REVIEW

Role of T-cell-mediated inflammation in psoriasis: pathogenesis and targeted therapy

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Abstract: Psoriasis is one of the most common chronic, inflammatory, T-cell-mediated autoimmune diseases. Over the past decade, increased knowledge of disease pathogenesis has fundamentally changed psoriasis treatment, with the introduction of biologics, and this has led to a multitude of improved selective targets providing potential therapeutic options. Indeed, numerous pathogenesis-based treatments are currently in development, as psoriasis has also become increasingly relevant for proof-of-concept studies. The purpose of this review was to summarize current knowledge of psoriasis immunopathogenesis, focusing on the T-cell-mediated immune response and its initiation. The authors describe recent advances in psoriasis treatment and discuss pathogenesis-based therapies that are currently in development or which could be envisioned for the future. Although current biologics are well tolerated, several issues such as long-term efficacy, long-term safety, and high costs keep driving the search for new and better therapies. With further advances in understanding disease pathogenesis, more genomic data from psoriasis patients becoming available, and potentially the identification of autoantigens in psoriasis, current research should lead to the development of a growing arsenal of improved targeted treatments and to further breakthrough immunotherapies.

Keywords: autoimmunity, autoimmune disease, immune response, immunopathogenesis

Introduction

Psoriasis is a chronic, inflammatory, T-cell-mediated autoimmune disease that affects mainly skin and joints. It is one of the most common inflammatory skin diseases, affecting 2%–3% of the population. Psoriasis is characterized by the presence of sharply demarcated, red plaques with adherent silvery-white scales and a tendency for symmetrical distribution over the body. The clinical presentation is mirrored histologically by dramatic hyperplasia of the epidermis (acanthosis) with loss of the granular layer, regular elongation of the rete ridges (papillomatosis), thickening of the corneal layer (hyperkeratosis), and incomplete keratinocyte differentiation with retention of nuclei in the stratum corneum (parakeratosis). The inflammatory infiltrate is made up mainly of macrophages, different types of dendritic cells, and T cells within the dermis, as well as neutrophils and some T cells in the epidermis. The redness of the lesions is caused by an increased vascularity – an increased number of dilated and tortuous capillaries in the dermal papillae.

However, psoriasis does not affect skin and joints only. It is a multisystem disease associated with a multitude of comorbidities and thus psoriasis has become increasingly important for all medical fields, beyond just dermatology and rheumatology. Psoriasis patients show an increased risk for cardiovascular events.[1,2] The prevalence

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1

of metabolic syndrome – a combination of obesity, dyslipidemia, impaired glucose regulation, and hypertension – is elevated in psoriasis patients.[3] The prevalence of depression is increased, and psoriasis can have a substantial psychological impact on patients.[4,5] In addition to this, psoriasis is often associated with other immune-mediated inflammatory disorders. Intriguingly, chronic inflammatory bowel disease, diabetes, and psoriasis have been associated with the same or similar susceptibility genes.[6,7] Although the mechanisms of inheritance are still poorly understood, nowadays psoriasis is accepted as a genetic disease with a complex interplay of genetic and environmental factors providing the basis for disease development.

Over the past decade, psoriasis has become more and more important as a model disease for scientists working on chronic inflammation and autoimmunity. Psoriasis has also become increasingly relevant as a first-choice disease for proof-of-concept studies investigating the efficacy of newer pathogenesis-based treatments.

The purpose of this review was to summarize current knowledge of psoriasis immunopathogenesis, focusing on the T-cell-mediated immune response and its initiation. This review will span a bridge from pathogenesis of psoriasis and its classical treatment to the new avenues of biologics – the authors describe recent advances in psoriasis treatment and discuss pathogenesis-based therapies that are currently in development or which could be envisioned for the future.
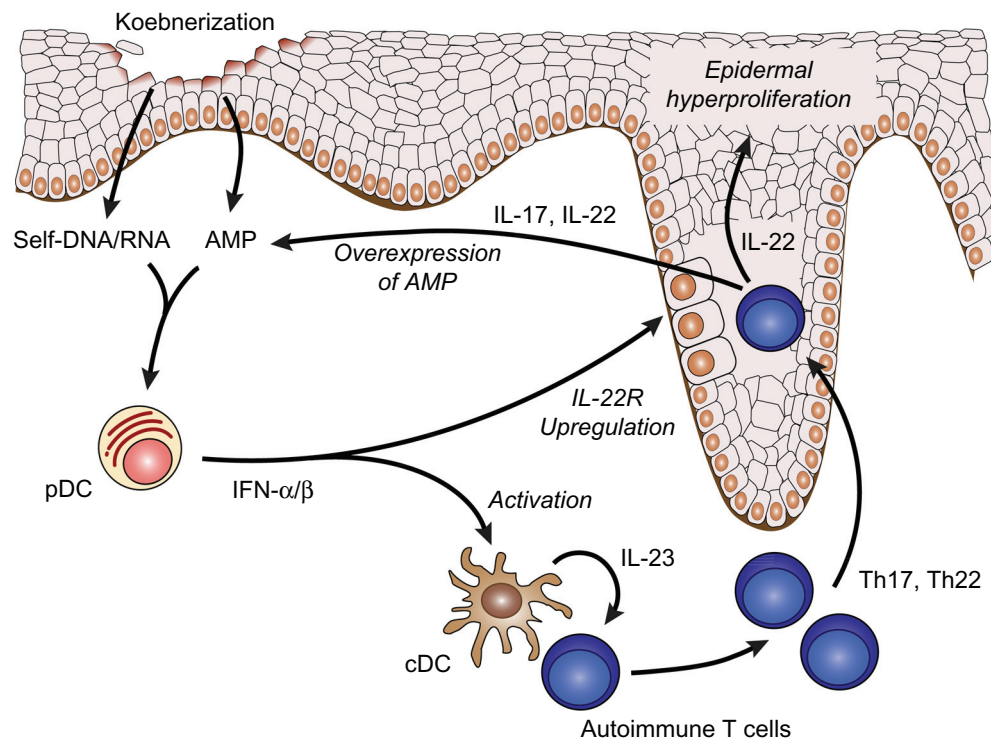
Pathogenesis

As clinical appearance is characterized by hyperkeratosis and silvery-white scales due to hyperproliferating keratinocytes, for a long time psoriasis was considered a keratinocyte disease. Only the effective use of cyclosporin A in psoriasis patients in the late 1970s[8] and therapeutic agents targeting T cells but not keratinocytes (eg, DAB389IL-2, anti-CD4)[9,10] led to a paradigm shift from epidermal keratinocytes to various immunocyte populations. Nevertheless, the discussion about the primary instigator of psoriasis is still ongoing. Recent evidence from mouse models and translational research strongly indicates that psoriasis is actually caused by a combination of both a primary defect in keratinocytes and an inappropriate innate and adaptive immune response–driven type I interferon (IFN) and that it is mediated mainly by resident and infiltrating T cells (Figure 1).[11–14]

In individuals with a genetic predisposition, external stimuli such as trauma (known as Koebner phenomenon), infections, stress, drugs, and alcohol can all trigger an initial episode of psoriasis. This initial trigger activates the innate immune system. Complexes of the antimicrobial peptide LL-37 and host DNA/RNA, both released by keratinocytes after common epidermal damage, activate plasmacytoid dendritic cells (pDCs) to produce large amounts of IFN.[13,15] Physiologically, pDCs are sensors of viral nucleic acid and induce protective immunity.[16] In psoriasis, IFN production by pDCs is an early key event in disease development by driving autoimmunity. IFN induces the activation and maturation of conventional dendritic cells (cDCs), which are key stimulators of T cells, thereby bridging the gap between innate and adaptive immunity.[12] Subsequently, autoreactive T cells proliferate and migrate into the epidermis, another key event in psoriasis pathogenesis and controlled by the expression of alpha 1 beta 1 integrin on effector T cells.[14] This T-cell expansion and migration into the epidermis precedes the onset of psoriasis and is essential for the development of characteristic epidermal changes. Although the putative (epidermal) autoantigen in psoriasis remains elusive, T cells show oligoclonal expansion, indicating a common antigen for autoimmune T cells.[17,18] In psoriasis, these autoreactive T cells are IFN-gamma-secreting type 1 T helper (Th1) cells[19] and Th17/Th22 cells producing interleukin (IL)-17 and IL-22.[20,21] Th1 and Th17 cells seem to show concomitant presence in various inflammatory pathologies, but they – along with Th22 cells – represent distinctly polarized Th cell types.[22–24] Research has recently focused on Th17/Th22 cells and IL-23,[25–27] which induces IL-17 and IL-22 production by T cells.[28] These cytokines are key mediators linking adaptive immune response and epithelial dysregulation in psoriasis.[29,30] IL-22 induces hyperproliferation of keratinocytes (leading to typical acanthosis), and both IL-17 and IL-22 increase production of the antimicrobial peptide LL-37.[31–33] In turn, the increased LL-37 production leads to continuous activation of the immune system, as described earlier. Therefore, these cytokines potentially not only cause the typical epidermal changes seen in psoriasis but also lead to a self-sustained feedback loop and chronification of the disease.[34] Indeed, in contrast to the transient skin expression of LL-37 in response to skin injury in healthy individuals,[35] high levels of LL-37 appear to persist in psoriatic skin lesions. Subsequently, the maintained production of IFN leads to uncontrolled activation of cDCs and eventually to autoimmunity.

Interestingly, IFN has recently been shown to specifically upregulate IL-22-receptor expression on keratinocytes and thereby increase responsiveness to IL-22.[36] Thus, in psoriasis pathogenesis, IFN seems to have multiple roles: it drives immune activation with the induction of IL-22- (and IL-17-) producing T cells through cDC activation and

Figure 1 Psoriasis pathogenesis: upon skin injury, known as koebnerization, antimicrobial peptides (AMPs) such as LL-37 produced by keratinocytes or deposited by infiltrating neutrophils form complexes with self-nucleic acids (DNA and RNA) released by dying cells.
Notes: These complexes are transported into intracellular compartments, leading to the activation of plasmacytoid dendritic cells (pDCs) via endosomal Toll-like receptors 7 and 9 and thereby leading to the production of type I interferons (IFN alpha [IFN-α], IFN beta [IFN-β]) early in psoriasis pathogenesis. Subsequently, type I IFNs trigger maturation and differentiation of conventional dendritic cells (cDCs), and these cDCs then stimulate autoreactive T cells through interleukin (IL)-23. Thereby, psoriatic autoimmune T cells are biased to produce T helper (Th)17 cytokines IL-17 and IL-22. Interestingly, these cytokines induce expression of AMPs in keratinocytes, suggesting a positive feedback loop that further sustains innate activation of pDCs and leads to type I IFN-driven autoimmunity. In addition, type I IFNs directly upregulate IL-22 receptor (IL-22R) on keratinocytes, increasing their responsiveness to IL-22, which inhibits terminal differentiation and induces hyperproliferation of keratinocytes leading to epidermal hyperplasia, a hallmark of psoriasis.

IL-23 induction; in addition, it provides the interface between immune activation and epidermal remodeling by increasing keratinocyte responsiveness to IL-22.[36,37] Intriguingly, IL-22 was indeed shown to be critical for the imiquimod mouse model, in which Toll-like receptor 7/8 activation induces IFN-driven psoriasiform skin inflammation.[38] A third potential effect of IFN could be an enhanced expression of major histocompatibility complex class I on keratinocytes, which may promote presentation of putative autoantigens to intra-epidermal T cells.[39] In psoriasis, this may lead to enhanced activation of pathogenic autoimmune T cells.

Taken together, a sustained LL-37-IFN-Th17/Th22 axis seems to be crucial for psoriasis pathogenesis. Intriguingly, several genetic variants that have been associated with psoriasis provide a direct genetic basis for this axis; these susceptibility genes include RAGE and IFN regulatory factor 5[40] (involved in activation of pDCs and IFN induction), certain major histocompatibility complex class I molecules[40,41] (involved in autoantigen presentation and activation of T cells), gene polymorphisms of IL-23

and IL-23 receptor[42,43] (involved in Th17 polarization and expansion), and gene copy number polymorphisms of anti-microbial peptides.[44]

In addition to the well-established role for conventional T cells in psoriasis pathogenesis already described in this review, recent studies have indicated a potential contribution of innate gamma-delta (γδ) T cells. Dermal γδ T cells constitutively express IL-23 receptor and rapidly produce large amounts of IL-17 upon stimulation with IL-23.[45–47] Thereby, γδ T cells may amplify Th17 responses and induce autoimmunity.[45] Intriguingly, in the imiquimod mouse model, γδ T cells were essential and sufficient to induce psoriasiform skin inflammation.[46,48] Although relevance for human disease remains to be shown, γδ T cells accumulate in psoriasis plaques and this indicates a possible functional role in psoriasis pathogenesis.[46] This hypothesis is further supported by the identification of a novel proinflammatory Vγ9Vδ2 T-cell subset that is rapidly recruited into psoriatic skin and potentially mediates an immediate tissue response upon koebnerization.[49] Similarly, natural killer (NK) cells and

natural killer T (NKT) cells have been proposed as essential players in psoriasis pathogenesis. Thus, further studies will have to show if γδ T cells, NK cells, or NKT cells also provide potential therapeutic targets for psoriasis.

Traditional therapy

Even without modern knowledge of psoriasis pathogenesis, patients have benefited from the constant improvement of conventional therapies. Most of the currently accepted systemic treatments for psoriasis were developed empirically or were found by pure chance. However, modern knowledge has shed light on the mode of action of some of these classic treatments. Fumaric acid and cyclosporine are mainly immunosuppressive, retinoids target keratinocytes, and methotrexate affects both keratinocytes and immune cells.[8,50–53] Even though these therapies continue to play an important role in psoriasis treatment, they have not fully met the needs of patients.[54] Although these therapies are effective in the majority of patients, potentially serious toxicities can in some cases limit their long-term use. Methotrexate has a potential for hepatotoxicity and is teratogenic. Cyclosporin may lead to impaired renal function and hypertension, increased risk of infections, and hypertrichosis. Concerns about lymphoma and a potential increase in other malignancies are known adverse effects after long-term treatments. Retinoids, which are preferentially used in cases of pustular psoriasis, are teratogenic and may lead to dyslipidemia and, in rare cases, to hepatotoxic side effects.

Targeted therapy

Over the past 15 years, the increasing knowledge of disease pathogenesis has fundamentally changed psoriasis treatment.

Based on the detailed insight into psoriasis that this increase in knowledge has provided, a new generation of therapeutic agents, called biologics, has been in development. These agents are derived from recombinant DNA technology and include monoclonal antibodies and receptor-antibody fusion proteins that specifically target the activity of T cells or cytokines responsible for the inflammatory nature of the disease. By inhibiting specific components of the immune system, biologics may not affect cells of other organs, thus limiting side effects. Dermatologists have subsequently moved from serendipitous choices among the available therapeutic options to interventions based on greater insight into psoriasis immunopathogenesis. The proof of principle of pathogenesis-based therapies in dermatology has created a multitude of opportunities for the development of new drugs with new therapeutic targets. Indeed, numerous biologics are currently moving through different phases of clinical development (Table 1) or are already available as therapeutic options for patients and doctors.

Tumor necrosis factor (TNF) alpha is a pleiotropic cytokine that plays an important role in inflammation and is an end-stage product of the inflammatory cytokine cascade.[55] Indeed, TNF levels are increased in the serum and cutaneous plaques of patients with active psoriasis and in joints of patients with psoriatic arthritis. Thus, TNF was a logical candidate for initial targeted therapies in chronic inflammatory diseases such as Crohn's disease, arthritis, and psoriasis. While the first studies were based on anecdotal experience with infliximab, a chimeric anti-TNF antibody, in a patient with Crohn's disease and concomitant psoriasis,[56] anti-TNF therapy has become the gold standard for psoriasis treatment. Today, several anti-TNF antibodies and fusion

Table 1 Psoriasis trials: a summary of clinical trials of targeted therapy for psoriasis currently in development

Molecule	Mechanism	Phase	Status	Sponsor	ClinicalTrials.gov identifier[a]	Indication
ILV-095	Anti-IL-22	I	Completed	Pfizer	NCT01010542	Safety in psoriasis
AIN457	Anti-Th17	II	Completed	Novartis	NCT00941031	Safety and efficacy in psoriasis
Ixekizumab	Anti-Th17	III	Recruiting	Eli Lilly	NCT01646177	Superiority to etanercept
MK3222	Anti-IL-23	III	Recruiting	Merck	NCT01722331	Safety and efficacy in psoriasis
BT-061	T regulatory cell activator	II	Completed	Biotest	NCT01072383	Safety and efficacy in psoriasis
ACT-128800	S1P1 agonist	II	Ongoing	Actelion	NCT01208090	Safety and efficacy in psoriasis
SCH527123	CXCR2 antagonist	II	Completed	Schering-Plough	NCT00684593	Efficacy in psoriasis
Tofacitinib	JAK3 inhibitor	II	Approved	Pfizer	NCT01710046	Efficacy in psoriasis
Ruxolitinib	JAK inhibitor	II	Completed	Incyte	NCT00820950	Efficacy in psoriasis
ASP015K	JAK3 inhibitor	II	Completed	Astellas Pharma	NCT01096862	Efficacy in psoriasis
Apremilast	PDE4 inhibitor	II	Ongoing	Celgene	NCT01172938	Efficacy in psoriatic arthritis
AN2728	PDE4 inhibitor	II	Completed	Anacor Pharmaceuticals	NCT01029405	Safety and efficacy in psoriasis
MK0873	PDE4 inhibitor	II	Completed	Merck	NCT01235728	Safety and efficacy in psoriasis

Note: [a]All trials are registered under ClinicalTrials.gov and detailed information can be obtained through the ClinicalTrials.gov identifier (NCT number).
Abbreviations: CXCR2, CXC chemokine receptor 2; IL, interleukin; Th, T helper; S1P₁, sphingosine-1-phosphate receptor 1; JAK, Janus kinase; PDE4, phosphodiesterase type 4.

proteins – with diverging efficacies, response onsets, and frequencies of side effects[57] – are approved for psoriasis treatment. Newer anti-TNF compounds such as different antibody fragments and antisense nucleotides are in the early phases of clinical development.

The recognition of the functional relevance of the IFN-IL-23-Th17/Th22 axis in psoriasis pathogenesis led to a fast developing group of reagents targeting this axis, with ustekinumab as the first approved and broadly used antibody of this class.[58,59] Ustekinumab targets p40, the common subunit of the two heterodimeric cytokines IL-12 and IL-23, thereby inhibiting both cytokines and their ability to drive Th1 and Th17 differentiation, respectively. Ustekinumab's efficacy in patients with moderate to severe psoriasis has been shown to be superior to that of etanercept, an anti-TNF fusion protein.[60] Briakinumab, another anti-IL-12/23 antibody, has shown very impressive response in phase III clinical trials.[61–63] However, the incidence of major adverse cardiovascular events (MACEs) associated with briakinumab treatment resulted in the withdrawal of its application in 2011. An independent meta-analysis was conducted to evaluate a potential association between IL-12/23 inhibition and MACEs.[64] Although the increased rate of MACEs in patients receiving IL-12/23 antibodies was not significant, questions about the cardiovascular safety of these compounds remain, particularly as low IL-17 serum levels have recently been shown to be associated with a higher risk of MACEs in patients with acute myocardial infarction.[65] These findings raise further possible concerns about the use of inhibitors of the IL-17 pathway in clinical settings associated with a high cardiovascular risk. Greater detailed insight can be expected from the multitude of biologic compounds targeting the IL-23-Th17/Th22 axis that are currently in development.

Targeting the subunit p19, which is specific to IL-23, has been shown to be efficient in a clinically relevant mouse model.[27] In addition, blockage of IL-23 but not IL-12 may decrease the long-term risk for malignancies, as IL-23 has been associated with tumor promotion[66] and IL-12 with antitumor and antimetastatic activity.[67,68] Several specific anti-IL-23 agents are currently in clinical and preclinical phases of development.

To achieve an even more specific intervention, recent research has focused on downstream Th17/Th22 effector cytokines, which mediate the adaptive immune response and provide the link to epidermal dysregulation in psoriasis. Anti-IL-22 antibodies are in clinical and preclinical studies, and multiple anti-IL-17 and anti-IL-17-receptor inhibitors are in development, showing promising clinical results.[69–71]

Furthermore, Th17 cytokines provide potential targets for therapeutic interventions, with IL-26 representing a very interesting candidate. IL-26 is a member of the IL-10 cytokine family and it is significantly upregulated in psoriasis.[72] Intriguingly, single-nucleotide polymorphisms in or near the human *IL26* gene have been associated with increased risk of developing autoimmune diseases.[73–75] Further studies will have to prove functional relevance for IL-26 in the pathogenesis of psoriasis and other auto immune diseases, as there is still little known about its biological functions.

As with anti-TNF blockers, increased risk for infections remains a concern for treatments targeting the IL-23-Th17/Th22 axis. IL-17 has been shown to play a crucial role for host defense against fungi.[76,77] Recent findings suggest that the IL-23/Th17 axis is a key factor regulating protective immunity against opportunistic fungi.[78] Ongoing clinical trials and national registries will have to show if these agents lead to an excess of particularly fungal infections in comparison with other immune modulators.

The therapeutic potential of targeting T-cell function in psoriasis has been shown by the effective use of efalizumab[79] and alefacept.[80] Efalizumab is an anti-CD11a antibody that inhibits T-cell activity by disrupting the interaction between leukocyte function–associated antigen-1 on T cells and intercellular adhesion molecule-1 on antigen-presenting cells. Efalizumab also prevents the adhesion of T cells to endothelial cells. Therefore, efalizumab blocks T-cell activation in the lymph node, T-cell trafficking into the skin, and reactivation of skin-resident T cells. Efalizumab was the first biologic to reach the market for psoriasis, but it was finally withdrawn because of a risk of progressive multifocal leukoencephalopathy and other infections. Alefacept is a fusion protein that binds to the CD2 receptor expressed on T cells, blocking the binding of leukocyte function–associated antigen-3 on antigen-presenting cells, which provides the costimulatory second signal for T-cell activation; thus, T-cell activation and proliferation is inhibited. In addition, alefacept induces NK cell–mediated apoptosis of memory and effector T cells.

Based on these experiences, numerous potential therapeutic interventions could be evaluated and, indeed, several specific inhibitors of T-cell activation are already in development. Like alefacept, the anti-CD2 antibody siplizumab blocks the secondary costimulatory signal necessary for T-cell activation. Siplizumab has already been tested in clinical trials for psoriasis but it has not shown sufficient clinical efficacy.[81] On the other hand, anti-CD4 antibodies have already been proven to be effective in psoriasis.[10,82] CD4

is expressed mainly on Th cells and T regulatory cells, but it is also expressed on pDCs, cDCs, and monocytes; thus, CD4-depleting antibodies are highly immunosuppressive. A potentially less immunosuppressive, nondepleting antibody is currently in phase II clinical trials for psoriasis and rheumatoid arthritis (BT-061, Biotest). Its distinct effects on the various immune cells expressing CD4 will have to be analyzed, as the functional role of CD4 on dendritic cells remains elusive.

During psoriasis pathogenesis, dermal cDCs migrate upon stimulation to the draining lymph node where they activate T cells, and these T cells in turn enter blood vessels and migrate to the skin. Therefore, another potential therapeutic option is inhibition of the recruitment of circulating immune cells. Recently, lymphocyte egress from secondary lymphoid organs and thymus was found to depend on sphingosine-1-phosphate receptor 1 within lymphocytes.[83,84] An oral sphingosine-1-phosphate receptor 1 agonist (ACT-128800, Actelion), currently in clinical development, deprives immune cells of this essential signal to egress from lymphoid organs and thus leads to the sequestration of T cells and reduces the availability of circulating effector T cells. Because of its mechanism of action, this novel immunosuppressive drug could be envisioned for the treatment of a variety of autoimmune disorders.

While activated cDCs certainly migrate to draining lymph nodes to activate T cells, skin-resident immune cells have been shown to be sufficient for initiation and maintenance of psoriasis.[85,86] Based on these findings, treatments should be considered for targeting skin-resident immune cells rather than systemic components of the immune system. Thus, possible future therapeutic options blocking the expansion and survival of tissue-resident immune cells might include the inhibition of local cytokines and chemokines, blockage of adhesion molecules and costimulatory molecules, targeting the skin microenvironment and extracellular matrix, and inhibiting emigration of dermal T cells into the epidermis. The last of these examples has already shown proven efficiency in a clinically relevant xenotransplantation model,[14] and antagonists of chemokine receptors (SCH527123, Schering-Plough, Kenilworth, New Jersey, USA) are currently in phase II clinical trials for psoriasis.

Other therapeutic targets currently being evaluated include protein kinase C (PKC) inhibitors, Janus kinase (JAK) inhibitors, mitogen-activated protein kinase inhibitors, and phosphodiesterase type 4 (PDE4) inhibitors. PKCs are involved in diverse signal transduction pathways that modulate a wide variety of cellular events including activation, proliferation, differentiation, apoptosis, and autophagy. Several PKC

isoforms play important roles in T-cell-mediated immune responses, with PKC theta being essential for T-cell activation and IL-2 secretion and PKC beta being relevant for IFN-gamma production and Th1 responses. Sotrastaurin is the first in a new class of selective oral PKC inhibitors that offer highly potent inhibition of early T-cell activation.[87] Sotrastaurin has been tested in clinical trials for transplant rejection and psoriasis and has shown promising results.[88]

The JAK family contains four members, JAK1, JAK2, JAK3, and tyrosine kinase 2, which phosphorylate and activate signal transducers and activators of transcription upon activation. JAKs have proven to be important for a multitude of immunological processes; they play an essential role in various autoimmune diseases and they also promote tumorigenesis.[89,90] The Janus kinase–signal transducer and activator of transcription pathway is the major signaling cascade downstream from cytokine and chemokine receptors. JAK3 is the only JAK family member that associates with just one cytokine receptor subunit, with the common gamma chain, which is exclusively used by the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines are crucial for the immune system but not for the function of other organs, thus JAK3-specific inhibitors should have limited side effects. However, the inhibition of JAK1 and JAK2 has also been proven to be beneficial for the treatment of inflammatory diseases. Currently, numerous inhibitors of selective JAKs or of different JAK family members combined are in development for prevention of transplant rejection, treatment of psoriasis, rheumatoid arthritis, Crohn's disease, and for various malignancies. Tofacitinib, a pan-JAK inhibitor with preference for JAK1 and JAK3, has shown good clinical response in psoriasis and is being evaluated as a systemic and topical therapy. Ruxolitinib, a specific JAK1/JAK2 inhibitor initially developed for treatment of myeloproliferative neoplasms, has been tested as a topical therapy in clinical trials for psoriasis. Additionally, a specific JAK3 inhibitor (ASP015K, Astellas Pharma, Tokyo, Japan) has entered phase III clinical trial for psoriasis.

PDE4 is an enzyme ubiquitously expressed in inflammatory cells that catalyzes the degradation of cyclic adenosine monophosphate (cAMP). cAMP is an intracellular second messenger that controls a network of pro- and anti-inflammatory mediators. Thus, inhibition of PDE4 leads to an accumulation of cAMP and thereby elicits a broad anti-inflammatory effect leading to downregulation of TNF, IL-23, and other proinflammatory cytokines. Apremilast has shown efficacy in psoriasis[91] and is currently evaluated mainly in psoriatic arthritis. Results from the phase III clinical trial have been made public

very recently and have demonstrated clinical efficacy and good safety for a treatment duration of 24 weeks. In addition, two topical PDE4 inhibitors (AN2728, Anacor Pharmaceuticals, Palo Alto, California, USA; MK0873, Merck, Darmstadt, Germany) are currently in clinical trials for psoriasis.

Conclusion

As discussed in this review, there are multiple new agents in clinical and preclinical development that are showing exciting potential. Of the therapies currently in development, agents targeting the IL-23/Th17 axis will most likely have the biggest immediate impact when entering the market within the next few years. Although IL-22 directly induces epidermal hyperproliferation but not IL-17 does not, and although functional relevance of IL-22 in psoriasis development has been shown in mouse models, IL-17 seems to be of greater importance than IL-22 in chronic inflammation of psoriasis.[29] While initial clinical data on IL-22 inhibition in psoriasis have not been very promising, both anti-IL-17 and anti-IL-17-receptor antibodies have shown excellent efficacy in clinical trials. With broad accessibility of IL-17 blockers after marketing and a growing patient population treated with these agents, remaining questions about the safety of long-term inhibition of the IL-23/Th17 axis and particularly of IL-17 should be addressed: 1) Relevance and pathomechanism of the described aggravation of Crohn's disease under anti-IL-17 therapy; 2) the potential association of low IL-17 serum levels with a higher risk of MACEs and the consequential possible risk of targeting the IL-17 pathway in patients with high cardiovascular risk. Nevertheless, anti-IL-17 antibodies and biologics targeting the IL-23/Th17 axis will probably be at the forefront over the next years, together with well-established anti-TNF therapy.

In which clinical settings small molecules such as JAK inhibitors or PDE4 inhibitors will be used remains to be seen. Depending on long-term safety, and largely also on costs of these compounds, these small molecules may already be used in moderate psoriasis as first-line systemic therapy along with methotrexate and fumaric acid, or otherwise in more severe disease prior to expensive antibody treatments. If costs are similar to currently available biologic agents, post-marketing will tell if the benefit of oral availability and the clinical efficacy of these small molecules are sufficient to gain substantial market share.

In the long run, increasing knowledge of psoriasis pathogenesis will certainly lead to the emergence of new promising targets such as IL-21 or IL-26 and, subsequently, to the development of additional therapeutic compounds.

Over the past decade, psoriasis has become more and more important as a model disease for research in the field of chronic inflammation and autoimmunity. Because of its easy accessibility and its frequency, psoriasis has also become increasingly relevant as a first-choice disease for proof-of-concept studies investigating the efficacy of newer therapies. Indeed, driven by fundamental and translational research, numerous pathogenesis-based therapies are under investigation and are currently moving through different phases of clinical development.

New insights into psoriasis pathogenesis have already led to a multitude of potentially new therapeutic targets. Although current biologics are well tolerated, several issues such as long-term efficacy, long-term safety, and high costs keep driving the search for new and better therapies. With further advances in understanding disease pathogenesis, more genomic data from psoriasis patients becoming available, and potentially the identification of autoantigens in psoriasis, current research should lead to the development of a growing arsenal of improved targeted treatments and to further breakthrough immunotherapies.

Disclosure

The authors report no conflicts of interest in this work.

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