as well as associations with diseases.

| IL-17 subtype | Receptor(s) | Producing cells | Effect on other cells | Associations with diseases |
|---------------|-------------|-----------------|-----------------------|---------------------------|
| IL-17A        | – IL-17-RA  | Th17 cells      | Proinflammatory effect on epithelial cells | Psoriasis                  |
|               | – IL-17-RC  | γδ-T cells, ILC3 cells, Neutrophil granulocytes, Mast cells | IL-17F in synergy with IL-17A | Atopic eczema               |
|               |             |                 |                       | Multiple sclerosis         |
|               |             |                 |                       | Rheumatoid arthritis       |
|               |             |                 |                       | Psoriatic arthritis        |
|               |             |                 |                       | Chronic inflammatory intestinal diseases |
|               |             |                 |                       | Inflammation with acute coronary syndrome |
| IL-17B        | – IL-17-RB? | Neutrophil granulocytes, B-lymphocytes, neurons | Increase of TNF-α production by fibroblasts | Rheumatoid arthritis       |
|               |             |                 | Associated with a poor prognosis in breast and stomach cancer | Psoriasis                   |
| IL-17C        | – IL-17-RA  | Primarily epithelial cells | Autocrine stimulation of epithelial cells | Atopic eczema               |
|               | – IL-17-RE  | Rarely immune cells | Proinflammatory effect on epithelial cells via the expression of cytokines, chemokines, and antimicrobial peptides. | Rheumatoid arthritis       |
|               |             |                 |                       | Chronic inflammatory intestinal diseases |
| IL-17D        | – ?         | Weak expression in lymphocytes and monocytes | Modulation of cytokine production by endothelial cells, release of proinflammatory cytokines such as IL-6, IL-8 and GM-CSF | Rheumatoid arthritis       |
|               | – ?         | Expression in skeletal muscle, brain, fat tissue, heart, lung, pancreas |                       | Psoriasis                   |
| IL-17E        | – IL-17-RA  | Epithelial and endothelial cells, T cells, Macrophages, Myeloid cells type 2, Dendritic cells, Eosinophil granulocytes, ILC2 cells | Induces the loss of cellular barrier function | Psoriasis                   |
| (also known as IL-25) | – IL-17-RB |                   | Modulation of proinflammatory cytokines such as IL-8, CCL-5 and GM-CSF | Atopic eczema               |
|               |             |                 | Reduced IL-17E expression in chronic inflammatory intestinal diseases | Allergic contact dermatitis |
|               |             |                 |                       | Bronchial asthma            |
|               |             |                 |                       | Rheumatoid arthritis        |
|               |             |                 |                       | Chronic inflammatory intestinal diseases |
| IL-17F        | – IL-17-RA  | Th17 cells, γδ-T cells, ILC3 cells | Synergistic effect with IL-17A | Psoriasis                   |
|               | – IL-17-RC  |                 | Proinflammatory effect on epithelial cells | Atopic eczema               |
|               |             |                 |                       | Multiple sclerosis          |
|               |             |                 |                       | Rheumatoid arthritis        |
|               |             |                 |                       | Psoriatic arthritis         |
|               |             |                 |                       | Chronic inflammatory intestinal diseases |
Minireview  Cytokines of the IL-17 family in psoriasis

IL-17B

The function of IL-17B in psoriasis is largely unknown, and only weak expression has been described in psoriasis lesions [2]. IL-17B is not produced by activated T lymphocytes, but it has been found in neutrophil granulocytes, B-cells, neurons, stroma cells and colorectal epithelial cells.

Synovial and pannus tissue in patients with rheumatoid arthritis (RA) has shown increased expression of IL-17B. IL-17B amplifies the effects of TNF-α in fibroblasts. This could be important for the immunogenesis of RA [15].

IL-17D

IL-17D is expressed in many cells and organs, but only weakly in immune cells such as lymphocytes and monocytes. IL-17D in vitro induced the production of IL-6, IL-8 and GM-CSF in endothelial cells. An inhibitory effect on the hematopoiesis of myeloid precursor cells was also detected [16]. Other studies have shown an association of IL-17D with viral and oncological diseases, particularly via recruitment of natural killer cells (NK cells). However, current data on IL-17D during tumor development are contradictory [17]. A deficiency in IL-17D led to a higher vulnerability to viruses in animal models.

IL-17C

IL-17C is not produced by T lymphocyte cells, but primarily by epithelial cells such as keratinocytes. A high concentration of IL-17C has been measured in human psoriasis plaques [18]. It can act as an autocrine stimulant in epithelial inflammation, particularly in combination with TNF-α. Overexpression of IL-17C in keratinocytes leads to psoriasiform dermatitis in mice [19]. IL-17C also leads to increased growth of sensory nerves. It was shown in a mouse model of herpes simplex infections of the skin that IL-17C can induce neuronal growth in a way similar to that of NGF (nerve growth factor) [18, 20, 21]. It has also been reported that depletion of IL-17C in mouse models of psoriasis and atopic dermatitis significantly reduces the inflammatory reaction. IL-17C therefore acts independently of T cells as an epithelial stimulant of immune reactions [19].

IL-17E (also known as IL-25)

IL-17E induces proliferation of keratinocytes and is able to activate innate immune cells. In psoriasis, IL-17E is strongly expressed by keratinocytes and activates specific subtypes of macrophages (M2 or tissue macrophages). In psoriasis lesions, IL-17E expression correlates positively with the number of neutrophil granulocytes and negatively with the number of T lymphocytes. This is surprising, since IL-17E was seen for a long time as a cytokine with a role in the Th2 immune response. An animal model of allergic asthma showed that inhibition of IL-17E by a neutralizing antibody resulted in a significant reduction of bronchial hyperreactivity, serum IgE concentration and histological signs of inflammation [22]. Similarly, IL-17E is also strongly expressed in atopic eczema [23, 24].

Like IL-17C, IL-17E appears to amplify innate inflammatory processes in the skin, independently of the cells that contribute to the adaptive immune system [25].

Clinical aspects of IL-17 subtypes in psoriasis

Contrary to earlier notions of the pathogenesis of psoriasis, we now understand that there are other important inflammatory cycles apart from the IL-17A/IL-23 axis. On the one hand, the epithelial IL-17 cytokines IL-17C and IL-17E stimulate innate immune cells and the production of antimicrobial peptides. On the other hand, IL-17F leads to a pronounced increase of the IL-17A effects on epithelial cells. Animal experiments have shown the importance of these independent inflammatory cascades. For instance, the mouse model of psoriasis showed that when IL-17C is blocked, other immune mechanisms are stimulated that can allow the disease to persist [26].

This is a possible immunological explanation for the secondary loss of efficacy. Inhibition of a cytokine of the IL-17A/IL-23 axis could therefore modulate the inflammatory reaction and induce epithelial IL-17 cytokines such as IL-17C and IL-17E. However, there is currently no scientific evidence for this in humans.

Therapeutic consequences

Various biologics are currently approved for the treatment of psoriasis. Inhibition is focused on TNF-α, IL-12 (in combination with IL-23 inhibition) and the IL-17 subtypes IL-17A and IL-17F, or the subunit of the IL-17 receptor. The latter prevents an interaction of IL-17A, A/F, F, C, and E with the IL-17 receptor. Table 2 shows the biologics that are currently approved in the EU and that inhibit the effects of IL-17 subtypes or those of the IL-17A/IL-23 axis.

With regard to IL-17 subtypes and associated inflammatory cycles, it might be easier to stratify patients with psoriasis in the future. It is conceivable that some patients have a primarily adaptively driven psoriasis [7, 27] that responds very well to IL-23 or IL-17A inhibition. From an immunological perspective, these could be patients who have only recently started to suffer from the disease, since
Table 2  Overview of biologics directed against the IL-23/IL-17 axis in psoriasis therapy.

| Substance         | Inhibited cytokine | Indication                        | Dosage and Application                                                                 | EMA approval status                                      |
|-------------------|--------------------|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------|
| Ustekinumab       | IL-23 and IL-12    | Plaque psoriasis                  | Initially 45 mg, 45 mg in week 4, then every 12 weeks; b.w. > 100 kg: initially 90 mg, 90 mg in week 4, then every 12 weeks. Children/adolescents: according to dosage table in week 0 and 4, then every 12 weeks. The patient can do the subcutaneous injection himself after proper training (FI last modified 09/2019). | Approved 01/2009, approval extended 09/2013               |
| Secukinumab       | IL-17A             | Plaque psoriasis                  | Plaque psoriasis: 300 mg in week 0, 1, 2 and 3, 300 mg per month starting in week 4. In case of concomitant moderate to severe plaque psoriasis or insufficient response to anti-TNF-α: 300 mg at week 0, 1, 2, 3 and 4, then monthly. In all other patients: 150 mg 0, 1, 2, 3 and 4, then monthly; dose may be increased to 300 mg. Patient can do the subcutaneous injection himself after proper training (FI last modified 10/2019). | Approved 01/2015                                        |
| Ixekizumab        | IL-17A             | Plaque psoriasis                  | Plaque psoriasis: 160 mg in week 0, then 80 mg in week 2, 4, 6, 8, 10 and 12; then 80 mg every 4 weeks. Psoriatic arthritis: 160 mg in week 0, then 80 mg every 4 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 05/2018). | Approved 04/2016                                        |
| Brodalumab        | IL-17 receptor A and thus IL-17A, IL-17C, IL-17E, IL-17F and IL-17A/F Heterodimer | Plaque psoriasis                  | 210 mg in week 0, 1 and 2, then 210 mg every 2 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 09/2017). | Approved 07/2017                                        |
| Guselkumab        | IL-23              | Plaque psoriasis                  | 100 mg in week 0, week 4, then every 8 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 11/2018). | Approved 11/2017                                        |
| Tildrakizumab     | IL-23              | Plaque psoriasis                  | 100 mg in week 0 and 4, then every 12 weeks. For patients with particular characteristics (e.g. high disease burden, b.w. ≥ 90 kg), 200 mg could be more effective. Patient can do the subcutaneous injection himself after proper training (FI last modified 09/2018). | Approved 09/2018                                        |
| Risankizumab      | IL-23              | Plaque psoriasis                  | 150 mg in week 0 and 4, then every 12 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 07/2019). | Approved 04/2019                                        |
| Bimekizumab       | IL-17A and IL-17F  | Plaque psoriasis                  | Not yet approved, currently in Phase-III studies                                         |                                                          |

Abbr.: b.w., body weight; FI, summary of product characteristics.
chronic development and activation of other inflammatory cascades (such as epithelial IL-17 cytokines) has not yet occurred. Patients with stable psoriasis vulgaris without significant inflammation could also fall into this category. However, other patients might profit from the inhibition of several IL-17 cytokines. It is conceivable that these are patients who have suffered from psoriasis longer, have eczematized forms or possibly more inflammatory forms, since for them, activation of additional IL-17 cytokines (and other mediators such as IL-36) might sustain disease activity [7, 27]. The stimulating effect of IL-17C on the growth of cutaneous nerves could also mean that patients with very itchy or inflammatory forms of psoriasis could benefit from the additional inhibition of IL-17C. Since IL-17E stimulates the inflammatory response of psoriasis on the one hand but also induces TH2 cytokines on the other hand, inhibition of IL-17E might positively affect accompanying allergic illnesses. Future studies must determine whether specific disease types can be defined and whether therapeutic decisions based on immunologic aspects can be made for selected psoriasis patients.

Conflict of interest
Felix Lauffer received honoraria for speaker and consulting activities from AbbVie, Leo Pharma, Lilly, Novartis, Roche and Sanofi. Kilian Eyrich received honoraria for speaker and consulting activities from AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Hexal, Janssen, Lilly, Novartis, Sanofi and UCB. Wolf-Henning Boehncke received honoraria for speaker and consulting activities from AbbVie, Almirall, Celgene, Janssen, Leo Pharma, Lilly, Novartis and UCB as well as a research grant from Pfizer. Khusru Asadullah received honoraria for speaker and consulting activities from AbbVie, Almirall, Antabio, Bayer, Emeritipharma, Galderma, Janssen-Cilag, Leo Pharma, L’Oréal, Novartis, Pierre Fabre, Sanofi Genzyme and UCB. Stefan Beissert received honoraria from AbbVie, Actelion, Bristol-Myers Squibb, Galderma, GSK, Janssen-Cilag, MSD, Novartis and Roche Posay. Honoraria for serving on advisory boards: AbbVie, Actelion, Angen, Celgene, Galderma, Janssen-Cilag, Leo Pharma, Lilly, Menlo Therapeutics, MSD, Novartis, Pfizer and UCB Pharma. Kamran Ghoreschi received honoraria for speaker and consulting activities from AbbVie, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen-Cilag, LEO Pharma, Lilly, MSD, Novartis, Pfizer and Roche. Michael P. Schön received honoraria for speaker and consulting activities from AbbVie, Celgene, Janssen-Cilag, Leo Pharma, Lilly, Novartis and UCB.

Medical writing support for this review was provided by Heike Hennig, MK+S – Medizin, Kommunikation +Service GmbH, and was funded by LEO Pharma GmbH.

References
1. https://www.who.int/ncds/management/psoriasis/en/ [Last accessed July 19, 2019].
2. Brembilla NC, Senra L, Boehncke WH. The IL-17 family of cytokines in psoriasis: IL-17A and beyond. Front Immunol 2018; 9: 1682.
3. Eisert L, Augustin M, Bach S et al. S2k guidelines for the treatment of psoriasis in children and adolescents – Short version part 1. J Dtsch Dermatol Ges 2019; 17: 836–70.
4. Eisert L, Augustin M, Bach S et al. S2k guidelines for the treatment of psoriasis in children and adolescents – Short version part 2. Dtsch Dermatol Ges 2019; 17: 959–73.
5. Nast A, Amelunxen L, Augustin M et al. S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 1 – Systemic treatment. J Dtsch Dermatol Ges 2018; 16: 645–69.
6. Nast A, Amelunxen L, Augustin M et al. S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 2 – Special patient populations and treatment situations. J Dtsch Dermatol Ges 2018; 16: 806–13.
7. Schön MP. Adaptive and innate immunity in psoriasis and other inflammatory disorders. Front Immunol 2019; 10: 1764.
8. Schön MP, Erpenbeck L. The interleukin-23/interleukin-17 axis links adaptive and innate immunity in psoriasis. Front Immunol 2018; 9: 1323.
9. Schön M, Denzer D, Kubitzka RC et al. Critical role of neutrophils for the generation of psoriasiform skin lesions in flaky skin mice. J Invest Dermatol 2000; 114: 976–83.
10. Krueger JG, Brunner PM. Interleukin-17 alters the biology of many cell types involved in the genesis of psoriasis, systemic inflammation and associated comorbidities. Exp Dermatol 2018; 27: 115–23.
11. Eyerich K, Dimartino V, Cavani A. IL-17 and IL-22 in immunity: driving protection and pathology. Eur J Immunol 2017; 47: 607–14.
12. Glatt S, Baeten D, Baker T et al. Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. Ann Rheum Dis 2018; 77: 523–32.
13. Ishigame H, Kakuta S, Nagai T et al. Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses. Immunity 2009; 30: 108–19.
14. Eyerich K, Foerster S, Rombold S et al. Patients with chronic mucocutaneous candidiasis exhibit reduced production of
Th17-associated cytokines IL-17 and IL-22. J Invest Dermatol 2008; 128: 2640–5.

15 Kouri VP, Olkkonen J, Ainola M et al. Neutrophils produce interleukin-17B in rheumatoid synovial tissue. Rheumatology (Oxford) 2014; 53: 39–47.

16 Starnes T, Broxmeyer HE, Robertson MJ et al. Cutting edge: IL-17D, a novel member of the IL-17 family, stimulates cytokine production and inhibits hemopoiesis. J Immunol 2002; 169: 642–6.

17 Seelige R, Washington A Jr, Bui JD. The ancient cytokine IL-17D is regulated by Nrf2 and mediates tumor and virus surveillance. Cytokine 2017; 91: 10–2.

18 Johnston A, Fritz Y, Dawes SM et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. J Immunol 2013; 190: 2252–62.

19 Vandeghinste N, Klattig J, Jaggerschmidt C et al. Neutralization of IL-17C reduces skin inflammation in mouse models of psoriasis and atopic dermatitis. J Invest Dermatol 2018; 138: 1555–63.

20 Peng T, Chanthaphavong RS, Sun S et al. Keratinocytes produce IL-17C to protect peripheral nervous systems during human HSV-2 reactivation. J Exp Med 2017; 214: 2315–29.

21 Ramirez Carozzi V, Sambandam A, Luis E et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. Nat Immunol 2011; 12: 1159–66.

22 Ballantyne SJ, Barlow JL, Jolin HE et al. Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. J Allergy Clin Immunol 2007; 120: 1324–31.

23 Senra L, Stalder R, Alvarez Martinez D et al. Keratinocyte-derived IL-17E contributes to inflammation in psoriasis. J Invest Dermatol 2016; 136: 1970–80.

24 Senra L, Mylonas A, Kavanagh RD et al. IL-17E (IL-25) enhances innate immune responses during skin inflammation. J Invest Dermatol 2019; 139: 1732–1742.e17.

25 Xu M, Lu H, Lee YH et al. An interleukin-25-mediated autoregulatory circuit in keratinocytes plays a pivotal role in psoriatic skin inflammation. Immunity 2018; 48: 787–798.e4.

26 Fritz Y, Klenotic PA, Swindell WR et al. Induction of alternative proinflammatory cytokines accounts for sustained psoriasiform skin inflammation in IL-17C/IL-6KO mice. J Invest Dermatol 2017; 137: 696–705.

27 Christophers E, van de Kerkhof PCM. Severity, heterogeneity and systemic inflammation in psoriasis. J Eur Acad Dermatol Venereol 2019; 33: 643–7.