REVIEW

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The etiopathogenesis of atopic dermatitis: barrier disruption, immunological derangement, and pruritus

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Abstract

Atopic dermatitis (AD) is a common chronic skin inflammatory disorder characterized by recurrent eczema accompanied by an intractable itch that leads to an impaired quality of life. Extensive recent studies have shed light on the multifaceted pathogenesis of the disease. The complex interplay among skin barrier deficiency, immunological derangement, and pruritus contributes to the development, progression, and chronicity of the disease. Abnormalities in filaggrin, other stratum corneum constituents, and tight junctions induce and/or promote skin inflammation. This inflammation, in turn, can further deteriorate the barrier function by downregulating a myriad of essential barrier-maintaining molecules. Pruritus in AD, which may be due to hyperinnervation of the epidermis, increases pruritogens, and central sensitization compromises the skin integrity and promotes inflammation. There are unmet needs in the treatment of AD. Based on the detailed evidence available to date, certain disease mechanisms can be chosen as treatment targets. Numerous clinical trials of biological agents are currently being conducted and are expected to provide treatments for patients suffering from AD in the future. This review summarizes the etiopathogenesis of the disease and provides a rationale for choosing the novel targeted therapy that will be available in the future.

Keywords: Atopic dermatitis, Immunology, Pathogenesis, Innate, Adaptive, Filaggrin

Background

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects one fifth of the population in developed countries [1]. The disease is characterized by recurrent eczema accompanied by a chronic intractable itch that leads to an impaired quality of life [2–4]. The onset of AD occurs primarily in childhood and is thought to precede allergic disorders mediated by an immunoglobulin E (IgE) sensitization to environmental antigens, namely, asthma and allergic rhinoconjunctivitis, the so-called atopic march [5–8]. Moreover, there are increasing evidence that AD is associated with systemic diseases and may be considered as a systemic disorder [9, 10]. The prevalence of AD in children is 15 to 25% [11]. Seventy percent of patients outgrow during late childhood

[12]. However, many remain affected [13, 14], and some may experience a new disease onset in adulthood [1].

Though extensive recent studies have shed light on the understanding of AD, the exact pathogenesis of the disease remains obscure. The complex interplay among genetics, environmental factors, microbiota, skin barrier deficiency, immunological derangement, and possibly autoimmunity contributes to the development of the disease [15–17]. This review aims to summarize the current understanding of the pathogenesis of AD with a focus on the major etiopathogenesis: barrier disruption, immunological derangement, and pruritus.

Skin barrier disruption
Stratum corneum and tight junction
The skin serves as a barrier to protect the body from outside dangers, such as microbes and toxic substances. The epidermis includes four main layers: the stratum corneum (SC), stratum granulosum (SG), stratum spinosum, and stratum basale. SC is the outermost part of the

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epidermis and is composed of denucleated corneocytes embedded in intercellular lipids (often called "bricks and mortar") [18], whereas tight junctions (TJs) are intercellular junctions that regulate the paracellular transport of water and solutes [19]. Skin barrier disruption in AD occurs as a result of an aberration of both components.

SC homeostasis relies greatly on filaggrin (FLG) and its metabolic process. The term filaggrin is short for "filament-aggregating protein," indicating that it is a protein that binds with keratin intermediate filaments and is responsible for the integral structural component [20]. FLG is formed and stored as profilaggrin polymers in keratohyalin granules in SG. At the interface between SG and SC, profilaggrin polymers are cleaved into FLG monomers by certain proteases, such as CAP1 [21] and SASPase [22, 23]. These monomers then assemble with keratin intermediate filaments to strengthen SC. Finally, at the upper SC, FLG is degraded into amino acids, urocanic acid (UCA), and pyrrolidine carboxylic acid (PCA). UCA is responsible for the acid mantle of the skin, and PCA provides natural moisturizing factors in the skin. This degradation process is mediated by proteases, namely, caspase 14 [24], calpain 1 [25], and bleomycin hydrolase [25].

Networks of TJs are found in the intercellular spaces of SG and regulate the paracellular transport of water, ions, and solutes [19, 26]. Strands of TJs are composed of the transmembrane portion in which claudins and occludins represent the most abundant constituents. Zonula occludens (ZO) is the major cytosolic scaffolding proteins responsible for the TJ assembly [27].

The importance of TJs in barrier function has been clearly demonstrated: mice with claudin-1 deficiency die within a day after birth with wrinkling skin [28]. Importantly, TJ aberration is associated with AD since human AD epidermis has a reduced expression of claudin-1, claudin-23 [29], and ZO-1 [30] and shows evidence of impaired barrier function. In addition, polymorphisms of CLDN1-encoding claudin-1 are found in AD patients [29].

Filaggrin and its role in the pathogenesis of AD
FLG is essential for controlling transepidermal water loss and maintaining SC hydration [31, 32] and for the cornification and organization of the epidermis [31, 33]. FLG is known to be decreased in the epidermis of AD patients [34], and null mutation in FLG is the strongest risk factor for AD [35]. FLG haploid insufficiency further confers the risk of developing of several atopic diseases, including asthma, food allergy, and allergic rhinitis [36].

FLG deficiency also leads to an increase in skin pH, which, in turn, enhances the function of serine proteases kallikrein (KLK)5, KLK7, and KLK14, which are responsible for corneocyte shedding [37]. These activated KLKs can increase the production of interleukin (IL)-1α and IL-1β from

corneocytes [38]. Moreover, by binding to the protease-activated receptor type 2 (PAR2) on keratinocytes, KLKs can induce thymic stromal lymphopoietin (TSLP) production that further promotes inflammation [39, 40].

The analysis with Flg mutant mice
The importance of FLG in the pathogenesis of AD is supported by the evidence that mice with Flg deficiency, e.g., flaky tail ($Matt^{ma/ma}Flg^{ft/ft}$) mice and Flg mutant ($Flg^{ft/ft}$) mice on a proallergic BALB/c background, exhibit a spontaneous AD phenotype [7, 41–43]. Of note, the flaky tail mice harbor double gene mutations, Flg and matted (ma), both of which affect the skin barrier in a different fashion. Abnormality in Flg leads to an aberrant profilaggrin polypeptide expression while ma mutation gives rise to the matted hair and spontaneous dermatitis phenotype [41, 44]. In addition, the derangement in proteases required for profilaggrin and Flg processing also gives rise to impairment of the skin barrier and SC dehydration, as observed in mice deficient in CAP1 [21], SASPase [22], and caspase 14 [24].

Furthermore, increased allergen penetration is observed in Flg-deficient mice, e.g., Flg-null mice [45] and flaky tail mice [46], and augmented responses in contact hypersensitivity are detected [45]. Allergen penetration results in inflammasome and protease activation [47]. Additionally, a reduction in FLG predisposes microbial colonization in the skin [32], partly due to the loss of the acid mantle resulting from the decrease in FLG breakdown products [48] combined with the indirect neutralizing effects of FLG to α-toxin of Staphylococcus aureus [49]. This effect is known to be mediated by the secretion of sphingomyelinase, an enzyme stored in the lamellar bodies of keratinocytes in which FLG is required for proper secretion [49–51]. Intriguingly, by promoting Flg expression in NC/Nga mice, development of the AD phenotype in the mice is attenuated, and upregulating FLG may be one of the approaches to improve AD [52].

Sweating is known to be attenuated in AD, which may be a result of acrosyringium obstruction caused by abnormalities in the sweat duct structures and/or derangement in the common sudomotor nerves that control sweating [53, 54]. Recently, it has been demonstrated that a sweat duct obstruction is observed in Flg mutant mice and that sweating is consequently reduced. These findings suggest that FLG may also contribute to the integrity of the acrosyringeal wall [55]. The immunologic modulation of FLG in the development of AD is summarized in Fig. 1.

Other SC components and their relationship with AD
Intercellular lipids are a fundamental part of SC and are regarded as the mortar in the brick and mortar model of the epidermis. These lipids are composed of ceramides,
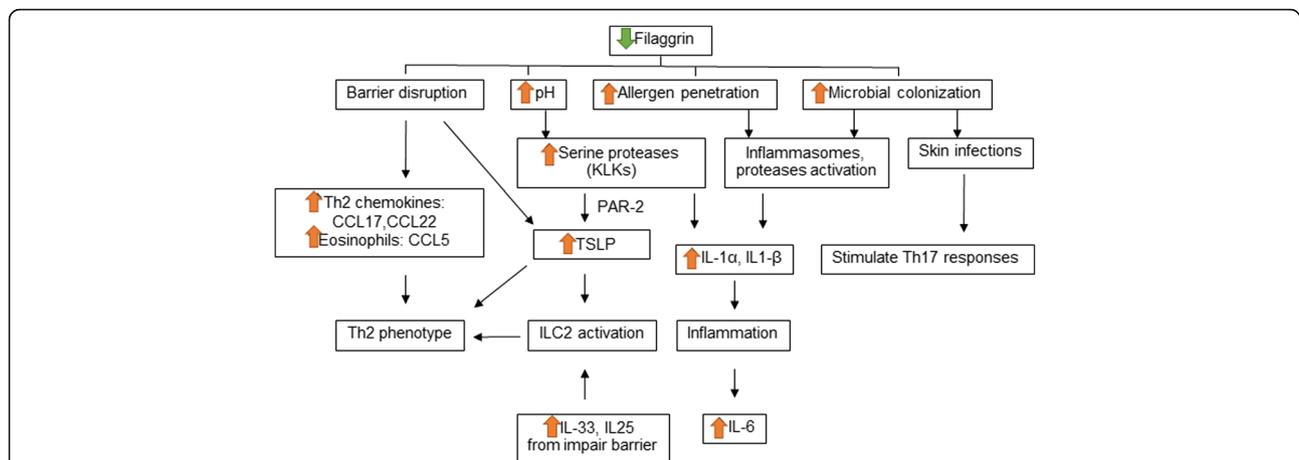
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Fig. 1 Immunologic modulation of filaggrin (FLG) in the development of atopic dermatitis. Decreased FLG exacerbates skin inflammation in many ways. Th2 phenotype skewing occurs because of barrier disruption and keratinocyte injuries that stimulate thymic stromal lymphopoietin (TSLP), Th2, and eosinophil-recruiting chemokines together with IL-33 and IL-25 released from keratinocytes. Moreover, the loss of the acid mantle in the epidermis also promotes TSLP secretion via protease-activated receptor type 2 (PAR-2) activation by increased serine proteases. Enhanced allergen penetration and microbial colonization activate inflammasomes and the Th17 pathway that complicate the pathogenesis of AD in a later state

free fatty acids, and cholesterol in a ratio of 1:1:1 M [18]. The lipid precursors are formed and stored in the lamellar bodies of SG and are released into the extracellular space when the keratinocytes differentiate into SC [18]. Abnormalities in the enzymes responsible for lipid processing and the transportation of lamellar bodies across the cells give rise to a myriad of barrier-insufficient skin diseases. For example, mutations of the genes that encode the enzymes 12R-lipoxygenase and epidermal lipoxygenase 3 are associated with autosomal recessive congenital ichthyosis (ARCI) [56]. It is of note that transmembrane protein 79/mattrin (Tmem79/Matt), a five-transmembrane protein of lamellar bodies, is essential in the lamellar body secretory system and that flaky tail ($Matt^{ma/ma}Flg^{ft/ft}$) mice and Tmem79 (ma/ma) mice with *ma* mutation exhibit spontaneous AD-like dermatitis [44, 57]. Moreover, in the human counterpart, a meta-analysis revealed that a missense mutation in the human *MATT* gene is associated with AD [57].

Corneocyte shedding is tightly regulated by serine proteases and serine protease inhibitors as mentioned above. Serine protease inhibitors include lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI), which is encoded by the serine protease inhibitor Kazal-type 5 (*SPINK5*) [58]. Disorders involving mutation and genetic polymorphisms of the genes that encode KLKs and LEKTI exhibit AD-like phenotypes [59–61]. For instance, Netherton syndrome is caused by *SPINK5* mutations. Patients with this disease exhibit severe dermatitis, allergic rhinoconjunctivitis, asthma, and a high serum IgE level [60]. Moreover, recent studies show that polymorphisms in *SPINK5* are related to AD [61, 62]. Skin barrier dysfunction and cutaneous inflammation due to aberrant immunologic

responses are critical for AD development [1, 63]. The initial trigger, however, remains a subject of debate. Although null mutation of the *FLG* gene poses the strongest risk for AD, 60% of individuals who carry the gene do not have AD symptoms [36]. On the contrary, a significant portion of AD patients do not have *FLG* mutation [36]. It is thus evident that additional factors are needed to develop the disease. In fact, recent genome-wide association studies reported ten new loci that are associated with AD and show a relationship with autoimmune regulation, especially in innate signaling and T cell activation [35, 64]. In the following section, immunological derangement in AD will be discussed.

The immunopathogenesis of AD
Keratinocytes
Acute skin barrier disruption promotes T helper (Th)2 skewing. Keratinocyte-derived cytokines such as TSLP [65], which is known to promote the AD-like phenotype [66], IL-25, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) influence innate lymphoid cells (ILCs) and increase the production of Th2 chemokines: CCL17 (thymus- and activation-regulated chemokine (TARC)), CCL22, and an eosinophil chemoattractant: CCL5 (regulated upon activation, normal T cell expressed and secreted (RANTES)) [67]. In addition to promoting Th2 cell recruitment, CCL17 has been reported to enhance keratinocyte proliferation and implicate in AD development [68].

ILCs, basophils, eosinophils, and mast cells
ILCs are a novel group of innate immune cells developed from a common lymphoid progenitor [69]. Although the

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morphology of ILCs resembles that of lymphoid cells, ILCs do not carry an antigen receptor. Instead, they have similar transcription factors as T cell subsets. Therefore, ILCs are capable of producing hallmark cytokines in the same fashion. ILCs can be divided into three groups: ILC1, ILC2, and ILC3. ILC2, characterized by having the transcription factor GATA3 and producing Th2 cytokines (IL-4, IL-5, and IL-13), is considered to be important in the pathogenesis of AD.

Several studies have shown that, although few ILCs are observed in normal human skin, in AD, the skin is infiltrated markedly by the ILC2 subset [70, 71]. IL-5 and IL-13 released from ILC2 are essential and sufficient to induce AD lesions in mouse models [71, 72]. In addition, ILC2 can drive Th2 responses in vivo [71]. Certain epithelial-derived cytokines and eicosanoids, namely, TSLP [71], IL-25 [73], IL-33 [73, 74], and prostaglandin D2 (PGD) [75, 76], can activate ILC2 whereas E-cadherin [73] is known to have an inhibitory effect. In addition, ILC2 can also respond to hematopoietic cell-derived cytokines, IL-2 and IL-7 [72]. Importantly, IL-4 from basophils can directly activate ILC2 and bring about AD-like inflammation [77]. The immunomodulatory actions of the aforementioned cytokines are mediated by ligation with the corresponding receptors that are present on the ILC2. In AD, where the epidermal barrier is breached, epithelial-derived cytokines (TSLP, IL-25, IL-33) are released. In addition, FLG deficiency that leads to a reduction in E-cadherin [73, 78] together with an increase in IL-4 derived from basophils and PGD2 from mast cells is present. These environments promptly recruit and activate ILC2 and initiate the cutaneous inflammation observed in AD. The complex interplay between the barrier dysfunction, ILC2, basophils, eosinophils, and mast cells is involved in AD [69, 79–82], as shown in Fig. 2.

In addition to cytokines and chemokines, the neurotransmitter dopamine is involved in mast cell activation and Th2 skewing in AD. Mast cells and Th2 cells bear dopamine receptors, the D1-like receptor group. Upon
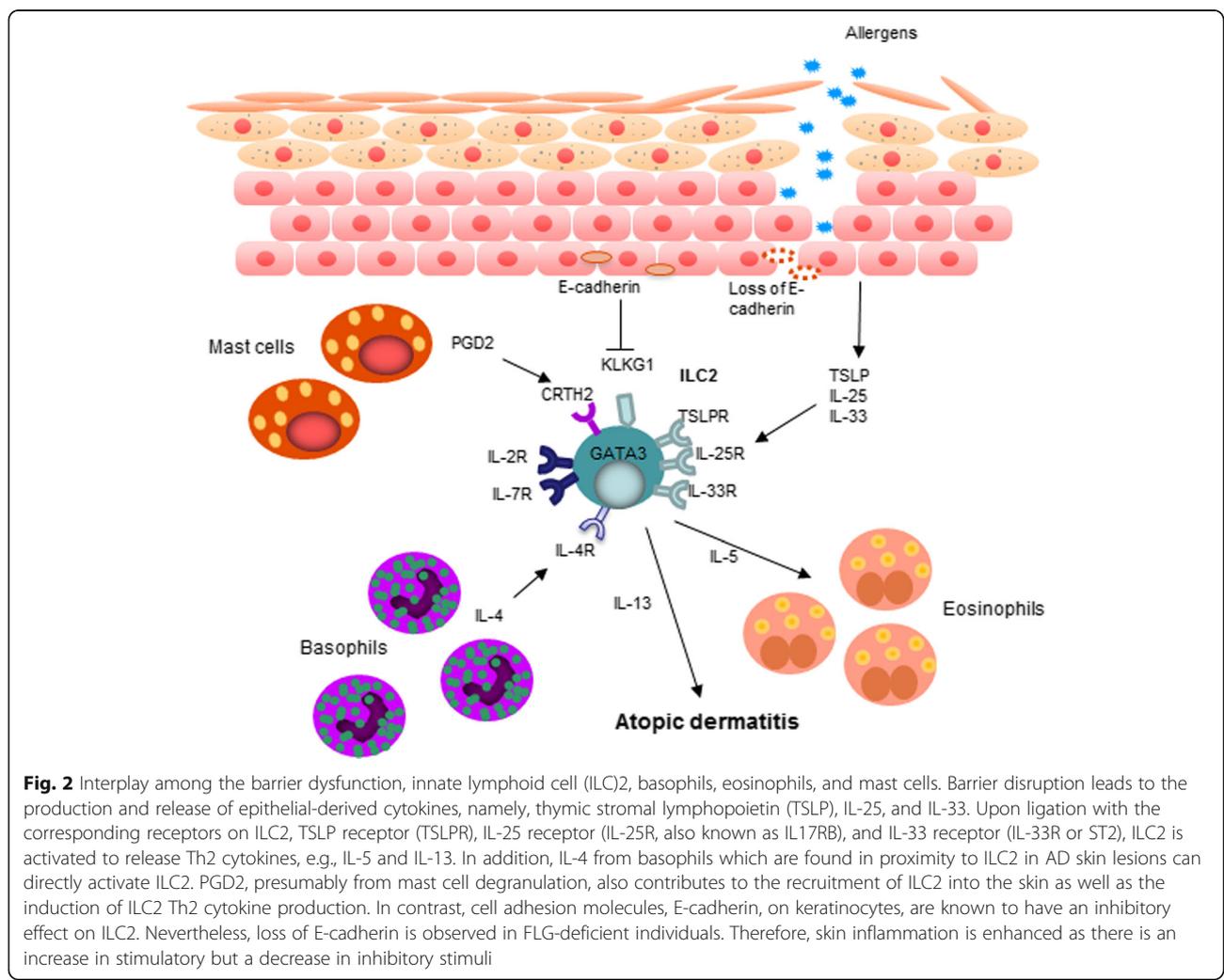

Fig. 2 Interplay among the barrier dysfunction, innate lymphoid cell (ILC)2, basophils, eosinophils, and mast cells. Barrier disruption leads to the production and release of epithelial-derived cytokines, namely, thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. Upon ligation with the corresponding receptors on ILC2, TSLP receptor (TSLPR), IL-25 receptor (IL-25R, also known as IL17RB), and IL-33 receptor (IL-33R or ST2), ILC2 is activated to release Th2 cytokines, e.g., IL-5 and IL-13. In addition, IL-4 from basophils which are found in proximity to ILC2 in AD skin lesions can directly activate ILC2. PGD2, presumably from mast cell degranulation, also contributes to the recruitment of ILC2 into the skin as well as the induction of ILC2 Th2 cytokine production. In contrast, cell adhesion molecules, E-cadherin, on keratinocytes, are known to have an inhibitory effect on ILC2. Nevertheless, loss of E-cadherin is observed in FLG-deficient individuals. Therefore, skin inflammation is enhanced as there is an increase in stimulatory but a decrease in inhibitory stimuli

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ligand binding, mast cells are degranulated and Th2 cells are activated, observed by an increase in the ratio of IL-4 to IFN-γ mRNA expression [83]. As psychoneuro-immunology plays a role in many skin diseases, results from the study might explain the worsening of AD symptoms after a psychological strain.

Dendritic cells (DCs)

DCs are professional antigen-presenting cells that capture antigens, allergens, and microbes, to prime naïve T cells into immunogenic or tolerogenic subsets, and act as a bridge between innate and adaptive immunity [84]. In the steady state of the skin, Langerhans cells (LCs) reside in the epidermis, and groups of dermal DCs (DDCs) are found in the dermis. It has been suggested that DCs initiate AD in humans, although it remains unclear which cutaneous DC subsets initiate epicutaneous sensitization.

LCs perform surface antigen surveillance and recognition by extending their dendrites through the TJs to take up the antigens [85]. LCs' function in this regard has been reported to induce Th2 responses as LCs efficiently drive naïve CD4$^+$ T cells into Th2 cells [86]. It is speculated that a breach in TJs may enhance penetration of foreign antigens, which are then taken up by LCs, amplifying Th2 cutaneous inflammation.

LCs are also responsible for the initiation of AD under the influence of TSLP [63, 87, 88]. Nakajima et al. demonstrated that LCs are essential to the induction of clinical manifestations and IgE elevation in a mouse model upon epicutaneous sensitization with the protein antigen ovalbumin (OVA) via the action of TSLP and its receptors presented on LCs [87]. TSLP is abundantly expressed in keratinocytes of lesional and non-lesional skin in AD patients as a result of both skin barrier dysfunction and proinflammatory cytokines, such as IL-1β, tumor necrosis factor (TNF)-α, IL-4, and IL-13 in AD [65, 89]. Importantly, TSLP can trigger DC migration to the draining lymph nodes [90], and LCs treated with TSLP drive naïve T cells to Th2 phenotypes [91]. All of these events lead to a Th2 bias in the acute stage of AD.

During the inflammatory state of AD, myeloid inflammatory DCs, namely, inflammatory dendritic epidermal cells (IDECs), are recruited [92]. DCs in the skin of AD patients are well characterized by the presence of a high-affinity receptor for IgE (FcεRI) that renders these DCs to induce T cell responses effectively [92]. A wide spectrum and amount of foreign surface and penetrating antigens, microbes, and allergens are encountered in AD skin due to the breach in the epidermis and the barrier dysfunction [92].

The cross-linking of FcεRI with IgE on the LC surface in an in vitro study leads to a release of chemokines, for example, IL-6, CCL22, CCL17, and CCL2, which can recruit Th2 cells and other immune cells, importantly, IDECs [93]. A patch test study showed that IDECs rapidly migrate into the epidermis of patch-tested lesions [94]. IDECs are key DCs in amplifying skin inflammation as they can migrate to the draining lymph nodes and prime naïve T cell into interferon (IFN)-γ- and IL-18-producing T cells [93]. Therefore, IDECs are considered to be important in the switching of Th2 to Th1 in chronic AD [94].

Another interesting feature of AD is a decreased plasmacytoid DC (pDC) number in AD skin compared to that expected to be observed in skin inflammatory conditions [95]. This can be explained by a lack of chemoattractant for pDCs, i.e., chemerin, in AD skin [96] and a paucity of skin-homing molecules in the blood pDCs of AD patients [97] in combination with the Th2 milieu in the skin [84]. pDCs are crucial in immune responses against viral infections. The reduced number and improper function of pDCs observed in AD skin can thus contribute to a susceptibility to viral infections [97].

Th2/Th1 paradigm shift

AD is traditionally viewed as a Th2-mediated allergic disease with increased IgE production, eosinophilia, mast cell activation, and overexpression of Th2 cytokines IL-4, IL-5, and IL-13 [63, 98]. Th2 polarization and barrier defects are closely related. TSLP, IL-25, and IL-33 are upregulated in the epithelium after environmental signals [11]. Keratinocytes are the main source of TSLP, which is crucial in the induction of Th2 skewing in AD skin by the activation of LCs and DCs [99]. In turn, Th2 cytokines IL-4 and IL-13 can induce keratinocytes to express TSLP [100]. In addition, Th2 cytokines can inhibit the expression of Toll-like receptors (TLRs), which dampens host defense against infections [100]. Moreover, IL-4 and IL-13 have negative impacts on skin barrier function. FLG, loricrin, and involucrin, the integral components of SC, are downregulated with Th2 cytokines, regardless of FLG genotypes [101, 102]. Keratinocyte differentiation is perturbed by Th2 cytokines via STAT3 and STAT6 activation, and topical Janus kinase (JAK) inhibitors can restore epithelial function by suppressing STAT3 signaling [103]. B cell class switching and increased IgE synthesis are also induced by IL-4. Based on this supporting evidence, suppression of Th2 cytokines appeared to be useful in alleviating AD symptoms [104–106]. Recently, a novel biological agent, the anti-IL-4 receptor antibody dupilumab, has been studied in clinical trials and found to be promising for the treatment of AD [107].

Th17

Th17 cells have the capacity to produce IL-17A, IL-17F, IL-22, and IL-26 upon stimulation [108]. Indeed, IL-17 can induce S100 protein and proinflammatory cytokine

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expression, which are responsible for eosinophil- and neutrophil-mediated inflammation [109, 110]. Many studies have suggested the involvement of Th17 in the pathogenesis of AD. For instance, it is reported that epicutaneous sensitization in mice with OVA typically leads to AD-like dermatitis and the cutaneous expression of IL-17 and IL-17-producing T cells in the draining lymph nodes and spleen, as well as increased serum IL-17 levels [111]. In addition, a study that used a repeated hapten application to induce AD in mice showed that IL-17A is necessary for the development of skin inflammation, IL-4 production, and IgG1 and IgE induction [112]. Interestingly, IL-17A is detected in the AD-like dermatitis of flaky tail mice [42, 46, 113]. Consistently, analysis of the peripheral blood of severe AD patients reveals an increased number of IL-17-producing cells [114, 115].

AD can be divided into two types: extrinsic and intrinsic AD. Patients with extrinsic AD typically have an elevated IgE level, harbor *FLG* mutation with a disruptive barrier, exhibit an early onset, and traditionally have a Th2-dominant response. On the other hand, intrinsic AD patients exhibit different features [116–118]. Patients with intrinsic AD usually do not show an elevated IgE level, do not harbor *FLG* mutation, exhibit with an adult onset, and are associated with more Th17 and Th22 immune activation than extrinsic AD patients [119]. Essentially, a study that compared phenotypes between European/American versus Asian AD showed that Asian AD skin exhibits more epidermal hyperplasia and parakeratosis that skewed toward psoriasis features. It is of note that higher Th17 activation is observed in Asian AD; this needs to be considered in the selection of treatments for different populations [120].

Antimicrobial peptides

Atopic skin is characterized by increased *S. aureus* colonization and/or infections with a loss of microbial diversity during flares [121]. This may be explained partly by the reduction in antimicrobial peptides (AMPs) of the skin. In homeostasis, AMPs, such as S100 protein psoriasin, ribonuclease (RNase) 7, dermcidin, and lactoferrin, are constitutively present in the epidermis and serve as one of the first-line protections against microbes. Upon challenges with danger signals/organisms, additional AMPs, namely, human beta-defensins (hBD)-2, hBD-3 and cathelicidin (LL-37), are upregulated [122]. In the past, it was thought that the reduction in hBD-2, hBD-3, and LL-37 levels in AD epidermis was one of the causes of *S. aureus* overgrowth [123]. This can be explained by the fact that skin inflammation in AD is predominantly mediated by Th2 cytokines (IL-4, IL-13) in the acute phase of the disease [63] and that the Th2 cytokine milieu is known to suppress the production of the AMPs [124]. Recent findings, however, have shown that

the induction of the AMPs hBD-2, hBD-3, and LL-37 was not impaired in AD [125]. These productions may not be sufficient to tackle the infections or the AMP functions may be disturbed [126]. Interestingly, *Escherichia coli* infection is rarely encountered in AD, and the major AMP family that combats this microbe is the S100 proteins, which consist of S100A7 (psoriasin), S100A8, and S100A9 [124]. An increase in S100 proteins in patients with AD has been reported [124, 125]. In addition, S100 proteins have proinflammatory properties that can further promote skin inflammation and inhibit keratinocyte differentiation, complicating the barrier dysfunction [126, 127].

Recent interesting studies have shown that TSLP exists in two different isoforms, i.e., short and long forms, both of which exhibit different functions. In the skin and gut, the short form is constitutively expressed, which is responsible for maintaining tissue homeostasis and acts as antimicrobial peptides [128, 129]. In contrast, the long form predominates and possesses proinflammatory activity under inflammatory states, such as in the lesional skin of AD [128, 130].

Pattern recognition receptors (PRRs) recognize vital and highly conserved molecular structures of microorganisms, so-called pathogen-associated molecular patterns (PAMPs), and danger signals, damage-associated molecular patterns (DAMPs). Upon receptor ligation, signaling pathways are stimulated and result in the production of cytokines with biological effects. In the skin, PRRs are found in keratinocytes and other innate immune cells [131] and are known to be involved in the pathogenesis of AD. TLRs are the most well-characterized PRRs. Other PPRs include NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs).

TLR2 is a major ligand for *S. aureus* [132] that has a unique ability to form either a homodimer or a heterodimer with TLR1 or TLR6 to expand their binding spectrum capability [133]. Bacterial lipoteichoic acid (LTA) found in *S. aureus*-infected AD lesions can bind to TLR2, which then exerts immunologic responses. Interestingly, a single nucleotide polymorphism (SNP) of TLR2 has been reported to be associated with severe AD and implicated in an increase in *S. aureus* infections [134, 135]. Moreover, intracellular muramyl dipeptide (MDP) derived from *S. aureus* peptidoglycan is recognized by NOD2, NLR family, within keratinocytes [136]. It is of note that NOD2-deficient mice exhibit an increased susceptibility to subcutaneous *S. aureus* infection [137], and polymorphisms in the NOD2 gene are associated with human AD [138].

Interestingly, peptidoglycan from *S. aureus* induces signaling through NOD-2 coupled with TLR stimulation which efficiently induces DCs to produce IL-12p70 and IL-23, which drive Th1 and Th17 responses, respectively [139]. This may in part explain the shift of Th2-

dominated to Th1/Th17-co-dominated inflammation in the chronic stage of AD where multiple PRRs are engaged [133].

S. aureus and AD

The cutaneous microbiome plays an important role in the skin during homeostasis and in the disease state. This is especially evident in AD in which skin colonization with *S. aureus* is found in almost 90% of lesional skin and 55 to 75% of non-lesional skin [5]. Skin infections and the toxin from *S. aureus* further exacerbate the cutaneous proinflammatory state [140]. Importantly, skin colonization with *S. aureus* produces superantigens that also stimulate Th17 responses by increasing IL-17 production [140, 141]. Indeed, in AD patients with skin infections, a rise in the percentage of Th17 cells in peripheral blood has been found [142]. *S. aureus* can worsen barrier impairment [143]; releases proteases, enzymes, and cytolytic toxins that induce cell injuries [143, 144]; and engages PRRs and exerts inflammation [145]. Its toxic shock syndrome toxin 1 (TSST-1) and enterotoxins (SEs) act as superantigens to activate a large number of T cells [146], promote T cell recruitment to the skin [147], and exert superantigen-specific IgE [148]. Additionally, *S. aureus* δ-toxin can stimulate mast cell degranulation [149]. These summarized events eventually deteriorate the disease state of AD [150].

Pruritus

Itch or pruritus is one of the most disturbing symptoms that characterize AD and can in fact significantly impair the quality of life of affected individuals [151]. Pruritus in AD is a result of the complex interplay among many factors. Although the exact pathogenesis remains unknown, recent studies have shown that hyperinnervation of the epidermis, an increase in several itch mediators/pruritogens, and central sensitization of itch are evident in AD.

Hyperinnervation of AD skin

The sprouting of nerve fibers is under a balanced homeostasis between nerve sprouting factors, e.g., nerve growth factor (NGF), amphiregulin, and gelatinase versus nerve retraction factors, e.g., semaphorin 3A (Sema3A) and anosmin-1 [152]. An increase in nerve fiber density in the epidermis is reported in AD [153, 154]. This is partly explained by the elevation of NGF that is observed in the plasma of AD patients [155] and a decrease in Sema3A that is detected in the lesional AD epidermis [156].

In addition to the hyperinnervation of the skin, a lower threshold for activation of the sensory nerve fibers is also observed in AD, and these events mutually function to increase the excitability of the sensory nerves [157].

This hypersensitivity of the primary itch-sensing neurons may contribute to alloknesis, pruritus resulting from non-pruritogenic stimuli [158], which is a well-observed phenomenon in AD patients [159]. Interestingly, artemin, a glial cell-derived neurotrophic factor (GDNF)-related family, is reported to be important in warm inducing itch because artemin is upregulated in fibroblasts from AD lesions, and an intradermal injection of artemin in mice leads to an increased number and sprouting of peripheral nerves together with thermal hyperalgesia [160, 161].

Itch mediators/pruritogens

Several itch mediators and their corresponding receptors are reported to be responsible for itch in AD: histamine (H), especially the role of H1 and H4 receptors (H1R and H4R) [157, 162], certain proteases (including tryptase, dust mites, and *S. aureus* [151]), substance P [63, 151], IL-31 [163, 164], TSLP [165], and endothelin-1 [166].

Recently, much interest has been focused on the role of IL-31-induced pruritus. IL-31 is predominantly produced by Th2 cells, and its receptor, which comprises IL-31 receptor α (IL-31RA) and oncostatin M receptor β (OSMRβ), is expressed in peripheral nerve fibers, dorsal root ganglions (DRGs), and keratinocytes [167, 168]. Upon its ligand binding, IL-31 signaling is mediated by activation of the JAK-signal transducer and activator of transcription (STAT) (STAT-1/5 and ERK-1/2), mitogen-activated protein kinase, and phosphoinositide-3-kinase (PI3K) signaling pathways [169, 170]. The IL-31 level is elevated in AD skin as well as in the serum [163, 171]. The IL-31 serum level correlates with the disease severity [172]. Clinical trials related to anti-IL-31 receptor (nemolizumab) and anti-IL-31 (BMS-981164) as treatments for AD are currently being conducted [173].

Central sensitization of pruritus in AD

The role played by the central nervous system in terms of the itch associated with AD has been investigated to a lesser extent compared to that of peripheral innervation. A study that used functional magnetic resonance imaging with arterial spin labelling, however, showed an increase in the activation of the anterior cingulate cortex and dorsolateral prefrontal cortex in human AD subjects compared with that of healthy controls [174]. These results suggest a central sensitization in AD individuals. Importantly, cognitive and affective processes play a pivotal role in the interpretation and perception of pruritus [151]. This is evident in AD, as several psychotropic drugs, including antidepressants, can attenuate the itch severity in some patients [175].

In addition to the brain itself, the activation of STAT3 in the astrocytes of the spinal dorsal horn has been shown to be involved in chronic pruritus. This activation

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results in the production of lipocalin-2 that enhances pruritus and may lead to a vicious itch-scratch cycle [176]. It is of note that astrocytes are a subtype of glial cells of the central nervous system [151].

The complex interplay among itch, barrier disruption, and immunologic aberration is illustrated in Fig. 3. Pruritus is known to induce scratching behavior that introduces or worsens breaches in the skin. On the other hand, in dry skin model mice, epidermal barrier dysfunction is observed together with an increase in the number of epidermal nerve fibers [177]. With regard to the relationship between pruritus and the immune responses, once the barrier is disrupted from scratching, e.g., in an experimental tape stripping procedure, Th2 chemokines (CCL17 and CCL22) and eosinophil-recruiting chemokines (CCL5) are increasingly produced by keratinocytes [67]. Moreover, tape stripping also results in TSLP production in the skin [65]. Consequently, Th2 skewing ensues. Conversely, immune responses can induce itch via the secretion of a myriad of cytokines that can act as pruritogens, namely, TSLP, IL-2, IL-31, IL-4, and IL-13 [157].

Novel AD treatments

Based on the growing knowledge of the complex pathophysiology of AD, many novel targeted therapies are currently in clinical trials. Table 1 summarizes these novel treatments [11, 173, 178–180].

Anti-IL-4 receptor, dupilumab

Based on the importance of IL-4 in inducing AD inflammation and barrier impairment, studies have examined how to attenuate its function. The central focus with a growing number of evidence is dupilumab, a fully humanized monoclonal antibody against the IL-4 receptor α subunit (IL-4Rα). This subunit is shared by IL-4 and IL-13; therefore, by blocking IL-4Ra, both IL-4 and IL-13 are inhibited [181].

Several phase II studies have shown the efficacy of dupilumab in improving clinical outcomes, biomarkers, and the transcriptome level in AD patients [181–183]. Moreover, a recent phase III study has confirmed the findings in a larger number of patients [184]. Although further studies with long-term follow-up periods are needed, dupilumab appears to be a promising treatment modality for AD.

IL-13 antagonist

IL-13 belongs to the Th2 cytokine lineage that can bind to both IL-4 and IL-13 receptors; therefore, the functions of IL-4 and IL-13 are considered to be similar [11]. IL-13 is important in B cell activation and differentiation and in promoting IgE production by B cells [178]. Lebrikizumab and tralokinumab are monoclonal antibodies against IL-13. Their roles in AD treatment are currently being explored in current phase II studies (ClinicalTrials.gov identifier: NCT02340234 and NCT02347176).

IL-23p40 antagonist

The fact that Th1 and Th17 cells are involved in the pathogenesis of AD has led to a trial of ustekinumab in AD. Ustekinumab is a fully human monoclonal antibody against the receptor p40 subunit, shared by IL-12 and
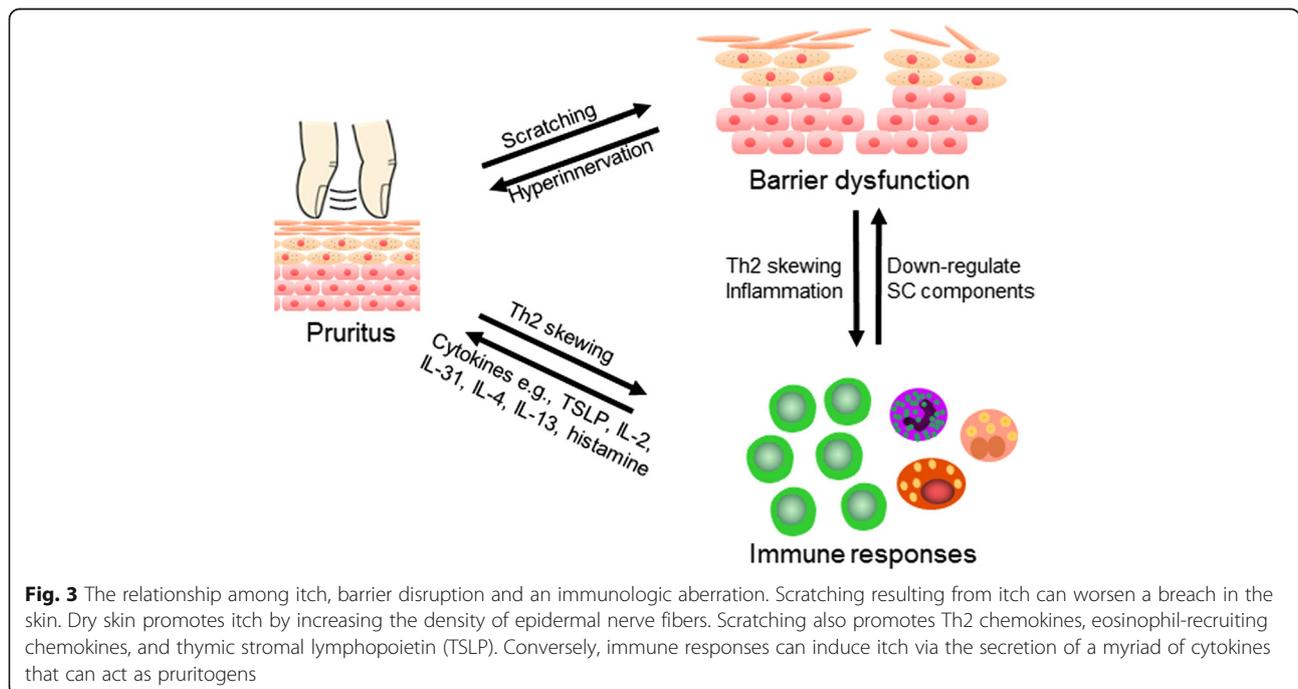

Fig. 3 The relationship among itch, barrier disruption and an immunologic aberration. Scratching resulting from itch can worsen a breach in the skin. Dry skin promotes itch by increasing the density of epidermal nerve fibers. Scratching also promotes Th2 chemokines, eosinophil-recruiting chemokines, and thymic stromal lymphopoietin (TSLP). Conversely, immune responses can induce itch via the secretion of a myriad of cytokines that can act as pruritogens

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Table 1 Novel AD treatments. The table is modified from Heratizadeh and Werfel [178], Lauffer and Ring [179], Noda et al. [180], Nomura and Kabashima [173], and Werfel et al. [11]

Mechanism of action	Route	Compound	Company	Type of clinical trial	Result
Targeting pathogenic cytokines and their cognate receptors					
IL-4/IL-13 receptor α-chain antagonist	SC	Dupilumab	Regeneron	Phase III	Improvement in clinical outcomes, pruritus, and quality of life
IL-13 antagonist	SC	Lebrikizumab	Roche	Phase II	Not yet available
	SC	Tralokinumab	AstraZeneca	Phase II	Not yet available
IL-23p40 antagonist	SC	Ustekinumab	Janssen	Phase II	Not yet available
IL-22 antagonist	IV	Fezakinumab	Pfizer	Phase II	Not yet available
IL-31 receptor antagonist	SC	Nemolizumab	Roche	Phase II	Improvement in pruritus and EASI score
IL-31 antagonist	SC, IV	BMS-981164	Bristol-Myers Squibb	Phase I	Not yet available
IL-1R1 antagonist	SC	Anakinra	Sobi	Phase I	Unpublished
IL-6	SC, IV	Tocilizumab	Genentech	Case series	Improvement in EASI score
Targeting pathogenic molecules					
PDE-4 inhibitors	Topical	Crisaborole	Anacor	Phase III	ISGA score success
	Topical	E6005	Eisai	Phase II	EASI score and SCORAD improvement
	Topical	DRM02	QLT	Phase II	Not yet available
	Oral	Apremilast	Celgene	Phase II	EASI score improvement
CRTh2 antagonist	Oral	ODC-9101	Oxagen	Phase II	Not yet available
	Oral	Fevipiprant	Novartis	Phase II	Not yet available
JAK inhibitor	Topical	Tofacitinib	Pfizer	Phase II	Decrease in EASI score
	Oral	Pf-04965842	Pfizer	Phase II	Not yet available
TSLP antagonist	SC	Tezepelumab	Amgen	Phase II	Not yet available
Targeting IgE					
IgE antagonist	SC	Omalizumab	Novartis	Stopped after proof-of-concept study	Heterogeneous results
	SC	Ligelizumab	Novartis	Phase II	Not yet available

Abbreviations: *PDE* phosphodiesterase, *CRTh2* chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes, *JAK*, Janus kinase, *TSLP* thymic stromal lymphopoietin, *SC* subcutaneous injection, *IV* intravenous, *ISGA* Investigator's Static Global Assessment, *SCORAD* SCORing Atopic Dermatitis, *EASI* Eczema Area and Severity Index

IL-23, which are required for the development and maintenance of Th17 and Th1 cells [179]. Notably, a recent phase II study showed no significant differences in clinical efficacy (SCORAD50) between ustekinumab and placebo in adult AD patients, which may be explained by an inappropriate dosing regimen [185]. Another phase II study is being evaluated (NCT01806662).

IL-31 receptor antagonist and IL-31 antagonist
IL-31 is an important mediator of both itch and inflammation [186, 187]. Nemolizumab, an IL-31 receptor antagonist, has been shown to significantly reduce itch and improve the Eczema Area and Severity Index (EASI) score in AD patients [188]. Additionally, a result from a phase I/Ib study suggests that nemolizumab is well tolerated and seems to be beneficial, especially in alleviating troublesome pruritus [189].

Phosphodiesterase (PDE)-4 inhibitors
PDE is a crucial regulator of cytokine production, and PDE-4 is the most abundant isoenzyme found in human leukocytes [190]. In addition, T and B cells, macrophages, monocytes, neutrophils, and eosinophils also express PDE-4 [191]. Inhibition of PDE-4 resulted in an accumulation of intracellular cyclic adenosine monophosphate (cAMP), which in turn inhibits proinflammatory cytokine transcription and production [192]. It is also known that AD mononuclear leukocytes exhibit increased cAMP-PDE activity that leads to inflammation [193].

PDE-4 inhibitors have been developed in both topical and orally administered forms. Clinical trials evaluating the efficacy of these drugs are detailed in Table 1. Topical PDE-4 inhibitors, e.g., crisaborole [194] and E6005 [195], demonstrate clinical efficacy for AD in phase II and III clinical trials, respectively. Moreover, apremilast,

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an oral PDE-4 inhibitor that has been used in various inflammatory diseases, including psoriasis, has shown promising results for AD in a recent phase II study [196].

Chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTh2)

CRTh2 is a prostaglandin D2 receptor that is expressed in Th2 cells, ILC2, eosinophils, and basophils [197, 198]. Activation of CRTh2 induces Th2 cell, ILC2, and eosinophil chemotaxis and promotes their cytokine production [197, 199]. CRTh2 inhibitors are currently in clinical trials for allergic diseases such as asthma and AD. For AD, the results are not yet available (NCT01785602 and NCT02002208).

JAK inhibitor

The JAK-STAT signaling pathway involves a family of cytoplasmic protein tyrosine kinases that is essential for the induction of the cellular responses of many pivotal pathogenic cytokines in AD, namely, IL-4/IL-13 [103]. Furthermore, the activation of eosinophils, the maturation of B cells, and the suppression of regulatory T cells (Tregs) are mediated through the JAK-STAT signaling pathway [200]. Indeed, JTE052, a JAK inhibitor, has been shown to decrease STAT3 activation and leads to an improvement in the skin barrier and an upregulation of filaggrin in a murine AD model [103]. Moreover, the JAK inhibitor can inhibit IFN-γ, IL-13, and IL-17A production from antigen-specific T cells and decrease differentiation and proliferation of effector memory T cells in the draining lymph nodes in the sensitization phase of a murine contact hypersensitivity (CHS) model [201]. Therefore, it appears to be promising as a treatment of various inflammatory dermatoses. JAK inhibitors have been investigated as a treatment for psoriasis and alopecia totalis [202]. In addition, a greater percentage change from baseline (a reduction) in the EASI score was observed in a phase II clinical trial involving topical tofacitinib [203]. Additional studies are currently underway (Table 1).

TSLP antagonist

As mentioned earlier, TSLP is crucial for Th2 skewing and is of great importance in inflammation and itching in AD. This makes TSLP as a promising target molecule to improve AD. Tezepelumab, its antagonist, is currently being studied (NCT02525094).

Other possible biologics for AD that have been studied include drugs that target IgE and B cells, as an increase in B cells and IgE is commonly observed in AD patients [204]. But the outcomes of the treatment with omalizumab, a humanized, monoclonal anti-IgE antibody, in multiple case reports and few control trials have appeared inconclusive [205–207].

In addition, rituximab, a chimeric monoclonal antibody against CD20 that depletes immature and mature B cells, also shows conflicting results [208–210]. Further investigation of omalizumab and rituximab for this indication has therefore been discontinued. Ligelizumab, a new anti-IgE antibody that exhibits a stronger IgE inhibitory effect compared to that of omalizumab [211] may, however, be beneficial for AD and is currently in a phase II trial (NCT01552629).

In summary, there are several promising therapies in the pipeline to satisfy the unmet needs of AD treatment [212]. Further insights into the disease mechanisms will tremendously improve the treatment outcomes and improve the quality of life for individuals with AD.

Conclusions

The skin barrier, innate and adaptive immunity, and pruritus mutually orchestrate skin inflammation in AD. The pathogenesis of the disease is complex and many aspects require further clarification. Based on the detailed evidence available to date, certain disease mechanisms can be chosen as treatment targets. Many clinical trials of biological agents are currently being conducted. These new drugs in the pipeline may satisfy the unmet needs in the treatment of AD.

Authors' contributions

PR, AO, CN, and KK conceived and designed the work. PR collected the data. PR, CN, AO, and KK analyzed and interpreted the data. PR, CN, and AO drafted the article. PR, AO, CN, KK critically revised the article. PR, AO, CN, and KK gave final approval of the version to be published.

Competing interests

The authors declare that they have no competing interests.

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Consent for publication

Not applicable.

Ethics approval and consent to participate

This review does not contain any identifiable information of patients that could be used to compromise patient confidentiality.

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