The Inflammatory Response in Psoriasis: a Comprehensive Review

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Published online: 30 March 2016

Abstract Psoriasis is a chronic inflammatory autoimmune disease characterized by an excessively aberrant hyperproliferation of keratinocytes. The pathogenesis of psoriasis is complex and the exact mechanism remains elusive. However, psoriasis is thought to result from a combination of genetic, epigenetic, and environmental influences. Recent studies have identified that epigenetic factors including dysregulated DNA methylation levels, abnormal histone modification and microRNAs expressions are involved in the development of psoriasis. The interplay of immune cells and cytokines is another critical factor in the pathogenesis of psoriasis. These factors or pathways include Th1/Th2 homeostasis, the Th17/Treg balance and the IL-23/Th17 axis. Th17 is believed particularly important in psoriasis due to its pro-inflammatory effects and its involvement in an integrated inflammatory loop with dendritic cells and keratinocytes, contributing to an overproduction of antimicrobial peptides, inflammatory cytokines, and chemokines that leads to amplification of the immune response. In addition, other pathways and signaling molecules have been found to be involved, including Th9, Th22, regulatory T cells, γδ T cells, CD8+ T cells, and their related cytokines. Understanding the pathogenesis of psoriasis will allow us to develop increasingly efficient targeted treatment by blocking relevant inflammatory signaling pathways and molecules. There is no cure for psoriasis at the present time, and much of the treatment involves managing the symptoms. The biologics, while lacking the adverse effects associated with some of the traditional medications such as corticosteroids and methotrexate, have their own set of side effects, which may include reactivation of latent infections. Significant challenges remain in developing safe and efficacious novel targeted therapies that depend on a better understanding of the immunological dysfunction in psoriasis.

Keywords Psoriasis · Inflammatory response · Cytokines · T cells · Dendritic cells · Biologics · Adverse effect

Introduction

Psoriasis, like most autoimmune diseases, is an immune-mediated dermatosis which is under the influence of genetics and epigenetic modifications that can be triggered by environmental factors [1–3]. Psoriasis is a very common disease, affecting approximately 2% of the world’s population [4]. Psoriasis may present with variable clinical manifestations, and because of this and the lack of a biological marker of disease, may be difficult to diagnose. As a result, psoriasis is still a clinical diagnosis which is defined by typical or atypical morphologic findings and appearances. The major clinical manifestations include characteristic skin lesions, including plaques, and/or pustular or guttate lesions. But there are several clinical forms of psoriasis.

The most common type of psoriasis is psoriasis vulgaris, which accounts for nearly 85-90% of all cases of psoriasis. Histologically, psoriasis is characterized by hyperproliferation and aberrant differentiation of keratinocytes, dilated, hyperplastic blood vessels, and inflammatory infiltration of
leukocytes predominantly into dermis. The skin patches are typically red, itchy, and scaly, which in addition to the physical toll, may result in psychological stress and poor quality of life. Like other systemic autoimmune diseases, psoriasis affects far more than the skin, and often presents with chronic inflammatory responses in joints, nails and other organs. The complexity and prevalence of the disease taxes financial and healthcare resources in many regions of the globe.

Immunological dysfunction in psoriasis involves the cross-talk between immune cells and cytokines. In the last 20 years, several important subsets of immune cells in psoriatic and other autoimmune diseases have been identified to play a role in pathogenesis, including Th1, Th2, Treg [5], and Th17 cells. The corresponding cytokines that may be involved include IFN-γ, TNF-α, IL-23, and IL-17. More recently, IL-9 secreting Th9 cells have been identified, and the inflammatory responses of keratinocytes, γδ T cells, T regulatory cells and other immune cell types in psoriasis have been explored. Evidence is emerging that new genetic variations and epigenetic modifications are associated with psoriatic disease. Often these epigenetic modifications result from an environmental trigger.

There is currently no known cure for psoriasis. Treatment goals are related to controlling symptoms and reducing morbidity. Conventional therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are only sufficient to manage mild disease. Research over the last decade has demonstrated a changing treatment framework based on redefinition of disease severity and treatment goals, taking into account the management of comorbid conditions and the reduction of risk [6].

Pathophysiology

Complex genetics plays a role in psoriasis. The role of genetics has been studied using family and twin studies, lineage studies, and genome-wide association studies (GWAS). Major histocompatibility complex (MHC), human leukocyte antigen C (HLA-C) and over 50 regions of susceptibility loci have been found to be associated with psoriasis [7–9]. Genetics is only a part of the pathogenesis. Without the simulation of certain environmental factors, epigenetic modifications and inflammatory responses, people with high genetic susceptibility may still fail to develop psoriasis, even though they are at significantly higher risk.

Psoriasis can be provoked by non-specific triggers such as trauma (from scratching, piercing, and tattoos), chemical irritants or microbial infections [6]. Researchers have found that Streptococcus infections can lead to T cell activation via the formation of superantigens [10, 11]. It has also been demonstrated that half of the Streptococcus cell wall-specific Th1 cells in psoriatic lesions are specific for Streptococcus peptidoglycan (PG), which is a strong pro-inflammatory stimulus in chronic inflammation [12]. PG interacts with keratinocytes, dendritic cells (DCs) and monocytes via pattern recognition receptors (PRR) such as Toll-like receptor 2, nucleotide-binding oligomerization domains (NOD)-1 and 2 and PG recognition proteins 1–4 in patients with psoriasis [13–15]. Subsequently, active leukocytes, cytokines (Th1, Th2, Th17, Th22, CD8⁺T, and γδ T cells), chemokines, adhesion molecules, growth factor, and subpopulations all act in an integrated way to generate the inflammatory responses seen in psoriasis [16, 17]. Once triggered by external and/or internal stimuli, activation of both the innate and adaptive immune system occurs, which result in the hyperproliferation and abnormal differentiation of keratinocytes, two of the critical contributors to the underlying pathophysiologic dysregulation in psoriasis.

Genetics and Epigenetics in Psoriasis

Psoriasis is not inherited in Mendelian fashion; however, there is a familial predisposition [18]. A positive family history significantly increases the relative risk among first-degree and second-degree relatives of patients compared to the general population [19]. Genetic studies have shown that HLA-Cw6 explains the largest part of the known heritability of psoriasis [20, 21]. GWAS have been successfully applied to exploration of the genetic architecture in psoriasis, and psoriasis-susceptibility loci (PSORS1) has been confirmed to be strongly associated with psoriasis, with an identification of over 12 different PSORS loci from genetic analysis of psoriasis-affected families [22]. Collectively, the gene variants relevant to psoriasis can broadly be classified into two kinds: skin-specific and immune-specific genes [23].

Evidence for a Role of Genetics in Psoriasis

Firstly, single nucleotide polymorphisms (SNPs) and copy number variation in genes of the late cornified envelope (LCE) family, which is involved in the epidermal cell and skin barrier formation and is highly expressed in psoriatic lesions, highlight significant roles for skin-specific genes [24–26]. The absence of these skin-related genes, including LCE3B/3C, is found significantly associated with a risk of psoriasis, which has been confirmed by two distinct studies from multiple samples from Spain (P = 1.38E-08) and from Italy and the USA (p = 5.4E-04), respectively [24]. Secondly, gene loci associated with psoriasis spans a series of functions mainly involved in adaptive immunity (antigen presentation and IL-23/Th17 axis) and innate immunity (NF-κB) [27]. HLA-Cw6 that lies within PSORS1 and possesses a highest odds ratio (OR) of nearly 3.0 compared with any other PSORS loci, encodes a major histocompatibility complex I (MHC1) antigen which is well known to mediated antigen presentation to CD8⁺ T cells [28]. In addition to HLA-
Cw6, ERAP1 is a newly found susceptible gene related to psoriasis that has been demonstrated to occur in replicated studies from 9079 European samples. A recent study reported that ERAP1 takes part in MHC-I peptide possessing by encoding an amino-peptidase which regulates the quality of peptides bound to MHC-I molecules, just like HLA-C [29].

In addition, there is accumulating evidence supporting a role of genes in the IL-23/Th17 pathway to psoriasis through GWAS [9, 26, 29, 30]. It has been identified that variants in or near the genes IL-12B, IL-23R, and IL-23A are strongly associated with psoriasis susceptibility [30, 31]. Interestingly, near the genes IL-12B, IL-23R, and IL-23A are strongly associated with psoriasis susceptibility [30, 31]. Paola et al. found that the IL23R R381Q gene variant does not directly inhibit activity of Th17 cells, but exerts a protective effect through selective attenuation of IL-23-induced cytokines in keratinocytes and endothelial cells by promoting NF-κB. It has been demonstrated that IFN-γ may be useful as a biomarker for psoriasis disease activity because of its positive correlation with PASI [32].

Epigenetic Regulation in Psoriasis

Although the critical role of heritability in psoriasis is difficult to refute, there is much that remains unexplained, and increasing data suggests an important role of epigenetic modifications in driving psoriasis [41–43]. A genome-wide methylation study from Han’s group demonstrated a hypomethylated level of 26 regions of the human genome in psoriasis patients compared to that of healthy controls. They further found that these regions are associated with histone modifications and transcription factor binding sites in the coding region, suggesting that there is epigenetic regulation in psoriasis [44, 45].

Immunological Changes in Psoriasis

Psoriasis is characterized by keratinocyte over-proliferation and the abnormal infiltration of effector T cells, dendritic cells, neutrophils and macrophages [58]. The effect of multiple cell types involved in psoriasis is mediated by a complex network of cytokines and their interactions.

The Role of Inflammatory Cytokines in Psoriasis

IFN-γ and TNF-α

IFN-γ and TNF-α act on keratinocytes and endothelial cells, leading to the activation, proliferation, and production of antimicrobial peptides. It has been demonstrated that IFN-γ is more relevant in the early stages of disease. IFN-γ induces the cross-phosphorylation of Janus kinase 1 (JAK2) and JAK3, which results in the downstream activation of STAT3. The subsequent activation of STAT factors is important for cell growth and is capable of regulating many genes expressed in psoriatic skin lesions [59]. IFN-γ promotes the release of cytokines (IL23, IL-1), chemokines (CXCL10, CXCL11), and adhesion molecules from DCs [60]. Studies suggest that IFN-γ may be useful as a biomarker for psoriasis disease activity because of its positive correlation with PASI [61].

TNF-α not only regulates the antigen-presenting ability of DCs but also promotes infiltration of T cells. This cytokine acts in part via phosphorylating NF-κB, the levels of which
are elevated in psoriasis [62]. TNF-α also possesses pro-inflammatory properties and in psoriasis can facilitate IL-23 production of DCs, suggesting that TNF-α acts as a regulator of the IL-23/Th17 axis. For this reason, TNF-α inhibitors such as etanercept serve their immune function partly by the suppression of IL-23, and by decreasing levels of Th17 effector molecules, including IL-17, IL-22, chemokines and β-defensin [63]. Yuko et al. have observed that TNF-α directly targets Th17 cells via attenuating a cytokine network of TNF/TNFRII signaling in psoriasis [64]. Blocking of TNF-α signaling has been more widely used in targeted biological therapy in psoriasis, with biological modulators such as infliximab, adalimumab, golimumab, certolizumab, and oncept, all of which have proven efficacy and relative safety in large, randomized, and controlled clinical trials [6, 65–69].

The IL-23/IL-17 Axis

IL-17 mRNA and protein levels are shown to be increased in the blood or skin biopsies from human psoriasis lesions [70]. IL-17 is primarily produced by Th17 cells, but recently, innate immune cells, including γδT cells, neutrophils and mast cells have been found to be involved in IL-17 secretion in psoriasis [71–73]. The IL-17 family includes at least six homodimeric cytokines, IL-17A though IL-17F. IL-17A and IL-17F are the most relevant to psoriatic disease. IL-17 is widely touted as a direct potentiator in enhancing keratinocyte proliferation and inhibiting keratinocyte differentiation via the downstream mediator REG3α, a protein with antimicrobial functions involved in wound repair [74]. The previous data has demonstrated IL-17A stimulates the production of chemokines and antimicrobial peptides by keratinocytes. Keratinocytes in turn promote Th17 cell recruitment and produce more IL-17, resulting in a positive feedback loop that perpetuates the inflammatory response of psoriasis [75, 76]. The role of IL-23 pathway has also been supported by observations that AIN457, an antibody neutralizing IL-17A, reduced PASI relative to baseline by 58% when compared to 4% of placebo-treated psoriasis cases [77].

A phase 2 clinical trial of LY2439821, namely ixekizumab, showed a higher efficacy by suppressing expression of cytokines and chemokines involved in the IL-17 pathway [78]. Conversely, IL-17 exhibits a protective influence on disease development by suppressing TNF-α-induced CCL27 production through induction of COX-2 in human keratinocytes, which ultimately alleviates keratinocyte dysfunction in psoriasis [79]. In fact, IL-17 appears to be a two-edged sword and is involved in both immune defense and disease development of many autoimmune disorders, including psoriasis.

The increase of IL-17 and IL-17-secreting cells is closely related to the altered balance between IL-23 and Th17 cells. IL-23 is pivotal in the survival and proliferation of Th17 cells [80]. IL-23 contributes to keratinocyte hyperproliferation and thus facilitates the development of psoriasis. Both IL-23 and IL-12 belong to IL-12 family. The IL-12 p40 subunit is shared by IL-12 and IL-23, which also have a unique subunit, p35 and p19, respectively. DCs and macrophages are the main sources of IL-12 and IL-23, the levels of which are increased in psoriasis skin. Emerging evidence has shown increased levels of p19 and p40 mRNA in lesion skin in contrast to non-lesional skin, while there is no difference in p35 levels [81]. In other words, it is IL-23 but not IL-12 that drives the pathogenesis of psoriasis. IL-23 protein levels in psoriatic skin lesions are also much higher compared to that in non-lesional skin [82]. All of the above information and single nucleotide polymorphism studies support the observation that IL-23 is a critical cytokine in disease pathogenesis [30, 83].

IL-22

IL-22, originating from Th17 and Th22 cells, induces IL-23-mediated keratinocyte hyperproliferation in vivo and in vitro, through STAT3 signaling [84]. Elevated levels of IL-22 are found in the blood of psoriatic patients [85], and IL-22 exerts its effects in tissues by binding to its heterodimeric receptor, consisting of the IL-10 receptor B and IL-22RA, which are exclusively expressed on epithelial cells such as keratinocytes in the skin [86]. The combination of IL-22 and IL-17 inhibits the differentiation of keratinocytes and increases their proliferation and mobility, which leads to retention of nuclei in the stratum corneum (parakeratosis), epidermal hyperplasia (acanthosis), and elongation of the epidermal rete ridges (papillomatosis), which are the hallmarks of skin psoriatic plaques [87].

IL-9

IL-9 expression in lesional skin from psoriasis patients was found to be markedly higher than that in healthy skin from the control subjects. Singh et al. and his group have demonstrated increased IL-9R and IL-9 expression in the skin and induction of a Th17-related inflammatory response after intradermal IL-9 injection in a psoriatic mouse model [88]. IL-9 is a pro-inflammatory cytokine that promotes secretion of IL-17, IL-13, IFN-γ and TNF-α in psoriasis. Both Th9 and Th17 cells are sources of IL-9. In another autoimmune disease model, anti-IL-9 monoclonal antibody not only blocks IL-9 signaling but also weakens Th17 function by suppressing IL-17 expression, suggesting that IL-9 may work as a mediator or target for inhibition of the IL-23/Th17 pathway [89, 90]. Additionally, a susceptibility gene for psoriasis is located on chromosome 5q31.1-q33.1, close to the location of the IL-9 gene [91]. The exact mechanisms by which these cytokines regulate the microenvironment of psoriasis still require further research.
Inflammatory Roles of T Cells in Psoriasis

**Th1 and Th2 Cells**

Th1 cells were originally considered to be the main mediator of the immune response in psoriatic plaques [92, 93]. Increased expression of both mRNA and protein levels of IFN-γ, TNF-α, and IL-12, but not IL-4, IL-5, or IL-10 have been documented in some studies [94–96]. On the other hand, Armanda et al. found that IL-4 ameliorated disease not only via promoting Th2 polarization, but also via direct inhibition of inflammatory cytokines in epidermal cells. This was supported by the observation that IL-4 leads to upregulation of epidermal GATA3 mRNA and protein in psoriatic skin and inhibition of IL-1β and IL-6 via transcriptional and post-transcriptional mechanisms [97]. IL-1β plays an important role in upregulating IL-6, IL-8, TNF-α, and hBD2 expression, differentiation of Th17 and Th22 cells, and stimulation of IL-17 and IL-22 secretion [98–100]. Thus by suppressing this pathway, the Th2 cytokine IL-4 is able to restore psoriatic skin to a healthy phenotype.

It has also been reported that genes encoding for Th1 cytokines but not Th2 are overexpressed in mesenchymal stem cells (MSCs) from psoriasis cases compared with healthy controls. This reflects an imbalance between the Th1 and Th2 paradigms [101]. There appears to be a bidirectional response pattern of Th1/Th2 balance, with a various skewing in different forms of psoriasis, when measuring specific cytokines and ratios of Th1/Th2 cells. In one of the most serious forms of psoriasis, erythrodermic psoriasis (EP), there is a higher expression of Th2 cytokines (IL-4, IL-10) than in the more commonly seen psoriasis vulgaris (PV). The Th1/Th2 ratio of EP is dramatically lower than in PV sufferers (P<0.01) [102]. It appears that the pathogenesis of psoriasis somehow involves the immune responses of both Th1 and Th2 cells; although, how the balance of Th1/Th2 skewing leads to psoriasis is not fully known.

What is known is that Th1 cells and IFN-γ levels are increased in psoriasis and lesional skin. Interferon-γ activates antigen-presenting cells early in the psoriatic cascade [103], and has been found to stimulate APC production of CCL20. CCL20, support migration of IL-17+ T cells, and also synergize with IL-17 in the production of β-defensin2 (HBD-2), an antimicrobial and chemotactic protein highly overexpressed by psoriatic keratinocytes [103]. Under the influence of Th1 cells, dysregulated keratinocytes release a rich source of AMP and IL-1 family cytokines including IL-1β and IL-18, which are further involved in the differentiation of Th1 and Th17 cells, respectively [104, 105]. This suggests that Th1 cells participate in the pathogenesis of psoriasis in conjunction with Th17 cells [106].

**Th17 Cells**

Th17 differentiation is dependent on the transcription factor RORγt, and the coexistence of IL-1β, TGF-β, IL-6 and IL-23 [107, 108]. Evidence is accumulating that effector T cells contribute to psoriasis immunopathogenesis, in which the Th17 subset is of central importance, in both human and mouse models. On the one hand, the number of IL-17-producing CD4+ T cell has been observed to be much higher in psoriatic skin lesions than in healthy skin [109, 110]. Th17 cells are crucial for secretion of IL-17, IL-12, IL-22, and IL-9, all of which directly or indirectly promote the inflammatory response of keratinocytes. Furthermore, antimicrobial peptides, cytokines and chemokines such as CCL20 and CXCL1, 3, 8–11 secreted by keratinocytes, act as chemoattractants to amplify the immune response in psoriasis [111–113]. In turn, activated Th17 cells enhance the inflammatory response of keratinocytes, creating a positive feedback loop around the IL-23/Th17 axis.

Recent murine studies also suggest that the Th17 pathway is essential to the pathogenesis of psoriasis. Topical imiquimod (IMD) may induce psoriasisform skin inflammation in mouse models, which is primarily mediated through the IL-23/Th17 axis [114]. Blocking of this axis using anti-IL-23 antibodies has showed great promise in suppressing the development of psoriatic diseases [115]. Neutralization of IL-22 using antibody or knockout mice inhibited IL-23-induced skin thickening [116]. Dysregulated of IL-17 signaling and Th17 cell pathway function thus promotes chronic inflammation in psoriasis. Reversing this dysfunction is the focus of current clinical trials in psoriasis.

**Regulatory T Cells**

Polarization of regulatory T (Treg) cells is primarily regulated by a combination of TGF-β, IL-4, IFN-γ, IL-2, and IL-6, as well as other T cell populations [117]. Mature Treg cells express Foxp3, TGF-β, IL-10, perforin, and granzyme A. Treg cells help maintain peripheral tolerance, thus limiting chronic inflammatory diseases and preventing autoimmune diseases [118–120]. Treg cells play important roles in maintaining homeostasis and may cause local suppression of other immune cells, including Th17 cells. IL-6, which is required for the differentiation of Treg cells, hampers the activation and proliferation of Th17 cells [121, 122]. Hence, it induces a balance between Tregs and Th17 cells. It has been shown that increased Treg cell counts may be seen in the skin lesions of psoriasis patients [123]. Treg cells usually suppress other pathogenic T cells like Th1 and Th17 cells in psoriasis. Dysfunction of Tregs by CD18 knockout allows the hyperproliferation of pathogenic T cells in psoriasis models. In the Cd18<sup>hypo</sup> PL/J mouse model, reduced CD18 expression resulted in impaired function and low proliferation of Treg cell, with 51.5 % gated CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>−</sup> Tregs by flow cytometry, compared to a much higher rate of 81.9 % in the wild type (Cd18<sup>wt</sup>). The dysfunction of Treg cells can be reversed by adoptive transfer of Cd18<sup>wt</sup> Tregs into Cd18<sup>hypo</sup> PL/J mouse, resulting in an improvement of the psoriasis [124].
Similar to this, ameliorated psoriasis-like skin lesions and lower Th17 cytokines but increased numbers of Treg cells are observed recently in IMQ-induced mice after combined treatment of glucosamine and low-dose cyclosporine [125]. Another study showed that CD4⁺CD25⁺ T cells differentiated in vitro from hematopoietic cells of patients with psoriasis are impaired in their regulatory capabilities [126].

γδT Cells, Th22 Cells, and Th9 Cells

A close relationship has been showed between psoriasis and other immune cells including newly identified IL-23-producing CD4⁺ T cells and IL-17 producing γδ T cells [88, 127]. γδT, Th22, and Th9 cells have been recently identified to play roles in the pathogenesis of psoriasis, with their main effector cytokines being IL17, IL-22, and IL-9, respectively, thus amplifying the function of the Th17 pathway in psoriasis. γδT cells produce IL-17 and promote a Th17 inflammatory response after their rapid activation by IL-23, IL-1β, or danger signals [128]. It has been established that epidermal hyperplasia and inflammation, along with IL-17 levels, are significantly decreased in T cell receptor δ-deficient (Tcrd−/−) mice [129–131]. In addition, IL-23-induced or IMQ-induced skin inflammation and acanthosis are observed only in wild-type (WT) mice rather than Tcrd−/− mice, suggesting that γδT cells are necessary for the development of psoriasis [114, 129]. In human studies, Cai et al. also found large numbers of IL-17-secreting γδT cells in lesions from patients with psoriasis, and dermal γδT cells are a significant source of IL-17 and CCR6 upon IL-23 stimulation in the skin [129].

Human γδT cells from blood are usually Vγ9Vδ2 T cells, which are increased in skin but decreased in the peripheral blood in psoriasis patients, suggesting that γδT cells redistribute from blood toward the skin in order to participate in the pathogenesis of psoriasis. Vγ9Vδ2 T cells release large amounts of psoriasis-relevant cytokines IFN-γ, TNF-α, and IL-9 and pro-inflammatory chemokines, CCL3, CCL4, and CCL5, confirming their important role in the pathogenesis of psoriasis [132].

IL-22-producing Th22 cells and IL-9-producing Th9 cells make up other two distinct subsets of effector T cells. IL-22 can lead to induction of cytokine-specific chemokines and augmentation of specific effector responses mediated by the IL-23/Th17 axis [133]. IL-9 works as a potent mediator of Th17 cell signaling. Studies of γδT, Th22, and Th9 cells in psoriasis, although still in their infancy, are expected to be a growing interest in the study of potential mechanisms of inflammatory responses and pathogenesis of psoriatic disease.

CD8⁺ T Cells

The PSORS1 gene lies within the class I region of the MHC. CD8⁺ T cells in the blood of psoriasis patients frequently carry the HLA-Cw6 allele, the most important susceptibility loci that has ever been found in psoriasis [134]. Johnston et al. found that CD8⁺ T cells recognized keratin self-antigens, which along with epitopes shared by Streptococcal M proteins were the target of CD8⁺ T cells in infiltrating psoriatic skin lesions [135]. In addition, the observation that perforin-mediated cytotoxicity of CD8⁺ T cells caused keratinocyte damage in psoriasis further strengthens the importance of CD8⁺ T cell in the disease pathogenesis [136]. In other words, apoptotic keratinocytes induced by CD8⁺ T cells initiate a vicious cycle of regenerative hyperplasia of epidermal keratinocytes, thereby promoting the development of psoriasis.

Other Immune Cell Types With a Role in Psoriasis

There are many other immunocytes that also exert inflammatory effects in psoriasis, notably dendritic cells (DCs) [137], natural killer (NKs) cells, and macrophages. In a broad sense, there are three types of dermal resident DCs: (1) epidermal Langerhans cells (LCs), (2) dermal myeloid DCs (mDCs), and (3) plasmacytoid DCs (pDCs) [138, 139]. Nestle et al. were the first to find the close relationship between DCs and psoriasis. They observed that in psoriasis plaques, skin-derived DCs mediate higher levels of IL-2 and IFN-γ production than DCs in healthy skin [140]. Additionally, compared to normal skin, there is an increased number of pDCs in psoriatic skin lesions (up to 16 % of the total dermal infiltrate) triggered by the Toll-Like Receptor (TLR) 7 agonist IMD [141].

Studies have identified that IFN-α signaling mediated by pDC is an initiator of psoriatic inflammation [142]. IFN-α produced by pDCs induces a upregulation of IL-17 and IL-23, which also polarizes Th17 cell differentiation and potentiates IL-17 production [143]. Lowes et al. found high levels of TNF-α and iNOS producing DC subsets in human psoriasis. Blockade of TNF-α using etanercept induced disease improvement in psoriasis [144, 145]. Similarly, CD11c⁺ DC cell counts were increased in psoriasis lesions and reduced after clinical response induced by efalizumab, alefacept, infliximab and NB-UVB [133].

Natural killer (NK) cells are a distinct subset of CD56⁺CD16⁺ cells which are well known for their ability to kill virally infected and cancer cells [146]. Studies from Ottaviani et al. have suggested that NKs are capable of producing large quantities of IFN-γ, inducing activation of keratinocytes and upregulation of MHC class I molecules [111]. More importantly, activated keratinocytes were observed to attract NK cells by secreting chemokines such as CXCL10, CCL5, and CCL20 [111].

In addition to DCs and NK cells, there is mounting evidence that neutrophils and macrophages may contribute to psoriasis. Neutrophils recruited by chemokines CXCL1, CXCL2, and IL-18 contribute to the recruitment of activated
Effector T cells. Moreover, neutrophils also produce AMPs and IL-17 in psoriasis patients [147, 148]. Infiltration of macrophages promotes keratinocyte proliferation and the development of psoriasis. In fact, cutaneous macrophages can produce many inflammatory mediators and cytokines, one of which is IL-23, a crucial participant in the pathogenesis of psoriasis [149] (Fig. 1).

**Treatment and Management**

**Traditional Therapy**

Conventional treatment of psoriasis mainly includes corticosteroids, Vitamin D analogues, phototherapy and systemic treatments [150]. The lack of biomarkers presents an additional roadblock to optimizing treatment [151]. Topical glucocorticosteroids and Vitamin D analogues, both of which regulate keratinocyte function and the inflammatory response, are usually sufficient to treat mild disease. Nevertheless, continuous corticosteroid use is associated with some risks [152] including loss of efficacy, cutaneous atrophy and rebound or pustular psoriasis. Vitamin D analogues fail to have a fast onset of activation, although they do not possess the more severe side effects of corticosteroid [153]. In the case of moderate-to-severe psoriasis, ultraviolet B light in combination with systemic drugs such as methotrexate is still an acceptable therapy, especially for those patients with arthritis or nail involvements. Methotrexate is widely used because of its reasonable price and high efficacy over protracted periods, and more than 75% of patients acquire 50% reduction in disease severity [154–156]. Nevertheless, the adverse effects that patients may suffer are potentially very serious, and include liver fibrosis and cirrhosis.

**Biological Modulators**

Biological modulators targeting molecules involved in the pathogenesis of psoriasis have been developed over the past 2 decades [157]. Biological therapies are usually advocated when traditional treatments have failed, are contraindicated or lead to severe adverse effects [158]. This is partially due to the high cost of biologicals. Generally, these newer treatments are categorized into several broad groups: TNF-α inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab and oncept), IL-12/IL-23 inhibitors (ustekinumab), IL-17 inhibitors (secukinumab), inhibitors of T cell activation and signaling (alefacept), and others. Among the biologics, etanercept is FDA approved for moderate-to-severe chronic plaque psoriasis, with a dosing regimen of 50 mg twice a week for 3 months followed by a maintenance dose of 50 mg per week [159, 160]. Comparison of improvements in PASI between etanercept and methotrexate showed no statistical difference over a 2-week treatment period. However, patients treated with etanercept had higher remission of arthritis and erythra than methotrexate after 6 weeks, suggesting that etanercept may be a better choice for maintenance in the long run ($P<0.05$).

In addition, combination therapy with etanercept plus methotrexate had acceptable tolerability and PASI 75 improvement compared with etanercept monotherapy in a 24-week treatment (77.3 vs. 60.3%, $P<0.001$) [161]. With regard to other biological modulators, the TNF-α inhibitor golimumab is approved for psoriatic arthritis, and the
IL12/IL-23 inhibitor ustekinumab is acceptable both in psoriasis and psoriatic arthritis. Numerous other biologics, which span an array of functions involved in blocking the JAK family of kinases (tofacitinib), correction of cytokine deviation (IL-10), and inhibiting phosphodiesterase-4 (apremilast) are in advanced phases of clinical trials [162, 163]. Each biological modulator acts on the immune system in a different way, but due to the redundancy of the immune system and genetic variation, none work equally well for every patient.

Adverse Effects

Compared to conventional treatments, biologics provides higher efficacy and sometimes better safety profiles, but have been found to possess new and unexpected adverse effects [164]. Blockade of Th17 and TNF-α induces the downstream inhibition of IL-17, IL-12, IL-23, and TNF-α itself, impairing immunity to fight against intracellular bacteria and granulomatous infections. Hence, TNF-α inhibitors may lead to reactivation of tuberculosis, while an impaired IL-23/Th17 pathway is closely associated with risk of salmonella infection, tuberculosis and mycobacterial disease [165–168]. A current study has estimated the different degrees of susceptibility to infection among common biologics in clinical treatment. In the infliximab cohort, there is cumulative incidence rate of infection of 2.49 %, which is much higher than the rates in ustekinumab (0.83 %), etanercept (1.47 %), and adalimumab (1.97 %). Indeed, infliximab exposure associated with other risk factors including increasing age, diabetes mellitus, smoking, and significant infection history led to a higher susceptibility to serious infection [169].

Followed by infection, cardiovascular disorders have been reported to occur with the use of the newer biologics. IL-17 inhibitors may block the anti-tumor effect which is mediated by IFN-γ and the anti-angiogenic effect of IL-17F, thus increasing the risk of malignancy in psoriasis patients [172]. Biologics are also much more expensive and the response is variable with only one third of psoriasis patients experiencing significant improvement [174]. At present, we are still far from finding a cure for psoriasis, but what we do know is that it is an incredibly complex autoimmune disease that will require a better understanding of its pathogenesis in order to develop new treatment modalities (Table 1).

Table 1  Summery of anti-psoriatic therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Efficacy</th>
<th>Common deficiency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticosteroids</td>
<td>Inhibition of inflammatory reactions, DNA synthesis, vasoconstriction, and immunosuppression</td>
<td>++++</td>
<td>Skin atrophy</td>
<td>[164]</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>Inhibiting epidermal hyperproliferation</td>
<td>+++</td>
<td>Low onset of activation, mild discomfort</td>
<td>[164]</td>
</tr>
<tr>
<td>Phototherapy (UVB, UVA)</td>
<td>Blockin TNF-α pathway</td>
<td>++ to +++</td>
<td>Infection, malignancy</td>
<td>[164, 169]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Immunosuppression</td>
<td>+ to ++</td>
<td>Liver fibrosis</td>
<td>[164]</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immunosuppression</td>
<td>++ to +++</td>
<td>Hypertension, malignancy, infection</td>
<td>[164]</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Blocking TNF-α pathway</td>
<td>+ to +++</td>
<td>Infection, malignancy</td>
<td>[164, 169]</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Blocking TNF-α pathway</td>
<td>+++ to +++</td>
<td>Infection</td>
<td>[169]</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Blocking TNF-α pathway</td>
<td>+++</td>
<td>Infection, lupus-like syndrome, malignancy</td>
<td>[164, 169]</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Blocking IL-12/IL-23 signaling</td>
<td>+++</td>
<td>Infection</td>
<td>[164]</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Blocking IL-17 signaling</td>
<td>Not indicated</td>
<td>Nasopharyngitis, headache</td>
<td>[173]</td>
</tr>
</tbody>
</table>

Global assessment: there are six levels for estimating efficacy

Poor − +/- +++ ++++ ++++

Conclusion

Psoriasis is more than just a Th1 type disease, and accumulating evidence is available to demonstrate the crucial roles of effector cell subsets including Th17, Th22, Th2, Treg, CD8 T cells, and other immune cells such as DCs, NKs cells, macrophages in the pathogenesis of psoriasis. Among the

 TNF-α inhibitors have been reported to be a potential cause of cardiovascular events. However, other meta-analysis showed conflicting observations in that only 1 of 3858 patients receiving TNF-α inhibitors experienced major adverse cardiovascular events (MACE) compared with 1 to 1812 patients receiving placebo (P=0.12), suggesting that there was no significant difference in the rate of MACE after TNF-α inhibitor treatment [170, 171]. The same observations can be made with regard to IL12/IL23 antibodies. The differences between these studies may be reflected by different patient populations and the statistical methods used, and the actual role of biologics in MACE still needs to be further investigated.

In addition, comorbidities such as nausea, diarrhea, nasopharyngitis, and headache may occur with biologics [172, 173]. IL-17 inhibitors may block the anti-tumor effect which is mediated by IFN-γ and the anti-angiogenic effect of IL-17F, thus increasing the risk of malignancy in psoriasis patients [172]. Biologics are also much more expensive and the response is variable with only one third of psoriasis patients experiencing significant improvement [174]. At present, we are still far from finding a cure for psoriasis, but what we do know is that it is an incredibly complex autoimmune disease that will require a better understanding of its pathogenesis in order to develop new treatment modalities (Table 1).
mechanisms involved in psoriasis, Th1/Th2 proportion, Th17/Treg balance, and IL-23/Th17 axis appear to be particularly important. Recently, IL-9-producing Th9 cells and IL-17-producing γδT cells have been found to play significant roles in the pathogenesis. New discoveries in the pathogenesis of psoriasis have already led to novel treatment modalities [175]. Further research in individual gene susceptibility and the role of environmental triggers and epigenetic modifications are needed to address the unmet need of personalized medicine in the treatment of autoimmune diseases such as psoriasis [176, 177].

Acknowledgments This work was supported by grants from the National Natural Science Foundation of China (Nos. 81220108017, 81430074, 81270024, and 30972745).

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