Check for updates

REVIEW

Recent advances in understanding psoriasis [version 1; peer review: 2 approved]

Franziska C. Eberle¹, Jürgen Brück¹, Julia Holstein¹, Kiyoshi Hirahara², Kamran Ghoreschi¹

¹Department of Dermatology, University Medical Center, Eberhard Karls University Tübingen, Tübingen, Germany

²Department of Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan

V1 First published: 28 Apr 2016, 5(F1000 Faculty Rev):770
<https://doi.org/10.12688/f1000research.7927.1>

Latest published: 28 Apr 2016, 5(F1000 Faculty Rev):770
<https://doi.org/10.12688/f1000research.7927.1>

Abstract

T helper (Th) cells producing interleukin (IL)-17, IL-22, and tumor necrosis factor (TNF) form the key T cell population driving psoriasis pathogenesis. They orchestrate the inflammation in the skin that results in the proliferation of keratinocytes and endothelial cells. Besides Th17 cells, other immune cells that are capable of producing IL-17-associated cytokines participate in psoriatic inflammation. Recent advances in psoriasis research improved our understanding of the cellular and molecular players that are involved in Th17 pathology and inflammatory pathways in the skin. The inflammation-driving actions of TNF in psoriasis are already well known and antibodies against TNF are successful in the treatment of Th17-mediated psoriatic skin inflammation. A further key cytokine with potent IL-17-/IL-22-promoting properties is IL-23. Therapeutics directly neutralizing IL-23 or IL-17 itself are now extending the therapeutic spectrum of antipsoriatic agents and further developments are on the way. The enormous progress in psoriasis research allows us to control this Th17-mediated inflammatory skin disease in many patients.

Keywords

psoriasis , T helper cells , skin inflammation , keratinocyte

Open Peer Review

Approval Status

	1	2
version 1
28 Apr 2016		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Thomas Herzinger**, Ludwig Maximilian University, Munich, Germany
2. **Mario Fabri**, University of Cologne, Cologne, Germany

Any comments on the article can be found at the end of the article.

Corresponding authors: Kiyoshi Hirahara (hiraharak@chiba-u.jp), Kamran Ghoreschi (kamran.ghoreschi@med.uni-tuebingen.de)

Competing interests: Kamran Ghoreschi has been a consultant, lecturer, or investigator for AbbVie, Almirall, Boehringer, Biogen, Celgene, Eli Lilly and Company, Janssen-Cilag, MSD Sharp & Dohme, Novartis Pharmaceuticals, and Pfizer.

Grant information: This work was supported by the Deutsche Forschungsgemeinschaft (DFG) Sonderforschungsbereich (SFB) 685 (to Kamran Ghoreschi) and SFB TR-156 (to Franziska C. Eberle and Kamran Ghoreschi).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2016 Eberle FC *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Eberle FC, Brück J, Holstein J *et al.* **Recent advances in understanding psoriasis [version 1; peer review: 2 approved]** F1000Research 2016, 5(F1000 Faculty Rev):770 <https://doi.org/10.12688/f1000research.7927.1>

First published: 28 Apr 2016, 5(F1000 Faculty Rev):770 <https://doi.org/10.12688/f1000research.7927.1>

Introduction

Psoriasis is one of the most common chronic diseases, affecting 2–3% of the adult population and 0.5–1% of children. Due to the frequency of the disease worldwide and its clinical characteristics, psoriasis has gained the interest of many scientists in academia as well as industrial research. The easy accessibility of the skin allows scientists to study cells and mediators in inflamed skin and their relevance in disease pathogenesis in detail. Recent advances in psoriasis pathogenesis improved our understanding of disease mechanisms and resulted in the development of new immunobiologics and small molecules that help to control the chronic inflammation¹. Here we summarize the recent findings on the cellular and molecular players that presumably contribute to psoriasis development. In general, psoriasis is considered to be an autoimmune disease and most scientists agree on the central importance of T cells in disease pathogenesis^{2–4}, yet the psoriatic inflammation may originate from epidermal epithelial cells and innate immune cells. Clearly, a close interaction between mediators and cells of the innate and adaptive immune systems and keratinocytes and endothelial cells is present in psoriasis^{5,6}.

Aberrant keratinocyte biology as a pathogenic driver in psoriasis

Decades ago, psoriasis was primarily thought to be caused by aberrant keratinocytes resulting in uncontrolled proliferation of the epidermal cell layers. Early studies on the cellular ‘turnover’ of epidermal cells supported this hypothesis⁷. The keratinocytes in psoriasis are characterized not only by strong proliferation but also by an altered expression of certain keratins like keratin 16. The concept of altered keratinocytes as pathogenic cells causing psoriasis has gained new attention since different reports published in the beginning of this millennium showed that genetic alterations in epidermal transcription factors can cause skin disorders that resemble human psoriasis clinically and histologically. Mice with altered expression of JunB/c-Jun or phosphorylation of STAT3 in keratinocytes develop skin inflammation with histological and molecular characteristics of psoriasis^{8,9}. Interestingly, in both models, the psoriatic skin inflammation seems to depend on the presence of immune cells including T cells and their cytokines. In fact, there is a close interaction between cytokines and keratinocytes. A number of cytokines present in psoriatic inflammation promotes keratinocyte proliferation. Intradermal injections of T helper 17 (Th17)-associated cytokines like interleukin (IL)-23 or IL-21 into mouse skin induce epidermal hyperplasia with morphological characteristics of human psoriasis associated with the infiltration of inflammatory T cells. On the other hand, keratinocytes themselves are a cellular source of cytokines. The most famous member is IL-8, a cytokine originally discovered in psoriatic scales¹⁰. Another example is the cytokine IL-15, which is expressed in psoriatic epidermis and protects keratinocytes from apoptosis. Interestingly, soluble IL-15R α has been shown to dampen the psoriatic inflammation by suppressing cytokine secretion from keratinocytes and the expansion of IL-17-producing T cells¹¹. Moreover, keratinocytes are a major source of IL-1 production¹². Factors such as cytosolic DNA can trigger inflammasome activation and IL-1 secretion by keratinocytes, which contribute to the psoriatic inflammation¹³. Other mediators that are linked to psoriasis pathogenesis and that are produced by keratinocytes include antimicrobial peptides like

S100A8/9, β -defensins, and cathelicidin (LL-37)³. Taken together, genetic alterations in transcription factors and environmental triggering factors affecting keratinocytes presumably facilitate the manifestation of psoriasis, yet psoriasis pathogenesis seems to be dominated by the activation of immune cells rather than alterations in keratinocytes.

Central role of immune cells

Several observations support the importance of immune cells in the pathogenesis of psoriasis. One is the transfer of the disease by bone marrow cells. Case reports from individuals undergoing bone marrow transplantation for hematological disorders have linked the disappearance of psoriasis as well as the development of psoriasis in the recipient to the skin status of the donor^{14,15}. The other observation is that immunosuppressive agents originally introduced for the prevention of organ transplant rejection showed unexpected benefits on the clinical course of psoriasis^{16,17}. Subsequently, immunosuppressive agents like cyclosporine or methotrexate have been established in the treatment of psoriasis. Genetic data on human leukocyte antigen (HLA) associations as well as data on the presence of oligoclonal T cells in lesional skin and their reactivity towards cutaneous antigens further underline the importance of immune cells in psoriasis pathogenesis. Putative autoantigens in psoriasis include keratins, heat shock proteins, the antimicrobial peptide LL37, and the melanocytic antigen ADAMTS-like protein 5 (ADAMTSL5)^{18–20}. The recent discovery of ADAMTSL5 as a potential autoantigen in psoriasis is a key finding. The recognition of this protein is restricted to epidermal CD8⁺ T cells of patients with psoriasis and a HLA-C*06:02 genotype. Stimulation of ADAMTSL5-specific CD8⁺ T cells results in IL-17A production²⁰. Of note, HLA-C*06:02 is known as the HLA locus with the strongest genetic association with psoriasis. In addition to the linkage to certain HLA genotypes, recent investigations revealed that psoriasis is also linked to polymorphisms in genes encoding certain cytokines, cytokine receptors, and transcription factors. Today, there is a widely accepted consensus that psoriasis is an immune cell-mediated disease.

A prototypic Th17 disease

Among the gene polymorphisms that have been linked to psoriasis are genes encoding *IL23A*, *IL23R*, *STAT3*, *RUNX3*, and *TYK2*. All of these genes are associated with the Th17 immune response¹. Th17 cells are characterized by the expression of their lineage-defining cytokine IL-17A. In addition, Th17 cells can produce other cytokines like IL-17F, IL-21, IL-22, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Some Th17 populations also secrete IL-9 or IL-10, depending on the signals they receive during initial activation. The differentiation and activation of the Th17 population from naïve T cells depend on cytokines like IL-6, IL-21, IL-1, TGF- β , and IL-23²¹. Strikingly, IL-23, its receptor, and its downstream signaling molecule STAT3 are all linked to the genetic susceptibility for developing psoriasis. Of note, the transcription factor STAT3 is also activated by IL-6 and IL-21 and, together with the other Th17-characterizing transcription factor ROR γ , STAT3 is responsible for IL-17A and IL-17F expression²². Skin-infiltrating Th17 cells seem to be the central players orchestrating psoriasis pathogenesis (Figure 1). They interact with tissue cells like keratinocytes and endothelial cells and with various immune cells including

Figure 1. Immune cells and T helper 17 (Th17)-associated cytokines implicated in psoriasis pathogenesis. Characteristic markers and cytokines related to the interleukin (IL)-17/IL-23 immune signature of T cells, dendritic cells (DCs), and associated immune cells in psoriatic skin inflammation.

dendritic cells (DCs) and neutrophilic granulocytes. The reactivation of memory Th17 cells is presumably responsible for the chronic course of the disease.

Contribution of skin-resident immune cells

It has become obvious that there is a critical population of memory T cells that resides in the tissue and is involved in the local immune response²³. Those specific memory T cells were named “resident-memory T” (T_{RM}) cells. T_{RM} cells preferentially reside in epithelial barrier tissues such as the respiratory tract, reproductive tract, and skin^{24–26}. T_{RM} cells can respond rapidly to pathogenic invaders in the epithelial barrier site, so T_{RM} cells are crucial for the protection of the host from harmful microorganisms. The pathogenic role of T_{RM} cells in immune-mediated diseases including skin diseases like psoriasis is gaining more evidence. A recent study revealed the augmentation of T_{RM} cells in the local inflamed skin of patients with psoriasis²⁷. Moreover, T_{RM} cells in psoriatic skin express higher levels of both *IL17A* and *IL22* compared to those in the skin of healthy individuals. The majority of T_{RM} cells in the epidermis express CD103. T_{RM} cells

residing in the dermis show lower expression of this marker²⁷. IL-9-producing T_{RM} cells have also been reported to be present in conditions of skin inflammation like in psoriasis²⁸. Besides T cells, DCs can reside in the skin. DCs are a key population of the immune system, bridging the breaks between innate and adaptive immunity. Among the heterogeneous DC population, CD1c⁺CD11c⁺ DCs represent a population of inflammatory dermal DCs. Ultraviolet exposure reduces the number of inflammatory CD1c⁺CD11c⁺ dermal DCs in patients with psoriasis²⁹, while the number of CD1c⁺CD11c⁺ so-called resident DCs remains unaffected³⁰. A potent marker that allows the discrimination of inflammatory CD1c⁺CD11c⁺ DCs from resident CD1c⁺CD11c⁺ DCs in patients with psoriasis is TNF-related apoptosis-inducing ligand (TRAIL)³¹. More intensive studies are needed to identify the environmental signals that induce specific features of T_{RM} cells and resident DCs in the skin under steady state and inflammatory conditions.

Phenotype of dendritic cells in psoriasis

In general, DCs are a heterogeneous population. In the skin, different types of DCs have been described. The distinct populations

are characterized by the expression of certain surface markers and mediators. In psoriasis, certain DC populations like plasmacytoid DCs (pDCs) and dermal myeloid DCs (mDCs) dominate the inflammatory skin, while the number of epidermal Langerhans cells seems to stay stable as compared to non-lesional skin. During initial inflammation, an increased number of pDCs is activated, which results in the release of type I interferon (IFN- α)³². Interestingly, complexes formed by self-DNA or self-RNA and the antimicrobial peptide LL37 have been shown to activate pDCs through Toll-like receptor 9 (TLR9) or TLR7/8, respectively^{33,34}. Recently, a novel mechanism of pDC activation has been described. As shown for antimicrobial peptides, the Th17-associated cytokine IL-26 can also form complexes with DNA from dying bacterial or host tissue cells and these complexes also promote IFN- α production by pDCs through TLR9 stimulation³⁵. These innate mechanisms seem to be relevant for pDC activation in psoriasis pathogenesis. The activation of pDCs is followed by an increase of CD11c⁺ mDCs, which express TNF, inducible nitric oxide synthase (iNOS), and IL-23. As mentioned above, inflammatory CD11c⁺ mDCs do not express CD1c in contrast to skin-resident CD1c⁺ mDCs. Another DC population that is capable of producing IL-23 is the so-called 6-sulfo LacNAc-expressing population (slanDCs)^{36,37}. Moreover, CD163⁺ macrophages can produce IL-23 (Figure 1). Taken together, the major function of DCs and macrophages in psoriasis pathogenesis is to provide the signals that promote the Th17 inflammation.

Non-T cell sources of IL-17A and IL-22 in psoriasis

As we discussed before, the IL-23/IL-17A and IL-23/IL-22 axes play a pivotal role in the pathogenesis of psoriasis³⁸. Besides Th17 cells, IL-17A and/or IL-22 are produced by other types of immune cells including innate lymphoid cells (ILCs) 3, and gamma delta ($\gamma\delta$) T cells^{39–41}. ILCs have recently been identified as a unique population of innate immune cells that lack antigen-specific receptors. They can be stimulated by cytokines and they produce a series of effector cytokines⁴⁰. ILCs are now recognized to be divided into three main groups based on the feature of producing lineage-defining cytokines and specific transcription factors^{40,42,43}. Among these groups of ILCs, ILC3 including lymphoid tissue inducer (LTi) cells are characterized by the production of IL-17A and/or IL-22 accompanied with high expression of Ror γ ^t^{40,44,45}. In the case of humans, ILC3 can be distinguished into several subpopulations based on expression patterns of natural killer (NK) cell markers like Nkp44 and Nkp46⁴⁶. Among these subpopulations, Nkp44⁺ ILC3 were reported to contribute to the pathogenesis of psoriasis, since IL-17A- and IL-22-producing Nkp44⁺ ILC3 were increased in both the peripheral blood and the skin of patients with psoriasis⁴⁷. The crucial role of ILC3 subpopulations in psoriasis pathogenesis is supported by the finding that Ror γ ^tCD56⁺ ILC3, which are capable of producing IL-22, are highly accumulated in the skin of patients with psoriasis⁴⁸. Another cellular source of IL-17A in the skin is the $\gamma\delta$ T cell population⁴⁹. The majority of dermal $\gamma\delta$ T cells express a T cell receptor (TCR) containing V γ 4 together with the chemokine receptor CCR6⁵⁰. In an experimental model of psoriasis-like inflammation in mice using the TLR7-agonist imiquimod, dermal V γ 4⁺ $\gamma\delta$ T cells persist in the skin and contribute to skin inflammation by producing IL-17A and IL-17F^{51,52}. Consistent with these findings, the increased number of $\gamma\delta$ T cells, which produce large amounts

of IL-17A, was detected in the affected skin of patients with psoriasis⁵³. More recently, mast cells have also been reported as producers of IL-17A and IL-22 in psoriasis⁵⁴. Similarly, neutrophils have been suggested as a further cellular source of IL-17A and IL-22. Of note, all immune cells mentioned also produce TNF, a factor well established in psoriasis pathogenesis and treatment. Taken together, various types of immune cells produce the psoriasis-driving cytokines TNF, IL-17A, and IL-22 (Figure 1).

Immunotherapies supporting the role of TNF and IL-17A in psoriasis

Based on the immunopathogenesis, antipsoriatic therapies target antigen-presenting cells (APCs), T cells, or their cytokines (Table 1). Modern small molecules like dimethyl fumarate and the PDE4 inhibitor apremilast both primarily act on APCs. By interfering with intracellular signaling pathways like NRF2 or second messengers like cAMP, they impair the production of pro-inflammatory DC cytokines like IL-23 and in contrast induce the release of anti-inflammatory IL-10. Since they also inhibit IL-12 and TNF production by APCs, dimethyl fumarate and apremilast treatment both result in the suppression of Th17 and Th1 responses^{55,56}. Thus, silencing IL-23 expression by DCs by small molecules or by RNA interference (RNAi) technology, as recently tested in preclinical settings of autoimmune disease, is an attractive approach^{57,58}. A new class of modern immunosuppressants is the class of JAK inhibitors⁵⁹. These compounds interfere with the signaling pathways of numerous cytokines and hormones. Selective JAK inhibitors inhibit the activation and differentiation of multiple Th cell subsets, but they also inhibit the effects of cytokines on non-T cells and non-immune cells⁶⁰. Thus, the mode of action of all of these compounds is not restricted to APCs and T cells. Although they may also affect other immune cells and tissue cells, they underline the importance of cytokine signaling in psoriasis⁶¹. To improve our understanding of psoriasis pathogenesis, it is more helpful to focus on therapeutics targeting single cytokines.

The first generation of antipsoriatic biologics targeting cytokines focused on TNF. These immunotherapeutics are highly effective in the treatment of psoriasis of skin and joints since they neutralize the effects of TNF on multiple cell types. In psoriatic skin, where TNF is mainly produced by DCs and macrophages, the neutralization of this cytokine rapidly decreases the expression of the Th17-promoting IL-23p40 and some other mediators^{62,63}. This initial action of TNF neutralization on IL-23 in the skin is followed by the reduction of IL-17A, IL-22, IFN- γ , and TNF. The second generation of anti-psoriatic biologics targeting cytokines focuses directly on the Th17 cytokines IL-23 and IL-17A. The neutralization of p40, a cytokine unit shared by IL-23 and IL-12, is also effective in the treatment of psoriasis and psoriatic arthritis and directly interferes with the activation of Th17 as well as Th1 cells. Importantly, selective inhibition of the IL-23 unit p19 also improves psoriasis. Currently, three antibodies targeting p19 are in phase 3 development for the treatment of psoriasis. Neutralization of IL-23 results in decreased numbers of skin-infiltrating T cells, mDCs, pDCs, and neutrophils, while epidermal Langerhans cells remain unaffected⁶⁴. Finally, IL-17A itself became a therapeutic target in psoriasis. The first monoclonal antibody directed against IL-17A is already approved for the treatment of psoriasis

Table 1. Modern immunotherapies targeting interleukin (IL)-17/IL-23. The table summarizes approved therapeutics and compounds that are in advanced stage development (according to www.clinicaltrials.gov) and some of their effects on the Th17 response. cAMP, cyclic adenosine monophosphate; DC, dendritic cell; HO-1, heme oxygenase-1; IL, interleukin; NRF2, nuclear factor (erythroid-derived 2)-like 2; PKC, protein kinase C; Th1, T helper type 1; Th2, T helper type 2; Th17, T helper type 17; TNF, tumor necrosis factor.

Immune-modifying category	Immunotherapeutic	Target(s)	Effect on the Th17 response
Small molecules with intracellular mode of action	Apremilast	cAMP/PKC signaling in DCs & macrophages	Inhibits IL-23 and TNF production, induces IL-10
	Dimethyl fumarate	NRF2/HO-1 signaling in DCs & macrophages	Inhibits IL-23 production, induces IL-10, promotes IL-4-producing Th2 cells
	Tofacitinib Ruxolitinib Baricitinib	JAK1/JAK3 JAK1/JAK2 JAK1/JAK2	Inhibit signaling by IL-22 and Th17-promoting cytokines IL-6, IL-21, and IL-23
Anti-cytokine antibodies and fusion proteins	Etanercept Adalimumab Infliximab Golimumab Certolizumab pegol	TNF/lymphotoxin TNF TNF TNF TNF	Impair DC activation and IL-23 production
	Ustekinumab	IL-12/IL-23p40	Impairs Th17 and Th1 responses
	Tildrakizumab Guselkumab BI 655066	IL-23p19 IL-23p19 IL-23p19	Impair Th17 responses
	Secukinumab Ixekizumab	IL-17A IL-17A	Inhibit effects of IL-17A
Anti-receptor antibody	Brodalumab	IL-17RA	Inhibits IL-17A and IL-17F signaling

and psoriatic arthritis⁶⁵. A second anti-IL-17A antibody recently received a positive opinion by the European Medicines Agency⁶⁶. Systemic neutralization of IL-17A lowers the expression of IL-17A, IL-17F, IL-22, TNF, IL-6, IL-8, and p40 in the skin⁶⁵. Of note, an antibody blocking the IL-17 receptor A (IL-17RA) is also effective in psoriasis and is in phase 3 development. These new approaches emphasize the significance of the Th17 pathway in psoriasis.

Remaining questions

Recent findings have helped us to improve our understanding of psoriasis pathogenesis. We now allocate the mechanisms of previously established antipsoriatic treatments to their effects on the Th17 pathway. This is best illustrated for the use of recombinant IL-4 or the small molecule dimethyl fumarate, which both suppress Th17 cell development^{55,67,68}. The new generation of antipsoriatic biologics directly targeting IL-23 or IL-17A underlines the central role of these cytokines in psoriasis pathogenesis. Although we have a battery of systemic treatments for our patients, we do not know which patient will respond adequately to a certain drug. There is still a significant number of primary and secondary non-responders. The lack and the loss of response are mainly observed in patients treated with oral therapeutics and TNF antagonists. Possibly, this will be similar in patients receiving modern drugs directly interfering with the Th17 axis. One of the most important future developments is the establishment of testing methods to predict the clinical response to certain targeted therapies using

immunobiologics or small molecules. Definition of useful biomarkers may help to identify responders in an early stage. Some markers like IL-8, IL-19, NOS2, or S100 proteins are typically expressed in psoriatic skin^{10,67,69–71}, but ideal biomarkers are still not established. Furthermore, we have to understand why the same body sites can develop psoriatic plaques, even after long periods of remission. One study demonstrates that epidermal CD8⁺ T_{RM} and also CD4⁺ T cells reside in the skin even after successful treatment and retain their capability of responding rapidly with the production of IL-17A and IL-22, respectively, upon *ex vivo* stimulation²⁷. Another issue to be studied is the exact mechanism that causes the development of paradoxical psoriasis in patients without prior history of psoriasis who receive TNF antagonists for the treatment of inflammatory colitis or rheumatoid arthritis. Unraveling these immunological mechanisms may also help us to understand the different phenotypes of psoriasis. One example is given by recent findings on pustular psoriasis. Genetic studies could link IL-36RN deficiency and CARD14 mutations to the susceptibility for generalized pustular psoriasis^{72,73}. Thus, interfering with inflammasome activation or IL-1 family cytokines may be of benefit in such patients⁷⁴. Similarly, it is of interest to understand why certain environmental factors like infections and drugs but also acquired immunodeficiency result in treatment-resistant cases of psoriasis. To complete our understanding of this chronic inflammatory disease affecting a large proportion of our global population, further research in immunology, genetics, epigenetics, microbiology, and molecular biology is needed.

Abbreviations

DC, dendritic cells; HLA, human leukocyte antigen; IL, interleukin; ILC, innate lymphoid cell; mDC, myeloid dendritic cell; NK cell, natural killer cell; pDC, plasmacytoid dendritic cell; Th cell, T helper cell; TLR, Toll-like receptor; T_{RM} cell, resident-memory T cell.

Competing interests

Kamran Ghoreschi has been a consultant, lecturer, or investigator for AbbVie, Almirall, Boehringer, Biogen, Celgene, Eli Lilly

and Company, Janssen-Cilag, MSD Sharp & Dohme, Novartis Pharmaceuticals, and Pfizer.

Grant information

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) Sonderforschungsbereich (SFB) 685 (to Kamran Ghoreschi) and SFB TR-156 (to Franziska C. Eberle and Kamran Ghoreschi).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

- Belge K, Brück J, Ghoreschi K: **Advances in treating psoriasis.** *F1000Prime Rep.* 2014; **6**: 4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nestle FO, Kaplan DH, Barker J: **Psoriasis.** *N Engl J Med.* 2009; **361**(5): 496–509.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lowes MA, Suárez-Fariñas M, Krueger JG: **Immunology of psoriasis.** *Annu Rev Immunol.* 2014; **32**: 227–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Boehncke WH, Schön MP: **Psoriasis.** *Lancet.* 2015; **386**(9997): 983–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Heidenreich R, Röcken M, Ghoreschi K: **Angiogenesis drives psoriasis pathogenesis.** *Int J Exp Pathol.* 2009; **90**(3): 232–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yazdi AS, Röcken M, Ghoreschi K: **Cutaneous immunology: basics and new concepts.** *Semin Immunopathol.* 2016; **38**(1): 3–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Weinstein GD, McCullough JL, Ross P: **Cell proliferation in normal epidermis.** *J Invest Dermatol.* 1984; **82**(6): 623–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zenz R, Eferl R, Kenner L, *et al.*: **Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins.** *Nature.* 2005; **437**(7057): 369–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Sano S, Chan KS, Carbajal S, *et al.*: **Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model.** *Nat Med.* 2005; **11**(1): 43–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Schröder JM, Christophers E: **Identification of C5ades arg and an anionic neutrophil-activating peptide (ANAP) in psoriatic scales.** *J Invest Dermatol.* 1986; **87**(1): 53–8.
[PubMed Abstract](#)
- Bouchaud G, Gehrke S, Krieg C, *et al.*: **Epidermal IL-15Rα acts as an endogenous antagonist of psoriasisform inflammation in mouse and man.** *J Exp Med.* 2013; **210**(10): 2105–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Gross O, Yazdi AS, Thomas CJ, *et al.*: **Inflammasome activators induce interleukin-1α secretion via distinct pathways with differential requirement for the protease function of caspase-1.** *Immunity.* 2012; **36**(3): 388–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Dombrowski Y, Peric M, Koglin S, *et al.*: **Cytosolic DNA triggers inflammasome activation in keratinocytes in psoriatic lesions.** *Sci Transl Med.* 2011; **3**(82): 82ra38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Eedy DJ, Burrows D, Bridges JM, *et al.*: **Clearance of severe psoriasis after allogeneic bone marrow transplantation.** *BMJ.* 1990; **300**(6729): 908.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Snowden JA, Heaton DC: **Development of psoriasis after syngeneic bone marrow transplant from psoriatic donor: further evidence for adoptive autoimmunity.** *Br J Dermatol.* 1997; **137**(1): 130–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mueller W, Herrmann B: **Cyclosporin A for psoriasis.** *N Engl J Med.* 1979; **301**(10): 555.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Harper JI, Keat AC, Staughton RC: **Cyclosporin for psoriasis.** *Lancet.* 1984; **2**(8409): 981–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Besgen P, Trommler P, Vollmer S, *et al.*: **Ezrin, maspin, peroxiredoxin 2, and heat shock protein 27: potential targets of a streptococcal-induced autoimmune response in psoriasis.** *J Immunol.* 2010; **184**(9): 5392–402.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lande R, Botti E, Jandus C, *et al.*: **The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis.** *Nat Commun.* 2014; **5**: 5621.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Arakawa A, Siewert K, Stöhr J, *et al.*: **Melanocyte antigen triggers autoimmunity in human psoriasis.** *J Exp Med.* 2015; **212**(13): 2203–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Ghoreschi K, Laurence A, Yang XP, *et al.*: **Generation of pathogenic T_H17 cells in the absence of TGF-β signalling.** *Nature.* 2010; **467**(7318): 967–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hirahara K, Ghoreschi K, Laurence A, *et al.*: **Signal transduction pathways and transcriptional regulation in Th17 cell differentiation.** *Cytokine Growth Factor Rev.* 2010; **21**(6): 425–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Park CO, Kupper TS: **The emerging role of resident memory T cells in protective immunity and inflammatory disease.** *Nat Med.* 2015; **21**(7): 688–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Iijima N, Iwasaki A: **T cell memory. A local macrophage chemokine network sustains protective tissue-resident memory CD4 T cells.** *Science.* 2014; **346**(6205): 93–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Gaide O, Emerson RO, Jiang X, *et al.*: **Common clonal origin of central and resident memory T cells following skin immunization.** *Nat Med.* 2015; **21**(6): 647–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Watanabe R, Gehad A, Yang C, *et al.*: **Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells.** *Sci Transl Med.* 2015; **7**(279): 279ra39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cheuk S, Wikén M, Blomqvist L, *et al.*: **Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis.** *J Immunol.* 2014; **192**(7): 3111–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Schlapbach C, Gehad A, Yang C, *et al.*: **Human T_H9 cells are skin-tropic and have autocrine and paracrine proinflammatory capacity.** *Sci Transl Med.* 2014; **6**(219): 219ra8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Heier I, Søyland E, Krogstad AL, *et al.*: **Sun exposure rapidly reduces plasmacytoid dendritic cells and inflammatory dermal dendritic cells in psoriatic skin.** *Br J Dermatol.* 2011; **165**(4): 792–801.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Zaba LC, Krueger JG, Lowes MA: **Resident and “Inflammatory” dendritic cells in human skin.** *J Invest Dermatol.* 2009; **129**(2): 302–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, *et al.*: **Identification of TNF-related apoptosis-inducing ligand and other molecules that distinguish inflammatory from resident dendritic cells in patients with psoriasis.** *J Allergy Clin Immunol.* 2010; **125**(6): 1261–1268.e9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Nestle FO, Conrad C, Tun-Kyi A, *et al.*: **Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production.** *J Exp Med.* 2005; **202**(1): 135–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

33. **F** Lande R, Gregorio J, Facchinetti V, *et al.*: **Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide.** *Nature*. 2007; 449(7162): 564–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. **F** Ganguly D, Chamilos G, Lande R, *et al.*: **Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8.** *J Exp Med*. 2009; 206(9): 1983–94. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. **F** Meller S, Di Domizio J, Voo KS, *et al.*: **T_H17 cells promote microbial killing and innate immune sensing of DNA via Interleukin 26.** *Nat Immunol*. 2015; 16(9): 970–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. Schäkel K, Kannagi R, Knip B, *et al.*: **6-Sulfo LacNAc, a novel carbohydrate modification of PSGL-1, defines an inflammatory type of human dendritic cells.** *Immunity*. 2002; 17(3): 289–301. [PubMed Abstract](#) | [Publisher Full Text](#)
37. Günther C, Blau K, Förster U, *et al.*: **Reduction of inflammatory skin (6-sulfo LacNAc) dendritic cells in psoriatic skin of patients treated with etanercept.** *Exp Dermatol*. 2013; 22(8): 535–40. [PubMed Abstract](#) | [Publisher Full Text](#)
38. **F** Nogralas KE, Zaba LC, Guttman-Yassky E, *et al.*: **Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways.** *Br J Dermatol*. 2008; 159(5): 1092–102. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. Chien YH, Meyer C, Bonneville M: **γδ T cells: first line of defense and beyond.** *Annu Rev Immunol*. 2014; 32: 121–55. [PubMed Abstract](#) | [Publisher Full Text](#)
40. Artis D, Spits H: **The biology of innate lymphoid cells.** *Nature*. 2015; 517(7534): 293–301. [PubMed Abstract](#) | [Publisher Full Text](#)
41. Schön MP: **The plot thickens while the scope broadens: a holistic view on IL-17 in psoriasis and other inflammatory disorders.** *Exp Dermatol*. 2014; 23(11): 804–6. [PubMed Abstract](#) | [Publisher Full Text](#)
42. Shih HY, Sciumè G, Poholek AC, *et al.*: **Transcriptional and epigenetic networks of helper T and innate lymphoid cells.** *Immunol Rev*. 2014; 261(1): 23–49. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Serafini N, Voshchenrich CA, Di Santo JP: **Transcriptional regulation of innate lymphoid cell fate.** *Nat Rev Immunol*. 2015; 15(7): 415–28. [PubMed Abstract](#) | [Publisher Full Text](#)
44. Takatori H, Kanno Y, Watford WT, *et al.*: **Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22.** *J Exp Med*. 2009; 206(1): 35–41. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Sciumè G, Hirahara K, Takahashi H, *et al.*: **Distinct requirements for T-bet in gut innate lymphoid cells.** *J Exp Med*. 2012; 209(13): 2331–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. **F** Cella M, Fuchs A, Vermi W, *et al.*: **A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity.** *Nature*. 2009; 457(7230): 722–5. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
47. **F** Villanova F, Flutter B, Tosi I, *et al.*: **Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44+ ILC3 in psoriasis.** *J Invest Dermatol*. 2014; 134(4): 984–91. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. **F** Dyring-Andersen B, Geisler C, Agerbeck C, *et al.*: **Increased number and frequency of group 3 innate lymphoid cells in nonlesional psoriatic skin.** *Br J Dermatol*. 2014; 170(3): 609–16. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
49. Gray EE, Suzuki K, Cyster JG: **Cutting edge: Identification of a motile IL-17-producing γδ T cell population in the dermis.** *J Immunol*. 2011; 186(11): 6091–5. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. **F** Pantelyushin S, Haak S, Ingold B, *et al.*: **Roryt⁺ innate lymphocytes and γδ T cells initiate psoriasis-like plaque formation in mice.** *J Clin Invest*. 2012; 122(6): 2252–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. **F** Ramírez-Valle F, Gray EE, Cyster JG: **Inflammation induces dermal Vγ4⁺ γδT17 memory-like cells that travel to distant skin and accelerate secondary IL-17-driven responses.** *Proc Natl Acad Sci U S A*. 2015; 112(26): 8046–51. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. **F** Hartwig T, Pantelyushin S, Croxford AL, *et al.*: **Dermal IL-17-producing γδ T cells establish long-lived memory in the skin.** *Eur J Immunol*. 2015; 45(11): 3022–33. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
53. **F** Cai Y, Shen X, Ding C, *et al.*: **Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation.** *Immunity*. 2011; 35(4): 596–610. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
54. **F** Mashiko S, Bouguermouh S, Rubio M, *et al.*: **Human mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis.** *J Allergy Clin Immunol*. 2015; 136(2): 351–9.e1. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Ghoreschi K, Brück J, Kellerer C, *et al.*: **Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells.** *J Exp Med*. 2011; 208(11): 2291–303. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Schafer PH, Parton A, Gandhi AK, *et al.*: **Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis.** *Br J Pharmacol*. 2010; 159(4): 842–55. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
57. Geisel J, Brück J, Glöckner I, *et al.*: **Sulfaphenazole protects from T cell-mediated autoimmune disease by inhibition of IL-23 and IL-12 in dendritic cells.** *J Immunol*. 2014; 192(8): 3530–9. [PubMed Abstract](#) | [Publisher Full Text](#)
58. Brück J, Pascolo S, Fuchs K, *et al.*: **Cholesterol Modification of p40-Specific Small Interfering RNA Enables Therapeutic Targeting of Dendritic Cells.** *J Immunol*. 2015; 195(5): 2216–23. [PubMed Abstract](#) | [Publisher Full Text](#)
59. Ghoreschi K, Laurence A, O'Shea JJ: **Selectivity and therapeutic inhibition of kinases: to be or not to be?** *Nat Immunol*. 2009; 10(4): 356–60. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Ghoreschi K, Jesson MI, Li X, *et al.*: **Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550).** *J Immunol*. 2011; 186(7): 4234–43. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Ghoreschi K, Gadina M: **Jakpot! New small molecules in autoimmune and inflammatory diseases.** *Exp Dermatol*. 2014; 23(1): 7–11. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. **F** Brunner PM, Koszik F, Reininger B, *et al.*: **Infliximab induces downregulation of the IL-12/IL-23 axis in 6-sulfo-LacNAc (sIa)⁺ dendritic cells and macrophages.** *J Allergy Clin Immunol*. 2013; 132(5): 1184–1193.e8. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
63. Tsianakas A, Brunner PM, Ghoreschi K, *et al.*: **The single-chain anti-TNF-α antibody DLX105 induces clinical and biomarker responses upon local administration in patients with chronic plaque-type psoriasis.** *Exp Dermatol*. 2016. [PubMed Abstract](#) | [Publisher Full Text](#)
64. **F** Kopp T, Riedl E, Bangert C, *et al.*: **Clinical improvement in psoriasis with specific targeting of interleukin-23.** *Nature*. 2015; 521(7551): 222–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
65. **F** Hueber W, Patel DD, Dryja T, *et al.*: **Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis.** *Sci Transl Med*. 2010; 2(52): 52ra72. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
66. **F** Griffiths CE, Reich K, Lebwohl M, *et al.*: **Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials.** *Lancet*. 2015; 386(9993): 541–51. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
67. **F** Ghoreschi K, Thomas P, Breit S, *et al.*: **Interleukin-4 therapy of psoriasis induces Th2 responses and improves human autoimmune disease.** *Nat Med*. 2003; 9(1): 40–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. Guenova E, Skabytska Y, Hoetzenecker W, *et al.*: **IL-4 abrogates T_H17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells.** *Proc Natl Acad Sci U S A*. 2015; 112(7): 2163–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. Witte E, Kokolakis G, Witte K, *et al.*: **IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis.** *J Invest Dermatol*. 2014; 134(11): 2757–67. [PubMed Abstract](#) | [Publisher Full Text](#)
70. Quaranta M, Knapp B, Garzorz N, *et al.*: **Intraindividual genome expression analysis reveals a specific molecular signature of psoriasis and eczema.** *Sci Transl Med*. 2014; 6(244): 244ra90. [PubMed Abstract](#) | [Publisher Full Text](#)
71. Schonhaler HB, Guinea-Viniegra J, Wculek SK, *et al.*: **S100A8-S100A9 protein complex mediates psoriasis by regulating the expression of complement factor C3.** *Immunity*. 2013; 39(6): 1171–81. [PubMed Abstract](#) | [Publisher Full Text](#)
72. **F** Marrakchi S, Guigé P, Renshaw BR, *et al.*: **Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis.** *N Engl J Med*. 2011; 365(7): 620–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. **F** Berki DM, Liu L, Choon SE, *et al.*: **Activating CARD14 Mutations Are Associated with Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris.** *J Invest Dermatol*. 2015; 135(12): 2964–70. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
74. Hüffmeier U, Wätzold M, Mohr J, *et al.*: **Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations.** *Br J Dermatol*. 2014; 170(1): 202–4. [PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Mario Fabri**

Department of Dermatology and Venereology, University of Cologne, Cologne, Germany

Competing Interests: No competing interests were disclosed.

2. **Thomas Herzinger**

Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research