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REVIEW

# Immune responses and therapeutic options in psoriasis

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## Abstract

Psoriasis is a chronic inflammatory disease of the skin that affects about 2–3% of the population and greatly impairs the quality of life of affected individuals. Psoriatic skin is characterized by excessive proliferation and aberrant differentiation of keratinocytes, as well as redness caused by increased dilation of the dermal blood vessels and infiltration of immune cells. Although the pathogenesis of psoriasis has not yet been completely elucidated, it is generally believed to arise from a complex interplay between hyperproliferating keratinocytes and infiltrating, activated immune cells. So far, the exact triggers that elicit this disease are still enigmatic, yet, it is clear that genetic predisposition significantly contributes to the development of psoriasis. In this review, we summarize current knowledge of important cellular and molecular mechanisms driving the initiation and amplification stages of psoriasis development, with a particular focus on cytokines and emerging evidence illustrating keratinocyte-intrinsic defects as key drivers of inflammation. We also discuss mouse models that have contributed to a better understanding of psoriasis pathogenesis and the preclinical development of novel therapeutics, including monoclonal antibodies against specific cytokines or cytokine receptors that have revolutionized the treatment of psoriasis. Future perspectives that may have the potential to push basic research and open up new avenues for therapeutic intervention are provided.

**Keywords** Epidermis · Dermatitis · CARD14 · Cytokine · Immunity

## Introduction

The skin is the largest organ serving as an interface between the host and the outside world. It provides a barrier that contains the body and prevents dehydration, as well as protects the body from external threats such as microbial agents and from physical dangers such as damage by daily wear and tear and UV light. In addition, the skin serves as a sensory organ and aids in regulating heat. Next to a physical barrier, the skin also acts as an immunological barrier that is important for the defense against invading pathogens. For instance, keratinocytes not only serve as structural components of the epidermis but also as important innate immune sensors. They contain several pattern recognition receptors that sense the presence of pathogen- or danger-associated molecular patterns and through the production of cytokines and proinflammatory mediators they participate in immune responses [1, 2]. Furthermore, keratinocytes are also an important source of antimicrobial proteins (AMPs) that can control microbial colonization [2, 3]. In addition, the skin hosts various resident immune cells that guard the skin and initiate immune responses. Langerhans cells are antigen presenting cells that populate the epidermis and that are tightly connected through their dendrites with keratinocytes. The exact functions of Langerhans cells are still under debate but by continuous sensing of the environment they instruct adaptive immune responses or induce tolerance to environmental antigens [4, 5]. A second type of immune cells that are abundantly present in both the epidermis and the dermis of healthy skin are tissue-resident memory T cells [2, 6, 7]. These adaptive immune cells establish memory after an initial infection and provide long term protection against commonly encountered pathogens [2, 8]. Compared to the epidermis, the dermis contains a more elaborate repertoire

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of immune cells under steady state including dendritic cells (DCs), macrophages, mast cells, innate lymphoid cells (ILCs), γδ T cells and conventional αβ T cells [6]. Because of this intricate and diverse immune network, the skin serves as an immune sentinel that can efficiently mount an immune response against invading pathogens. Moreover, immune cells and keratinocytes also contribute to the repair of the disturbed epithelial barrier to reestablish homeostasis [2]. However, when immune responses in the skin are targeted to harmless self-antigens or if they spin out of control, they contribute to the development of inflammatory skin diseases such as psoriasis.

Psoriasis is a common chronic inflammatory skin disease that affects 2–3% of the world's population and greatly impairs the quality of life of affected individuals. Psoriasis vulgaris or plaque psoriasis, the most prevalent disease type, is characterized by well-demarcated, red, scaly plaques. However, psoriasis represents a clinical spectrum including more rare subtypes such as pustular, erythrodermic and guttate psoriasis [9], which can be distinguished based on the clinical morphology of the plaques. For instance, pustular psoriasis is characterized by the presence of multiple tender sterile pustules [9]. Psoriasis-affected skin has a thickened epidermis with scaly patches, due to excessive proliferation and aberrant differentiation of keratinocytes, and redness that is caused by increased dilatation of the dermal blood vessels, and infiltration of immune cells [10]. Histologically this is characterized by thickening of the epidermis, also known as acanthosis, and thickening of the stratum corneum, also known as hyperkeratosis. Furthermore, because of the abnormal differentiation, the granular layer is lost, while cells in the stratum corneum retain their nuclei (parakeratosis). Finally, another prominent hallmark of psoriasis is immune cell infiltration, such as the accumulation of neutrophils in the epidermis and in the stratum corneum, also known as the pustules of Kogoj and Munro abscesses, respectively [10].

In certain cases, the cutaneous immune response becomes no longer restricted to the skin and results in systemic inflammation leading to the development of comorbidities. Thus, psoriasis is associated with an increased risk for cardiovascular disease and almost 30% of patients suffer from psoriatic arthritis [11, 12]. Similarly, patients with psoriasis or psoriatic arthritis exhibit increased rates of inflammatory and functional gastrointestinal disorders [13, 14]. Therefore, understanding the molecular and cellular mechanisms driving psoriasis development and 'run away' inflammation, is necessary to improve the current treatment options and help in disease prevention. In this review we will focus on the inflammatory pathways and the immune response driving psoriasis pathology.

## Etiology and genetic background of psoriasis

Even though the exact etiology of psoriasis is still largely unknown, the concordance rate of psoriasis in monozygotic twins of approximately 70% illustrates that there is a strong genetic component. Through linkage disequilibrium studies in psoriasis-affected families, several psoriasis susceptibility (*PSORS*) loci have been identified [10]. However, most of the genes responsible for this observed susceptibility remain unknown [10, 15]. Moreover, only for *PSORS1*, *-2* and *-4* the linkage association could be replicated in independent studies [16]. *PSORS1* is the first discovered susceptibility locus and is one of the strongest heritable risk factors for psoriasis, which lies in the major histocompatibility complex (MHC) region on chromosome 6p21. Although several possible candidate genes for *PSORS1* have been identified, there is general consensus that *HLA-Cw6* is the allele responsible for psoriasis susceptibility [17]. Since *HLA-Cw6* encodes an MHC class I molecule that presents cellular antigens to $CD8^+$ T cells, it is hypothesized that HLA-Cw6 can bind potential self-antigens and in this way links antigen presentation to psoriasis [15, 16]. So far, only LL37 and ADAMTSL5 have been identified as possible autoantigens that bind HLA-Cw6 [18, 19]. In 2012, Jordan et al. showed that *CARD14,* a scaffolding protein involved in NF-κB activation, is the gene responsible for psoriasis susceptibility in *PSORS2* [20]. Psoriasis-associated mutations in CARD14 result in increased NF-κB activation and expression of proinflammatory mediators in primary human keratinocytes [21, 22]. *PSORS4* maps to chromosome 1q21, where the epidermal differentiation cluster is located. This cluster is involved in terminal keratinocyte differentiation, which links psoriasis to skin barrier function [16]. The exact genes in *PSORS4* responsible for psoriasis association are not yet known, but deletion of *LCE3B* and *LCE3C* was shown to be a risk factor for psoriasis [23].

Recently, analysis of single nucleotide polymorphisms (SNP) in genome-wide association studies, exome-wide association studies and immune chips have revealed several new loci linked to psoriasis susceptibility, with at least 63 different psoriasis susceptibility loci being currently identified [16]. Candidate genes often belong to molecular pathways implicated in psoriasis pathology, such as innate and adaptive immune responses or skin barrier function. For instance, several SNPs in genes linked to the IL-23/IL-17 axis, such as *IL12Bp40*, *IL23Ap19, IL23R* and *TRAF3IP2* have been discovered. Besides, there is a genetic association with genes involved in antigen presentation (*HLA-C, ERAP1* and *ERAP2*) as well. Pathways involved in innate immunity, such as

antiviral signaling (*IFIH1*, *DDX58* and *RNF114)* and NF-κB signaling (*CARD14*, *TNFAIP3*, *TNIP1* and *NFKBIA*) also appear to be linked with psoriasis susceptibility [15]. Finally, changes in copy number variance have been detected in psoriasis patients. Beside the deletion of *LCE3B/C,* an increase in the copy number of β-defensin is associated with psoriasis susceptibility [24]. Together, these genetic links with psoriasis can help to point out and reveal the key pathways implicated in psoriasis pathogenesis.

Not only genetics but also environmental triggers play a role in the occurrence of psoriasis. For instance, psoriasis can be triggered by physical trauma also known as the Koebner phenomenon. Psoriasis lesions often occur on parts of the body that endure more mechanical force such as elbows and knees, and several provoking factors such as physical trauma, friction, tattoos and burns have been described [25]. Therefore, mechanotransduction in the skin might be involved in the onset of psoriasis [26]. Psoriasis prevalence also seems to be influenced by geographical distribution with the highest frequency in populations of northern Europe and the lowest in populations of eastern Asia [27]. Furthermore, also stress can serve as a trigger for the onset and frequency of psoriasis flares [28]. Finally, psoriasis has been associated with the exposure to certain microbiota. In particular, streptococcal infections have been linked to psoriasis occurrence. In addition, T cells recognizing streptococcal protein M can cross-react to keratin and are often found in peripheral blood of psoriasis patients [29]. Several reports described microbiota changes in psoriatic lesions compared to healthy skin that may contribute to differential T cell polarization [30, 31]. However, the available data is often controversial, possibly due to the differences in applied protocols or microbial variability across human subjects. Also changes in the intestinal microbiome in psoriasis patients have been described, with consistent increase in *Firmicutes*/*Bacteroidetes* ratio [32]. Furthermore, mice bred in a germ-free facility or treated with broad-spectrum antibiotics (either topically or systemically) are partially protected from imiquimod-induced skin inflammation, accompanied by reduced frequencies of Th17 and Th22 cells [31, 33, 34], suggesting that the microbiome regulates psoriasis-associated immune responses. However, it is still unclear whether these changes are instrumental to the development of psoriasis or are secondary to the skin pathology. In conclusion, the interplay between the genetic background and the environment governs the development of psoriasis and makes it a multi-factorial disease. However, more research is needed to elucidate the exact mechanisms that serve as the tipping point for disease initiation.

## Key inflammatory cytokines that drive psoriatic inflammation

### IL-23

Although originally thought to be a Th1-driven disease, the discovery of Th17 cells shifted the view on psoriasis as an IL-23/IL-17-dependent pathology [35]. IL-23 belongs to the IL-12 family of cytokines and consists of two subunits: p19 which is unique for IL-23 in man (and shared with IL-39 in mice) and p40 which is shared with IL-12. Initially, the key pathogenic role in psoriasis was attributed to IL-12, since administration of anti-IL-12 antibodies protected mice from the development of psoriasis-like skin inflammation, surprisingly in an IFNγ-independent manner [36]. However, the antibody that was used targets the p40 subunit and, thus, also neutralizes IL-23. The increased p19 and p40 expression but not IL-12-specific p35 expression in psoriatic lesions provided the first evidence that not IL-12, but IL-23 is a pivotal player in psoriasis [37]. Furthermore, intradermal injection of IL-23 in mice is sufficient to induce skin inflammation [38], while genetic deletion of IL-23 protects from imiquimod-induced psoriasis-like inflammation [39]. Finally, the remarkable efficacy of anti-IL-23 therapeutics (discussed below) further illustrates the central role of IL-23 in the pathogenesis of psoriasis [35].

IL-23 is mainly produced by DCs and macrophages, but also keratinocytes were identified as a source of IL-23 [40]. Binding of IL-23 to its receptor, a heterodimeric complex composed of IL23R and IL12Rβ1 subunits, leads to activation of receptor-associated Jak kinase family members, Jak2 and Tyk2. Activated kinases in turn phosphorylate tyrosine residues in the cytoplasmic tail of IL23R facilitating recruitment and activation of STAT3, a key transcription factor which mediates gene expression downstream of IL-23 receptor activation. IL-23 is mainly notorious for inducing IL-17 production in responder cells, such as Th17, which is often referred to as the IL-23/IL-17 axis [35].

### IL-17

IL-17A, often referred to as IL-17, is the best characterized IL-17 family member. It is considered as the most potent mediator of psoriatic inflammation. IL-17A expression is increased in psoriatic lesions and in the blood of patients with psoriasis [41]. IL-23-induced epidermal hyperplasia is reduced in IL-17A-deficient mice or upon IL-17A neutralization [42]. Although Th17 cells have been considered for a long time to be a major source of IL-17, it

is expressed by a wider range of cells in psoriatic lesions, such as γδ T cells, ILC3s, neutrophils and mast cells, which also express IL-23R [43, 44]. Therefore, psoriasis is now no longer considered as a strictly Th17-mediated disease but more as an IL-17-driven disease. IL-17 binds to a heterodimeric receptor consisting of IL17RC and IL17RA and not only induces Act1-mediated NF-κB activation, but also activates the C/EBP transcription factor family [45, 46] and enhances the stability of specific mRNAs (Fig. 1). In addition, IL-17A (as well as IL-36) stimulation was shown to induce expression of IκBζ, a co-factor of NF-κB, followed by inflammatory gene expression in keratinocytes [47, 48], while keratinocyte-specific deletion of IκBζ protects from imiquimod- or IL-36-induced skin inflammation [49]. Consequently, IL-17 receptor activation in keratinocytes induces expression of several proinflammatory cytokines, chemokines and AMPs, which sustain and perpetuate the inflammatory reactions during psoriasis [43, 45, 46]. Next to IL-17A, also IL-17F and IL-17C play a role in psoriatic skin inflammation. IL-17A and IL-17F are often co-expressed, bind the same receptor and act in a similar way, while IL-17C is produced by epithelial cells and can thus signal in an autocrine manner [50, 51]. Importantly, IL-17 family members might have different contributions to psoriasis development. Thus, inhibition of IL-17A alone was insufficient to inhibit the development of skin inflammation in IL-36α or STAT3 transgenic mice treated with phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) [52–54]. However, antibody-mediated blockade of the IL-17 receptor efficiently inhibited psoriasis-like pathology [54]. Similarly, IL-17 receptor-deficient mice were resistant to imiquimod-induced skin inflammation, comparably to IL-23 knockout mice [39]. Finally, several IL-17A- and IL-17 RA-neutralizing biologics have shown high efficacy in psoriasis patients (discussed below).

## TNF

TNF is another inflammatory cytokine that has been implicated in psoriasis pathology since a long time. As such, high levels of TNF, TNFR1 and TNFR2 are present in lesional skin [55]. Furthermore, TNF was the first cytokine target in psoriasis whose inhibition showed good therapeutic efficacy

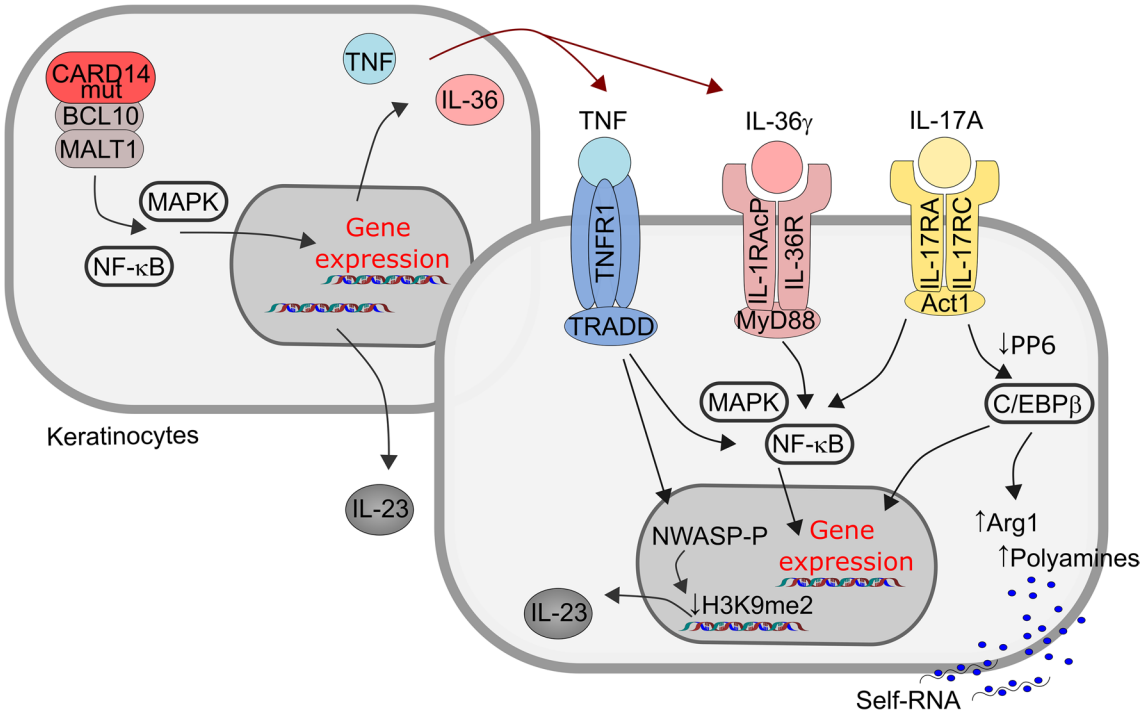


**Fig. 1** Major inflammatory signaling pathways in keratinocytes driving psoriasis. Hyperactivating CARD14 mutations drive the formation of a CARD14-BCL10-MALT1 complex, leading to downstream NF-κB and MAPK signaling and the initiation of pro-inflammatory gene expression, including IL-23, TNF and IL-36. These cytokines can then act in an auto- or paracrine manner and, in turn, initiate NF-κB and MAPK signaling in keratinocytes and other cells. In addition, IL-17 (produced by T cells and ILC3) binding to its receptor can also induce the NF-κB, as well as C/EBPβ. The latter mediates expression of Arginase 1, leading to increased production of polyamines that can stabilize self-RNA and facilitate its uptake by dendritic cells, thus contributing to downstream inflammatory responses. TNF has also been shown to trigger N-WASP phosphorylation in keratinocytes, preventing it from repressing IL-23 expression by controlling H3K9 methylation of the IL-23 promoter

[43]. TNF is a versatile cytokine that not only shapes inflammatory immune responses, but is also involved in cell death, cell cycling and tissue remodeling [56, 57]. It is a homotrimeric cytokine that can induce NF-κB and MAP kinase activation [58] (Fig. 1) either in a soluble or membrane-bound form that is expressed by a plethora of cell types such as macrophages, DCs, neutrophils, T and B cells and keratinocytes [35]. However, the exact roles of TNF in psoriasis pathogenesis are not completely understood yet. TNF might be involved in both the initiation phase and the chronic phase of the disease. For instance, by stimulating the production of IL-23 by DCs, it can promote disease development [43, 59]. The therapeutic effects of TNF inhibition are also linked to a strong reduction in IL-17-dependent genes [60]. In line with this, TNF potentiates IL-17 signaling by enhancing proinflammatory gene expression in keratinocytes in a synergistic way [61]. Furthermore, it has been recently shown that TNF also induces IL-23 expression in keratinocytes [62]. More specifically, TNF induces the phosphorylation and inactivation of the neural Wiskott-Aldrich syndrome protein (N-WASP) that was in turn shown to repress IL-23 expression by regulating histone methylation. TNF-induced phosphorylation of N-WASP reduced chromatin association of the latter and increased IL-23 expression in keratinocytes [62] (Fig. 1). This shows that TNF can amplify the psoriatic mechanisms that are at play and is, therefore, regarded as a regulator of the IL-23/IL-17 axis.

## IL-36

In addition, the IL-1 family cytokines IL-36α, -β and -γ (also known as IL1F6, IL1F8 and IL1F9, respectively) are upregulated in lesional skin of psoriasis patients and implicated in psoriasis development. Thus, IL-36α deficiency protects from imiquimod-induced skin inflammation [63], while loss-of-function mutations in *IL36RN*, a natural antagonist of IL-36, have been identified as the genetic basis in several cases of generalized pustular psoriasis [64, 65]. Expression of another IL-36 subfamily member with anti-inflammatory properties, IL-38, is reduced in the epidermis of lesional skin in patients with psoriasis, as well as other neutrophil-driven skin diseases [66, 67]. IL-38 deficiency in mice exacerbates imiquimod-driven skin inflammation, possibly via suppressing IL-17 production by γδ T cells, while treatment with recombinant IL-38 ameliorates disease progression [67, 68]. Specific deletion of the *IL36R* in keratinocytes results in similar levels of protection from psoriasiform inflammation observed in mice lacking IL36R globally [69], demonstrating that keratinocytes are the primary cells that orchestrate dermal inflammation in response to IL-36. However, the specific biological role of IL-36 signaling during psoriasis is not entirely clear yet [70]. IL-36 cytokines produced by keratinocytes after IL-17 and TNF stimulation can in turn further enhance proinflammatory cytokine and AMP expression by keratinocytes [71] (Fig. 1). Recently, IL-36R signaling in keratinocytes was shown to play a major role in the induction of imiquimod-induced psoriasis-like dermatitis by triggering the production of IL-23/IL-17/IL-22 cytokines and neutrophil infiltration [72]. Moreover, IL-36 is also implicated in the cross-talk between immune cells and keratinocytes by promoting DC and macrophage activation [73, 74]. Finally, IL36γ might also promote angiogenesis by inducing endothelial branching [75].

## Other cytokines

Several other cytokines are also implicated in psoriasis development, many of which are in one or another way linked to the IL-23/IL-17 axis. For example, IL-22 was shown to induce tissue remodeling in psoriatic lesions by affecting keratinocyte migration, differentiation and gene expression [76–78]. IL-22 is expressed in response to IL-23 by Th17 cells [79], but can also be produced by other T cell subsets and innate immune cells. Psoriatic-like lesions in the imiquimod model were strongly reduced in IL-22-deficient mice, suggesting an important role of this cytokine in psoriasis [80]. However, an IL-22 receptor antagonist was discontinued because of a lack of efficacy [81], questioning the driving role of IL-22 in psoriasis in humans.

The development of psoriatic lesions in patients that are treated with the type I interferons IFNα or -β for viral infections or multiple sclerosis provided the first evidence that type I interferons are involved in psoriasis pathogenesis [82–85]. Furthermore, neutralization of IFNα could prevent the development of psoriatic lesions upon xenotransplantation of non-lesional skin from psoriasis patients to mice, which points to a major role for type I interferons during the initiation phases of psoriasis [86]. Remarkably, therapeutic targeting of IFNα by MEDI-545, an anti-IFNα monoclonal antibody, did not show clinical improvements in psoriasis patients, though this might reflect the initiating role of type I interferons in psoriasis [87].

Lesional skin and serum of psoriasis patients also contains increased levels of IFNγ and these levels were also shown to correlate with disease severity [88]. Furthermore, even in healthy volunteers, a single intradermal injection of IFNγ could induce transcriptomic changes that are overlapping with those observed in lesional skin [89]. Therefore, IFNγ was considered a Th1-mediated driver of psoriasis for a long time. However, after the discovery of the cardinal IL-23/IL-17 axis and because of the poor therapeutic efficacy of IFNγ-neutralizing antibodies, IFNγ is no longer regarded as the central driver of psoriasis [90]. Still, IFNγ might be involved in the early phases through activation of antigen-presenting cells and it may also affect inflammation by synergizing with other cytokines such as IL-17 [43, 91].

Finally, it should be mentioned that also IL-9, IL-18, IL-19, IL-20, IL-21, IL-24, Il-27, IL-29 and IL-33 have been linked with psoriasis [92–96]. However, their specific importance and the mechanisms by which they influence psoriatic disease still require further research.

## Current model of psoriasis pathogenesis

Although the pathogenesis of psoriasis is not completely elucidated, substantial advances have been made over the last decade. Research on psoriasis has long been fuelled by the paradigm that psoriasis is driven by T cell-mediated immune responses targeting keratinocytes. However, as described above, psoriasis cannot be explained solely on the basis of T-cell activation. Instead, a complex interplay between infiltrating, activated immune cells and hyperproliferating keratinocytes is now believed to be at the base of the disease (Fig. 2).

## Role of keratinocytes in disease initiation

The exact triggers that initiate psoriatic disease are not yet known. However, the association with the Koebner phenomenon suggests that trauma can be a trigger. Furthermore, also microbial agents and certain medicines (e.g., lithium, type I IFN blockers) have been correlated with psoriasis onset [10]. Because some of these triggers are encountered regularly, genetic predisposition probably plays a considerable role in shaping the right microenvironment for the pathogenic events to occur. According to the current model for psoriasis pathogenesis, trauma or infectious agents can trigger keratinocytes which respond by releasing self-nucleic acids, AMPs, and alarmins like the cytokine IL-36 (Fig. 2) [43]. Certain AMPs such as LL37, hBD2, hBD3 and lysozyme form complexes with self-nucleic acids. By inducing TLR7/9 signaling in plasmacytoid DCs (pDCs) these AMP-nucleotide complexes

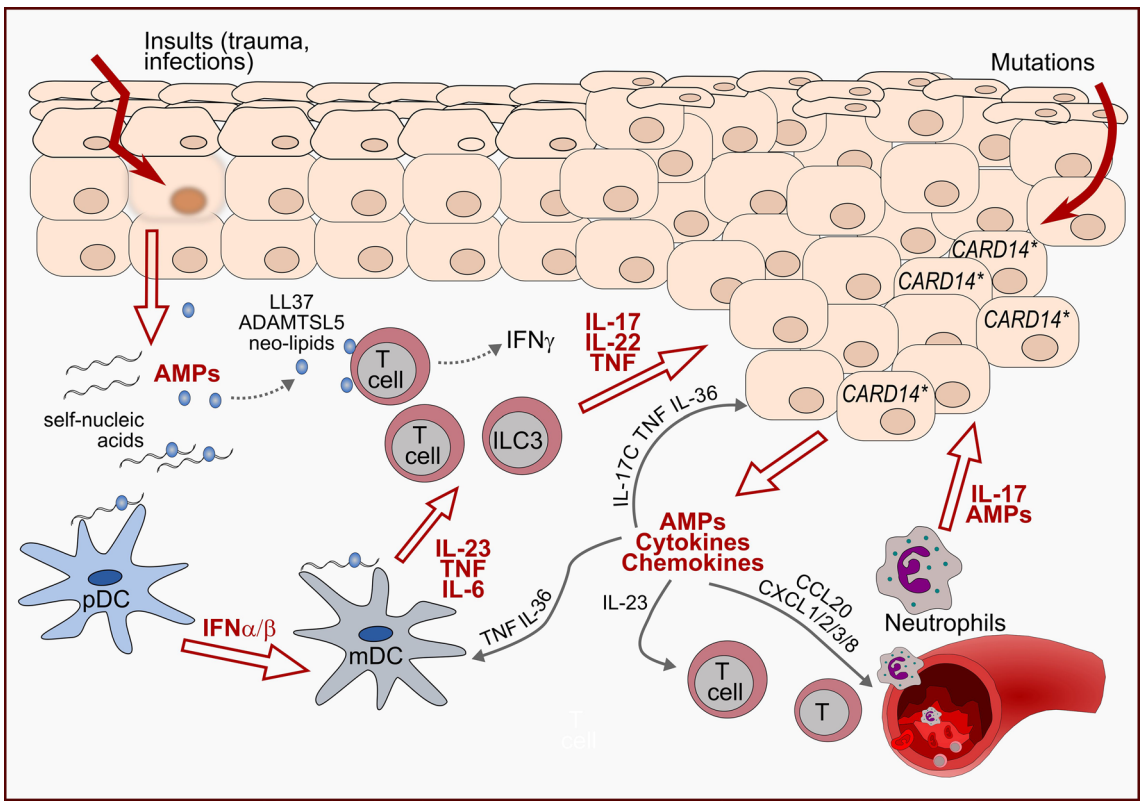


**Fig. 2** Mechanistic model depicting the inflammatory response in psoriasis. Insults that damage keratinocytes drive the release of self-nucleotides and antimicrobial peptides (AMPs) such as LL37, which together with ADAMTSL5 and neo-lipids are suggested to activate autoreactive T cells. Furthermore, AMPs form complexes with self-nucleic acids that stimulate plasmacytoid dendritic cells (pDCs) to produce IFNα and -β, which enhance myeloid DC (mDC) cell differentiation and secretion of IL-23, TNF and IL-6. These cytokines can activate T cells and type 3 innate lymphoid cells (ILC3s), which, in turn, produce IL-17 and other proinflammatory cytokines such as TNF, IL-17F, IL-22 and IFNγ. This cytokine cocktail activates keratinocytes to produce several AMPs, cytokines and chemokines acting on T cell, mDCs, neutrophils and keratinocytes. In addition, keratinocyte-intrinsic defects, such as hyperactivating CARD14 mutations, can induce this proinflammatory cascade culminating in the recruitment and activation of IL-17-producing cells, which further propagate and amplify the inflammatory response

breach the innate tolerance to self-DNA [97–99]. An elegant study by Lou and colleagues have recently shown that IL-17 stimulation of keratinocytes can rewire the metabolic urea cycle leading to the production of polyamines that protect released self-RNA [100] (Fig. 1). More specifically, IL-17 stimulation results in the downregulation of protein phosphatase 6 enabling phosphorylation and activation of the transcription factor C/EBPβ, which in turn leads to increased expression of Arginase 1 and production of polyamines [100]. Upon TLR7/9 stimulation, pDCs quickly respond by producing type I interferons. IFNα and -β, in turn, activate myeloid DCs (mDCs) which become inflammatory mDCs known as Tip-DCs [43] (Fig. 2). Furthermore, self-RNA complexed with LL37 can also directly activate mDCs by engaging TLR7/8 [97, 100]. Noteworthy, IL-17-induced polyamines were shown to facilitate self-RNA uptake by myeloid DC [100]. The dermal inflammatory mDCs release IL-6, NO, TNF, IL-12, IL-20 and IL-23, which seems to be dependent on TNF [59, 101] and ultimately initiate a chronic IL-17-mediated inflammatory response.

Various factors (e.g., chemicals, viral or endogenous nucleic acids, mutations) may cause damage and even cell death of keratinocytes. Dysregulation of necroptotic cell death markers has been documented in the epidermis of human psoriasis lesions as well as in imiquimod-induced psoriasiform skin of mice [102]. Moreover, inhibition of necroptotic cell death was shown to reduce imiquimod-induced inflammatory responses in the skin, indicating a proinflammatory effect of necrotic cell death in the pathogenesis of psoriasis [102]. Recently, several studies reported an important role for endogenous Z-DNA sensing by Z-DNA-binding protein 1 (ZBP1) in keratinocytes in which necroptosis and skin inflammation was initiated by disruption of the kinase RIPK1 [103, 104]. However, the causal role of necroptotic cell death in psoriasis, as well as the underlying molecular mechanisms, in more physiological conditions remain to be determined.

Intrinsic defects in cytokine and growth factor signalling in keratinocytes may be responsible for their aberrant hyperproliferation and differentiation, as well as inflammatory cell infiltration and activation. For instance, enhanced expression of IL-23 specifically in keratinocytes (IL-23 transgene or deletion of N-WASP, a negative regulator of IL-23 expression) leads to the development of psoriasis-like skin inflammation and psoriatic arthritis in mice [62, 105]. Recent evidence based on the imiquimod-induced psoriasis model also suggests that IL-36R signaling in keratinocytes mediates early expression of IL-23 and is indispensable for the induction of neutrophil infiltration but not keratinocyte hyperproliferation [72]. In addition, hyperactivating mutations in the *CARD14* gene, which is specifically expressed in keratinocytes and mucosal tissues, have been linked to psoriasis-susceptibility in human patients [20]. Specific CARD14 mutations enable its interaction with the downstream signaling proteins, BCL10 and MALT1, which induces NF-κB and p38/JNK MAP kinase signaling and expression of several proinflammatory mediators in keratinocytes [21, 106] (Figs. 1, 2). Importantly, keratinocyte-specific expression of the psoriasis-associated mutant CARD14 (E138A) was recently shown to be sufficient for driving the development of psoriasis-like skin inflammation in mice [107, 108]. Collectively, these studies highlight the instrumental role that keratinocytes are playing in initiating inflammatory responses in psoriasis.

## Role of T cells in the initiation and amplification of inflammation

Autoreactive T cells producing IFNγ and IL-17 might be another, alternative pathogenic mechanism that can initiate psoriasis [43]. Moreover, the strong predisposition linked to the *HLA-Cw6* allele favors an autoimmune disease mechanism. So far, LL37, ADAMTSL5 and neo-lipids have been identified as self-antigens (Fig. 2), evidenced by the existence of LL37- and ADAMTSL5-specific autoreactive T cells in psoriasis patients [18, 19, 109, 110]. However, deep sequencing of the T cell repertoire in lesional skin showed that the αβ and γδ T cell populations are highly polyclonal [111]. Therefore, the exact way of how these self-antigens and autoreactive T cells might initiate psoriasis is not entirely clear and still requires further research.

By the production of IL-23, activated inflammatory mDCs can steer and sustain T cell responses [112]. The essential role of T cells in the disease mechanism was first illustrated by the therapeutic efficacy of drugs that deplete or inhibit activated T cells such as alefacept and denileukin diftitox [10]. Furthermore, both $CD4^+$ T helper (Th) cells and $CD8^+$ cytotoxic T (Tc) cells were shown to be crucial for the development of skin lesions, and both $CD4^+$ and $CD8^+$ T cell numbers are increased in lesions and peripheral blood of psoriasis patients [43]. So far, Th1, Th17 and Th22 (a distinct T cell population that only produces IL-22) cells and their $CD8^+$ counterparts Tc1, Tc17 and Tc22 have been implicated in the disease [113, 114]. However, because of the strong clinical impact of anti-IL-17 therapeutics but not of IFNγ and IL-22 inhibitory drugs, Th17/Tc17 cells seem to play a more prominent role. Upon activation, these T cell populations produce a cytokine cocktail with IL-17 as the most potent ingredient. Next to 'conventional' T cells, also γδ T cells and ILC3s are enriched in lesional skin and serve as additional sources of IL-17 upon IL-23 stimulation [115–118] (Fig. 2). ILC3s, an innate immune system's counterpart of Th17 cells, secrete IL-17, IL-22 and GM-CSF in response to antigen-independent activation by microbial products or inflammatory cytokines, thus

modulating cross-talk between innate and adaptive immune systems [119]. Importantly, intradermal injection of ILC3s was sufficient to drive the development of psoriatic lesions in healthy human skin transplants implanted in SCID mice, even in the absence of Th17 cells [120].

Psoriasis recurrence is often observed in healed skin upon cessation of treatment, suggesting that a certain predisposition facilitating recurrence remains in the tissue. Indeed, engraftment of non-lesional skin from psoriatic patients onto immunocompromised mice resulted in the development of psoriatic lesions that was dependent on local T cell proliferation [121]. It was subsequently shown that resolved psoriatic lesions contain psoriasis-specific tissue-resident memory T cells that produce IL-17 and IL-22 [122, 123]. Furthermore, even never-lesional skin from patients with psoriasis harbors T cells capable of inducing psoriasis-associated responses further underscoring the pathogenic role that T cells play in the initiation of psoriasis development [124].

### Role of keratinocytes in the amplification of inflammation

Several of the cytokines produced by T cells and ILC3s act on keratinocytes and will thus further amplify the inflammatory response in psoriasis. Deletion of IL-17RA in T cells or myeloid cells had no effect on the development of imiquimod-induced skin inflammation, while deletion of IL-17RA in keratinocytes inhibited neutrophil infiltration and disease development, highlighting the instrumental role of keratinocyte-derived signals in psoriasis pathogenesis [125]. TNF, IL-22 and IFNγ have synergistic effects on IL-17 signaling and thus enhance the effects of IL-17 on keratinocytes [43]. In response to stimulation with these cytokines, keratinocytes become a source of AMPs, cytokines and chemokines, which have various effector functions (Fig. 2) [43]. In psoriatic plaques, keratinocytes produce excessive amounts of AMPs including LL37, S100A proteins (S100A7, S100A8 and S100A9), β-defensins, RNase7, REG3A and lipocalin-2 [3]. These AMPs are small proteins that have anti-bacterial, -fungal, -protozoal and -viral activities and can prevent microbial colonization. In addition, they also have immunomodulatory functions that further feed the inflammatory pathways at play. For instance, next to its capacity to activate TLR7/8/9 signaling, LL37 might serve as a self-antigen and can regulate the expression of cytokines such as IL-36γ by keratinocytes [110, 126]. Furthermore, AMPs are involved in a wide range of psoriatic processes that contribute to the formation of psoriatic plaques such as chemotaxis of immune cells, increased proliferation and aberrant differentiation of keratinocytes and angiogenesis [3, 127]. Next to AMPs, psoriatic keratinocytes also produce a vast amount of cytokines including TNF, IL-1 family members, IL-6, IL-8, IL-17C, IL-19 and IL-36γ [43], which can induce both paracrine and autocrine signaling. For instance, IL-19 and IL-20 act on keratinocytes and induce hyperproliferation leading to epidermal hyperplasia, while IL-1β is an important mediator of Th17 differentiation [128, 129]. Notably, keratinocytes can also be a source of IL-23 and in this way might shape a favorable microenvironment for IL-17-producing cells [40, 62]. Finally, upon stimulation with psoriatic cytokines, keratinocytes also produce several chemokines that serve as attractants for immune cells. CXCL1, -2, -3 and -8 are strongly upregulated by psoriatic keratinocytes and attract neutrophils to psoriatic lesions, which further contribute to the production of AMPs and proinflammatory mediators, in particular IL-17 [44, 130]. In addition, CCL20, a chemokine that recruits CCR6-positive cells, is markedly induced by keratinocytes in psoriatic plaques. Because most psoriatic IL-17-producing cells such as Th17 cells and γδ T cells bear a CCR6 receptor, this again induces higher IL-17 signals in the skin [43]. Together, the inflammatory mediators that are produced by keratinocytes upon IL-17 stimulation establish a feedforward loop that fuels IL-17 production by immune cells resulting in a vicious cycle of inflammation in psoriasis.

## Mouse models of psoriasis

Our improved understanding of psoriasis pathogenesis stems in a large part from studies that rely on the use of mice as a disease model. However, it is important to remember that although mouse and human skin share similar features, also significant differences exist. Mouse skin is thinner, has more densely distributed hair follicles [131] and also contains a cutaneous muscular layer called panniculus carnosus, which is usually absent in human skin. On the other hand, human epidermis contains more distinct cell layers compared to murine epidermis [132]. The skin transcriptomes of mice and human only partially overlap [132] and also skin-resident immune cells show some differences. For instance, murine epidermis contains special dendritic epidermal γδ T cells that are involved in the defense against infections and in wound healing [133], while T cells in the human skin predominantly express an αβ T cell receptor [132, 134]. Furthermore, spontaneous development of psoriasis seems to be unique to humans and mouse models fail to exactly reproduce psoriasis pathology. For instance, comparative transcriptomics between several mouse models shows that these mouse models share multiple gene expression patterns with human psoriasis but cannot completely mirror all involved pathways [135, 136]. Notwithstanding these differences, several mouse models, which closely resemble psoriasis pathology, serve as valuable tools for preclinical research and drug development. Ideally, psoriasis models should meet three criteria: they should have histological hallmarks that

are similar to those in psoriasis, a similar disease mechanism and respond to therapeutics that have shown to be effective in psoriasis patients [131, 137]. Different strategies to induce psoriasis-like disease in mice have been employed and can be subdivided in spontaneous models, genetically engineered models, induced models and xenograft models [134, 138], which reproduce typical characteristics of human psoriasis to a varying degree (Table 1).

## Spontaneous models

The first psoriasis-like mouse models that have been described were caused by homozygous spontaneous mutations. For instance, mice with asebia ($Scd1^{ab}$/$Scd1^{ab}$), chronic proliferative dermatitis ($Sharpin^{cpdm}$/$Sharpin^{cpdm}$) and flaky skin ($Ttc7^{fsn}$/$Ttc7^{fsn}$) mutations develop skin inflammation with histological features that resemble those in psoriasis [139–141]. However, the role of T cells in these models is limited and they don't respond to treatment with anti-psoriatic drugs such as cyclosporine A [134]. Therefore, psoriasis models caused by spontaneous mutations are considered to have limited applications.

## Genetically engineered mouse models

Over the last two decades, several genetically engineered mouse strains that develop psoriasis-like inflammation have been established. These involve both transgenic animals that overexpress certain genes and animals with a (conditional) deletion in certain genes. Transgenic (over) expression of genes induced by the K5 and K14 promotor leads to epidermal-specific expression and is often employed to obtain mouse lines that develop psoriasis-like inflammation. Among these, several mouse lines that overexpress cytokines and mediators associated with psoriasis have been generated. For example, K14-IL-23, K5-IL-17C and K14-IL-$17^{ind/+}$ mouse lines all develop skin inflammation that resembles psoriasis to a greater or lesser extent [105, 142, 143]. Furthermore, expression of a constitutively active STAT3 (Stat3C), a transcription factor that mediates IL-23 signaling, induces psoriasis-like inflammation in K5-Stat3C mice [144]. The most recent mouse model involves expression of human psoriasis-associated mutant CARD14(E138A) [107, 108, 145, 146]. Inducible keratinocyte-specific expression of CARD14(E138A) was shown to be sufficient for the development of skin inflammation

**Table 1** Major mouse models of psoriasis

| Examples | Characteristics | Advantages | Disadvantages |
|---|---|---|---|
| **Spontaneous mouse models** [139–141] | | | |
| $Scd1^{ab}$/$Scd1^{ab}$<br>$Sharpin^{cpdm}$/$Sharpin^{cpdm}$<br>$Ttc7^{fsn}$/$Ttc7^{fsn}$ | (Mild) acanthosis<br>Parakeratosis<br>(Sparse/strain-dependent) immune cell infiltration | | Limited role of T cells<br>Do not respond to cyclosporin<br>Complex pathologies in several organ systems |
| **Genetically engineered mouse model** [105, 108, 142, 144] | | | |
| K14-IL23<br>K14-IL-$17^{ind/+}$<br>K5-STAT3C<br>K14-CARD14(E138A) | Acanthosis<br>Parakeratosis<br>Immune cell infiltration | Allows to investigate the function of a specific gene | Single gene alterations do not always reflect psoriasis complexity |
| **Topical application** [39] | | | |
| Aldara cream | IL-23/IL-17-driven<br>Partially T cell-dependent<br>Acanthosis<br>Parakeratosis<br>Angiogenesis | Cheap<br>Easy<br>Can be induced at a specific age | Represents acute phase only<br>Systemic effects<br>Highly dependent on γδ Tcells<br>Limited similarity in gene expression with psoriatic skin<br>Lack of standardized protocols |
| **Intradermal injection** [38, 151] | | | |
| IL-23 | Acanthosis<br>Parakeratosis<br>Immune cell infiltration<br>Large gene expression overlap with humans | Easy<br>Can be induced at a specific age<br>High resemblance to psoriasis<br>Respond to clinical biologics | Lack of standardized protocols<br>May circumvent DC activation and reduce their contribution<br>Not suitable for chronic use |
| **Xenograft models** [121, 154, 155] | | | |
| Human skin transplantation onto immunocompromised mice | Hyperplasia<br>Parakeratosis<br>Preserved hypervascularization<br>Immune cell infiltration | Closely mimics human disease<br>Preserves immunologic and genotypic characteristics of human skin | Technically difficult<br>Require large skin fragments<br>Do not recapitulate co-morbidities<br>Phenotypic variation |

Typical features of human psoriasis that are present in each model and major advantages/disadvantages are mentioned

in the ears with several characteristics of psoriasis such as acanthosis and parakeratosis, neutrophilic infiltration and a TNF/IL-23/IL-17 cascade-related cytokine profile [108], illustrating the important role of keratinocytes in the initiation of psoriasis. Mutant CARD14-driven skin inflammation can be reduced upon treatment with IL-23-, TNF- and (to some extent) IL-17-neutralizing antibodies [107, 145, 146]. Importantly, CARD14(E138A) expression still induces psoriasiform skin inflammation in RAG-1-deficient mice that lack T and B cells, suggesting that inflammation caused by keratinocyte-intrinsic hyperactive CARD14-driven signaling is independent of adaptive immunity ([107]; our own unpublished observations).

Finally, also mouse strains that are deficient for certain genes have been described to develop psoriasiform inflammation. For instance, mice lacking JunB and c-Jun transcription factors in epidermal cells develop skin inflammation that includes many hallmarks of psoriasis [147]. In general, genetically engineered mouse models allow to investigate the effect of a single gene on skin inflammation in vivo and in this way help to elucidate the events and key mediators that promote psoriasis. However, because psoriasis is a multifactorial disease, single genetic alterations might not completely represent the complex phenotype observed in psoriasis.

## Topical application and intradermal injection models

As an alternative approach to genetic models, topical application of imiquimod cream or intradermal injection of IL-23 has been used. In 2009, Van der Fits et al. described that topical application of imiquimod-containing cream (Aldara®) could induce psoriasis-like inflammation in mice [39]. Originally, Aldara cream has been used as a treatment for genital warts caused by human papilloma virus and (pre)cancerous skin lesions. Remarkably, an exacerbation of psoriatic lesions in patients was noticed as a side effect of this treatment [39]. Imiquimod is a TLR7/8 agonist and a potent immune activator that can induce IL-23 production by dendritic cells and in this way drive psoriasiform changes [148]. However, it has been shown that also other components of the Aldara cream such as isostearic acid contribute to the psoriasiform inflammation through inflammasome activation in a TLR7-independent way [149]. The Aldara-induced skin inflammation is an IL-23/IL-17-driven model, partially dependent on T cells presenting several histological hallmarks of psoriasis such as acanthosis, parakeratosis and angiogenesis [39, 138]. For this reason and because of the easy applicability, this model has been widely used to study the impact of several genes and chemical substances on psoriasis-like inflammation. Nonetheless, similar to other mouse models, there are some limitations to the use of the imiquimod model. This model mainly represents the acute phase of psoriasis-like inflammation but does not correspond to its chronic nature. Moreover, several systemic effects such as splenomegaly and dehydration occur during the treatment, probably caused by accidental ingestion during grooming and effects on other organ systems such as the intestine. In this way the observed skin inflammation is affected by mechanisms that are not completely relevant to psoriasis pathology [150].

Intradermal injection of IL-23 is another way to model psoriatic inflammation. Injection of IL-23 induces erythema and ear swelling, which is characterized by acanthosis, parakeratosis and infiltrating immune cells such as $CD4^+$ T cells, dendritic cells, neutrophils and macrophages [38, 151]. IL-23-induced psoriasis was shown to be mediated by both IL-22 and IL-17 [42, 79]. Hedrick et al. described two phases in this model, an early T cell-independent phase, followed by a second, more chronic, T cell-dependent phase [151]. Furthermore, analysis of the gene expression profile showed significant overlap between this model and human psoriasis [135]. Next to IL-23 injections, also intradermal IL-17, IL-21 and IL-22 injections have been shown to induce psoriasiform skin inflammation, although IL-23 injections mirror psoriasis pathology more closely [151–153].

## Xenograft models

Finally, in an attempt to better preserve immunologic and genotypic characteristics of human skin, xenograft models were developed. Here, skin explants from lesional or non-lesional psoriatic skin together with infiltrating immune cells are transplanted onto immunocompromised mice, such as nude mice, SCID (*Prkdc*$^{scid}$) mice and AGR129 mice [121, 154, 155]. Transplantation in each of these strains shows a T cell-dependent disease course, illustrating the essential role of T cells in psoriasis pathogenesis. Interestingly, non-lesional psoriatic skin transplanted onto AGR129 mice (Rag-2-deficient mice lacking IFN I and II receptors) leads to the spontaneous development of psoriatic lesions, suggesting that all necessary immune 'components' to develop psoriatic lesions are also present in non-lesional skin [121, 138]. Unfortunately, xenograft models are technically difficult and require large skin fragments. In addition, because skin fragments are transplanted, these models cannot recapitulate more systemic co-morbidities of psoriasis such as psoriatic arthritis [134]. Nevertheless, these humanized mouse models offer the highest resemblance to human psoriasis serving as good models for preclinical studies and drug development.

In a further attempt to circumvent the restrictions of mouse models and reconstruct human epidermis in vitro, several three-dimensional (3D) skin models have been established and are now commercially available [156]. These

human skin equivalents rely on the co-culture of primary cells (e.g., keratinocytes, fibroblasts) supported by extracellular matrix components. However, to more faithfully reproduce the intricated interplay of skin keratinocytes and resident immune cells, 3D skin models require exogenous addition of immune cells or artificial substitution with cytokine stimulation. A further layer of complexity is added by the need to simulate infiltration of the skin models with non-resident immune cells, such as neutrophils or macrophages. Shin et al. have recently recapitulated T cell migration into reconstructed epidermis by supplementing human skin constructs with in vitro polarized T cells derived from psoriasis patients [157]. These skin constructs showed increased epidermal proliferation and psoriasis-associated cytokine profile and responded to psoriasis treatments [157]. However, although promising, 3D skin models are technologically complex, heterogenous and still currently inadequate to fully reproduce the complex multi-factorial in vivo environment necessary to study psoriasis pathology. Nevertheless, despite these limitations, 3D skin models have been used to study the role of cytokine signaling in cutaneous responses or for drug testing [156] and can nicely complement existing mouse models.

## Current therapies for the treatment of psoriasis

So far, there is no cure for psoriasis, since the current therapeutics manage the disease by controlling symptoms. The psoriasis area and severity index (PASI) is often used to score the severity of psoriasis and as a measure to follow up the efficacy of therapeutics. PASI is determined as a combined score for erythema (redness), induration (thickness) and scaling and it also takes into account the body surface area that is involved. A treatment is often considered successful if the PASI score is reduced with 75% compared to baseline, also termed PASI75 [10]. Psoriasis patients with mild psoriasis are usually treated with topical treatments containing coal tar, salicylic acid, vitamin D3, anthralin, retinoids or corticosteroids. Patients that do not respond to topical treatments or patients that suffer from moderate to severe psoriasis can benefit from phototherapy with UV-B radiation or UV-A radiation in combination with psoralen [158]. Furthermore, also systemic drugs including cyclosporin, methotrexate and acitetrin are used for moderate to severe psoriasis. However, these systemic drugs have immune-suppressive capacities and can lead to toxicity when administered chronically [159].

The development of biologics, most often monoclonal antibodies, was a great breakthrough in psoriasis treatment. These biological drugs specifically target key players in psoriasis pathogenesis. Therefore, they have greater efficacy and a better safety profile compared to traditional systemic drugs [160]. Table 2 gives an overview of currently used biologics for the treatment of psoriasis and psoriatic arthritis.

The first approved biologics for psoriasis were biologics that interfered with the activation of T cells. Efalizumab and alefacept both block co-stimulation of T cells by antigen presenting cells. However, because of severe side effects or lower effectiveness compared to the newer biologics, these drugs were withdrawn from the market [160]. Abatacept (trade name Orensia), is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4 that binds CD80/CD86 and in this way prevents co-stimulation of T cells. It is used for the treatment of rheumatoid arthritis and was in 2017 approved by the FDA for treatment of psoriatic arthritis.

TNF inhibitors, another class of biologics, interfere with TNF function and in this way reduce inflammatory signaling. Several anti-TNF biologics are currently used to treat psoriasis. Etanercept was the first approved drug and is a human TNF-receptor fusion protein. Next, also other TNF inhibitors were developed: infliximab, adalimumab and golimumab are monoclonal antibodies, while certolizumab consist of an antibody Fab fragment conjugated to polyethylene glycol. They all bind both to soluble and membrane-bound TNF [159, 160]. Nowadays, also biosimilars for etanercept, infliximab and adalimumab are approved by the FDA. These biosimilar agents are highly similar to the

**Table 2** Biologics for the treatment of psoriasis and psoriatic arthritis

| Therapeutic agent | Target | Trade name |
|---|---|---|
| Etanercept | TNF | Enbrel® |
| Infliximab | TNF | Remicade® |
| Adalimumab | TNF | Humira® |
| Certolizumab pegol | TNF | Cimzia |
| Golimumab* | TNF | Simponi Aria® |
| Secukinumab | IL-17A | Cosentyx® |
| Ixekizumab | IL-17A | Taltz® |
| Netakimab | IL-17A | Efleira® |
| Bimekizumab* | IL-17A and IL-17F | |
| Brodalumab | IL-17 receptor A | Kyntheum®(Europe) Siliq®(US) |
| Guselkumab | p19 subunit of IL-23 | Tremfya® |
| Mirikizumab** | p19 subunit of IL-23 | |
| Tildrakizumab | p19 subunit of IL-23 | Ilumya™ |
| Risankizumab | p19 subunit of IL-23 | Skyrizi™ |
| Ustekinumab | p40 subunit of IL-12 and IL-23 | Stelara® |
| Abatacept* | CD80/CD86 | Orencia® |

*Only approved for psoriatic arthritis

**Not approved yet

already approved biologics, however, because of the biologic origin of these products, it is almost impossible to manufacture an exact generic copy [159]. TNF inhibitors generally show an improved efficacy compared to traditional systemic drugs; ~ 50–80% of patients reached PASI75 [35]. However, they are, like almost any drug, linked with side-effects. For instance, infusion reactions are observed in 4% of patients and because of the immunosuppressive properties, patients can be more sensitive to infections [159]. Furthermore, loss of efficacy can also occur through time due to the development of anti-drug antibodies or because of adaptations in the pathogenic mechanisms. Surprisingly, TNF inhibitors have also been linked to the development of paradoxical skin lesions that had psoriasiform and eczematous-like characteristics [35].

Next to TNF inhibitors, also biologics that directly target the IL-17/IL-23 axis have been developed. Ustekinumab targets the p40 subunit that is shared by IL-12 and IL-23 and in this way inhibits both Th1 and Th17 pathways in psoriasis. 50 to 80 percent of patients showed an improvement of 75 percent in the PASI score in phase III clinical trials with ustekinumab [35]. In addition, guselkumab, tildrakizumab and risankizumab have recently been approved for treatment of psoriasis. They are IL-23-specific inhibitors that target the p19 subunit of IL-23. Comparative testing with ustekinumab and etanercept, showed that these IL-23-specific therapeutics are superior and can reach a PASI90 in more than 50 percent of patients [35, 161]. In addition, also another IL-23-specific inhibitor, mirikizumab, is being developed and undergoes clinical testing. Finally, also IL-17 inhibitors have shown great promise for the treatment of psoriasis. So far, there are three biologics that target IL-17 on the market. Secukinumab, ixekizumab and netakimab are monoclonal antibodies that target IL-17A directly. Recently, superiority to Secukinumab in achieving complete psoriasis skin clearance in a Phase 3b study was reported for Bimekizumab, which is a monoclonal antibody that targets both IL-17A and IL-17F. Brodalumab is an IL-17RA inhibitor and thus inhibits signaling by several of the IL-17 family members: IL-17A, IL-17C, IL-17F and heterodimers of IL-17A and F, as well as IL-17E (IL-25). Compared to ustekinumab and etanercept, these IL-17 inhibitors showed better efficacy and they could even reduce the PASI score with 100% in 30 to 60 percent of psoriasis patients [35, 159]. Unfortunately, similar to anti-TNF biologics, also anti-IL-23 and anti-IL-17 biologics are accompanied with side effects such as increased susceptibility for infections. For instance, because of its biological functions, blocking of IL-17 might sensitize to fungal infections such as Candida infections [162]. Nevertheless, anti-IL-23 and anti-IL-17 biologics show great efficacy with relatively good safety profiles compared to the traditional systemic therapies.

Even though biologics revolutionized the treatment of psoriasis, the perfect therapy does not exist yet. The benefits require ongoing administration of treatment and there are currently no known therapies for psoriasis that can induce long-lasting tolerance. Moreover, there is still a subset of patients that does not respond to these novel biologic therapies [35]. Furthermore, treatment with biologics is very expensive and might not always be an affordable option. Therefore, novel, more targeted drugs to treat psoriasis are being developed using small molecule inhibitors. For instance, in 2014, the FDA approved the use of Aprimelast (Otelza®), a phosphodiesterase 4 (PDE4) inhibitor to treat psoriasis [159]. Inhibition of PDE4 increases intracellular cAMP levels and this reduces the production of proinflammatory cytokines and promotes anti-inflammatory signaling [163]. In addition, other small molecule inhibitors such as Tofacitinib and Ruxolitinib that target Janus kinases in the JAK/STAT signaling pathways, are being tested for the treatment of psoriasis [164].

## Future perspectives

Our knowledge about the disease mechanisms that lead to psoriasis has greatly increased over the last years. However, also considerable questions remain. For instance, next to the above-mentioned cellular players, also several other cell types such as mast cells, macrophages and NK cells are involved in psoriasis pathogenesis; however, their exact roles are not fully understood. Furthermore, both deregulated innate immune responses and autoimmune responses seem to be at the base of this disease, but how these responses interact and feed into each other to initiate the disease is still unclear. Finally, also the breaks that keep inflammatory processes in check and restore homeostasis in the skin are enigmatic. For instance, regulatory T cells (Tregs) are a subset of T cells responsible for suppressing immune responses, but their role in psoriasis still needs clarification. The numbers of Tregs are elevated in lesional skin of psoriasis patients [165], but some reports have indicated that Tregs are functionally impaired and might even acquire Th17-like proinflammatory characteristics in response to IL-23 [166–170]. Similarly, IL-10-producing regulatory B cells of psoriasis patients were reduced in number and showed decreased IL-10 production [171, 172]. Genetic association studies are also indicating novel therapeutic targets. For example, psoriasis patients harboring hyperactivating CARD14 mutations that are associated with psoriasis might benefit from CARD14 signaling inhibitors. In this regard, we have recently reported that a small molecule inhibitor of MALT1, a protease that is activated by CARD14 and that mediates signaling leading to increased psoriasis-associated gene expression (e.g., TNF, IL-23), attenuates the

development of psoriatic-like dermatitis in a newly developed CARD14(E138A) transgenic mouse model [108]. Moreover, genetic associations also point to a role for defects in negative regulators of proinflammatory signaling pathways in psoriasis. For instance, SNPs in inhibitors of NF-κB signaling (*TNFAIP3*, *TNIP1* and *NFKBIA)* or JAK-STAT signaling *(SOCS1))*, can predispose to psoriasis [15, 173]. Such observations indicate that a better knowledge of the link between psoriasis susceptibility genes and the response to certain treatments might allow to stratify patients and thus enable personalized medicine. For instance, SNPs in *TNFAIP3* have been linked to a better response to anti-TNF therapy [174]. Furthermore, also natural cytokine antagonists might prevent excessive skin inflammation as evidenced by the close connection of loss-of-function mutations in *IL36RN* with generalized pustular psoriasis [64, 65]. The association of these negative regulators with psoriasis indicates that this disease is not merely caused by an excessive inflammatory response, but also by a failure to adequately dampen inflammatory response and to restore homeostasis. In addition, ever growing evidence supporting the role of keratinocytes as initiators of psoriatic inflammation might further shift the focus to topical therapies rather than systemic biologics. Clearly, further studies are needed to obtain better insights in the etiology and inflammatory signals that drive psoriasis, which would ultimately lead to the development of more targeted and more effective therapies that will also benefit refractory patients. Ideally, such treatments would also have an effect on comorbidities of psoriasis such as psoriatic arthritis, cardiovascular disease, inflammatory bowel disease and other immune-related disorders.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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