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Focus: Skin

Current Developments in the Immunology of Psoriasis

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Abstract

Psoriasis is a frequent inflammatory skin disease. Fundamental research on the pathogenesis of psoriasis has substantially increased our understanding of skin immunology, which has helped to introduce innovative and highly effective therapies. Psoriasis is a largely T lymphocyte-mediated disease in which activation of innate immune cells and pathogenic T cells result in skin inflammation and hyperproliferation of keratinocytes. B cells have thus far largely been neglected regarding their role for the pathogenesis of psoriasis. However, recent data shed light on their role in inflammatory skin diseases. Interestingly, interleukin (IL)-10-producing regulatory B cells have been assumed to ameliorate psoriasis. In this review, we will discuss the development of disease, pathogenicity, and current developments in therapeutic options. We describe different roles of T cells, B cells, and cytokines for the immunopathology and disease course of psoriasis.

Keywords: Psoriasis, Lymphocytes, Regulatory B cells, Cytokines, Biologics

Psoriasis

Psoriasis is an immune-mediated inflammatory disease with autoimmune pathogenic traits that affects the skin and joints. The worldwide prevalence of psoriasis is 2 to 3%, which tends to be lower in some regions of Asia and Africa but higher in Scandinavian populations [1-3]. Known environmental triggers and associations include streptococcal infections, physical trauma (*e.g.* tattoos, surgical incisions), certain medications (such as antidepressants, antihypertensive drugs, anti-cytokine therapy), smoking, as well as alcohol abuse, respectively [4-6]. Psoriasis is characterized by the excessive proliferation and aberrant differentiation of keratinocytes resulting clinically in erythematous scaly plaques of variable sizes. Psoriasis was initially believed to be a variant of leprosy until 1841 when von Hebra [7] identified it as a separate disease entity. Psoriasis patients typically have demarcated chronic erythematous plaques covered by silver white scales mainly on the knees, elbows, scalp, umbilicus, and lumbar region [8]. The disease is often associated with psoriatic arthritis, metabolic syndrome, cardiovascular problems, diabetes mellitus, and other comorbidities. Psoriasis patients have a higher risk for chronic inflammatory bowel disease and chronic kidney disorders. Moreover, the prevalence of depression, anxiety, and suicidality is increased [6,9]. Taken together, different factors contribute to the development of psoriasis causing adverse effects on patients' quality of life and disease burden.

Pathogenesis

Psoriasis is a complex genetic disorder that is triggered by various risk factors involving a variety of processes such as inflammation, antigen presentation, cell signaling, and transcriptional regulation [10]. The hallmark of psoriasis is sustained inflammation leading to uncontrolled keratinocyte proliferation and dysfunctional differentiation (Figure 1). Psoriatic plaque formation is believed to be a combination of inflammation in epidermal layers resulting from interaction of keratinocytes with many different cell types in the skin. Histological studies often show dramatic alterations in psoriatic skin characterized by profound thickening of the epidermis (acanthosis), hyperkeratosis and parakeratosis. In "meta-analyses" of transcriptomes of lesional *versus* non-lesional psoriatic skin by cDNA microarrays transcripts more than 1000 genes were found to be differently expressed [11,12]. There is a genetic predisposition to psoriasis, and many psoriasis susceptibility (*PSORS*) loci have been identified that appear to be involved in the pathogenesis of the disease. In one of the latest meta-analyses of genome-wide association studies, 15 new loci were identified, which increased the number of *PSORS* loci in European patients to 36. Among those are several loci that code for components of the NFκB signal transduction cascade such as *REL, NFKBIZ* (encoding IκB-zeta), *NFKBIA* (encoding IκBα), *TRAF6, CARD14,* and *ILF3* [13,14]. The latter is an RNA-binding protein affecting the transcription factor Nuclear factor of activated T cells (NFAT) expression. These genome-wide studies display the complexity of gene expression alterations during psoriasis development. Among a variety of risk factors promoting the development of psoriasis, HLA-C*06:02 is a predominant risk gene. T cell hybridoma studies with a unique T-cell receptor (Vα3S1/Vβ13S1) have shown that T cells detect the melanocyte-derived autoantigen ADAMTS-like protein 5 in a HLA-C*06:02-restricted manner [15]. Several reports have also suggested an important role of the nervous system for the pathogenesis of psoriasis. The latter appears to be co-responsible for the symmetric plaque distribution on the body and interactions between immunomodulatory networks and peripheral sensory nerves have been described [16-18]. Clinical data also suggest that the surgical denervation of psoriatic lesions or local anesthesia not only diminish the local sensation but also leads to reduced regional inflammation [18]. In this context, emotional stress may be also linked to the onset and/or exacerbation of psoriasis [19].

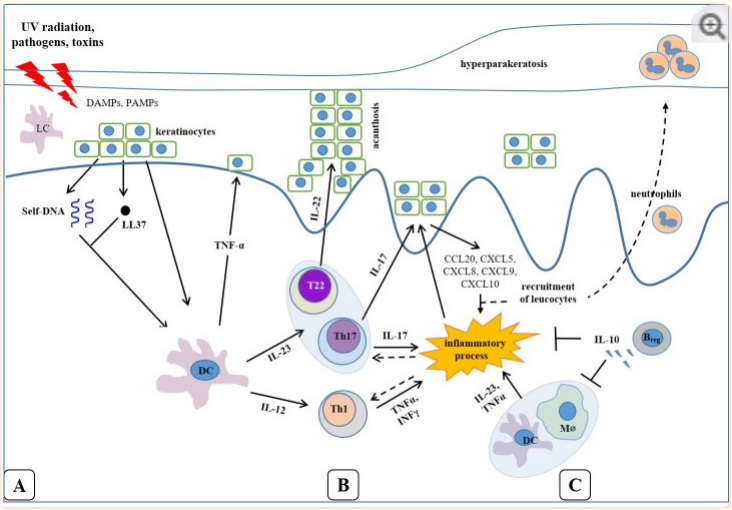

Figure 1

The pathogenesis of Psoriasis. **A**) Damaged keratinocytes during exposure to microbial or mechanical injury foster activation of antigen-presenting cells (APC) such as macrophages and dermal dendritic cells (DC). **B**) APCs including Langerhans cells (LC), DCs and potentially B cells interact with T cells leading to their activation and pro-inflammatory cytokine production. **C**) Regulatory B cells (B_{reg}) may modulate inflammation. B_{reg} secrete IL-10 that interferes with activation of other leukocytes including macrophages (MØ) and T cells to counteract inflammation

Basic research using human and mouse data has illustrated the pivotal role of the immune system in psoriasis development. Traditionally, psoriasis is considered as a T cell-controlled systemic inflammatory disease modulated by genetic susceptibility along with environmental factors. The massive infiltration of lymphocytes, macrophages, and neutrophils into the skin is a hallmark of psoriatic lesions. Therefore, it is clear that the disturbance of the innate and adaptive cutaneous immune responses along with non-immune cells lead to development and sustainment of psoriatic inflammation [20,21]. The pathogenesis of psoriasis is commonly acknowledged with two phases, (i) the initiation phase and (ii) the maintenance of the pathological state phase.

Keratinocytes and Innate Immunity Cells in the Skin

The skin is the largest, multi-layered organ of the body comprising multiple cell types [22]. In psoriasis there is an intense crosstalk between innate immune cells (*e.g.* dendritic cells (DCs), macrophages, neutrophils), adaptive immune cells (B and T cells) and resident skin cells (*e.g.* keratinocytes, melanocytes, and endothelial cells). These interactions appear to amplify and sustain chronic inflammation.

DCs, being professional antigen-presenting cells (APCs), play a major role in the initial stages of disease. Though DC activation in psoriasis is not entirely clear, proposed mechanisms involve recognition of released antimicrobial peptides (LL37, S100 proteins, and β-defensins) by keratinocytes in response to injury. These peptides (mainly LL37) are overexpressed in psoriatic skin [23] and bind to DNA of damaged cells. Such binding may result in activation of plasmacytoid DCs to produce IFNα in psoriatic plaques. IFNα leads to maturation/activation of myeloid DCs. These activated DCs are transformed into APCs to interact with naïve T cells and start producing high amounts of TNF-α, IL-23, IL-12, and IL-6. Those cytokines activate cascades of inflammatory responses by promoting keratinocyte proliferation and recruitment of neutrophils to sites of inflammation. Keratinocytes perpetuate the inflammatory milieu via production of antimicrobial peptides, secretion of cytokines (IL-6, IL-1β, and TNF-α) and chemokines (*e.g.* CCL20, CXCL5, CXCL8, CXCL9, CXCL10) [24]. Abundant accumulation of neutrophils in psoriatic lesions is a typical feature of psoriasis. Neutrophils granules are accumulated by IL-36, which is mainly secreted by keratinocytes and dendritic cells in the skin [25,26]. IL-36 is expressed in three isoforms (*i.e.* IL-36α, β, and γ), all of them belonging to the IL-1 family. After binding to its receptor IL-36Rα, IL-36 promotes transcription of various inflammatory mediators through activation of NF kappa B. On the other side, IL-36 also interacts with other inflammatory cytokines like IL-17 thereby increasing inflammation. Genetic mutations/polymorphisms in genes regulating IL-36 cause uncontrolled inflammation as well as excessive neutrophil accumulation at sites of inflammation [10]. Interestingly, there is evidence that neutrophil depletion significantly relieves patients who did not respond to conventional therapeutic approaches [15,27].

Macrophages (MPs) derive from monocytes and represent tissue-resident phagocytic and antigen-presenting cells. There is manifold evidence that MPs contribute to inflammatory processes in psoriasis. Elevated numbers of MPs are found in psoriatic lesions [28]. MPs are an important source of TNF-α, a key mediator in chronic inflammation [29]. Additionally, it was shown that IFN-γ can activate the expression of proinflammatory cytokines such as CXCL9 [28] assigning them a role as target as well as acting cells in psoriasis.

In the emerging field of the innate immune system lymphoid cells without antigen-specific receptors, innate lymphoid cells (ILC), contribute to antimicrobial defense and balance between pro- and anti-inflammatory factors. Among the three different subtypes ILC3 appear to be most important in psoriasis due to their ability to produce IL-22 and IL-17A [30]. ILC3 are present in the blood and skin of affected patients to a greater extent as compared to healthy individuals [30]. Moreover, their number in the peripheral blood and in the affected skin decrease with disease remission indicating a negative correlation between cell number and disease activity. In a mouse model in which psoriasis-like skin lesions are induced by imiquimod, ILC3 – besides γδ T cells – were the major source of IL-17 and IL-22 rather than Th17 cells [30]. This suggests a so far underestimated role of ILC3 in the pathogenesis of psoriasis and requires further investigation.

T cells

T cells play a central role in defense against different pathogens and tumors. Successful treatment of psoriasis patients with cyclosporine A (CsA) has highlighted the crucial role of T cells in its pathophysiology [31]. CsA treatment leads to T cell suppression [32]. T cell signaling is a highly organized process in recognizing antigens presented by APCs in the skin. Psoriasis pathogenesis involves crucial interplay between T cells ($CD8^+$, Th1, autoreactive T cells, Th17, and Th22) and dermal DCs [33,34]. Cytokines IL-12 and IL-23 released by dermal DCs promote Th1, Th17, and Th22 responses. These helper T cells stimulate epidermal hyperproliferation and alter epidermal differentiation leading to their decreased apoptosis [35,36]. The role of $CD4^+$ T cells in psoriasis was convincingly shown by transferring human skin transplants to immunodeficient SCID mice followed by injection of autologous $CD4^+$ T cells from psoriasis patients that resulted in psoriasis development [37]. Th1-type $CD4^+$ T cells producing high levels of IFN-γ and TNF-α are important players in triggering psoriasis [6].

Tissue residential T cells (T_{RM}) provide a pivotal role in local protection from environmental dangers challenging body surfaces. T_{RM} induce antimicrobial,inflammatory, and cytotoxic tissue responses. IL-17 and IL-22 producing T_{RM} are enriched in active and resolved psoriatic lesions, thereby influencing the onset and maintenance of a psoriatic plaque [38,39]. Skin sensations and some form of itch are transmitted by sensory fibers that express TRPV1 (The transient receptor potential cation channel subfamily V member 1) cation channels. These fibers co-express the sodium channel Nav1.8. It has been shown recently that these receptors interact with dermal dendritic cells, thereby regulating the IL-17/IL-23 pathway and hence controlling immune responses [40]. Skin inflammation is strongly diminished in IL-17 receptor-deficient mice suggesting a vital role of IL-17 in the generation of psoriasis-like lesions in mice [41]. While Th17 cells are a main source of IL-17 production, other cells including natural killer cells, myeloid cells, γδ T cells, lymphoid-tissue inducer-like cells, and invariant natural killer T cells have also been reported to release IL-17 [42-44]. Increased expression in lesional skin [45] and higher IL-17 serum levels are typical features of psoriasis [46]. Although Th17 and other IL-17-producing cells protect the epidermal barrier against bacterial and fungal infections, when overproduced, they contribute to chronic inflammation and autoimmune diseases [47]. The successful therapeutic application of antibodies against IL-17 and the IL-17 receptor underpins the importance of Th17 cells concealing that IL-17 works as “driving force” in the generation and maintenance of psoriasis [48-51]. However, after deciphering that IL-23 derived from DCs promotes Th17 development it became obvious that the IL-23/Th17 axis plays a major role for the development of psoriasis [52]. Therefore, inhibition of IL-23 is an alternative approach to control the production of IL-17 [46]. Other T cell subsets involved in the pathophysiology of psoriasis include dermal γδ T cells that are capable of producing IL-17A independent of IL-23 stimulation [53].

B Cells

B cells contribute to innate and adaptive immune responses by antibody production and antigen presentation. B cells play an essential role in the protection against different infectious and inflammatory diseases. They are generally believed to be a positive regulator of the pathogenesis of various inflammatory diseases by producing autoantibodies and providing T cell help. B cell depletion by anti-CD20 mAbs (*e.g.* Rituximab) studies have shown promising effects in treating different autoimmune diseases [54-56]. However, regulatory roles of B cells have been discovered in the past few decades. Such B cell subsets have been collectively named regulatory B cells (B_{reg}). In 1996, Wolf *et al.* reported compelling data of adverse disease affects from mice deficient for B cells after inducing experimental autoimmune encephalomyelitis (EAE) [57]. Using an intestinal inflammation model, Mizoguchi *et al.* [58] showed that the $CD1d^{high}$ B cell subset protects from inflammation mainly by IL-10 production. Similarly, Fillatreau *et al.* showed that IL-10 produced by B cells plays a vital role in ameliorating inflammatory autoimmunity [59]. B_{regs} exert an immunosuppressive function by secreting IL-10 that plays an important role in dampening various inflammatory and allergic diseases [59-62].

B_{regs} do not appear to be a distinct B cell lineage but rather a differentiated stage of different B cell subsets. It remains to be clarified which factors initiate the development or maturation of B cells into a B_{reg} phenotype. Several subsets of B_{regs} have been identified in mice and humans. In mice, B cell subsets including $CD5^+$ B1a and $CD5^-$ B1a are found in peritoneal and pleural cavities. The well characterized murine B_{regs} population is defined by $CD5^+CD1d^{hi}$ surface expression. Other B cell subsets with IL-10-mediated regulatory functions are marginal zone (MZ) B cells ($CD19^+CD21^{hi}CD23^-CD24^{hi}IgM^{hi}IgD^{lo}$ $CD1d^{hi}$), precursors of MZ B cells and $CD138^+$ plasma cells [63-66]. In humans, an IL-10-producing $CD19^+CD38^+CD24^+$ immature transitional B cell subset is commonly defined as B_{reg}. The other defined populations include $CD19^+CD24^{hi}CD38^{hi}CD1d^{hi}$ and $CD19^+CD24^{hi}CD27^+$ B cell subsets [67-70]. The immunosuppressive function of B_{regs} critically depends on intrinsic Toll-like receptor (TLR) signaling. TLR agonists induce IL-10 secretion by naïve B cells *ex vivo* [60].

Compared to the number of investigations on the role of T lymphocytes in psoriasis, there are only a few reports studying B lymphocytes in this disease. Currently, the role of B cells – in particular of B_{regs} – for the development and/or maintenance of psoriasis in humans is unclear. This is in part due to the rare appearance of B cells in lesional psoriatic skin. Depletion of B cells by the anti-CD20 mAb rituximab in patients suffering from other autoimmune diseases or lymphomas resulted in the development of psoriatic skin lesions in individual cases [71,72]. The use of genetically altered mice which lack B cells and mainly IL-10-producing B cells showed that defective B_{reg} development results in chronic inflammation [61,73]. Previously, it had been shown that B_{regs} have the capacity to ameliorate the severity of autoimmune diseases [61,74,75]. B_{regs} are decreased in patients with psoriasis [76]. Recently, a study was published on the suppression of imiquimod (a TLR7 agonist) -induced, psoriasis-like skin inflammation by B_{reg} in mice [77]. We showed previously that mice bearing B cells deficient for the transcription factor “nuclear factor of activated T cells” (NFATc1) harbored more B_{regs} and ameliorated imiquimod-induced psoriasis [60]. Since treatment of human psoriasis with recombinant IL-10 improved disease symptoms [78,79], it might be assumed that B_{regs} may influence the course of psoriasis by producing IL-10.

There is also growing evidence that skin resident B cells play a vital role in driving diseases through various mechanisms. These skin-associated B cells are involved in skin homeostasis as well as in regulating the repair of the wounded skin and the cutaneous microbiome [80]. B cells are key effector cells and secrete inflammatory cytokines like IL-6, IL-4, GM-CSF, and IFN-γ [81]. Such effector functions have also been shown by skin-resident B cells in a recent study where inflamed mouse skin was shown to harbor increased numbers of IL-6-producing B cells in a scleroderma mouse model. Blocking IL-6 but not IL-10 led to reduced inflammatory symptoms of the disease [82]. These data indicate various functional properties of B cells in the skin and refer to a potential window of opportunity for selectively targeting distinct B cell subsets to treat skin diseases (Figure 1).

Cytokines

IL-1: IL-1 is a key mediator of inflammatory responses to bacterial and viral infections but also to injury [83]. The IL-1 family consists of multiple members such as IL-α and IL-β that are produced by macrophages, monocytes, and other cell types. These peptides are recognized by the IL-1 receptor type 1 (IL-1R) and its accessory protein (IL-1RAcP), which subsequently activate a complex network of intracellular signaling (including MyD88 and Interleukin-1 receptor-associated kinases, IRAKs) [84]. This finally leads to the induction of transcription factors such as NFκB resulting in inflammatory immune responses.

IL-1β is known to play a critical role in psoriasis. Elevated mRNA levels can be found in lesional skin compared to healthy skin and the same is true in an imiquimod-induced mouse model of psoriasis [85]. It induces T cell proliferation and enhances IL-17 production [85], thereby fueling inflammatory processes in psoriasis.

IL-1-targeting therapies such as the IL-1-receptor antagonist anakinra, however, have failed to improve chronic plaque psoriasis, but showed efficacy in some patients with generalized pustular psoriasis [86]. Recently, some molecules upstream from IL-1 were discovered to play a possible role in psoriasis, *i.e.* the inflammasome components NLRP1 and NLRP3, which are involved in the control of IL-1β maturation [87].

IL-23: IL-23 is an important cytokine in anti-bacterial and anti-fungal immune defense. It is a heterodimeric molecule composed of two subunits, p19 and p40, the latter of which is shared with IL-12 [88]. Diverse cell types produce IL-23 including macrophages and DCs. It binds to a receptor complex consisting of IL-23R and IL-12Rβ1 and leads to the activation of transcription factors including STAT-3 [89,90]. IL-23 is a key regulator of the Th17-driven pathogenesis of psoriasis [91] even though it cannot activate naïve T cells alone since these cells do not express the corresponding receptors [92]. IL-6, IL-1, and TGFβ promote differentiation of CD4 cells into Th17 cells via the transcription factor RORγt [89,93], which can be stimulated by IL-23 to produce proinflammatory cytokines including IL-17 and TNFα [89,94]. IL-23 is overexpressed in human psoriatic skin [95] and injection of IL-23 into the skin of wild-type mice can cause psoriasis-like lesions [96]. Its crucial role for the molecular pathogenesis of psoriasis led to the development of

anti-IL-23 mAbs, which showed excellent efficacy in the treatment of psoriasis [94].

IL-17: The IL-17 family consists of 6 members, IL-17A, B, C, D, E, and F, amongst which IL-17A and IL-17F are the most similar while sharing about 50% of their sequence [97]. The main source of IL-17 are Th17 cells deriving from CD4 T cells [91], but also neutrophils, mast cells, NK cells, macrophages, and B cells are capable of producing this cytokine [98]. Hetero- or homodimers of IL-17A and IL-17F bind to the receptors consisting of the subunits IL-17RA and IL-17RC, while the receptor for IL-17E is formed by IL-17RA and IL-17RB and the one for IL-17C by IL-17RA and IL-17RE [97]. IL-17RA and IL-17RC are expressed by epithelial cells, fibroblasts, and different immune cells [97,99]. IL-17 induces the expression of proinflammatory molecules, *e.g.* IL-1β, IL-6, GM-CSF, G-CSF, and TNF-α in fibroblasts and macrophages. The latter also secrete chemokines such as CXCL9 and CXCL10 [99,100]. Epithelial cells are stimulated to secrete antimicrobial peptides and CCL20 [99,101]; secreted chemokines lead to the recruitment and skin invasion of neutrophils. Thus, IL-17 plays an important role in the defense of bacterial and fungal infections at the epithelial barrier [99,102].

The proinflammatory impact of IL-17 on the immune system may cause autoimmunity as this has been shown for different diseases including rheumatoid arthritis, inflammatory bowel disease, and psoriasis [103-105]. Furthermore, IL-17 supports inflammatory processes in lifestyle-associated metabolic disorders like hepatic steatosis and arteriosclerosis [106,107]. IL-17 antagonists are not only effective in treating psoriasis, but may also contribute to improvement of frequent comorbidities [108,109].

IL-22: IL-22 is part of the IL-10 cytokine family, even so in some ways it differs from other members of this group. Its active form is a monomer as which it binds to its receptor composed of heterodimeric subunits, IL-22R1 and IL-10R2 [110,111]. These receptors are found on non-hematopoietic cells, *i.e.* epithelial cells and fibroblasts in diverse tissues [110]. Intracellular signaling of the IL-22 receptor is driven via phosphorylation of STAT3 as well as STAT1 and STAT5 [112]. Additionally, IL-22 activates the p38 and ERK MAPK pathways [112]. Cells producing IL-22 include CD4 (Th1, Th17, and Th22 cells) and CD8 lymphocytes, innate lymphoid cells and NK cells [110,111]. Also some non-lymphoid cells like macrophages and fibroblasts are capable of synthesizing IL-22 [111]. Crucial for IL-22 production are the transcription factor RORγt, IL-23, and the aryl hydrocarbon receptor (AhR), since $CD4^+$ cells secrete IL-22 only when this receptor is present [113,114].

Imbalances in IL-22 secretion and signaling have been observed in various autoimmune diseases [114]. In psoriatic lesional skin IL-22 expression was found to be increased and serum levels are correlating with disease activity [115]. IL-22 induces keratinocyte migration and hinders their differentiation leading to epidermal thickening and scaling [90,115]. Additionally, it induces the secretion of chemokines and antimicrobial peptides promoting neutrophil invasion and inflammation. Therefore, IL-22 was considered a potential target for psoriasis treatment [13]. Phase I trials with IL-22 inhibitors, however, had to be discontinued due to lack of efficacy [86].

IL-12: IL-12 was initially named natural killer cell-stimulating factor because it was discovered in transformed B cells activating NK cells and T cells [116]. It exists as a heterodimer consisting of a p35 and a p40 unit [116,117], the latter of which is shared with IL-23. DCs, macrophages, and neutrophils produce IL-12. Two subunits, IL-12Rβ1 and IL-12Rβ2, form its receptor, which is mainly found on T cells and NK cells. Binding of IL-12 to the receptor activates the JAK/STAT pathway [117].

IL-12 plays an important role in Th1 responses and in the induction of IFN-γ [117]. Since IL-12 increases IFN-γ and TNF-α, which are key molecules in psoriasis pathogenesis, IL-22 was also expected to be crucial. However, an increased expression of the IL-12 p35 subunit in psoriatic skin could not be detected [118]. It is now known that successfully targeting the p40 subunit in psoriasis treatment exert its effects via inhibition of IL-23 [94].

IFN-γ: Interferon-γ is a type 2 interferon and an important molecule in inflammatory responses and for the defense of viral and bacterial infections. The main source of IFN-γ are $CD4^+$ and $CD8^+$ lymphocytes and NK cells, but also APCs and B cells release this cytokine [119]. IFN-γ secretion is driven by IL-12 and IL-18. When APCs sense pathogenic patterns, IL-12 and chemokines like macrophage inflammatory protein (MIP)-1α are released that attract NK cells, which, in turn, are triggered to produce IFN-γ by the secreted IL-12 [120]. The IFN-γ receptor consists of two IFNGR1 chains, where the ligand binds and two IFNGR2 chains responsible for signal transduction leading to an activation of the JAK/STAT signaling pathway [120]. IFN-γ enhances antigen processing and presentation and drives CD4 cells towards a Th1 response.

IFN-γ can be found in psoriatic lesions. Serum levels are higher in affected patients than in healthy controls and appear to correlate with disease activity [52,121,122]. It promotes IL-1 and IL-23 production by APCs driving a Th17 response [123]. Interestingly, patients with a higher decrease of IFN-γ serum levels showed longer remission periods as compared to patients with less reduction of blood levels [52]. However, anti-IFN-γ therapy failed to show efficacy in improving psoriatic lesions [124].

TNF-α: TNF-α is an important proinflammatory cytokine in acute and chronic inflammation, has anti-tumor-activity and helps defending infections [125]. TNF-α is synthesized membrane-bound and is released by matrix metalloproteinases in its soluble form [126]. Many different cell types produce TNF-α including macrophages, monocytes, lymphocytes, and keratinocytes. TNF receptors are expressed on every nucleated cell, and there are two main isoforms: TNFR1 or TNFR2 [125]. TNFα induces CD4 cell proliferation, production of different chemokines and cytokines such as IL-1, but also promotes apoptosis in different cell types.

TNF-α is known as a critical player in different autoimmune disease such as Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis [29]. Serum levels of TNF-α may correlate with disease activity [127] and TNF-α inhibitors have been proven to be effective in the treatment of plaque psoriasis.

Biologicals

There is a multitude of substances to treat psoriasis – from topical treatments and immunosuppressive agents to biologics. In the recent years many newly developed biologics have been approved by the Federal Drug Agency (FDA) and the European Medicines Agency (EMA) (see overview in Table 1). Patients with moderate to severe plaque psoriasis clearly benefit from their high efficacy.

TNF-α inhibitors: TNF-α inhibitors were the first biologics approved for the treatment of moderate to severe psoriasis. There are at the moment three approved monoclonal antibodies, *i.e.* infliximab, adalimumab. and certolizumab (the latter being a $F_{ab'}$ antibody fragment), as well as one fusion protein consisting of the recombinant TNF-α receptor 2 and the F_c fragment of IgG1 (etanercept) [128]. Infliximab has been proven to be most effective among this group of psoriasis therapies, followed by adalimumab and etanercept. Infliximab showed a decrease in the psoriasis area and severity index (PASI) of at least 75% (*i.e.* PASI75) in 80% of treated patients at treatment week 10 [129].

It is well known that TNF-α inhibitors are associated with the risk of reactivation of latent tuberculosis infection. Tuberculosis (TB) associated with TNF-α inhibitors, in contrast to classical TB, is more likely to be disseminated, atypical, extrapulmonary, and life-threatening [130]. Therefore, TB testing is mandatory in patients prior to starting therapy.

Despite of their efficacy in psoriasis there is evidence that TNF-α inhibitors may occasionally elicit new manifestations or worsening of psoriasis as paradoxical effect [131]. This is independent of the underlying disease and can resolve after termination of treatment [132]. More investigations are

needed to fully understand the underlying mechanisms.

Up to now, there is no evidence of teratogenicity of TNF-α inhibitors. However, it is recommended to restrict the use of these drugs to the first two trimesters [133]. Since certolizumab is a pegylated F_{ab} fragment, it cannot be diaplacentally transported, so its use during the whole pregnancy is possible [134].

IL-12/23 inhibitors: Among this group of drugs, one substance (ustekinumab) targets the p40 subunit and therefore both IL-12 and IL-23. The monoclonal antibodies guselkumab, tildrakizumab and risankizumab target exclusively the p19 subunit of IL-23 [128]. The latter have been proven to be more effective than ustekinumab suggesting that neutralizing p19 leads to a more potent inhibition of IL-23 [135]. Compared to TNF antagonists, IL-23 blockade shows a higher efficacy while the safety profile remained similar [136]. All the antibodies directly targeting IL-23 have first line approval in adult patients with moderate to severe plaque psoriasis. Ustekinumab is approved as second-line therapeutic by the EMA but as first-line treatment by the FDA. Moreover, it is approved by FDA and EMA for therapy in children beginning from the age of 12 [128].

Similar to the TNF-α inhibitors TB screening has to be performed prior to initiating therapy. In general, no significant safety issues were observed during clinical trials, most frequent adverse events were upper respiratory tract infections [137]. Thus, IL-23 and IL12/IL-23 inhibitors are a good therapeutic option treating chronic plaque psoriasis.

IL-17 inhibitors: Three monoclonal antibodies targeting IL-17 signaling are approved for the first-line therapy of moderate to severe plaques psoriasis in adults, namely secukinumab and ixekizumab, which inhibit IL-17A, and brodalumab that blocks the IL-17 receptor A. Considering their similar mode of action, all three antibodies show comparable efficacy in psoriasis, which has been proven to be higher than the efficacy of ustekinumab [128].

Due to some cases of suicidal ideation and completed suicides among patients treated with brodalumab, special care must be taken in patients with psychiatric comorbidities like depression [128], which is quite common among psoriatic patients [138].

Other relevant side effects mainly manifest as infections, especially mucocutaneous *Candida* infections [139]. As for the other biologics, TB testing is mandatory before initiation of psoriasis.

Recently, some biosimilars of effective biologics have become available for TNF-α inhibition. Studies showed that there are no significant differences with respect to efficacy and safety [140].

Conclusions

T lymphocytes unequivocally play a crucial role for the development of psoriasis, however, not all aspects of the disease can be exclusively explained by the mode of action of T lymphocytes. Different cytokines and the cellular contribution of other cells including (but not limited to) DCs, neutrophils, macrophages, keratinocytes, and B cells refer to a more complex cascade of events that finally results into the development of psoriasis. Despite the identification of early players in triggering this disease, the exact sequence of events during initiation and propagation of the psoriasis cascade remains largely unknown. Deciphering the role of regulatory immune cells (*e.g.* B_{regs}) may contribute to a better understanding of the pathogenesis and to a further improvement of our therapeutic strategies controlling psoriasis.

Table 1

Biologics approved for the treatment of plaque psoriasis and/or psoriatic arthritis.

Name	Structure	Indication	Approval state	PASI75[1]	PASI90[1]	Approval state for PsA	Specifics
TNF antagonists							
Infliximab	chimeric human/ murine mAb	adult psoriasis	FDA, EMA	80-87% at week 10 [141,142]	57-58% at week 10 [141,142]	yes	i.v. every 8 weeks, CI: patients with NYHA III/IV
Etanercept	soluble TNFR2:IgG1Fc human fusion protein	adult psoriasis, FDA: children (≥4 yrs of age), EMA (≥6 yrs of age)	FDA, EMA	44-56% at week 24 [143,144]	21-32% at week 24 [143,144]	FDA/EMA: yes, but adults only	s.c. weekly or twice weekly, CI: patients with NYHA III/IV
Adalimumab	human mAb	adult psoriasis, EMA: children (>4 yrs of age)	FDA, EMA	71-78% at week 16 [145,146]	45-51% at week 16 [145,146]	EMA: yes, but adults only, FDA: no	s.c. biweekly, CI: patients with NYHA III/IV
Golimumab	human mAb	adult PsA only [146]	FDA, EMA	n.a.	n.a.	yes	s.c. monthly, CI: patients with NYHA III/IV
Certolizumab	humanized Fab-fragment, Polyethylene glycol-conjugated	adult psoriasis	FDA, EMA	67-81% at week 16 [148]	36-53% at week 16 [148]	yes	may be used in pregnancy, s.c. biweekly or every 4 weeks, CI: patients with NYHA III/IV
IL-17 antagonists							
Secukinumab	human mAb	adult psoriasis	FDA, EMA	77-82% at week 12 [149]	54-59% at week 12 [149]	yes	s.c. every 4 weeks, caution in patients with IBD
Ixekizumab	humanized mAb	adult psoriasis	FDA, EMA	89% at week 12 [150]	70% at week 12 [150]	yes	s.c. every 4 weeks, caution in patients with IBD
Brodalumab	human mAb	adult psoriasis	FDA, EMA	80-92% at week 12 [151,152]	69-74% at week 12 [151,152]	no	s.c. every 2 weeks, CI: active Crohn´s disease. Caution in patients with depression
IL-12/IL-23 antagonists							
Ustekinumab	human mAb	adult psoriasis FDA/EMA: adolescent patients (≥12 yrs)	FDA, EMA	67% at week 12 [153,154]	42% at week 12 [153,154]	yes	s.c. every 12 weeks
IL-23 antagonists							
Guselkumab	human mAb	adult psoriasis	FDA, EMA	86-91% at week 16 [155,156]	70-73% at week 16 [155,156]	no	s.c. bimonthly
Tildrakizumab	humanized mAb	adult psoriasis	FDA, EMA	61-64% at week 12 [157]	35-39% at week 12 [157]	no	s.c. every 12 weeks
Risankizumab	humanized mAb	adult psoriasis	FDA, EMA	87-89% at week 12 [158]	75% at week 16 [158]	no	s.c. every 12 weeks

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[1]under administration of approved dose; mAb, monoclonal antibody; PsA, psoriasis arthritis, FDA, Food and Drug Administration; EMA, European Medicines Agency; TNF, tumor necrosis factor; TNF-R2, TNF receptor 2; n.a., not applicable; IBD, inflammatory bowels disease; s.c., subcutaneous; i.v., intravenous; CI, contraindication.

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Glossary

DCs	dendritic cells
APC	antigen-presenting cells
IL-10	Interleukin-10
B_{reg}	regulatory B cells
T_{reg}	regulatory T cells

Author Contributions

KM conceptualized the manuscript. FG and KM wrote the manuscript with the help of AK, ES, and MG. All authors were involved in critically reading and revising the manuscript.

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