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Elevation of IgE in patients with psoriasis: Is it a paradoxical phenomenon?

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Immunoglobulin E (IgE) elevation is a hallmark of allergic conditions such as atopic dermatitis (AD). The pathogenesis of AD is typically associated with high levels of IL-4 and IL-13 produced by activated T helper 2 (Th2) cells. Psoriasis, on the other hand, is an inflammatory skin disease mainly driven by Th17 cells and their related cytokines. Although the immunopathologic reactions and clinical manifestations are often easily distinguished in the two skin conditions, patients with psoriasis may sometimes exhibit AD-like manifestations, such as elevated IgE and persistent pruritic lesions. Given the fact that the effective T cells have great plasticity to re-differentiate in response to innate and environmental factors, this unusual skin condition could be a consequence of a cross-reaction between distinct arms of T-cell and humoral immunity. Here we review the literature concerning the roles of IgE in the development of AD and psoriasis, showing that elevated IgE seems to be an important indicator for this non-typical psoriasis.

KEYWORDS

Immunoglobulin E, atopic dermatitis, psoriasis, T helper 2 cell, T helper 17 cell

Introduction

Immunoglobulin E (IgE) elevation is a useful clinical indicator for atopic dermatitis (AD) and other allergic diseases. Antigen-specific IgE *via* binding IgE receptors on master cells and basophils plays a central role in the initiation of mediator release from these cells, which often leads to immediate hypersensitivity reactions such as systemic anaphylaxis, bronchospasm, and urticaria. However, elevated IgE is also found in some chronic inflammatory allergic diseases such as rhinitis, asthma and AD (1, 2), and even non-allergic diseases such as psoriasis (3).

AD causes dry, itchy and inflamed skin lesions. Psoriasis is also a chronic inflammatory skin disease with patches of rashes and abundant silvery scales. Both conditions tend to be long-lasting and flare up from time to time. In contrast to the relatively young ages of onset in AD patients, psoriasis is common in adults. The primary immune cell effectors in the two diseases are believed to be different (4, 5). Many studies have shown that the elevated IgE and persistent pruritus in AD patients are driven by activated Th2 immune response (6–8). By contrast, pruritus in psoriasis patients is often mild or even absent (9, 10), and the immune mechanism of psoriasis

appears to be activated by Th17 cells and is associated with high levels of IL-17A and IL-17F (11). However, when psoriasis patients exhibit severe pruritus as well as high levels of eosinophils and IgE (12–14), it remains unknown whether these conditions are comorbid characteristics of AD and psoriasis or simply manifestations of a kinetic spectrum of the individual diseases. In this review, we will focus on the involvement of IgE in the pathogenesis of both AD and psoriasis, and examine the possible IgE-mediated pathogenic mechanisms in AD and psoriasis.

Biological functions of IgE

IgE is one of the five immunoglobulins. It consists of two heavy chains (H chains) and two light chains (L chains), which are linked *via* disulfide bonds to form a tetrapeptide chain molecule similar to other monomer immunoglobulin molecules (15). Structurally, IgE molecule has no hinge region that differs from IgG, IgA, and IgD (16). The main function of antigen specific IgE is to induce release of mediator molecules from mast cells or basophils after binding to the high-affinity IgE receptor (FcεRI) on these two types of immune cells (17). The mediator molecules such as histamine, prostaglandins, and leukotriene 2 will then enormously increase vascular permeability, bronchospasm, and others (18, 19). Mast cells and basophils are both derived from $CD34^+$ hematopoietic progenitors. Mast cells are long-lived resident cells in tissues that differentiate from other blood-derived progenitor cells (20). Mast cells are found in areas that are often exposed to the external environment and microbiota, such as mucosa of the gastrointestinal tract and respiratory tract (21). Basophils, once mature in the bone marrow, enter the blood circulation and then are activated in blood vessels and transported to inflammatory sites to perform functions similar to the mast cells (22–24).

The Th2 immune response plays a central role in activating IgE-mediated activation of mast cells and basophils (25, 26). In addition to those effector molecules that are released from mast cells and basophils to cause clinical symptoms, the mediator molecules also include growth factors, cytokines and chemokines. Of them, the cytokines such as IL-4 and IL-13 are required for priming both Th2 cell differentiation and aiding the switching of B cells to IgE-producing plasma cells (27–29). Interestingly, IL-22 is highly produced by activated mast cells within the plaque lesions of psoriasis and AD. The immunopathogenic roles of IL-22 have been well established in the development of both diseases (30). When the allergic host is re-exposed, the allergen will cross-link with IgE already bound to the membrane and activate mast cell or basophils to release allergic mediators. This cascade of reactions culminates in the typical symptoms of type I hypersensitivity (31).

New evidence has suggested that the biological function of IgE is beyond the Type I hypersensitivity reactions. A number of studies have proven that IgE alone can provide survival signals to mast cells even in the absence of allergens (32, 33) or survival cytokines (34). Like normal antigen-binding IgEs, the so-called cytokinergic IgEs could bind FcεRI receptors on the surface of mast cells. However, this cross-linking stabilizes FcεRI receptors, which then prevents the degradation process of mediator cells (35). IgE has even been found to be involved in the antigen-presenting process (36, 37). Indeed, in terms of the magnitude of T cell activation, the antigen-IgE complex is several folds stronger than either the antigen-IgG complex or antigen alone (37). This process depends on the endocytosis of the antigen-IgE complex through CD23 expressed on B cells or FcεRI on dendritic cells (DC), which is named IgE-facilitated antigen presentation (FAP) (38). The FAP mechanism is thought to be presented in most allergic and atopic diseases, and is also responsible for the relapse of atopic diseases.

Despite the short half-life of IgE, sustained IgE production appears important to maintain allergen-specific IgE levels in allergic patients, most likely due to long-lived plasma cells and memory cells (39, 40). IgE-producing plasma cells and IgE^+ memory cells have been detected in the blood of allergic patients, but these cells produce only about 0.2% of IgE in serum because of few such cells in the blood. Therefore, it is likely that most IgE-producing and IgE memory cells may exist elsewhere (41). For instance, lymphoid tissues at sites of allergen exposure (e.g., nasal mucosa and intestinal mucosa) contain IgE^+ memory cells that can be activated (42) or plasma cells in the bone marrow (43, 44).

Elevated IgE has been associated with the severity of patients with exogenous AD and normal IgE levels have been found in patients with intrinsic AD (45, 46). Recently, IgE autoreactivity that targets keratinocytes and a variety of autoantigens has increasingly received attention in research of AD immunopathogenesis (47–49). These IgE autoantibodies also play an important role in exacerbating and prolonging the severity of AD. By contrast, when paradoxical eczema appears in patients with psoriasis, the IgE elevation tends to vary with stages of psoriasis (50) and biological drug treatments the patients received (51, 52).

Immunopathological relationship between atopic dermatitis and IgE

Pathogenesis of atopic dermatitis

Failure to maintain the skin barrier could initiate the onset of an atopic condition such as AD (53). Genetic defects in AD patients are mainly involved in mutations of the filaggrin (FLG) gene (54–57). Some FLG mutations would affect the development of the stratum corneum and change pH on the skin surface (58). As a result, the thymic stromal lymphopoietin (TSLP) is produced by the barrier-disrupted epidermis, which

effectively induces a Th2/Th22 immune response in AD lesions (6, 59). Increased IL-4/IL-13/IL-25 and IL-22 form a positive feedback loop that further suppresses FLG expression in the stratum corneum barrier (60) and increases allergen penetration and systemic IgE sensitization (61).

IgE mediated type 2 inflammatory reaction in atopic dermatitis

Skin barrier defects and atopic immune environments work together to promote the development of a series of IgE-mediated allergic diseases, known as atopic march, in a sensitized patient (62). The highly produced IgE tends to skew the adaptive response toward type 2 inflammatory reaction diseases in each of these atopic conditions (6). Serum IgE levels are elevated in about 80% of AD patients sensitized to air and food allergens (7). Even less common, AD patients can be caused by the excessive autoantibody reactive to IgE. In this case, auto-reactive IgE antibodies induce an allergic, autoimmune process that tends to be persistent and chronic inflammation course (63). Meanwhile, the increased sensitivity to autoantigens observed in AD patients may concur with other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (63–65).

Potential association between psoriasis and IgE

Pathogenesis of psoriasis

The immune effectors of psoriasis include Th1, Th17, and Th22 and their corresponding cytokines such as IFN-γ, IL-17, and IL-22 (5, 66, 67). At the onset of psoriasis, the cytokines secreted by Th17, keratinocytes and other skin-resident cells, could work together to induce an extensive inflammatory response and recruit Th1 and Th22 cell subsets into psoriatic lesions. These effector cells then promote the cytokine secretion to magnitude inflammatory responses. This process has been known as "feed-forward" in the pathogenesis of psoriasis (11, 68). Of note, clinical studies demonstrate that antagonists of IL-17 alone are sufficient to remiss the disease (69, 70). Thus, it is believed that Th17 cells are the main driver of psoriasis pathogenesis.

Keratinocytes play an essential role in psoriasis. Following the activation, keratinocytes indirectly attract immune cells into the skin by releasing chemokines, such as CXCL8, which is the major recruiter for neutrophil accumulation in the epidermis (71). Other keratinocyte-produced chemokines, such as CCL2, CCL5, CXCL10, and CXCR3 ligands, participate in attracting monocytes and Th1 cells (72). In addition, ADAMTSL5, highly expressed in keratinocytes, can act as an autoantigen in psoriasis (73). When activation of psoriatic Th17 cells is not driven by exogenous antigens in psoriasis, chronic activation of endogenous autoantigens could be the alternative mechanism for inflammatory reactions due to insufficient Tregs and immune checkpoints responses (74). Because Th17 cells can promote the production of both ADAMTSL5 and another skin autoantigens, LL37, the such positive feedback loop may exacerbate the course and chronicity of this disease (75). Finally, activated keratinocytes and immune cells would release endothelial growth factor that increases capillary density and permeability in psoriatic lesions.

IgE in psoriasis

The presence or absence of a Th2 immune response is the discretionary sign to discriminate psoriasis from AD. However, accumulating evidence shows that some psoriasis patients have high levels of serum IgE and tend to have pruritic AD-like manifestations (3, 12, 76, 77). It seems that serum IgE levels are higher in patients with more severe psoriasis (3) or with longer skin lesions (50). A study in Austria divided patients with psoriasis into mild (PASI < 10) and moderate-to-severe (PASI ≥ 10) groups and found that the allergic conditions appeared in 29.0% of patients in the moderate-to-severe group and 23.8% in the mild psoriasis group, although Type I hypersensitivity reactions in both groups were similar to the general population (12). In terms of the IgE level, 34.7% of the psoriasis patients showed elevated IgE in the PASI ≥ 10 group compared with 19.1% in patients with PASI <10 (78).

IgE levels in patients with psoriasis vary with stages and types of disease. A radio allegro sorbent test (RAST) is a commonly used method to measure the serum IgE in the clinical setting. A previous study showed that RAST was positive in 58 and 22% of patients with chronic plaque psoriasis and active psoriasis, respectively (79). Several studies showed similar results, in which the positive RAST tests were significantly higher in patients with chronic plaque psoriasis(CPP) than those with progressive psoriasis (50, 80). However, contradictory results have also been reported. For example, the proportion of patients with elevated serum IgE in psoriasis vulgaris (PV) group was 77%, which was significantly higher than that in CPP group (29.7%) (81). For PV and generalized pustular psoriasis (GPP), the percentage of patients with an elevated IgE accounted for 46 and 76.2%, respectively, compared with 15.6% in healthy controls (82). Compared with 76.5% of patients with psoriatic erythroderma (PE) that showed elevated IgE, only 37.9% CPP patients showed high IgE (50). Similarly, another study found that 81.3% of PE patients had elevated serum IgE, which was significantly higher than that of controls (6.3%) (83). All these studies suggested that PE patients are more likely to have high serum IgE and that patients with moderate-to-severe psoriasis with joint symptoms have higher serum IgE levels than patients without joint symptoms (84).

The pathological impacts of elevated IgE may differ in different forms of psoriasis that may determine the clinical outcomes. Patients with a longer period of skin lesions had higher total IgE concentrations (50), and serum IgE levels correlated positively with C-reactive protein (CRP) in patients with GPP and PV (82). In addition, the populations of IgE^+ cells and $Fc\varepsilon RI^+$ cells are substantially higher in psoriatic lesions relative to non-lesional areas of the skin in the same patient, suggesting that $Fc\varepsilon RI^+$ cells may also be involved in the development of psoriasis (85, 86). However, there are also contradictory result. In one study, high serum IgE in patients with psoriatic arthritis (PsA) seemed to suffer fewer episodes of atopic symptoms when compared with PV and control groups (87), suggesting that atopic disorders somehow protect against the development of PsA. Results from several studies may provide a clue to explain the significance of the elevated IgE in PsA and PE patients. First, the elevated serum IgE levels in PsA seem to be a consequence of an altered Th1/Th2 balance (84); the Th1 / Th2 response was skewed toward the Th2 axis in PE patients (83). Th1 lymphocytes may produce cytokines in the early phase of psoriasis, whereas Th2 lymphocytes cytokines for activating IgE produce appear at the late stage of psoriasis. Therefore, as others have suggested, caution should be exercised in using Th2-inducing reagents when treating patients, particularly PsA and PE patients (81). Second, it is interesting to observe that the IgE elevation was correlated to a down-regulation of CD23 in B cells harvested from synovial fluid from PsA patients (88). CD23 is a low-affinity IgE receptor. How this down-regulated CD23 affects IgE-mediated inflammation in PsA is unclear.

Overproduction of IgE is mainly driven by Th2-associated cytokines, such as IL-4 and IL-13 (89). However, IL-17 also participates in inducing the differentiation of IgE-secreting cells and promoting the synthesis of IgE (90). Keratinocytes do not produce IL-4 or IL-13 but express IL-4 and IL-13 receptors on the surface of the cells (91). Given that the over-proliferation of keratinocytes and high production of IL-17 are common in psoriasis patients, one can imagine that both keratinocytes and IL-17 may contribute to the elevated serum IgE in psoriasis. For example, upregulated IL-21 cytokine has been noted in psoriasis, which has been speculated to be involved in IgE production in psoriasis (92, 93). Proinflammatory cytokines such as IL-6, IL-17, IL-21and CD40/CD40L may play critical roles in the elevation of IgE in psoriatic lesions (86, 94).

To date, a number of biologics have been used to effectively treat psoriasis, including psoriasis patients with high serum IgE levels. Ustekinumab downregulates IL-17 by binding promoters of IL-12 and IL-23 (IL-12 and IL-23 inhibitor), which can significantly reduce IgE^+ and $Fc\varepsilon RI^+$ cells in patients with high serum IgE levels. Since IL-17 has been shown to promote IgE production from human B cells, the downregulation of IL-17 by ustekinumab may thus decrease IgE (92). However, it is noteworthy that ustekinumab paradoxically initiated or exacerbated AD-like symptoms (95, 96). Risankizumab, an IL-23 inhibitor, was reported to cause the elevation of serum IgE in patients with psoriasis. Others reported that patients with plaque psoriasis developed an extensive urticaria rash with intense itching after 1 month of treatment with efalizumab (52). Taken together, allergies appear to be common in patients with psoriasis. These results suggest that allergen exposure should be avoided or combined with anti-allergy therapy, particularly in patients treated with biologicals (78). Nonbiological agents, such as azithromycin or methotrexate, can also decrease the serum IgE levels (86).

Despite accumulating evidence showing that an elevated level of total serum IgE is associated with psoriasis, the involvements of IgE in psoriasis pathogenesis are not fully clarified. The elevated IgE level in psoriasis patients suggests a possible shift of Th17 toward Th2 immune responses, which makes it difficult to distinguish between psoriasis and AD. Since the biologics for psoriasis treatment have a profound effect on modulating different subsets of T-helper cells, results from studies on the immunopathogenesis of psoriasis could become more complicated under biologic therapies (97).

IgE is a link or epiphenomena for atopic dermatitis and psoriasis

Overlap between psoriasis and atopic dermatitis

Traditionally, AD and psoriasis are considered two distinct diseases by virtue of their immunopathogenic mechanisms, clinical characteristics, and the ages of onset (98). However, when one views the dynamic process of each individual disease, some AD patients with high levels of Th1 and Th17 cytokines may mimic psoriasis and show psoriasis-like lesions. On the other hand, some psoriasis patients may present with AD-like lesions with high IgE and severe pruritus. The coexistence of psoriasis and AD includes different conditions such as psoriasis in patients with AD, psoriasis in children with AD, AD in children with psoriasis, contact dermatitis in psoriasis, and a phenotypic shift to eczema as a result of biologic therapy for psoriasis (99–104). Therefore, the coexistence ratio is also different (Table 1).

Common genetic predispositions have been noted (105) for the two diseases, in which the mutations are found on chromosomes 1Q21, 3Q21, 17Q25, and 20P12 (106). In addition, associations with AD were found on chromosomes 1Q21, 17q25, and 20P, regions that closely correspond to known psoriasis sites (107). A study in Japan found a marginal association between AD and two psoriasis susceptibility SNPs, IL-13(rs1295685) and ZMIZ1(rs1250546) (108). Although it is generally believed that the FLG gene mutation contained in the epidermal differentiation complex (EDC) on chromosome

TABLE 1 The distribution of subtypes of Psoriasis and AD in the published articles.

Subtypes	Percentage (%)
Psoriasis in patients with AD (97, 99)	3–16.7%
Psoriasis in children with AD (98)	0.2%
AD in patients with psoriasis (97, 99)	2–9.5%
AD in children with psoriasis (98)	1%
Contact dermatitis in psoriasis (100, 101)	32.7–77.7%
Phenotypic shift to eczema as a result of biologic therapy for psoriasis (102)	6.0% (Infliximab) 2.7–12.1% (Ixekizumab) 3.9–8.0% (Secukinumab) 4.4% (Ustekinumab)

1Q21.3 is more closely related to the development of AD than psoriasis (109, 110). Variants of the FLG mutation have been reported to increase the risk of psoriasis in Chinese patients (111). Interestingly, the two diseases had another common region on the genome, chromosome 5Q31.1-Q33.1, where IL-13 was associated with both AD and psoriasis (109). There is evidence supporting a significant correlation between IL-13 and psoriasis/ psoriatic arthritis (112, 113).

Clinical symptoms also overlap or coexist between the two diseases, which may present a challenge for clinical diagnosis. Studies have found that patients with overlapping AD and psoriasis have a high incidence of hand involvement (101). Because adult AD patients are more likely to appear on body flexion, the lesions on the hand often exhibit atypical manifestation (114, 115). As a large number of proinflammatory cytokines and chemokines are involved and released into the circulation in AD and psoriasis, the systemic inflammatory spectrum of clinical manifestations has also been described as "psoriatic march," "march of psoriasis" or "inflammatory skin march" (116). Itching is one of the hallmark symptoms of AD and occurs in many psoriasis patients (117–119). The mediators causing this symptom include neuropeptide substance P, its receptor NK-1R, and β-endorphin precursor gene (POMC), which are upregulated, and a downregulated κ-opioid receptor gene (OPRK1). MRGPR, an enzyme of cytosolic group IV PLA2 family members and TRPV1 are also significantly elevated in pruritus skin (120). Studies have shown that upregulated phospholipase A2 IVD, Substance P, Nav1.7, or TRPV1 genes in itchy skin are positively correlated with the intensity of pruritus in AD and psoriasis. Also, cytokines such as IL-17A, IL-23A, and IL-31 are upregulated in atopic pruritus and psoriatic skin (120).

Atopic dermatitis presents with psoriasis-like features

AD can be categorized into the extrinsic and intrinsic types, in which exogenous AD is frequently associated with activation of Th2 and elevated IgE and intrinsic AD shows activation of Th17 response besides activation of Th2. In adults, extrinsic AD with a decreased Th17 response tends to have nonflexural area involvement (121). S100A9/12, regulated by IL-17 and IL-22, was also significantly increased in skin lesions in intrinsic AD and it was positively correlated with SCORAD scores (122). In the acute phase of AD, thymic stromal lymphopoietin (TSLP) produced by keratinocytes can trigger Th2 polarization to produce IL-4 and IL-13, which in return acts on keratinocytes to further increase TSLP levels. This process thus creates a positive feedback loop (6).

AD starts in early childhood but has a tendency to persist throughout life with different clinical manifestations (123, 124), which are the consequence of dominated immune responses. For example, the Th2 response is detectable in the blood of infantile AD patients and the Th17 response in skin lesions then develops with increasing age along with Th2 and Th22 responses (59). However, when comparing no age difference in the expression of Th2 and Th22, a more pronounced Th17 response can be clearly detected in childhood AD patients than in adulthood AD patients (125). This may be related to age-related changes in the skin immune system, the regulatory and protective properties of which tends to skew a strong Th17 response in early life (126).

The clinical manifestations of AD may vary considerably in AD patients of different ethnicities. Lesions in Asian AD patients are more likely covered by scales than in European and American patients, and epidermal hyperkeratosis and neutrophilic infiltration are more common in Asian AD patients than European and American patients (55, 124, 127, 128). In addition to exhibiting psoriasis-like features, Asian AD patients often show a robust Th17 response (IL-17A, IL-19 and S100A12) in the skin lesions (129) and are more susceptible to *S. aureus* colonization, perhaps due to a lack of AMPs, damage to the skin barrier and dysbiosis of the microbial ecology. In this case, not only can *S. aureus* directly disrupt skin barrier function, but it can also cause Th17 polarization by upregulating pro-inflammatory cytokines. This may explain why some AD patients have lesions that are more similar to psoriasis (130, 131). Taken together, pathological mechanisms at different stages of the disease and different ages of the patients all contribute to a more psoriasis-like presentation in AD patients.

Psoriasis mimics atopic dermatitis

The function of Th17 cells and IL-17A, the signature cytokine of Th17 cells, are pivotal for the development of psoriasis (68, 132). IL-17A is also involved in the induction of Th2 cell-specific allergen activation and plays an important role in increasing serum IgE levels (133). There is a large amount of literature showing that Th17 cells are directly or indirectly involved in the development of allergic atopic diseases (134, 135). Unlike AD, Th2 cell response was downregulated in psoriasis patients, showing ethnic differences. A strong Th2

response was detected in the lesions of Chinese patients (136). IL-17 family has five other members (IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F), which may play similar or opposite roles of IL-17A in regulating immune responses, *via* perhaps the Th1/Th2 balance or the Th17/Th2 balance (137). Taken together, these studies suggest that different members of the IL-17 superfamily can play different roles that can change the balance of Th1/Th2, which is part of the reasons that two diseases occur in the same patient.

IL-4 is considered a marker of Th2 cells, but interestingly, high levels of IL-4 can be found in patients with mild PASI scores (138). Since IL-4 can exert an anti-inflammatory effect by reducing the expression levels of IL-1 and IL-6 in the skin of patients with psoriasis, this phenomenon may be the result of the immune system trying to balance the main inflammatory responses. Such a balancing process can be demonstrated in psoriasis patients receiving biologic treatment. A study found that biologics that inhibit the TNF-α and IL-17/IL-23 axis induce atopic eczema, eosinophilia and increase serum IgE (104). Naïve $CD4^+$ T cells differentiate into different subpopulations of Th cells in response to different stimuli. Whether this inhibition of IL-17 skews the immune responses toward a specific Th identity, or repolarize into new Th cell subsets are poorly understood. However, studies have found that Th17 cells are plastic, and in the presence of appropriate signals, they also shift to the Th2 phenotype that will turn human circulating memory $CD4^+$T cells into the Th cells that produce IL-17A and IL-4 (139, 140). A previous study re-evaluated the spectrum plasticity and found that several new cytokine patterns were produced after repolarization. Repolarization of Th17-trained cells revealed severe instability in this spectrum. These cells can re-differentiate to the Th2 phenotype not only in the context of Th2 stimulation but also in the presence of neutral conditions (Th0). Thus, nascent Th17 cells may change cytokine expression toward the Th2 pattern under specific changes in an inflammatory microenvironment caused by preconditions

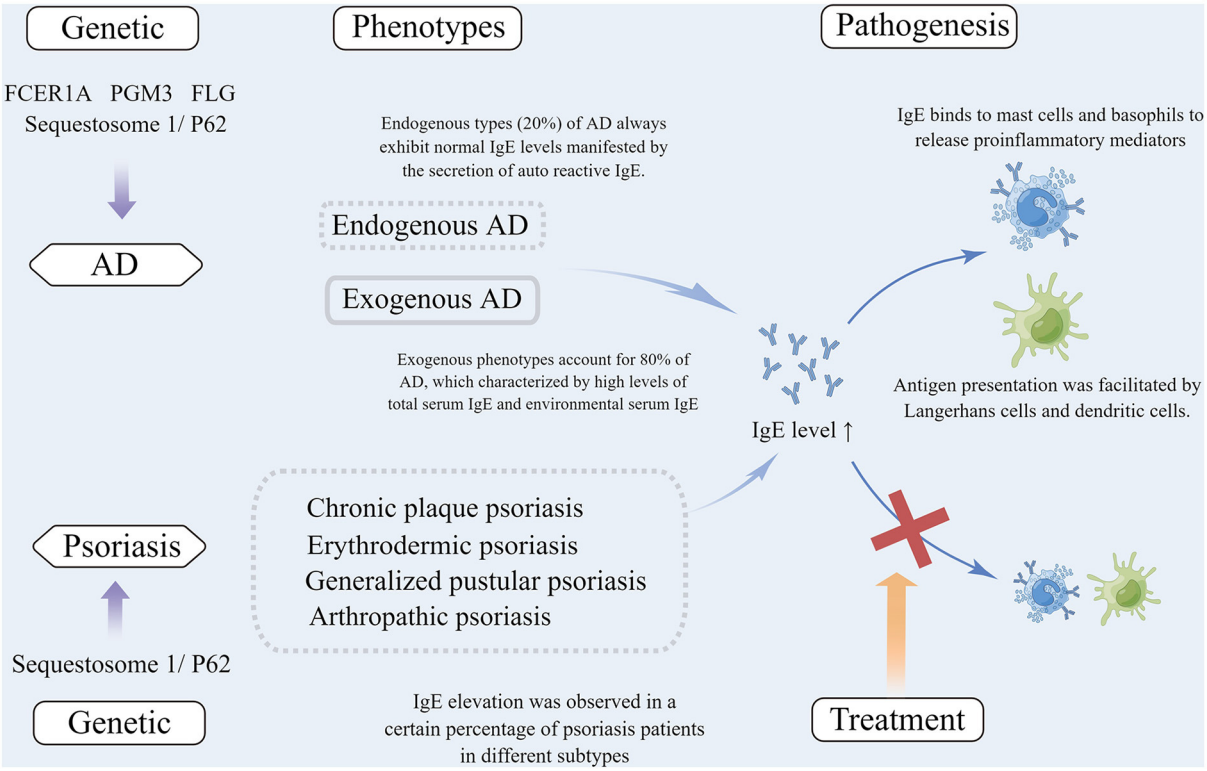

FIGURE 1
(1) Mutations of several genes are associated with IgE elevation in atopic dermatitis, including FCER1A, PGM3, FLG and Sequestosome 1/P62, among which Sequestosome 1/ P62 mutation was also observed in psoriasis patients with elevated IgE; (2) Exogenous phenotypes account for 80% of patients with AD, which are characterized by high total serum IgE and allergen-specific IgE. Patients with endogenous types (20%) of AD always exhibit normal IgE levels manifested by the secretion of autoreactive IgE. IgE elevation was observed in a certain percentage of patients with different subtypes of psoriasis; (3) In the pathogenesis of AD, IgE binds to immune and non-immune cells that expressed high-affinity IgE receptors (FcεRI) (e.g., dendritic cells, Langerhans cells, mast cells, basophils, and keratinocytes) to release proinflammatory mediators or to facilitate antigen presentation. In psoriasis, IgE can be bound to the above cells that expressed high-affinity receptors to be involved in the pathogenesis; (4) Anti-IgE treatment is often effective in AD patients, but there are no reports concerning anti-IgE treatment for psoriasis. AD, Atopic dermatitis; IgE, Immunoglobin E; FcεRI, Fc epsilon receptor Iα; PGM3, Phosphoglucomutase 3; FLG, Filaggrin.

(141). This further suggests that progression of the disease is a dynamic process with many strands in a possible network.

The skin barrier acts as a physical barrier and immune barrier, and the destruction of the skin barrier is associated with the process of AD pathology and the development of psoriasis. In psoriasis, keratinocyte proliferation and differentiation can be interfered with mutations in keratin (142), as well as decreased expression of the epidermal differentiation markers loricrin and FLG (143, 144). Dysregulation of tight junction proteins and E-cadherin, as well as CX26 overexpression, can also affect intercellular junctions (145–148). In addition, disorders of ceramide subtypes and skin lesions result in cuticular extracellular matrix dysfunction, low expression of aquaporin-3 (AQP3), and fibroblasts in psoriasis, all contribute to the dysfunctional physical barrier (149–153). For the immune skin barrier, keratinocytes trigger psoriatic inflammation by producing autoantigens (154) and promote DC autoantigen recognition by producing polyamines that prevent autoantigen RNA degradation (155). In addition to further contributing to psoriatic inflammation by producing proinflammatory cytokines (156, 157), keratinocytes can also produce chemokines that induce immune cell infiltration into the dermis (158) and contribute to psoriatic inflammation by means of direct contact between keratinocytes and T cells (159). Innate immune cells, including dendritic cells, neutrophils, macrophages, and mast cells, also produce cytokines, particularly THF-α, IL-17, and IL-22 (160–164), thus having a similar effect in driving inflammatory response in psoriasis. Dysregulation

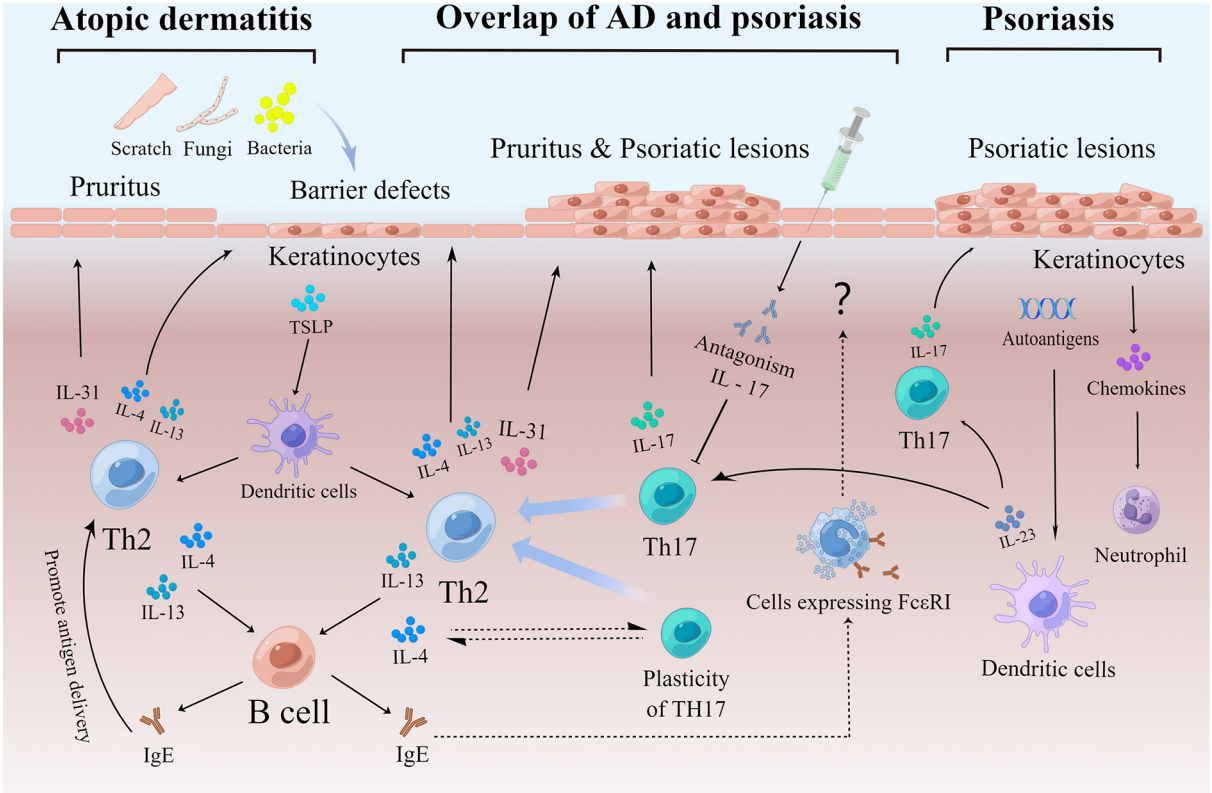

FIGURE 2
(1) An important pathogenesis of AD is the destruction of the skin barrier, which makes it easier for pathogens and allergens to invade and activate Th2. Keratinocytes play an important role in the inflammatory response to AD. Keratinocytes produce thymic stromal lymphopoietin (TSLP) to promote the differentiation of inflammatory Th2 cells. Th2 cells can produce cytokines, including IL-4, IL-13, and IL-31. IL-4 and IL-13 stimulate B cells, to produce IgE antibodies and aggravate skin barrier defects. IL-31 causes itching and stimulates scratching, which in turn damages the skin barrier. In addition, IgE promotes antigen presentation, which tilts the reaction toward Th2 and exacerbates the process. (2) Childhood AD patients, endogenous AD patients, Asian AD patients, etc. also show elevated Th17, thus exhibiting a partial overlap with psoriasis. In addition, certain percentage of psoriasis patients present with AD-like symptoms such as elevated serum IgE and pruritus, which may be due in part to Th17 remaining plastic and shifting to Th2 in response to stimulation mainly by IL-4. In addition, some patients with psoriasis show a shift to an eczematous phenotype following the use of IL-17 inhibitors, which may be due to a suppressed Th17 response and a relatively enhanced Th2 response. IgE produced during this process may act through cells expressing IgE high-affinity receptors. (3) Upon activating by a variety of stimuli, dendritic cells secrete IL-23 and further stimulate Th17 differentiation to produce IL-17. The IL-17/IL-23 axis plays a central role in the pathogenesis of psoriasis. Keratinocytes also play an important role in psoriasis by releasing chemokines to recruit neutrophils. In addition, keratinocytes with high expression of autoantigens may play a role in maintaining the pathological state of psoriasis. AD, Atopic dermatitis; IgE, Immunoglobin E; Th, T helper cells; DC, Dendritic cell; IL, Interleukin.

of immunosuppressive cells is closely related to psoriasis pathology. Regulatory T cells (Treg) are the most characteristic immunosuppressive cells. Suppression of Tregs results in increased penetration of γδ, CD4+, and CD8+T cells, an increased presence of IL-17 and tumor necrosis factor-α, and increased severity of skin lesions (165). Regulatory B cells (Breg), which exert immunosuppressive effects by producing the anti-inflammatory cytokine IL-10, was reduced in the circulation of patients with psoriasis (166). Moreover, the anti-inflammatory effect of Myeloid suppressor cells (MDSCs) was decreased in patients with psoriasis (167).

Patients with psoriasis have elevated serum IL-31 levels, which are associated with the presence of pruritus in these patients (168, 169). Persistent scratching of the skin would further damage the skin barrier in patients and lead to Koebner's phenomenon (170). Scratching could activate sensory neurons, force them to release proinflammatory neuropeptides, and again exacerbate skin barrier disorders in psoriasis (171).

Previous studies have strongly linked changes in the skin barrier with the development of allergic reactions (172), and dysfunction of the epithelial barrier is thought to initiate a range of allergic inflammatory diseases, including asthma and atopic dermatitis (173–175). FLG is a key component of the cuticle, and its genetic defects are believed to be involved in the development of psoriasis and AD and other IgE sensitization (176). Thus, in the skin with a broken barrier, alterations in the epidermal microenvironment appear to be particularly suited for producing allergen-specific IgE and type 2 inflammatory diseases (177), which are observed in some psoriasis patients who develop AD-like lesions.

IgE is a link or epiphenomena for psoriasis and atopic dermatitis

In mouse models, there are two types of IgE induced *via* natural and adaptive ways (178). Adaptive IgE is usually produced by B cells and plasma cells, with characteristics such as variable region gene polysomatic high mutation. Natural IgE, unlike adaptive IgE, is produced by B cells and does not require the co-stimulation of antigen selection and T cells. Therefore, B cells that naturally produce IgE have less polysomatic high mutation and can respond to their own antigens (179). Some studies have found that high IgE VH mutation and the increased CDR3 diversity along with high serum IgE content in AD and psoriasis patients (178). In addition, it was found that the serum IgE level of Sequestosome 1/ P62 DKO mice returned to be normal, which was increased in psoriatic lesions, suggesting that this gene has a similar IgE regulation mechanism in psoriasis and AD (180).

Some studies have found that the up-regulation of ICOS on TH22 cells may play an essential role in the pathogenesis of AD in Han Chinese (181). Activation of the Th22 pathway plays an important role in the pathologic process of both psoriasis and AD (182). The development and biological functions of T cell subsets are critically regulated by the Inducible T cell co-stimulator (ICOS) and ITS ligand (ICOSL). The number of $ICOS^+$ Tfh cells was also found to be positively correlated with the course of psoriasis (183). Additionally, it has been shown that ICOS-mediated stimulation promotes B cell differentiation and IgE production (184). Thus, the elevated IgE levels may be related to this pathway.

In addition, DC and T cell markers (CD3, ITGAX/CD11c and CD83) were expressed at higher levels in AD and psoriasis tissues (185). The serum total IgE level and IgE^+ and $Fc\varepsilon RI^+$ cells were significantly increased in psoriatic skin lesions, which were mainly expressed on mast cells, dendritic cells and macrophages (86). However, it is unclear whether the initial high IgE level initiates the inflammatory process or whether the increased number of proinflammatory cells leads to increased IgE production. $CD3^+$ cells are the main cell population infiltrating psoriatic plaques (30) and in both acute and chronic AD lesions (6). However, IgE synthesis requires homologous interactions between the TCR/CD3 complex on T cells and MHC class II antigens on B cells, as well as contributions from cell adhesion molecules (186). CD83 is a marker of B cell activation and is important for B cell activation. In a B cell-specific CD83 conditional knockout model, bacterial clearance was inhibited, and the model showed a characteristic transformation to a Th2 response produced by high IgE (187) and marked by IL-4 and IL-13 production (188). The massive release of thymic stromal lymphopoietin (TSLP) from the barrier-disrupted epidermis also triggers a Th2/Th22 immune response, as a major T-cell response often observed in AD lesions. Furthermore, IgE-antigen complexes promote antigen delivery and skew the adaptive response toward type 2 immunity, which results in chronic skin barrier dysfunction and inflammation.

The reciprocal regulation of Th1 and Th2 cells is always observed in psoriasis and other infectious diseases, with induction of Th1 cells and release of Th1-associated cytokines IFN-γ and TNF-α resulting in the inhibition of Th2 cells (189). Accordingly, it has been postulated that Th1-triggered diseases may be involved in the suppression of Th2 cells (190). Accumulating clinical data show that allergy appears to be equally abundant in patients with mild or moderate-to-severe psoriasis (78, 191). The genetic and phenotype, pathogenesis, and treatment of AD and psoriasis associated with elevated IgE levels were summarized in Figure 1.

Potential causes of IgE stimulation in atopic dermatitis and psoriasis

An important mechanism for AD development is the disruption of the skin barrier that increases the transmissibility

of external allergens and promotes the Th2 immune response through antigen-presenting cells such as Langerhans cells and dendritic cells, both of which could lead to increased IgE production (192). In addition, AD was found to have IgE autoantibodies and a wide range of autoantigenic epitopes (193–195). Autoreactive antibodies also seem likely to play a role in co-morbidities of AD and enhance atopic marching, as well as other inflammatory diseases (193). The presence of both exogenous and autologous allergens may then accelerate the immune response.

IgE is usually associated with type I hypersensitivity reactions and is not present in non-allergic diseases such as psoriasis. Although the roles of IgE in psoriasis pathogenesis remain unclear (188), the high levels of IgE in psoriasis (Figure 2) have become evident, as shown from numerous clinical and experimental studies of patients with chronic plaque psoriasis, erythrodermic psoriasis, generalized herpetic psoriasis, and psoriasis with comorbid arthropathy (50, 79, 80, 82–84). The data also show that serum IgE levels seem to be higher in patients with more severe psoriasis and with lesions of longer duration (3, 50, 78), highlighting the possibility that IgE could be a key indicator of AD-like psoriasis and play a potential role in the pathogenesis of AD and psoriasis. Based on these observations, psoriasis patients with AD-like symptoms and high IgE should avoid exposure to allergens and be aware of any lesion changes and possible shifts to eczema or urticaria (51, 52, 97) under biologic therapies.

Conclusions and future perspectives

Although AD and psoriasis have traditionally been considered two clinically distinct diseases, it has become clear that overlapping clinical manifestations exist, and even the underlying pathogeneses of these diseases have become somewhat blurred. Clinically, pruritus, as well as other phenotypes of type 2 inflammatory diseases (e.g., elevated IgE and eosinophils), are typical features of AD and yet are observed in 37-75% of patients with psoriasis. Current evidence supports the notion that AD and psoriasis share some clinical and immunopathogenic characteristics based on the following: (1) some patients are genetically susceptible to both diseases; (2) Th17 cells in psoriasis patients may still have the plasticity to re-differentiate toward Th2 phenotypes under certain conditions; (3) clinical treatments can change the manifestations of either disease. To answer whether AD-like psoriasis is a part of a spectrum that may stretch between psoriasis and AD, we must look further at AD patients with symptoms that overlap with those of psoriasis. Here we have conducted a comprehensive literature review to clarify the impact of Th cell plasticity on different immune inflammatory environments, including high levels of IgE in the progression of AD and psoriasis.

Author contributions

LS and CL: elaborated the figures and wrote the manuscript. LS, HX, and DS: reviewed topics and concepts. DS: conceived, reviewed, and discussed concepts in the manuscript. All authors contributed to critical revisions of the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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