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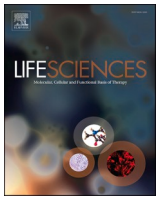

Advances in psoriasis research: From pathogenesis to therapeutics

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ABSTRACT

Psoriasis is a chronic inflammatory condition affecting approximately 2 % to 3 % of the global population. The pathogenesis of psoriasis is complex, involving immune dysregulation, hyperproliferation and angiogenesis. It is a multifactorial disease which is influenced by genetic and environmental factors. The development of various therapeutic agents, such as JAK inhibitors, small molecules, and biologics with potential anti-psoriatic properties was possible with the vast understanding of the pathogenesis of psoriasis. Various signalling pathways, including NF-κB, JAK-STAT, S1P, PDE-4, and A3AR that are involved in the pathogenesis of psoriasis as well as the preclinical models utilised in the research of psoriasis have been highlighted in this review. The review also focuses on technological advancements that have contributed to a better understanding of psoriasis. Then, the molecules targeting the respective signalling pathways that are still under clinical trials or recently approved as well as the latest breakthroughs in therapeutic and drug delivery approaches that can contribute to the improvement in the management of psoriasis are highlighted in this review. This review provides an extensive understanding of the current state of research in psoriasis, giving rise to opportunities for researchers to discover future therapeutic breakthroughs and personalised interventions. Efficient treatment options for individuals with psoriasis can be achieved by an extensive understanding of pathogenesis, therapeutic agents, and novel drug delivery strategies.

1. Introduction

Psoriasis is an autoimmune disorder that causes chronic inflammation in the skin, affecting nearly four million people worldwide [1]. This condition is characterised by persistent inflammation and excessive skin cell growth. Although the patients' well-being and life expectancy are affected by psoriasis, the cure for this disease has not been achieved [2]. However, several treatment options are available to alleviate skin manifestations. Topical therapies, phototherapy, oral systemic therapies, and biologic therapies are standard treatment options for the treatment of psoriasis [3]. However, these treatments exhibit various side effects affecting patients' satisfaction [4]. A study indicated that patients with moderate-to-severe psoriasis who received topical therapies had significantly low overall satisfaction (66.7) compared to patients receiving phototherapy, biologic monotherapies or biologic-methotrexate combinations (83.3) [5]. Moreover, the effectiveness of therapies observed in clinical trials is not observed in a significant number of patients in actual situations due to inappropriate therapy selection, such as the presence of unexplored psoriasis variants, and the negligence of key comorbidities [6,7]. Despite extensive research, complete elucidation of the disease pathogenesis has not been achieved. Recently, novel approaches, such as system biology have been utilised to elucidate the pathogenesis of the disease [8]. Consequently, there is a growing demand for understanding the pathogenic pathways in psoriasis to identify novel molecular targets and new therapeutic approaches to treating psoriasis with minimal side effects. This review aims to discuss the pathogenesis of psoriasis, explore potential therapeutic molecules, and discuss innovative drug delivery approaches.

2. Intracellular signalling pathways involved in the pathogenesis of psoriasis

The phases that comprise the pathogenesis of psoriasis are initiation and maintenance. During the initiation phase, triggers, such as drugs, infection, skin injury or stress led to the development of psoriasis, and then the disease progresses into a chronic condition during the maintenance phase [9]. The inflammation in psoriasis starts and then persists due to the disruptions of the adaptive and innate cutaneous immune responses [9,10]. In psoriatic skin, AMPs are overexpressed by keratinocytes in the presence of these triggers. The activation of dendritic cells

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(DCs) occurs in the presence of antimicrobial peptides (AMPs). AMPs that are commonly linked to psoriasis are S100, β-defensins, and LL37 (cathelicidin) proteins [11]. The activation of plasmacytoid dendritic cells (pDCs) occurs upon stimulation of toll-like receptor 9 (TLR 9) in pDCs by DNA-bound LL37 [12]. The initiation in the pathogenesis of psoriasis relies on the activation of pDC, which results in the expression of type I interferon, such as interferon-beta (IFN-β) and interferon-alpha (IFN-α). The promotion of phenotypic maturation of myeloid dendritic cells (mDC) as well as differentiation of T helper 1(Th1) and T helper 17 (Th17) are elicited by the signalling of type I interferon [13–15]. The progression of inflammation into the maintenance phase is driven by T cell subsets which activate the adaptive immune response [16]. Upon the T lymphocyte activation by antigens, the expression of cytokines is further elevated leading to increased expression of T lymphocytes, keratinocyte proliferation and severeness of inflammation [17]. Various inflammatory pathways are known to play a major role in the pathogenesis of numerous chronic diseases. The major inflammatory pathways that lead to the pathogenesis of psoriasis are nuclear factor-kappa

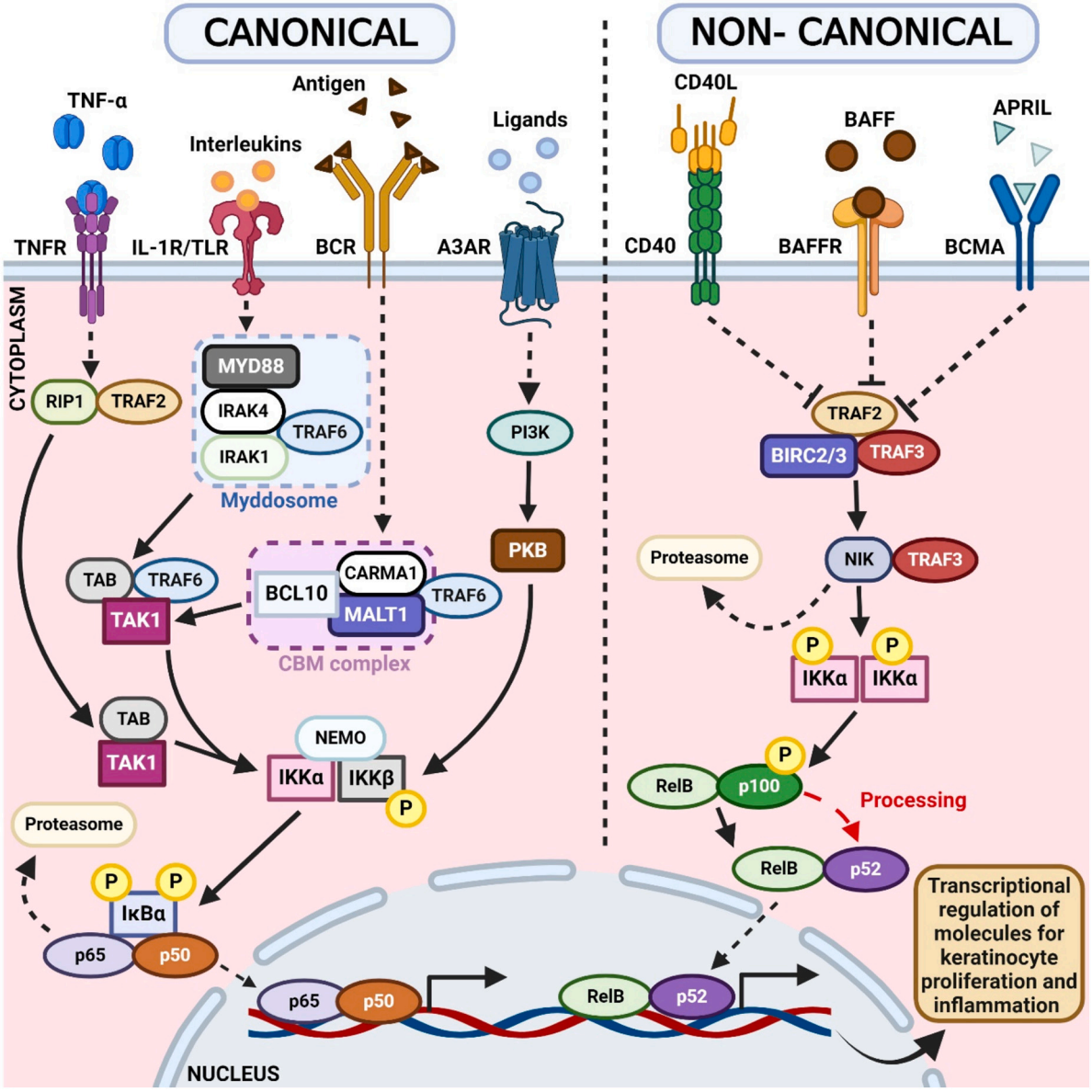

Fig. 1. Canonical and non-canonical NF-κB signalling pathways in the pathogenesis of psoriasis. The activation of receptors, such as cytokine receptors (TNFR), TCR/BCR or TLRs are responsible for the induction of the canonical NF-κB signalling pathway. Once these receptors are activated, specific signalling complexes and adaptor proteins respective to these receptors are recruited. Catalytic subunits (IKKα and IKKβ) and regulatory subunit (NEMO) comprise the IKK complex. The phosphorylation of the IKK complex results from the engagement of signalling complexes and adaptor proteins. The phosphorylated IKK complex causes the release of NF-κB dimer, p50/p65, which is translocated to the nucleus to induce gene expression of pro-inflammatory mediators. A3AR signalling is also part of the canonical NF-κB signalling. Upon activation of A3AR, the PI3K/AKT signalling pathway is induced resulting in the phosphorylation of the IKK complex. On the other hand, the induction of non-canonical NF-κB signalling is caused by the activation of receptors, such as CD40, BAFFR or BCMA. Activation of these receptors results in the inactivation of the TRAF/BIRC complex, which causes the stabilisation of NIK. Accumulation of NIK leads to IKKα phosphorylation, which then causes the phosphorylation of RelB/p100. The p100 subunit undergoes partial proteosomal processing, resulting in the release of RelB/p52 dimers, which are translocated to the nucleus to induce gene expression of pro-inflammatory mediators. Abbreviations: TNFR; tumour necrosis factor receptor; TCR, T cell antigen receptor; BCR, B cell antigen receptor; TLRs, Toll-like receptors; IKKα, I kappa B kinase alpha; IKKβ, I kappa B kinase beta; NEMO, NF-κB essential modulator; A3AR, A3 adenosine receptor; PI3K/AKT, Phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B; CD40, cluster of differentiation 40; BAFFR, B-cell activating factor receptor; BCMA, B-cell maturation antigen; TRAF, TNF receptor-associated factor; BIRC, Baculoviral IAP repeat-containing proteins; NIK, NF-κB inducing kinase.

B (NF-κB), Janus kinase-signal transducers and activators of the transcription (JAK/STAT), sphingosine 1-phosphate (S1P), phosphodiesterase 4 (PDE-4), and A3 adenosine receptor (A3AR) (27).

2.1. NF-κB pathway

In psoriatic skin lesions, the expression of NF-κB is significantly upregulated. NF-κB signalling pathway modulates keratinocytes and immune cells, leading to the pathogenesis of psoriasis [18]. NF-κB is vital in regulating immune reactions and other physiological processes, including inflammation. The NF-κB activation causes the transcription of various genes needed for the expression of cytokines that regulate inflammation, cell survival, proliferation, and differentiation of immune cells [19]. In the epidermis of psoriatic patients, the nuclear positivity of NF-κB was significantly elevated and it correlates to the intensity of epidermal hyperplasia [20].

In psoriasis, the activation of canonical NF-κB is initiated upon the degradation of I kappa B kinase (IκBα) by a multi-subunit IκB kinase (IKK) (Fig. 1). Various stimuli, ranging from cytokines to stress agents can trigger the activation of IKK. This leads to rapid nuclear translocation of p50/p65 and p50/c-Rel dimers. On the other hand, the specificity of the noncanonical NF-κB pathway towards stimuli is selective as only specific stimuli can trigger the pathway. The processing and ubiquitination of p100 are carried out with the aid of NF-κB-inducing kinase (NIK). The phosphorylation of p100 then leads to the production of mature NF-κB2 p52 along with translocation of the

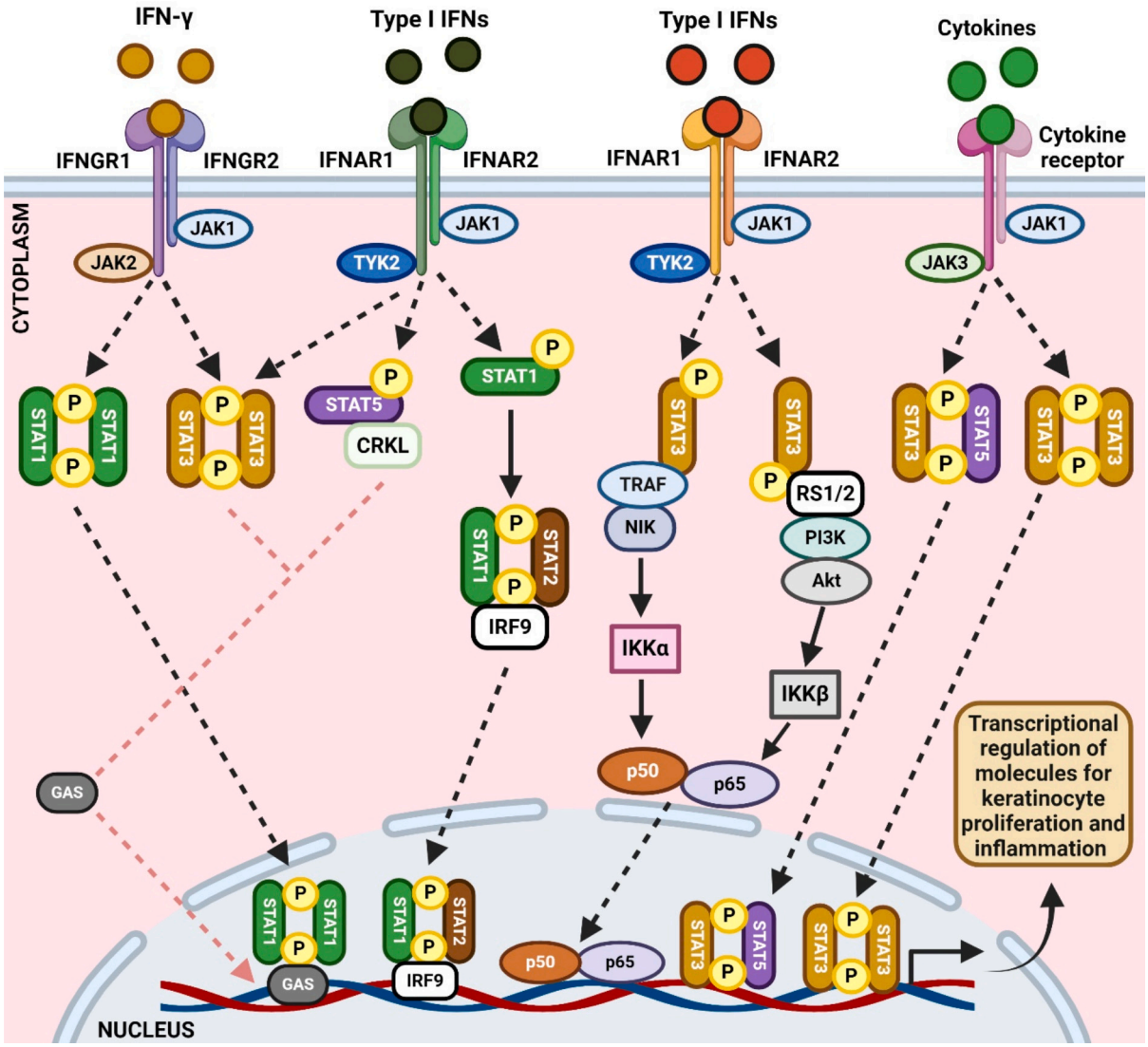

Fig. 2. JAK-STAT signalling pathway in the pathogenesis of psoriasis. IFNGR1 and IFNGR2, which are associated with JAK1 and JAK2, respectively are responsible for the canonical type II IFN signalling. Upon phosphorylation of STAT1, the homodimers are translocated to the nucleus and bind to GAS elements. This results in the transcription of IFN-γ induced genes which are responsible for immune activation. The phosphorylation of STAT3 is also triggered by IFN-γ signalling. In the type I IFN pathway, the receptors that are involved are IFNAR1 and IFNAR2, which are linked with TYK2 and JAK1, respectively. In this pathway, the ISGF3 complex consisting of phosphorylated STAT1 and STAT2 with IRF9, is translocated to the nucleus for the IRG transcription via ISRE regulatory sequence. NF-κB or CRKL pathway is vital for non-canonical type I IFN signalling. Upon phosphorylation of CRKL by TYK2, the complex consisting of CRKL and STAT5 binds to the GAS elements in the nucleus. The NF-κB pathway is induced via PI3K/AKT AND TRAFs after the activation of IFNAR1/2 associated with JAK1 and TYK2. The phosphorylation of STATs is caused by the activation of specific receptors, which then causes the STAT complexes to translocate to the nucleus to modulate gene expression of molecules necessary for inflammation and keratinocyte proliferation. Abbreviations: IFNGR, interferon-gamma receptor; GAS, gamma-activated sequence; IFNAR, interferon alpha receptor; ISGF3, interferon-stimulated gene factor 3; IRF9, interferon regulatory factor 9; IRG, interferon regulated gene; ISRE, interferon-stimulated response element; CRKL, CRK like proto-oncogene, adaptor protein; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; TRAF, TNF receptor-associated factor; IFNAR, interferon-alpha receptor.

noncanonical NF-κB complex p52/RelB to the nucleus. The pro-inflammatory cytokines produced via the downstream activity of NF-κB lead to the upregulation of toll-like receptor 2 (TLR2) and caspase-5, which are part of innate immunity. The initiation of TNF-α and interleukin (IL)-23/IL-17 pathways as well as recruitment of dendritic cells and Th17 cells are upregulated by NF-κB signalling [21].

2.2. IL-23/IL-17 pathway

In the IL-23/IL-17 pathway, the expression of IL-23 triggers the expression of IL-17 via IL-17-producing immune cells, leading to inflammation [22]. IL-17 cytokines play a key role in the downstream signalling of IL-23. IL-17A, a common IL-17 cytokine linked to psoriasis, induces the expression of keratinocyte-derived antimicrobial peptides upon binding to its receptors to trigger innate immunity. Signalling pathways triggered by IL-17A also lead to leukocyte recruitment via chemokines as well as expression of various pro-inflammatory genes. These actions lead to the amplification of the IL-23/IL-17A axis contributing to increased severity of inflammation. In psoriasis, epidermal hyperplasia is induced by IL-17A via the expression of IL-19 and IL-36 by keratinocytes [23,24].

The IL-17 receptor, especially interleukin-17 receptor A (IL-17RA) is also critical in psoriasis. IL-17RA is targeted by various cytokines, such as IL-17A, IL-17C, IL-17E, and IL-17F and the activation of this receptor in the keratinocytes leads to the expression of IL-1, IL-22, and CXCL2 as well as infiltration of neutrophils which are responsible for the development of psoriasis. However, IL-17RA expressed in T cells, neutrophils or macrophages are not involved in the development of psoriasis. Hence, keratinocytes are vital in the pathogenesis of psoriasis [25].

2.3. JAK-STAT pathway

JAK-STAT pathway is involved in intracellular signalling modulating physiological and pathological processes responsible for inflammatory conditions, such as psoriasis (Fig. 2). Four types of JAK proteins [JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)] and seven STATs are present in mammals [26]. When the JAK-STAT pathway is activated, the gene transcription of various cytokines, including proinflammatory cytokines is triggered, driving the pathogenesis of psoriasis. In psoriatic skin lesions, the activation of dendritic cells and the differentiation of Th1 and Th17 cells is triggered by STAT1 and STAT3. STAT3 is also responsible for the proliferation of keratinocytes with the aid of IL-22, IL-36, and IL-19.

The development and function of immune cells are affected by different JAKs induced by specific cytokine receptors. The dimerisation of JAKs leads to heterodimers which causes autophosphorylation that attracts STAT protein. Upon activation, the dimerised STAT proteins move to the cell nucleus, which is the site of gene transcription regulation of various cytokines, including pro-inflammatory cytokines that are part of the pathogenesis of psoriasis [26]. In both keratinocyte and immune cells, the hyperactivation of STAT3 modulates apoptosis, cell proliferation, and differentiation. In keratinocytes, the activation of

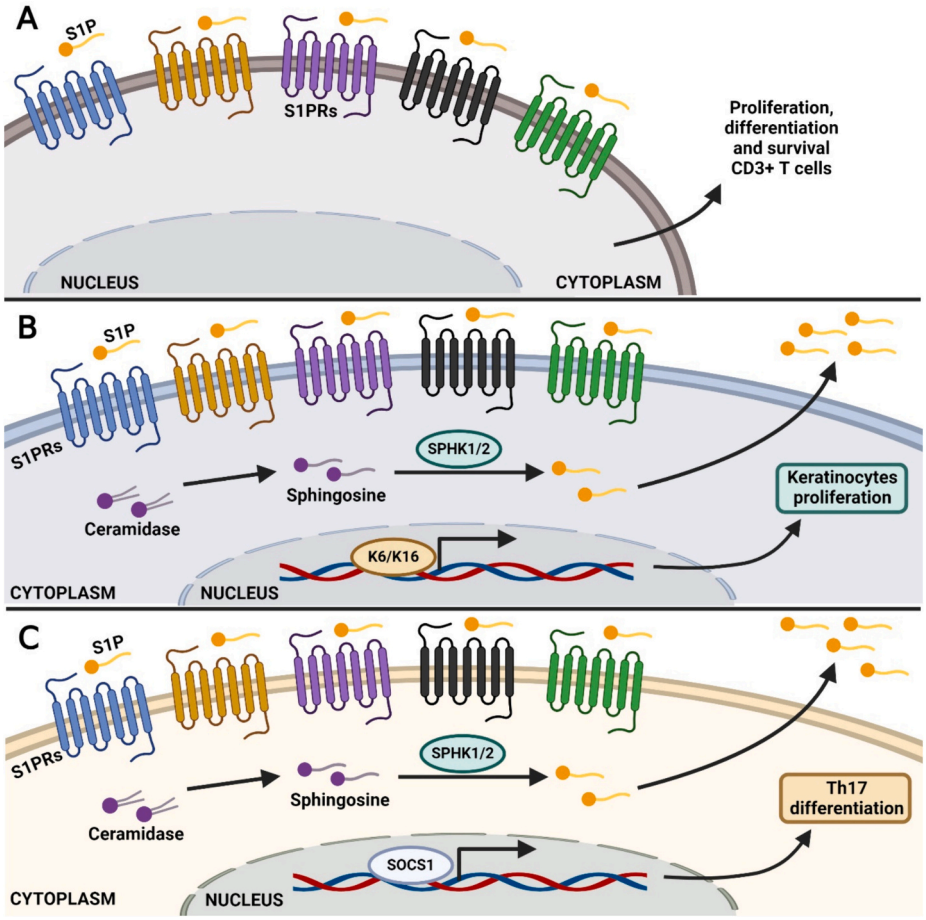

Fig. 3. S1P signalling pathway in the pathogenesis of psoriasis. (A) In CD3 + T cells, the activation of S1PRs by S1P leads to the increased proliferation, differentiation, and survival of CD3 + T cells. (B) In keratinocytes, the activation of S1PRs causes the overexpression of S1P and also up-regulates the expression of keratins K6 and K16, which are responsible for hyperproliferation of keratinocytes. (C) In Th17 cells, the activated S1PRs cause the overexpression of S1P and also induce the expression of pro-inflammatory cytokines. The expression of SOCS1, which is responsible for the differentiation of Th17 cells is up-regulated. Abbreviations: S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SPHK, sphingosine kinase; SOCS1, suppressor of cytokine signalling 1.

STAT3 leads to the promotion of proliferation and production of antimicrobial peptides as well as inhibition of cell differentiation. Concluding that the development of psoriasis is greatly affected by STAT3 [25]. Additionally, TYK2 is essential for the modulation of downstream signal transduction originating from extracellular receptors, such as IFNs, IL-12, and IL-23. These downstream signals can be inhibited by the binding of small molecule ligands to the receptor [27].

2.4. S1P pathway

S1P couples to the G protein-coupled receptors S1P1-5 to behave as an intracellular second messenger that modulates the proliferation, survival and migration of cells responsible for angiogenesis and inflammation (Fig. 3) [28,29]. S1P induces the differentiation of cells but inhibits the proliferation of keratinocytes and it is significantly elevated in psoriatic patients [30]. Inhibition of S1P suppresses the Th17 cell and keratinocyte differentiation, leading to amelioration of psoriasis [31].

3. Models in the research of psoriasis

In psoriasis, researchers have developed various in vitro and in vivo models mimicking psoriasis to gain insights into the components involved in the pathogenesis of the disease and potential therapeutic strategies. These models have been used to study various subtypes of psoriasis and its characteristics [32].

3.1. In vitro models

A reliable and physiologically relevant model should possess a specific profile linked to the psoriatic phenotype [33]. In vitro models are developed to overcome animal models' restrictions and ethical concerns. The simplest in vitro models in psoriasis are two-dimensional (2D) cell cultures, consisting of monolayer cultures and co-cultures [34]. Monolayer keratinocyte cultures, which consist of a single type of cell are an easily reproducible model system, commonly used for pharmacological and biological studies and drug screening in psoriasis [35–37]. Cell lines that are commonly used to establish psoriasis models are immortalised human keratinocyte lines (HaCaT) and normal human epidermal keratinocytes (NHEK) [38]. The controlled addition of cytokines to these cells induces features of psoriasis by mimicking the disease pathogenesis. Various cytokines are used to induce innate (TNF-α, IL-6, and IL-1α) or adaptive (IL-17A) immune responses in the keratinocytes [39,40]. Moreover, oncostatin-M (OSM), a potent activator of keratinocytes with similar effects as other cytokines is used to induce genes associated with innate immunity, angiogenesis, adhesion, and motility [39]. Studies have shown that cytokine-induced keratinocytes expressed high levels of inflammatory markers, such as AMPs, chemokines, cytokines and major histocompatibility complex (MHC) molecules corresponding to psoriasis [22]. On the other hand, the co-culture approach is widely used in understanding cell-to-cell interactions of the disease as well as the effect of drugs on these interactions [41]. Co-culture involves the two or more different cell populations grown with some degree of contact between them. A common co-culture system used for psoriasis is keratinocytes grown with macrophages or lymphocytes [35,42]. Macrophages or lymphocytes are grown in a cell culture insert placed on top of keratinocytes to provide a barrier between the different cell lines. The controlled addition of inducers, such as lipopolysaccharide (LPS) to the macrophages induces gene transcription of the proinflammatory cytokine, leading to inflammatory effects [43,44].

Although 2D cell cultures have provided vital insights into psoriasis, nevertheless, they lack complex structures and interactions within tissues. This resulted in the development of three-dimensional (3D) models that can exhibit the interactions of skin cells and their milieu, reflecting the disease's complexity. Adult keratinocytes and de-epimerized dermis are commonly used in developing 3D models [45]. One strategy is to grow epidermal cells on the dead de-epidermised dermis. The de-epidermised dermis is a cell lacking structure that allows researchers to observe all morphological signs of differentiation except for keratin patterns [46–48]. Chiricozzi (2014) utilised reconstructed human epidermis (RHE) to study the genomic effect of IL-17 in psoriasis. This model consists of cornified, granular, spinous, and basal layers derived from normal human-derived epidermal keratinocytes to construct epidermal skin with full thickness [48]. Alternatively, there are commercial models available for psoriasis research. MatTek Corporation (MatTek Corporation, Ashland, MA, USA) utilised collagen gels incorporated with fibroblasts harvested from psoriatic patients and healthy human epidermal keratinocytes to develop a model with psoriasis phenotype, such as keratinocyte hyperproliferation and upregulated levels of pro-inflammatory cytokines that closely resembles the morphology of lesional psoriatic human skin [45,49].

Although in vitro models are vital in the investigation of the molecular mechanism of the disease, including evaluating the function and physiology of cells as well as their response to stimulators and inhibitors, nevertheless the lack of microenvironments and blood vessels in these models fails to mimic the complexity of the disease [50].

3.2. In vivo models

An animal model exhibiting a sustainable phenotype of the disease allows researchers to elucidate the pathogenesis of the disease and identify novel or vital cellular and molecular targets of the disease. This results in the emergence of potential therapeutic drugs or approaches [51]. In psoriasis, the most commonly used models are rodents. Mice with psoriasis-like or psoriasiform phenotypes are used to mimic human psoriasis as they express phenotypes, such as hyperproliferation of keratinocytes, T-cell infiltration, Munro-like neutrophilic microabscesses, and acanthosis (epidermal thickening). The expressed phenotype is dependent on immune cell activation and responds to immune suppression as the mice models are interleukin (IL)-23/IL-17A/tissue necrosis factor (TNF) and T-cell-dependent [52]. There are different types of mice models for psoriasis, including spontaneous, transgenic/knockout, intradermal injection of cytokines, topical application of imiquimod, and xenograft [53].

The first animal models initially used in the psoriasis research were mice with spontaneous mutations. Common psoriasis spontaneous models are Asebia (Ab), flaky tail, chronic proliferative dermatitis, and flaky skin (Fsn) mice. These models exhibit certain genetic backgrounds and allelic mutations resulting in psoriasis-like dermatitis [53]. Although, these models exhibit certain characteristics of psoriasis-like phenotypes, however, the spontaneous models are not widely used in psoriasis research because they lack T-cell infiltration in the skin [52].

Since psoriasis is a multifactorial disorder, which involves the interaction of different genetic susceptibility loci and gene products [54]. Transgenic or “knockout” mice models can be used for genotype-phenotype studies that allow researchers to study the pathophysiological of psoriasis. The knockout approach is used to determine the role of certain factors in psoriasis or psoriasiform phenotypes [53]. For example, in IL-20R2 knockout mice (IL-20R2$^{-/-}$), inhibition of IL–23–dependent epidermal hyperplasia was observed [55]. Moreover, the deletion of S100A9, a calprotectin, modulating complement component 3 (C3) that is responsible for T-cell-dependent inflammation, in imiquimod-induced mice significantly alleviated psoriasis-like phenotype [56]. Transgenic overexpression of molecules that are commonly elevated in psoriasis, such as transforming growth factor alpha (TGF-α), IL-6, IL-1a, interferon-gamma (IFN-γ), and vascular endothelial growth factor (VEGF) is another approach to investigate the role of these molecules in chronic inflammation [53]. An example is using TGF-β1 transgenic mice for preclinical therapeutic studies in psoriasis [57,58]. However, there are inherent limitations in the ability of fixed transgenes to mimic the reversible hyperplasia observed in psoriasis, resulting in changes in inflammatory cytokines levels after

treatment intervention [59]. Overall, using transgenic or "knockout" mice models in psoriasis has allowed the discovery of genes vital for producing cytokines, adhesion molecules, proteases, signalling molecules, proangiogenic factors, and other regulatory processes.

Another approach for animal models in psoriasis is intradermal injection of cytokines. The common model is the intradermal injection of IL-23 resulting in a TNF-α– and IL-20R2–dependent psoriasis-like inflammatory phenotype [55]. These models can be used to study the role of specific mediators, and the interplay between cytokines, chemokines, and their receptors in psoriasis [60]. The drawback of animal models induced with cytokines is that manipulation of cytokine profile or other components of the immune system can lead to the induction of phenotypes not exclusive to psoriasis-like inflammation. For example, the intradermal injection of IL-23 can also cause epidermal barrier defects, which are characteristic of atopic dermatitis [60].

Topical application of imiquimod (Toll-like receptor 7/8 agonist) is the most common model used to study psoriasis-like inflammation in mice [61]. The advantage of this model is that it is economical and easy to establish. Daily application of 5 % imiquimod creams such as Aldara on ears or depilated backs of mice results in the development of inflammatory response mimicking human psoriasis [62]. However, the drawback of this model is that the immunopathology differs from that of human psoriasis. In this model, dendritic cells and T cells play vital roles and the expression of inflammation-associated genes exhibits very limited similarities compared to human psoriasis [63,64]. Moreover, the topical application of the imiquimod can result in weight loss and systemic cytokine elevation due to possible ingestion of the cream. As a result, these factors should be taken into consideration when evaluating imiquimod-induced skin [65]. Nevertheless, this animal model remains an attractive and convenient model system to mimic and study certain aspects of psoriasis.

Despite the advantages exhibited by these various mouse models, confounding factors such as mouse strain and sex influence the phenotype. For example, in the imiquimod-induced model, the gene expression of C57Bl/6 mice resembled human psoriasis more closely than in BALB/c mice [66]. Moreover, in vivo models fully derived from animal exhibit limitations and do not completely resemble human conditions [53].

As a result, this gave rise to the xenograft approach, which involves engrafting human skin and/or immune cells onto immunodeficient animals [53]. The transplant of human psoriatic skin preserves many phenotypic, immunologic, and genetic traits of psoriasis [67]. However, the limitation of this model is that the transplantation procedure involves a wound-healing process that could affect the interpretation of the results, the evaluation of drugs that inhibit specific human cytokines can be compromised due to the crosstalk between human and murine immune systems and lastly, xenotransplantation models require patients who are willing to donate skin, thus limiting the sample size [68,69]. Therefore, xenograft models should be applied only when novel targets or selected drugs have been validated in other primary models [70].

Overall, these preclinical animal models have supported various clinical advances. These models can mimic individual or multifactorial components of human psoriasis, but none to date have replicated the complete pathogenesis or disease complexity. Nevertheless, with the complexity of the pathogenesis in psoriasis, no single model can be expected to include all the pathogenic mechanisms and aspects that manifest in affected humans [52].

4. Technological advancements enhancing psoriasis research

4.1. Transcriptomic analyses

Transcriptomic analyses allow the identification of differentially expressed genes (DEGs) between disorders by comparing their respective gene expression profiles. The data obtained from transcriptomic studies aid in understanding the molecular pathogenesis of psoriasis, which results in identifying potential therapeutic targets [71]. In a study, the involvement of IL-1 as a dominant immune response in the inflammation of psoriatic lesions was indicated through the comparison of IL-1-induced keratinocytes and that of psoriatic skin [72]. Moreover, the variation between different subtypes of psoriasis can be determined via comparative transcriptomic analyses. A study showed that with the aid of transcriptomic analyses on different psoriasis subtypes, such as plaque, palmoplantar, and scalp psoriasis, the signalling pathways specific to the subtypes as well as their molecular heterogeneity were established. This provides researchers with the opportunity to develop appropriate therapies specific to each of the subtypes [73]. Transcriptomic studies can also be used to identify the differences between conditions that often have overlapping clinical and histopathologic features, such as atopic dermatitis (AD) and psoriasis. A study indicated that the genetic expression that differentiates AD and psoriasis exhibits a distinctive pattern, especially in the expression of the chemokines. These insights allow the identification of leukocyte infiltration pathways distinct to these two skin conditions [74]. Moreover, another study also indicated the importance of A20, also known as the TNAIP3 gene, a negative regulator of NF-κB that inhibits inflammation. In psoriasis, the keratinocytes lack A20, leading to systemic inflammation and aggravation of inflammation by upregulation of chemokines and cytokines [75].

4.2. T-cell receptor (TCR) deep sequencing

TCR deep sequencing has been utilised to study the diversity, clonality, and specificities of TCR as well as to determine the changes in the intensity of TCR in different diseases and treatments [76]. In psoriasis, cutaneous leukocyte antigen $(CLA)^-$ blood fraction is responsible for the abundance of clonally expanded T cells in the skin lesion. This indicates that the T cells target other parts of the body and are not specific to the skin. Moreover, higher levels of clonality were observed among circulating cells without the expression of skin-homing factor CLA. Since not all clonally expanded T cells are from skin-homing, it is concluded that psoriasis is a condition with systemic inflammation [77]. This results in psoriasis patients exhibiting a risk of developing psoriatic arthritis and other inflammatory conditions [78]. Another study also reported that polyclonal T cells were significantly higher in active psoriatic skin compared to ameliorated psoriatic skin [63]. Moreover, it was proven that skin-homing T cells are vital in the initiation of inflammation in psoriasis [79]. Overall, TCR deep sequencing can be used to identify clones specific to psoriasis and patient-specific T cell clones that can be potential markers for the disease and to allow understanding of individual responses to treatments [80].

5. Emerging compounds in the psoriasis research pipeline

5.1. Targeting novel immune pathways or receptors

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor with higher potency compared to other PDE-4 inhibitors that were initially approved to treat severe chronic obstructive pulmonary disease [81].

As PDE-4 is activated, the production of inflammatory cytokines is upregulated via the NF-κB pathway meanwhile the degradation of intracellular cyclic adenosine monophosphate (cAMP) (Fig. 4), which is involved in the maintenance of immune homeostasis leads to the downregulation of anti-inflammatory cytokines, such as IL-10 [82]. When PDE-4 is inhibited, inflammation is ameliorated due to the suppression of inflammatory cytokines caused by the accumulation of cAMP [81]. This is because the protein kinase A (PKA) pathway is activated upon accumulation of cAMP. The PKA pathway is responsible for the elevation of anti-inflammatory cytokines and suppression of pro-inflammatory cytokines via gene transcription modulated by activating transcription factor 1 (ATF-1) and cAMP response element-binding (CREB) proteins [82]. In trials, roflumilast ameliorated plaque

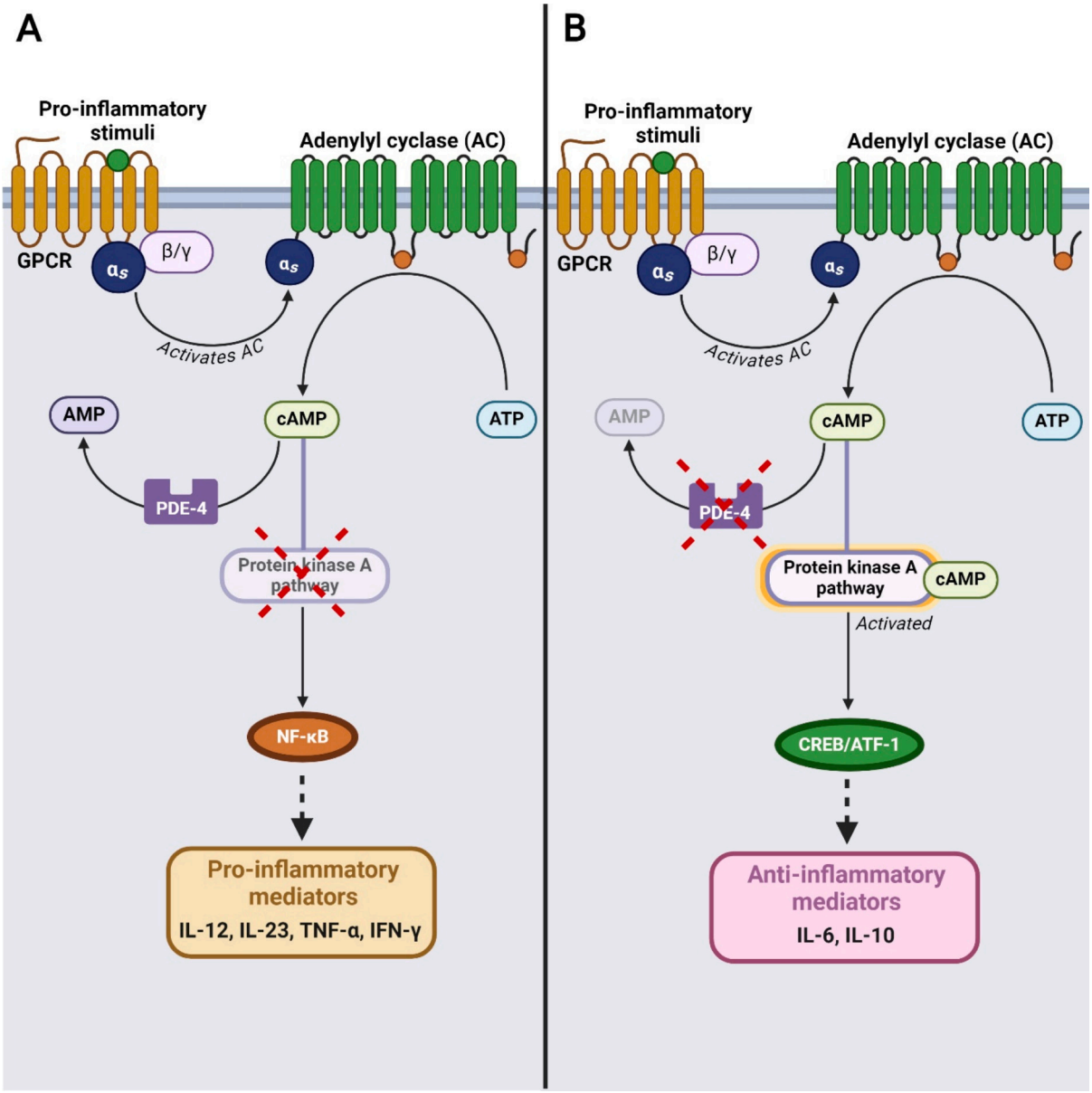

Fig. 4. PDE-4 signalling pathway in the pathogenesis of psoriasis. (A) PDE-4 causes the degradation of cAMP which is vital for the homeostasis of the immune system. This results in the activation of the NF-κB pathway, resulting in the expression of pro-inflammatory cytokines whereas anti-inflammatory cytokines are inhibited. (B) When PDE-4 is inhibited, the accumulation of cAMP activates PKA which is responsible for the induction of CREB and ATF-1, which is involved in the expression of anti-inflammatory cytokines. Abbreviations: cAMP, cyclic adenosine 3,5-monophosphate; PKA, protein kinase A; CREB, cAMP response element binding protein; ATF-1, cAMP-dependent transcription factor 1.

psoriasis in patients and exhibited greater efficacy than the placebo [83]. On 29th July 2022, roflumilast gained approval from the U.S. Food and Drug Administration (FDA) to be used as a topical cream to treat plaque psoriasis [84].

Mufemilast is another PDE4 inhibitor that is currently being tested for psoriasis but no data have been reported to date.

Piclidenoson (CF101) is an agonist that targets the A3 adenosine receptor (A3AR), a Gi protein-coupled cell surface receptor that is responsible for inflammatory activity (Fig. 1) [85]. Upon binding of piclidenoson to the A3AR, the NF-κB and AKT are down-regulated via downstream signal transduction pathways. This eventually leads to macrophage inflammatory protein-1 alpha (MIP-1α) and TNF-α inhibition as well as suppression of auto-reactive T cell proliferation and chemokine production [86–89]. A phase II/III study of piclidenoson against plaque psoriasis indicated a significant improvement in the Psoriasis Area and Severity Index (PASI) score in the presence of piclidenoson. Piclidenoson exhibits effectiveness higher than apremilast with a good safety profile [90].

Tapinarof is a one-of-a-kind small molecule topical agent that targets aryl hydrocarbon receptors. The aryl hydrocarbon receptor is vital in antioxidant activity, skin-barrier–protein expression, and regulation of cytokine. The expression of skin-barrier proteins filaggrin and loricrin as well as IL-17 are modulated by tapinarof when it binds to the aryl hydrocarbon receptor [91–93]. Several phase II clinical trials have shown that tapinorf improves the Physician's Global Assessment (PGA) and PASI score of patients with plaque psoriasis. However, patients have reported mild or moderate adverse effects [94,95]. In phase III trials, a single application of tapinarof cream daily for 12 weeks significantly improved the PGA and PASI of patients with mild-to-severe plaque psoriasis. However, patients reported adverse effects, such as headache, nasopharyngitis, and upper respiratory tract infection. Tapinarof then progressed to phase 3 Long Term Extension (LTE) study which indicated

that patients receiving the cream achieved clearance and maintenance of the condition. This resulted in the approval of tapinarof by the FDA on 24th May 2022, making it the first and only FDA-approved steroid-free topical medication [96].

5.2. Biologics

Bimekizumab is a humanized monoclonal IgG1 antibody that selectively inhibits IL-17A and IL-17F. It is a novel IL-17 inhibitor that targets both IL-17F and IL-17A [97]. Currently, bimekizumab is undergoing clinical trials for the treatment of psoriasis as well as psoriatic arthritis (PsA). In a phase III trial, bimekizumab was effective against patients with PsA or psoriasis who did not respond to TNF-α inhibitor [98]. Trials have also indicated that bimekizumab against PsA exhibits effectiveness similar to adalimumab (standard of care for PsA) and increased effectiveness compared to secukinumab (IL-17A inhibitor) [99,100]. The positive outcome of the phase III trials led to the approval of bimekizumab by the FDA in October 2023. Bimekizumab is the first IL-17A and IL-17F inhibitor to be approved to treat adults with moderate to severe plaque psoriasis [101]. Sonelokimab is a monovalent nanobody derived from camelid that specifically targets human IL-17A, IL-17F, and human serum albumin. A phase II study indicated patients treated with sonelokimab achieved almost clear or clear investigator's global assessment (IGA) scores which was not achieved by any patients in the placebo group. The safety profile of sonelokimab was acceptable and similar to secukinumab [102]. Izokibep is a novel molecule inhibiting IL-17A derived using Affibody technology [103]. Affibody technology is used to derive small protein molecules that are capable of binding to various peptides or target proteins with high affinity. These molecules belong to the family of antibody mimetics as they resemble monoclonal antibodies [104]. A phase II trial carried out to evaluate izokibep against patients with PsA, indicated that a significant proportion of patients treated with izokibep achieved ACR50 compared to the placebo group. The safety profile of izokibep is acceptable and it is well tolerated in patients [105]. Netakimab is a humanized monoclonal antibody targeting IL-17A. When netakimab was tested against patients with plaque psoriasis in a phase II trial, it significantly improved the condition of the patients and the efficacy of netakimab was constant throughout the treatment period [106]. Netakimab was also effective in patients with PsA who failed to respond to other therapies. The safety profile of netakimab was similar to placebo and other IL-17 inhibitors [107]. A phase III trial indicated that netakimab resulted in a significant proportion of patients with moderate-to-severe plaque psoriasis achieving PASI 75 compared to placebo and the ability to maintain clearance throughout the one-year treatment [106]. Vunakizumab is a novel monoclonal antibody targeting IL-17A tested against plaque psoriasis. Patients treated with vunakizumab experienced significant improvement compared to the placebo control in various trials [108].

JNJ-2113 is a novel and first oral antagonist that targets interleukin-23 receptor (IL-23R) with high affinity [109,110]. JNJ-2113 selectively inhibits IL-23 signalling and the corresponding downstream production of inflammatory cytokines. In the pathogenesis of psoriasis, the IL-23/IL-23R signalling pathway plays a vital role [109,111]. When JNJ-2113 was tested against patients with plaque psoriasis who did not respond to systemic therapy, patients experienced alleviation of skin condition and achieved PASI 75. Further studies indicated that some patients achieved PASI 100 with the treatment of JNJ-2113 [112]. Picankibart (IBI112) is a potent monoclonal antibody selectivity targeting IL-23p19 similar to guselkumab. In splenocytes, picankibart inhibited the production of IL-17 induced by IL-23 signalling. The treatment of picankibart alone and with the combination of anti-IL-1R antibodies resulted in the alleviation of psoriasis. The synergistic effect observed with the combination picankibart and anti-IL-1R antibodies indicates the potential of combination therapy for psoriasis. The safety aspect of picankibart stated that it is well tolerated [113].

Spesolimab is a humanized anti-IL-36 receptor monoclonal antibody. When tested against generalized pustular psoriasis (GPP) patients in several phase II trials, patients treated with spesolimab achieved lesion clearance within the first week of the treatment [114]. Additionally, spesolimab induced a rapid effect against pathways associated with GPP by downregulation of immune cells associated with inflammation signalling. However, in patients with palmoplantar pustulosis (PPP), spesolimab was capable of alleviating the phenotypic presentation [115]. Based on the phase II trial that indicated a significant proportion of patients experience reduced GPP flares when treated with spesolimab compared to placebo, resulted in the FDA approval of the drug on 19th March 2024. Spesolimab is the first targeted therapy for the treatment of GPP [116]. Imsidolimab is an antibody specifically targeting the IL-36 receptor. In a phase II trial, GPP patients treated with imsidolimab exhibited an instant effect in alleviating the phenotypic condition. Imsidolimab progressed to the phase III trials as it has an acceptable safety profile and is well-tolerated [117]. Two phase III trials have indicated that a single intravenous dose of imsidolimab significantly ameliorated GPP and maintained the effect by preventing any occurrence of flare as compared to placebo [118].

5.3. JAK inhibitors

Deucravacitinib (BMS-986165) is a one-of-a-kind inhibitor that specifically targets TYK2 through allosteric inhibition, distinguishing it from other tyrosine kinase inhibitors [119,120]. Based on phase II trials, deucravacitinib significantly improved the condition of patients with psoriasis and PsA [121,122]. Currently, a Phase III trial indicated that patients with psoriasis treated with deucravacitinib achieved almost clear or clear static Physician's Global Assessment (sPGA) scores and PASI 75, surpassing the efficacy of apremilast. This concludes that deucravacitinib is effective against psoriasis and PsA [123]. Based on the outcome of the phase III trial and the good tolerability and safety profile, deucravacitinib was approved by the FDA on 9 September 2022. Deucravacitinib is the first oral drug approved to treat adults with moderate-to-severe plaque psoriasis that selectively inhibits TYK2 [124]. Baricitinib is a reversible JAK inhibitor mainly targeting JAK1 and JAK2 [125,126]. In a phase II trial, a significant proportion of patients treated with baricitinib achieved PASI 75 and PASI 90 indicating its effectiveness against psoriasis. However, intolerance of baricitinib at higher doses was observed with the occurrences of anaemia, neutropenia, and lymphopenia. With careful monitoring, baricitinib shows promise as an anti-psoriatic agent [127].

Upadacitinib is an orally taken JAK inhibitor that targets specifically JAK1 [128]. In the phase III trial, patients who received upadacitinib achieved significant improvements in psoriatic arthritis compared to the placebo group [129]. Based on the phase III trials, the FDA approved upadacitinib on 14th December 2021 for patients with active PsA who did not respond to TNF blockers [130].

JAK inhibitors that are still in the early stage of clinical trials for psoriasis with limited data reported are ivarmacitinib.

5.4. Small molecules

IMMH002 is a novel S1P1 agonist that can inhibit the activation of peripheral pathogenic lymphocytes by signals from secondary lymphoid organs and the thymus. The study concluded that IMMH002 alleviated the phenotypic condition as indicated by the improvement in the PASI score. The accumulation of T lymphocytes is induced in the thymus but inhibited in peripheral blood and skin by IMMH002 through lymphocytes' homing induction [131]. Lymphocytes' homing causes the dispersion of immunologic repertoire, resulting in the movement of lymphocyte subsets to specialized microenvironments. These microenvironments are not only responsible for the modulation of differentiation and survival of lymphocyte subsets but also vital for guiding immune effector cells to sites of microbial invasion or antigenic [132]. Results indicated that T lymphocyte distribution can be rapidly

modulated by IMMH002, indicating it is a potential drug for psoriasis treatment [131] (Table 1).

6. Drug delivery and novel therapeutic approaches

6.1. Nanotechnology and nanotherapeutic approaches

In psoriasis, the skin is a barrier that affects the effective delivery of drugs to the affected areas. Moreover, current therapies exhibit limitations, including patient adherence, poor drug absorption and safety concerns due to toxicity to other tissues. The development of new drugs is also time-consuming and costly. Hence, there is a crucial need for innovative therapies, such as novel drug carrier systems to achieve improved delivery while maintaining the safety profile [135]. A study indicated that apremilast-loaded microemulsion (APR-ME) exhibiting Newtonian behaviour exhibited anti-inflammatory properties with enhancements, such as significant tolerability and timed-release effect [136]. Researchers also developed methotrexate-loaded nanostructured lipid carriers (MTXNLCs) gel that was advantageous over conventional methotrexate (MTX) gel since the MTXNLC gel demonstrated improved anti-psoriatic activity with timed-release effect and decreased adverse effect [137].

6.2. Probiotic and prebiotic approaches

Various research has indicated the vital role of gut microbiota in autoimmune diseases, including psoriasis. In psoriatic patients, elevated inflammatory molecules induce gut microbiota dysbiosis and abnormal immune response [138]. Gut microbiota dysbiosis in autoimmune diseases, such as psoriasis results in various effects, such as suppression of regulatory T cells (Tregs) and bacterial function as well as translocation of bacteria, impairment of epithelial barrier and inflammation [139,140]. Moreover, dysbiosis leads to the amplification of the inflammatory milieu via alteration in the gut microbiota and TLR expression in antigen-presenting cells as well as Th17/Tregs imbalance [141,142]. Probiotic and prebiotic supplementation could be a potential

Table 1
Summary of emerging compounds in the psoriasis research pipeline.

Target	Name/label	Classification	Description	References
Phosphodiesterase-4 (PDE-4)	Roflumilast	Small molecules	Exhibits higher potency compared to other PDE-4 inhibitors and is found to exhibit greater efficacy than the placebo in ameliorating plaque psoriasis. Approved by FDA on 29th July 2022 to treat plaque psoriasis.	[81,83,84]
Phosphodiesterase-4 (PDE-4)	Mufemilast	Small molecules	No data are available.	[133]
A3 adenosine receptor (A3AR)	Piclidenoson (CF101)	Small molecules	Targets A3 adenosine receptor to inhibit activation of NF-κB and AKT. Significant improvements were observed when piclidenoson was tested against plaque psoriasis in the phase II/III study.	[90]
Aryl hydrocarbon receptors	Tapinarof	Small molecules	Improvement in the PGA and PASI scores was observed after the treatment with tapinarof. However, mild or moderate adverse effects were present among patients. It is the first and only steroid-free topical medication approved by FDA on 24th May 2022.	[94–96]
IL-17F and IL-17A	Bimekizumab	Biologics	Clinical trials have indicated that bimekizumab was effective against psoriasis and PsA, and its activity was comparable with adalimumab, the standard of care for PsA. It is the first IL-17A and IL-17F inhibitor to be approved to treat adults with moderate to severe plaque psoriasis.	[98,99,101]
IL-17A, IL-17F, and human serum albumin	Sonelokimab	Biologics	The treatment of sonelokimab in psoriatic patients resulted in achieving almost clear or clear IGA scores with acceptable safety profile that is similar to secukinumab.	[102]
IL-17A	Izokibep	Biologics	A novel molecule derived using Affibody technology. A phase II trial indicated that izokibep is effective against PsA with acceptable safety profile.	[105]
IL-17A	Netakimab	Biologics	Significantly effective against plaque psoriasis in a phase II trial. The safety profile is comparable to placebo and other IL-17 inhibitors. A phase III trial indicated significant amelioration of patients with moderate-to-severe plaque psoriasis and the ability to maintain clearance throughout the one-year treatment.	[106,107]
IL-17A	Vunakizumab	Biologics	Various trials have shown vunakizumab was significantly effective against psoriasis and with better efficacy compared to the placebo.	[108]
IL-23R	JNJ-2113	Biologics	Down-regulates inflammatory cytokines by inhibiting IL-23 signalling. Plaque psoriasis patients experienced alleviation of skin condition after treated with JNJ-2113.	[112]
IL-23p19	Picankibart (IBI112)	Biologics	The treatment of picankibart alone and in combination with anti-IL-1R antibodies was effective against psoriasis. The potential of being developed as combination therapy due to synergistic effect. It is well-tolerated.	[113]
IL-36 receptor	Spesolimab	Biologics	In several phase II trials, spesolimab was highly effective against GPP compared to palmoplantar pustulosis. It is the first targeted therapy approved by the FDA for the treatment of GPP.	[114–116]
IL-36 receptor	Imsidolimab	Biologics	Alleviated the phenotypic presentation of patients with GPP in the phase II trial. It has an acceptable safety profile and is well-tolerated. Imsidolimab also prevented any occurrence of flare in GPP patients.	[117,118]
TYK2	Deucravacitinib (BMS-986165)	JAK inhibitor	In phase II trials, the condition of patients with psoriasis and PsA was significantly improved. In the phase III trial, patients with psoriasis achieved improvement in sPGA and PASI scores. Higher efficacy compared to apremilast. The first oral drug approved by the FDA to treat adults with moderate-to-severe plaque psoriasis that selectively inhibits TYK2.	[121–124]
JAK1 and JAK2	Baricitinib	JAK inhibitor	A reversible JAK inhibitor that exhibited significant improvement in patients with psoriasis in phase II trials. However, adverse effects were observed at higher doses.	[127]
JAK1	Upadacitinib	JAK inhibitor	In phase III trials, significant improvements, better than the placebo group were observed in patients with psoriasis. The FDA approved upadacitinib to treat patients with active PsA.	[129,130]
JAK1	Ivarmacitinib	JAK inhibitor	No data are available.	[134]
S1P1	IMMH002	Small molecules	Rapidly modulates T lymphocyte distribution, leading to inhibition of peripheral pathogenic activation. Ameliorated phenotypic condition of psoriatic patients in clinical trials.	[131]

therapeutic strategy in the management of psoriasis by treating gut microbiota dysbiosis [138]. A study indicated that certain probiotic strains alleviated psoriasis in IMQ-induced psoriasis-like mice by targeting the IL-23/Th17 axis and inhibiting the expression of inflammatory factors. However, more studies are needed to fully elucidate the potential benefits of probiotics and prebiotics for psoriasis [143].

6.3. Topical delivery enhancements

Topical therapy is a common treatment option for psoriasis, especially if it is localized. However, the enhancement of topical delivery is needed to overcome limitations, such as low efficiency in delivery through skin penetration as well as allergies and irritation [135]. A perforated microneedle (PMN) was developed for adoptive cell therapy in psoriasis. The enzyme-degradable microneedle matrix facilitates cell migration and releases of fatty acid in the hyperinflammatory area of psoriasis, enhancing the Treg suppressive functions via the fatty acid oxidation (FAO)–mediated metabolic intervention. Treg cells administered through PMN substantially ameliorated psoriasis syndrome with the assistance of fatty acid-mediated metabolic intervention in a psoriasis mouse model [144]. Recently, researchers have developed a bioelectronic patch comprised of sensors, a gel derived from gelatine and starch, and bacterial cells, such as *S. epidermidis* which are naturally found on human skin and known to be anti-inflammatory. When the bioelectronic patch is integrated into the skin, the bacteria secrete anti-inflammatory compounds whereas the sensors monitor the skin conditions, such as humidity and temperature. Initial studies of the patch on mice with psoriasis-like skin lesions have shown that significant improvement in the condition and continuous monitoring of the skin was achieved [145].

6.4. Gene and RNA-based therapies

Recent advances in genomics have led to the discovery of various genetic variants involved in the pathogenesis of psoriasis, acting as molecular signatures of the disease. Hence, gene and RNA-based therapies are potential therapeutic approaches to overcome drug response variability as well as give rise to personalised therapy [35]. In a study, small interfering RNA (siRNA) has been utilised to inhibit the NF-κB pathway. The IL-siRNA is used to target NF-kappa-B inhibitor zeta (NFKBIZ), an upstream target in the NF-κB pathway that is responsible for the expression of psoriasis-related antimicrobial peptides and proinflammatory cytokines [146]. Additionally, ionic liquids were used to deliver IL-siRNA effectively while maintaining the therapeutic efficacy of the siRNA. Another study targeted genes encoding the IL-17A receptor (IL-17RA) with topically administered liposomal spherical nucleic acids (L-SNAs). In the psoriatic mouse model, IL-17RA L-SNAs significantly inhibited the expression of mRNA related to the pathogenesis of psoriasis, leading to amelioration of the psoriatic lesion [147].

6.5. Personalised medicine

A personalised approach is necessary to develop patient-specific therapies based on genetic makeup to prevent variation in drug response [148]. In a study, early gene-expression profiling was used to determine the long-term efficacy and clinical response of untested drugs. The effects and responses of drugs in numerous patients are predicted through various analyses to determine and provide the most effective treatments [149]. Recently, a machine learning algorithm was used to predict the response rate of patients to different psoriasis biologics. This study prevents the use of a trial-and-error approach in biologic treatment as well as gives rise to precision medicine [150]. Thus, the integration of "-omics"-derived data and analytics provides the opportunity to evaluate the clinical response of patients to specific biological treatment to determine the group of patients who potentially have significant drug response with low adverse effects [148].

7. Conclusion

Understanding the pathogenesis of psoriasis is vital for the identification of biological targets, essentially for the development of novel therapies. Recent advancements and novel approaches in psoriasis research allow researchers to identify novel cells, cytokines, signalling pathways, and molecular targets that play a role in the pathogenesis of psoriasis. These discoveries drive researchers to develop novel treatments with higher efficiency and selectivity as well as minimum side effects. Although there is no cure for psoriasis, nevertheless, there are treatment options ranging from small molecule inhibitors to advanced biologics and gene-based therapies for psoriatic patients. Enhancements in drug delivery and personalised medicine also gained the attention of researchers in the effort to develop therapies with enhanced efficacy and safety. However, to date, the pathogenesis of this disease has not been completely elucidated regardless of the rapid advancements. New oral therapies should be tested along with approved biologics to position them in the treatment landscape based on their effectiveness [151]. The long-term goal of psoriasis research is to develop tailored approaches with higher effectiveness to manage this challenging condition.

CRediT authorship contribution statement

Dineshwar Sugumaran: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Audrey Chee Hui Yong:** Supervision, Funding acquisition. **Johnson Stanslas:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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