



Invited review article

Recent advances in atopic dermatitis and psoriasis: Genetic background, barrier function, and therapeutic targets



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ABSTRACT

Atopic dermatitis (AD) and psoriasis are common inflammatory skin diseases. Although clinical pictures of these two diseases are quite different, they share some common pathological backgrounds such as barrier dysfunction and enhanced IL-22 expression. To explain the clinical differences of the diseases, it has been proposed that Th2/Th22-polarized immune status together with an attenuated Th17 axis may cause insufficient induction of antimicrobial peptides and more severe barrier dysfunction in AD. While skin barrier dysfunction is commonly seen in AD and psoriasis, a Th2-dominant cytokine milieu down-regulates immunity against infections, which are commonly seen in lesional skin of AD. In the era of biologics, increase in the understanding or new discoveries of molecules involved in the development of various diseases will instantly lead to a new therapeutic strategy. In this review, we give an overview of recent advances in AD and psoriasis, especially on genetic background, barrier function, and therapeutic targets.

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1. Introduction

Atopic dermatitis (AD) and psoriasis are common inflammatory skin diseases. As time moves on, the main players of these diseases drawing researchers' attention have been changing. Twenty years ago, researchers tried to divide various diseases into two categories; T-helper 1 (Th1) diseases and T-helper 2 (Th2) diseases. Th2 subset has been an important therapeutic target for AD

patients because eosinophilia and high serum levels of IgE and thymus and activation-regulated chemokine (TARC) suggest its critical roles in the development of AD. Although Th2 subset is still important, barrier dysfunction and resultant diminished epidermal defense have been drawing more attention since the discovery of loss-of-function mutation of filaggrin in AD patients [1]. With regard to psoriasis, the disease was thought to be induced by dysregulated turnover of keratinocytes. After the therapeutic effect of cyclosporine was discovered, psoriasis had been thought to be mainly mediated by T cells, especially Th1 cells. The concept further evolved when the importance of interleukin (IL)-23, IL-17, and IL-22 in the pathogenesis of psoriasis was discovered [2].

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Fig. 1. Clinical pictures of skin lesions of AD (left) and psoriasis (psoriasis).

Currently, various biologics targeting IL-17-related cytokines are available or under development.

Clinical pictures of AD and psoriasis are quite different (Fig. 1). In AD lesions, scratch marks, exudation, and dry skin in the surrounding area are remarkable. Bacterial, fungal, and viral infections are frequently seen. In contrast, lesional skin of psoriasis is characterized by thick silvery-white scale over well-defined red thickened skin. Some researchers, however, report similar pathological background between the two diseases. IL-17 is reported to be expressed not only in psoriasis lesional skin but also in AD skin [3]. On the other hand, decrease in filaggrin expression has been shown in patients with psoriasis [4]. To explain the clinical differences of these diseases, it has been proposed that Th2/Th22-polarized immune status together with an attenuated Th17 axis may cause insufficient induction of antimicrobial peptides and more severe barrier dysfunction in AD (Fig. 2). While skin barrier dysfunction is commonly seen in AD and psoriasis, a Th2-dominant cytokine milieu down-regulates immunity against infections, which may reflect the commonly seen infectious lesions in the skin of AD [2].

Acceleration in the understanding of the pathogenesis of the diseases provides us with chance to develop new therapeutic strategies. In this review, we give an overview of recent advances

in AD and psoriasis, especially on genetic background, barrier function, and therapeutic targets.

2. Genetic background of AD

Although loss-of-function mutation of filaggrin has been reported to be a predisposing factor for AD [1], filaggrin knockout mice, on both the C57BL/6 and BALB/c backgrounds, did not develop spontaneous dermatitis under SPF conditions [5], suggesting that exposure to environmental factors might be critical. The cohort study of children in Ishigaki Island, which has a tropical climate with high humidity and high temperature throughout the year, demonstrated that the filaggrin loss-of-function mutation frequency was not significantly different between the AD and non-AD groups [6]. The results also suggested the importance of environmental factors for development of AD.

The prevalence of single-nucleotide polymorphisms (SNPs) in filaggrin gene varies depending on race and community. As some mutations are difficult to differentiate, restriction enzymes should be carefully selected [7]. Two recent papers following the previous genome-wide association studies (GWAS) of AD have suggested association of SNPs in *ZNF365*, *RTEL1*, *IL13*, and *ZMIZ1* loci with development or subphenotypes of AD [8,9].

3. Barrier function in AD

The stratum corneum (SC) is a well-known structure responsible for the cutaneous barrier. Ceramide hydrolysis by ceramidase in SC yields both sphingoid bases and free fatty acids. Recent study revealed that sphingoid base composition influences lamellar membrane architecture in SC, suggesting that altered sphingoid base profiles could contribute to the barrier abnormality in AD [10]. Pyrrolidone carboxylic acid (PCA), a natural moisturizing factor, and caspase-14, which cleaves filaggrin monomers to free amino acids and their derivatives such as PCA, are also important for skin barrier. The quantity of PCA and caspase-14 was shown to be decreased in inflammatory lesions compared to non-lesion in AD patients [11]. The amounts of PCA and caspase-14 in the lesion of AD patients correlated with clinical severity as determined by eczema area and severity index score and the skin barrier functions. These differences in AD skin compared to normal or non-lesional skin may be therapeutic targets to improve skin barrier function.

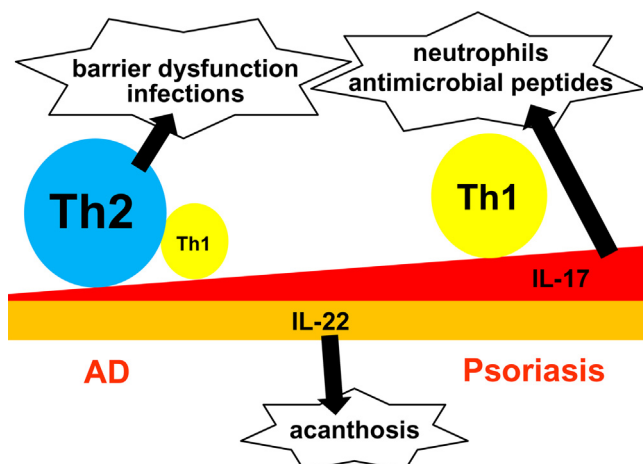


Fig. 2. Difference in the balance of Th2 and IL-17 between AD and psoriasis.

The role of *Staphylococcus aureus* (*S. aureus*) in skin barrier dysfunction in AD was also recently reported [12]. Normal human keratinocytes treated with *S. aureus* extracts increased expression of IL-6 and significantly reduced expression of the terminal differentiation markers keratin 1, keratin 10, loricrin, and filaggrin. Anti-IL-6 antibody inhibited the decrease in keratin 10 mRNA or protein expression, suggesting that *S. aureus* inhibits the terminal differentiation of keratinocytes by stimulating IL-6 secretion. Thus, skin barrier dysfunction in AD may not only cause frequent bacterial infection but also may result from inflammation induced by infectious agents such as *S. aureus*.

4. New therapeutic targets for AD

Current therapeutic options for moderate to severe AD in children and adults are unsatisfactory and discovery of new therapeutic targets is a pressing issue. Recent reports on future treatment of AD mainly focus on inflammatory components such as TARC, IL-31, and thymic stromal lymphopoietin (TSLP), and prevention of itch sensation (Fig. 3).

Serum levels of TARC have served as a reliable biomarker of disease progression of AD [13]. It was recently reported that combination of tumor necrosis factor (TNF)- α and IL-4 induced expression of TARC mRNA and appreciable amounts of TARC protein by dermal microvascular endothelial cells and dermal fibroblasts, but not by primary normal human epidermal keratinocytes in vitro [14]. TARC production by those dermal cells was not inhibited by dexamethasone or tacrolimus, suggesting that anti-inflammatory therapy may decrease TARC in AD patients indirectly, via its inhibitory effects on TNF- α and IL-4 production. Eotaxin-3 is another major Th2 chemokine. Eotaxin-3 is highly expressed in epidermal keratinocytes of lesional AD skin [15]. Analyses on human dermal fibroblasts showed abundant expression of CCR3, a receptor of eotaxin-3. Stimulation of dermal fibroblasts with eotaxin-3 induced intracellular Ca(2+) mobilization, as well as enhanced fibroblast migration and repair capacity, which may be related with tissue remodeling in AD.

IL-31 is a relatively new cytokine strongly related with pruritus. In AD skin, many CD11b cells express this cytokine [16]. Keratinocytes and nerve fibers in the dermis of AD and the neurons of normal human dorsal root ganglia express IL-31 receptor A, suggesting that IL-31 signaling may be a contributing factor in the persistence and exacerbation of AD skin lesions.

TSLP is produced by epidermal keratinocytes, and it induces Th2-mediated inflammation by activating dendritic cells, mast cells, and T cells. TSLP expression is enhanced in AD lesional skin

[17]. The effect of antimycotic agents, which sometimes improve the symptoms of AD, on TSLP expression was recently reported [18]. The antimycotics itraconazole, ketoconazole, luliconazole, terbinafine, butenafine, and amorolfine suppressed the secretion and mRNA expression of TSLP from keratinocytes stimulated by polyinosinic-polycytidylic acid plus IL-4. SC pH is also important for TSLP expression because neutralization of SC pH can stimulate activity of serine protease. Activated serine protease, in turn, induces TSLP production of through protease-activated receptor-2. SC neutralization induced cutaneous inflammation with elevated serum levels of TSLP, TARC, and IgE in flaky-tail mice [19]. Thus, maintenance of pH of SC and application of antimycotic agents may be useful to decrease TSLP expression levels in AD skin.

Breaking the itch-scratch cycle in AD patients is very important for controlling skin conditions. E6005, a topically effective phosphodiesterase 4 (PDE4) inhibitor, is a promising antipruritic drug. PDE4, which catalyses the conversion of cyclic AMP to 5'-AMP, plays a critical role in the pathogenesis of inflammatory disorders. In mouse model, topical E6005 increased cutaneous cAMP content and inhibited proteinase-activated receptor 2-associated itching [20]. Electroacupuncture is also useful to treat pruritus in AD. High-frequency electroacupuncture alleviated pruritus of AD-like lesions in rats induced by capsaicin injection through the release of dynorphin [21].

Dopamine is a unique therapeutic target. It transduces signals via five subtypes of G protein-coupled receptors. Among these subtypes, the D1 and D5 receptors belong to the D1-like group. Administration of SCH 23390, the D1-like receptor antagonist, did not affect Th1-type contact hypersensitivity but suppressed the immediate-type reaction and the late phase reaction in AD mouse model [22]. In addition, SCH 23390-treated mice showed higher interferon- γ and lower IL-4 mRNA levels in the ear skin of challenged mice than did non-treated mice, suggesting that the D1-like receptors is a good therapeutic target in AD.

5. Genetic background of psoriasis

It is widely accepted that development of psoriasis is dependent on the patient's genetic background and environmental factors [23]. The search for genes responsible for familial psoriasis through genome-wide linkage scans identified several putative susceptible loci. Genetic loci other than the psoriasis susceptibility region 1 and gene variants have been identified through several gene specific studies as well as GWAS performed among different populations [9,24]. Among others, SNPs in genes encoding IL-22 have been recently linked to psoriasis susceptibility [25]. In the Japanese population, the polymorphisms in IL22 had the important influence on the susceptibility to psoriasis vulgaris, but not to AD. Vitamin D analogues have been used in psoriasis intervention alone or in combination with other treatments. The study on association of polymorphisms of the vitamin D receptor gene with psoriasis was recently performed on large sample size [26]. In the Han population of northeastern China, an association between one of the vitamin D receptor gene polymorphisms (*Apal*) and psoriasis was identified, similar to previous studies based on small sample size in the Korean, Turkish, Croatian, or Egyptian population. Hayashi et al. found that the *TNF receptor-associated factor 3-interacting protein 2* gene polymorphisms is associated with psoriasis vulgaris, but not with AD, in the Japanese population [27]. This gene encodes a protein involved in IL-17 signaling, which interacts with members of the nuclear factor-kappa-B transcription factor family.

There are emerging evidences that psoriasis is associated with other chronic diseases with an inflammatory component, such as the metabolic syndrome, diabetes mellitus and cardiovascular diseases. Recently variants in some genes have been found to

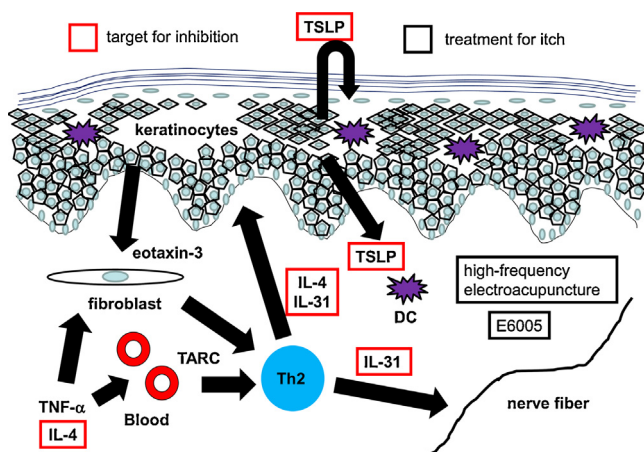


Fig. 3. Therapeutic targets for AD.

increase the risk for developing such other chronic diseases in patients with psoriasis. Variation at *IL12B*, *IL23R*, and *IL23A* would contribute not only to psoriasis susceptibility but also to risk of developing type 2 diabetes in the Caucasian population [28]. Genetic variants at *CSMD1* were associated with cigarette smoking and those at *TNIP1/ANXA6* were associated with alcohol use, affecting the risk for psoriasis, in the Han Chinese population [29]. This study provided an empirical evidence that these genes and environmental factors interacting together contributed to the increased risk for psoriasis.

Generalized pustular psoriasis (GPP) is an uncommon variant of psoriasis, with an acute, subacute, or occasionally chronic eruption, with sterile pustulosis as its central feature. There has been increasing knowledge of the genetic background of GPP. Currently, two genes, *IL-36 receptor antagonist* (*IL36RN*) and *CARD14*, which encode proteins secreted by keratinocytes or keratinocytes-localized proteins, are thought to be the causative or susceptibility genes in GPP [30]. To date, 17 *IL36RN* mutations, including the mutations reported only in 1 or 2 cases, have been identified in GPP patients from the African, European, or Asian populations [30–32]. Thus, at least some cases with GPP are associated with deficiency of *IL-36RN*. It is, however, not determined whether specific therapeutic strategies should be applied to GPP with *IL-36RN* deficiency. Recombinant *IL-36RN* could be one of the most promising therapies for those patients.

Other than genetic backgrounds, epigenetic network might be causative elements in psoriasis. Among epigenetic factors postulated to be responsible for disease pathogenesis, DNA methylation is one of the keys. Broadly, it is an epigenetic silencing mechanism, responsible for diverse biological regulations including genome instability, cellular differentiation, imprinting and X-linked inactivation. Dermal mesenchymal stem cells (MSCs) isolated from psoriatic patients showed aberrant promoter methylation of several genes, compared to normal MSCs [33]. This study suggested a possible role of dermal MSCs in psoriasis pathogenesis.

6. Barrier function in psoriasis

Many reports indicated the abnormal expression of filaggrin and loricrin in patients with psoriasis [4]. On the other hand, overexpression of involucrin was found in lesional skin of psoriasis [34]. In normal skin, involucrin was only detected in the granular layer and upper stratum spinosum. By contrast, in psoriatic lesional skin, involucrin was identified in whole stratum spinosum. Neuronatin, which is a neuronal developmental and differentiation molecule, was also up-regulated in the epidermis of psoriasis and regulated involucrin expression [35].

7. New therapeutic targets for psoriasis

Treatment of psoriasis can be divided into three main categories of pharmacological intervention: topical therapy, phototherapy, and pharmacotherapy with immunomodulatory drugs, such as traditional oral agents (methotrexate, retinoids and cyclosporine) and/or biologic agents. Newer insights into traditional therapies have been investigated, such as down-regulation of *IL-22* receptor by calcipotriol and a role of *CD147* to promote resistance to methotrexate [36,37]. In addition, recent reports have revealed therapeutic targets in the development of psoriatic skin lesions (Fig. 4).

TNF-α inhibitors significantly reduce disease activity among patients with psoriasis and psoriatic arthritis. While the treatment is beneficial for many patients, the treatment itself is expensive and has potential serious side effects. Some patients lose therapeutic response after several cycles of therapy, partially due to induction of antibodies to the biologics. To assist the

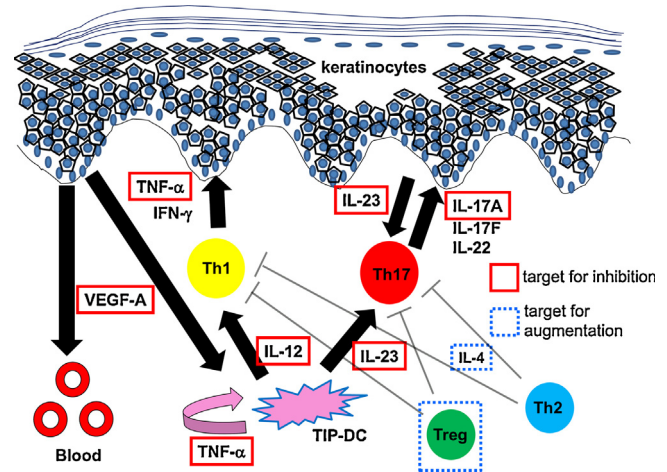


Fig. 4. Therapeutic targets for psoriasis.

selection of patients for the treatment, measuring antinuclear antibodies and anti-double-stranded DNA antibodies prior to the treatment was recently suggested. Lower concentrations of anti-double-stranded DNA antibodies predicted better response to adalimumab treatment [38]. The clinical trial with anti-*IL-22* antibody has terminated in 2011 because of lack of efficiency. In K5.Stat3C transgenic mice, which develop psoriasis-like lesions after wounding stimuli or topical treatment with 12-*O*-tetradecanoylphorbol 13-acetate [39], *IL-22* deficiency failed to suppress the development of psoriatic lesions [40]. Newer biologic reagents such as brodalumab, ixekinumab, and secukinumab which target either *IL-17* receptor (brodalumab) or *IL-17* itself (ixekinumab and secukinumab) are under development. In clinical trials, these biologic reagents showed good therapeutic efficacy against psoriasis [41].

Based on the fact that psoriasis is dominantly mediated by Th17 and Th1 cells, pharmaceutical interventions, aiming at a shift to a Th2 environment in the inflamed skin, have been proposed as a therapeutic strategy for the treatment of psoriasis. In mouse models of psoriasis, F8-*IL-4*, a fusion protein of the F8 antibody (specific to the alternatively-spliced extra domain A of fibronectin) with murine *IL-4*, selectively localized to inflamed skin lesions following intravenous administration and mediated a therapeutic benefit [42]. The antibody-mediated pharmacodelivery of cytokines can be a new therapeutic tool for the treatment of psoriasis. On the other hand, in some psoriatic patients, impaired function of FOXP3+ regulatory T cells has been identified [43]. Recently, it was clarified that some psoriatic patients showed cytoplasmic retention of FOXP3 and these patients had higher serum *IL-17* levels and disease severity [44]. In psoriasis, c-Jun N-terminal kinase (JNK)-phospho-c-JUN (ser63/73) pathway was essential for FOXP3 nuclear translocation. Thus, selective manipulation of JNK in regulatory T cells can be a promising choice for the development of drugs in the treatment of psoriasis.

Epidermal hyperplasia is another characteristic feature of psoriasis. Direct interactions between keratinocytes and T cells are important in the development of psoriasis [45]. The Ras-Raf-mitogen-activated protein kinase (MAPK) pathway, which was associated with keratinocyte proliferation, was up-regulated in the hyperplastic epidermis of psoriasis. This Raf-MAPK-dependent psoriatic-like epidermal hyperplasia required Stat3 signaling in keratinocytes [46], which played an important role in psoriasis [39]. Thus, inhibition of Stat3 signaling can ameliorate epidermal hyperplasia in psoriatic skin. On the other hand, the sphingolipid sphingosine-1-phosphate exhibited anti-proliferative and anti-inflammatory effects in mouse models of psoriasis [47]. Topical

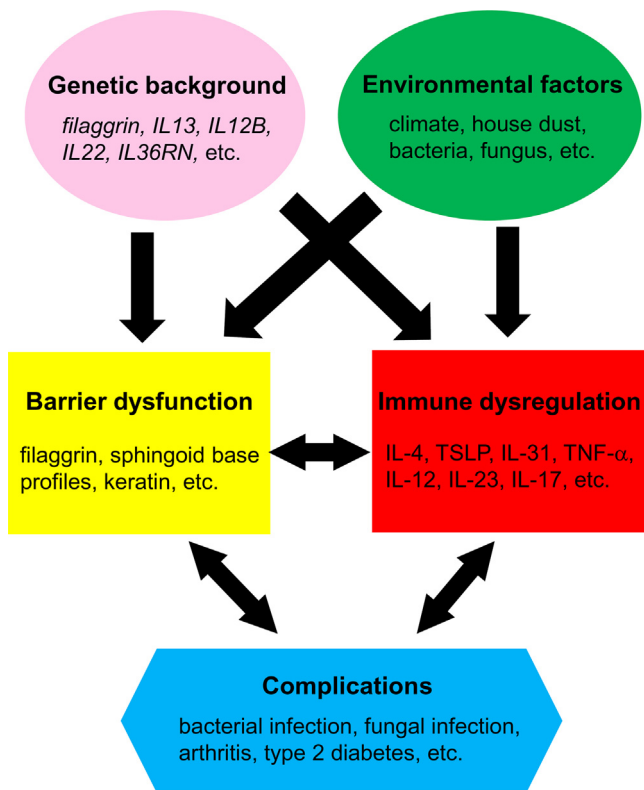


Fig. 5. Various factors surrounding AD and psoriasis.

administration of sphingosine-1-phosphate might be a new option for the treatment of mild to moderate psoriasis lesions.

Vascular endothelial growth factor (VEGF)-A is a major regulator for angiogenesis and is produced by proliferative keratinocytes in psoriatic skin. VEGF-A promoted IL-17A-producing $\gamma\delta$ T cell accumulation in mouse skin and served as a chemotactic factor for plasmacytoid dendritic cells [48]. Consistently, treatment of VEGF-Trap, a soluble fusion protein that binds VEGF with high affinity, improved psoriasis-like skin inflammation in KC-Tie2 mice through decrease of T cell infiltration and Th17 cytokine expression in the skin [49]. Thus, blocking of the VEGF-A can be a potential therapeutic target for psoriasis.

Gene expression regulation by micro RNAs (miRNAs) in the post-transcriptional level is considered as another important epigenetic mechanism. In recent years, there have been evidences implying the role of miRNAs in the pathogenesis of psoriasis based on studies on miRNAs expression in the skin, peripheral blood mononuclear cells, or serum [50]. Further studies are needed to elucidate miRNAs mechanisms of action, which may be useful for novel therapeutic approaches.

8. Conclusion

Both genetic background and environmental factors induce barrier dysfunction and immune dysregulation in AD and psoriasis, which are frequently associated with various infections and systemic inflammatory diseases (Fig. 5). In the era of biologics, discovery of a new molecule playing critical roles in the development of AD and psoriasis will instantly lead to a new therapeutic strategy. While data and evidence to unravel the pathogenesis of AD and psoriasis are accumulating, more sophisticated treatment is urgently needed for patients with severe type of diseases. Further investigation using lesional skin, blood samples, cell culture system, and mouse models should be strongly encouraged.

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