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REVIEW

Humoral and Cellular Autoreactivity to Epidermal Proteins in Atopic Dermatitis

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Abstract Atopic dermatitis (AD), a chronic relapsing inflammatory disease of the skin, is an important public health concern affecting 10–20 % of children worldwide. The etiology and pathogenesis of AD involve the interplay of genetic and environmental factors, including abnormalities in skin integrity and a skewed immune system usually driven by a Th2 phenotype in childhood with a switch to Th1 in the chronic phase of disease. Children and adults with AD commonly have elevated IgE levels directed to multiple different antigens, including aeroallergens, food allergens, and microbial proteins. IgE targeting self-antigens from epidermal proteins have been detected in up to 91 % of patients, particularly in severe persistent AD. It has been suggested that the occurrence of autoreactivity develops in early childhood. However, it is not clear yet if autoreactive IgEs in patients with AD are pathogenic or just an epiphenomenon. The fact that these autoantibodies are associated with severity and are not present in other allergic or skin diseases favors the pathogenicity of IgE-mediated autoreactivity in AD. In this review, we evaluate the pathogenesis of AD and the emerging role of autoreactivity to various keratinocyte antigens involving both the humoral and cellular components of the immune system.

Keywords Autoimmunity · Epidermis · Immunoglobulin E · Malassezia

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disease that affects 25 % of children and 2–3 % of adults (Eichenfield et al. 2014; Ring et al. 2012). However, recent studies have suggested an increase in the adulthood prevalence of the disease (Mortz et al. 2015). AD is an important public health concern affecting 10–20 % of children worldwide with higher prevalence in industrialized countries with a two- to three-fold increase in the past three decades (Bieber 2010). AD is characterized by severe dry skin, erythema, and pruritus, and deeply affects the quality of life of affected individuals and its relatives (Coutanceau and Stalder 2014; Lewis-Jones 2006; Schmitt et al. 2011). It is often associated with a personal and family history of type I allergic diseases, including food allergy, asthma, and allergic rhinitis, in a progressive sequence commonly denominated as the atopic march (Spergel 2010; Spergel and Paller 2003). However, about 20 % of patients with AD have no sensitization to food or aeroallergens, with variations between children and adults (Folster-Holst et al. 2006; Schafer et al. 2000). This condition is known as intrinsic AD, as opposed to patients with IgE-mediated sensitization known as extrinsic AD.

Evidence for autoreactivity and autoimmunity in AD patients is as old as the 1920s when two investigators reported that individuals with severe forms of atopy exhibited immediate-type reactions on skin testing with

aqueous human dander extracts (Valenta et al. 2000). Then, it was shown that human skin extracts induced proliferation in leukocytes from AD patients (Hashem et al. 1963). The concept of autoallergy in AD was then discarded for years (Valenta et al. 2000), until it was discovered that some fungi (e.g., molds) and animal antigens had some similarities to human antigens/proteins that could be associated with some manifestations and disease course in AD patients. The demonstration that human IgE recognizes both exogenous allergens and related human antigens has led to the hypothesis that autoreactivity may play a role in AD pathogenesis (Valenta et al. 1996).

The purpose of this article is to review the role of humoral and cellular autoreactivity in the pathogenesis and clinical presentation of AD.

Natural History, Clinical Manifestations, and Pathogenesis of AD

Almost 45 % of cases of AD are diagnosed during the first 6 months of life, 60 % during the first year, and 85 % before 5 years of age (Illi et al. 2004). The disease can be continued to adulthood in 10–20 % of patients (Mortz et al. 2015), and albeit rare, the disease can start in adults, making AD a prevalent and potentially severe disease encountered by both pediatricians and adult-care physicians. The clinical manifestations and skin distribution of AD may vary with age providing a wide range of presentations. Family history is frequent, with a concordance of up to 80 % in monozygotic twins and up to 20 % in dizygotic twins (Schultz Larsen and Holm 1985). New data have emerged concerning different phenotypes (Ricci et al. 2014) and courses (Garmhausen et al. 2013) of AD that may translate into a variety of AD subtypes and not a single uniform disease as traditionally viewed. Understanding the pathogenesis of AD, which we will explore in the following section, is highly relevant for definition of these different subtypes of AD. Further in this review, we evaluate the emerging role of autoreactivity to various keratinocyte antigens involving both the humoral and cellular components of the immune system that may define a particular phenotype within AD.

As with any complex disease, the pathogenesis of AD involves interplay of many factors, both genetic and environmental. Two strong pillars of disease have been clearly identified. First, impairment in the epidermal barrier has been consistently demonstrated in AD patients (Baroni et al. 2012). An altered epidermal surface prompts transepidermal water loss and the penetration of allergens and microorganisms (or their components) into the skin. These processes lead to irritation, pruritus, and scratching causing mechanical injury to the epidermis. One of the most important and studied impaired protein in this barrier is filaggrin (acronym for filament associated protein). It plays a key role in aggregating keratin filaments into compact bundles in the keratinocytes and "collapses" granular cells to form physiologic corneocytes and a homeostatic stratum corneum (Levin et al. 2013). Other important impaired components of the skin barrier include lipids from the lamellar bodies, such as ceramides (Madison 2003), involucrin, loricrin, keratolinin, and among others (Baroni et al. 2012). A second pillar of AD is the immunological alterations characterized by imbalances in T helper (Th) subsets. There is a predominance of Th2 immunity at the beginning of the disease with a predominance of interleukin (IL)-4, IL5, and IL-13 followed by a switch to a Th1 immunologic response (with predominance of interferon (IFN)-γ and IL-12) in later chronic stages (Peng and Novak 2015). Th2 lymphocytes activate B cells to switch immunoglobulin class to the IgE, a phenomenon that usually occurs early in the life of AD patients. These IgEs are not only directed against multiple allergens including food and aeroallergens, but also to staphylococcal and other skin microbial proteins, and as we will discuss further in this review, IgEs may be directed to self-antigens in a large proportion of affected patients.

Microbial colonization and infection also plays a role in the skin inflammation of AD. Inflammation produced by Th2 cytokines (IL-4, IL-13) causes a downregulation of antimicrobial peptides (namely, cathelicidin and β-defensins) that have antistaphylococcal and antiviral effects (Ong et al. 2002). AD patients are colonized by *S. aureus* in up to 90 % of patients driving additional inflammation in a vicious loop (Aly et al. 1977; Ong et al. 2002; Rajka et al. 1981). In addition, the *S. aureus* enterotoxin seems to contribute to pathogenesis of AD; it induces further expression of IL-18 leading to constant skin inflammation (Orfali et al. 2009) and by the production of specific enterotoxin antibodies (Orfali et al. 2015).

Role of Autoreactivity in AD

Given the finding that individuals with severe AD were found to have immediate-type reactions on skin testing with aqueous human dander extracts (Hampton and Cooke 1941), autoimmunity/autoreactivity was hypothesized as a possible mechanism of AD, not without controversy (Zeller et al. 2008). It is not yet clear if autoreactive IgEs in patients with AD are pathogenic or just an epiphenomenon, or whether it is genetic predisposition or epigenetic/environmental factors that influence the generation of autoreactivity in AD. The presence of autoreactivity in AD may be involved in the pathogenesis of this complex and heterogeneous disease and may explain in part phenotypic

differences among AD patients, possibly constituting a new subgroup of AD (Altrichter et al. 2008; Hradetzky et al. 2015). In the following paragraphs, we will explore the current evidence of autoreactivity in AD and its association with disease severity.

Autoimmune Phenomena in AD Patients

More recently, AD has been reported to occur simultaneously with autoimmune diseases, such as celiac disease, vitiligo, and alopecia areata, suggesting that it may be part of a more widespread disturbance of the immune system (Mohan and Silverberg 2015; Ress et al. 2014). In addition, 19–26 % of adult AD patients with severe facial lesions display positive antinuclear antibodies (ANA) ranging from 1:40 to 1:640 (Higashi et al. 2009; Tada et al. 1994). The ANA patterns in one study were homogeneous type (9/19 patients), homogeneous and speckled (7/19), speckled and other (2/19), and speckled and nucleolar (1/19) (Higashi et al. 2009). However, there are no detailed reports of the specific antinuclear antibodies detected in this group of patients. ANA positivity may be associated to photosensitivity of AD. The relationship between the titers of ANA and AD severity is not clear either (Higashi et al. 2009). In contrast, there are some authors that have not found this association in children with AD (Ress et al. 2015). Another interesting study found higher levels of anti-phospholipid antibodies in AD patients (25 %) in comparison with healthy controls (4 %; $p = 0.03$). Moreover, in this subset of antiphospholipid positive AD patients, SCORAD index was nine times higher than in AD patients with normal antibodies (Szakos et al. 2004). However, the association of antiphospholipid antibodies with AD severity has not been replicated by others (Ricci et al. 2005).

Humoral Autoreactivity

The evidence of a humoral immune response against self-antigens in AD is supported by two main considerations: the chronic relapsing course of the disease, as observed in autoimmune diseases; and the ability of some autologous human components to elicit immediate hypersensitivity skin reactions in patients with severe AD (Cipriani et al. 2014). These considerations are supported by a systematic review involving 1253 patients with AD and 1391 control participants that found "autoreactivity" (not specified/any type) in 18–91.4 % of AD patients compared to 0–11.7 % in control subjects. In the subset of patients with AD that specifically reported serum IgE autoantibodies with capacity to bind to human proteins, the authors found a 38.2 % of prevalence of autoreactivity compared with a 6.4 % prevalence in controls [weighted risk-ratio 13.2 (1.75–99.4)] (Tang et al. 2012). These autoantibodies mostly target keratinocyte components of AD patients. Using immunofluorescence microscopy, one study showed that serum IgE-binding is most pronounced at sites of cellular contact (junctional structures) (Altrichter et al. 2008). It has been suggested that the occurrence of autoreactivity develops in early childhood between 2 and 6 years of life, which would be the critical period for IgE autosensitization (Bieber 2010).

Self-Antigen Candidates

As a result of different mechanisms, the self-antigens associated with AD-autoreactivity derive from different cells and tissue lines (Table 1) (Cipriani et al. 2014). AD-related autoallergens are mostly intracellular proteins expressed in keratinocytes that are thought to be released

Table 1 Autoantibodies and its target antigens that have been described in atopic dermatitis patients

Autoantibody	Target antigen	Function (when available)
Hom s 1 antibody	Squamous cell carcinoma antigen recognized by T cells (SART-1) antigen in epidermis	Cell cycle arrest and apoptosis
Hom s 2 antibody	Human nascent polypeptide-associated complex (α-NAC) in epidermis	Activator of transcription
Hom s 3 antibody	BCL7B	Tumor suppressor oncogene
Hom s 4 antibody	Epidermal subfamily of calcium-binding proteins	
Hom s 5 antibody	Cytokeratin type II	Component of the cytoskeleton
Anti-hMnSOD antibody	The human protein manganese superoxide dismutase (hMnSOD) has high mimicry with *Malassezia sympodialis* allergen (Mala s 11)	Participates in redox reactions
Anti-DFS70/LEDGF antibody	The lens epithelium-derived growth factor/dense fine speckles 70 kDa protein (LEDGF/DFS70)	Multiple functions including involucrin expression and preserving corneal layer integrity and function
Anti-thioredoxin antibodies	Thioredoxin (hTrx). As an antigen, it cross-reacts with *Malassezia sympodialis* thioredoxin (Mala s 13)	Ubiquitous redox-sensing cytoplasmic enzyme

by tissue damage induced by activities, such as scratching or during the chronic inflammatory phase allowing contact of immune cells (antigen-presenting cells: APC) with these "cryptic" antigens (Fig. 1) (Cipriani et al. 2014; Tang et al. 2012). In addition to intracellular antigens, IgE directed against keratinocyte cell surface has been observed in some autoreactive patients, suggesting the recognition of freely accessible surface proteins as targets of autoreactivity (Altrichter et al. 2008). However, specific cell surface antigens have not been identified to date. Recognized self-antigens include the family of *Homo sapiens* antigens (Hom S) that are primarily intracellular and expressed mainly in keratinocytes. They share the characteristic of not having known cross-reactivity to exogenous allergens (Hradetzky et al. 2015).

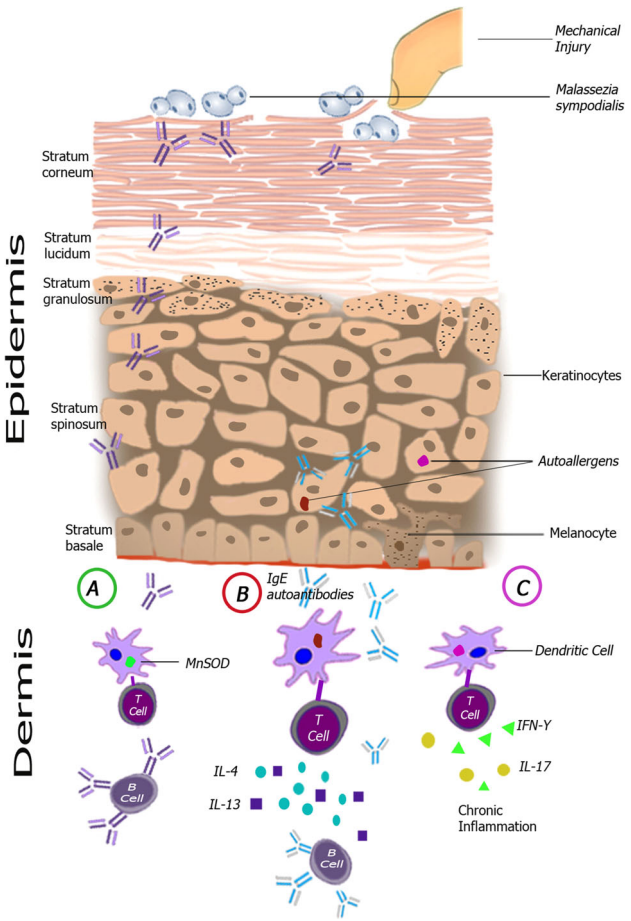

Fig. 1 Pathogenesis of autoreactivity in atopic dermatitis. **a** Mechanical injury causes epidermal inflammation driving the production of IgE autoantibodies against fungal proteins of Malassezia sympodialis that, in turn, can cross-react with the human protein MnSOD. **b** Autoallergens are mostly intracellular proteins expressed in keratinocytes, for example, Hom s1, which is one of the most frequently recognized autoantigens by IgE autoantibodies. **c** Activated autoreactive T cells in the lesional skin of patients with AD can produce IFN-γ and IL-17 that may play a role in the development of chronic eczema

Hom s 1 has been one of the most frequently recognized antigens by IgE autoantibodies. It has an almost identical sequence with the squamous cell carcinoma antigen recognized by cytotoxic T cells (SART-1). SART-1, a cytoplasmic pro-apoptotic protein, is expressed in suprabasal keratinocytes and dermal fibroblasts and endothelial cells (Valenta et al. 2000).

Hom s 2 is the α-chain of the human nascent polypeptide-associated complex (α-NAC) and can induce an immune response dependent of APC (Cipriani et al. 2014; Valenta et al. 2000). IgE-autoantibodies against α-NAC have been found in serum of AD patients and may be associated with AD flares (Natter et al. 1998). In addition, α-NAC specific T cells can be detected by flow cytometry in the blood and lesional skin of patients with AD (Heratizadeh et al. 2011). These T cells produce IFN-γ and IL-17 that may play a role in the development of chronic eczema (Heratizadeh et al. 2011). Furthermore, the cultured supernatants from peripheral blood mononuclear cells from Hom s 2 sensitized patients induced disintegration of respiratory epithelial cell layers and keratinocyte apoptosis, both reversible with the addition of anti-IFN-γ antibodies, demonstrating a key role of IFN-γ (Mittermann et al. 2008).

Hom s 4 codes a novel subfamily of calcium-binding proteins strongly expressed in epidermal keratinocytes and dermal endothelial cells, with cross-reactivity to exogenous calcium-binding allergens from fish (Carp parvalbumin, rCyp c 1) and plants (rPhl p 7 from timothy grass pollen). Aichberger et al. (2005) have found a prevalence of IgE against Hom s 4 in ~10 % of 100 AD patients. Hom s 4 has an intrinsic property to induce lymphoproliferative responses and Th1 switch with release of IFN-γ, but elicits only a weak histamine release from basophils (Aichberger et al. 2005).

As shown in previous paragraphs, Hom s 2 and Hom s 4 may, therefore, be considered as examples of Th1-driving autoantigens that have escaped tolerance, possibly because of their intracellular nature. If they are released from epidermal and dermal cells in an inflammatory milieu such as in AD, they may induce autoantibody formation and Th1 responses (Mittermann et al. 2008).

Other less studied Hom s autoantigens are Hom s 3 (BCL7B) and Hom s 5 (cytokeratin type II) that can also induce immediate type skin reactions in AD patients (Natter et al. 1998).

Hom s 1–5 antigens represent only a fraction of the target antigens recognized by autoreactive IgE (Altrichter et al. 2008), as other autoantigens have also been described. Antibodies to the human protein manganese superoxide dismutase (hMnSOD), an enzyme that cross-reacts with fungal proteins, have also been found in AD patients. hMnSOD induced IgE autoreactivity in vitro in

43 % of patients (Schmid-Grendelmeier et al. 2005). In this study, all patients with IgE against hMnSOD were co-sensitized with Malassezia sympodialis, suggesting that this autoreactivity may be elicited by molecular mimicry (Fig. 1). Eczematous reactions in sensitized AD patients evidenced by patch testing with hMnSOD are less frequent (21 %) (Guarneri et al. 2015; Schmid-Grendelmeier et al. 2005).

The dense fine speckles 70-kDa protein (DFS70), also known as lens epithelium-derived growth factor (LEDGF), is a major autoantigen found in about 30 % of AD patients (Ochs et al. 2000). DFS70/LEDGF was initially isolated as a transcriptional cofactor and exhibits DNA-binding and transcriptional activity. It also activates heat-shock protein 27 (Sharma et al. 2003) and involucrin in keratinocytes in vitro (Kubo et al. 2002). In addition, it promotes cell survival and stress resistance (Singh et al. 2001). Antibodies against DFS70/LEDGF have also been found in other autoimmune skin disease, such as alopecia areata (Okamoto et al. 2004). In the epidermis, DFS70/LEDGF has different patterns of expression. It is a nuclear antigen in the basal layer, and it becomes expressed mainly in the cytoplasm in more differentiated superficial layers. In the stratum corneum, it is expressed in keratohyalin granules (KG) (Sugiura et al. 2007). Thus, it is transported from nucleus to the cytoplasm and is accumulated in KG. KG contains involucrin, a very important protein for the maintenance of the stratum corneum integrity. Antibodies targeting DFS70/LEDGF in AD may alter epidermis homeostasis (Sugiura et al. 2007). Interestingly, autoreactive AD patients not only produce specific IgE to DFS70/LEDGF but can also produce specific IgG4 against DSF70/LEDGF (Watanabe et al. 2011). However, the importance of anti-DSF70 autoantibodies is controversial in AD and other diseases, as these have been found in up to 11 % of healthy individuals without manifest disease (Schmeling et al. 2015; Watanabe et al. 2004).

Role of the Cellular Immunity in AD Autoreactivity

Despite the important role of T cells in the genesis and maintenance of skin inflammation, and in contrast with the antibody production to self-antigens, the role of autoreactive T cells in the pathogenesis of AD has been much less studied.

Evidence for Autoreactive T Lymphocytes

Molecular mimicry has been implicated as the main mechanism of cellular autoreactivity in AD (James and Kwok 2011). In contrast to Hom s autoallergens, some antigens have been described that have cross-reactivity to exogenous allergens (Hradetzky et al. 2015). A good example of this is human Thioredoxin (hTrx), a ubiquitous redox-sensing cytoplasmic enzyme. As an antigen, it cross-reacts with *Malassezia sympodalis* thioredoxin (Mala s 13). Mala s 13-specific T cell lymphocytes generated from patients with AD are cross reactive with hTrx and are mainly $CD4^+$ and cutaneous leukocyte-associated antigen-positive, implying skin homing (Balaji et al. 2011). The study included only three patients who were sensitized to Malassezia species and 11 non Malassezia-sensitized controls. Three patients generated $CD4^+$ T-cell clones fully cross-reactive to hTrx. Interestingly, human primary keratinocytes stimulated with IFN-γ release hTrx, and this is augmented if tumor necrosis factor-α is present; however, stimulation with IL-4 did not lead to the release of hTrx (Balaji et al. 2011). T cells that recognized hTrx could only be detected in patients with AD and *Malassezia* species colonization, implying that *Malassezia* species-specific responses are required to elicit self-reactivity through molecular mimicry (Balaji et al. 2011; James and Kwok 2011).

As discussed in the humoral specific response, Schmid-Grendelmeier et al. (2005) also demonstrated that fungal MnSOD (Mala s 11) and its human counterpart (hMnSOD) are capable of inducing specific T-cell proliferation in patients with AD, in addition to the specific IgE sensitization to hMnSOD. However, this finding has not been replicated by others (Guarneri et al. 2015).

Despite mainly producing a humoral response, some authors have noted high frequencies of circulating autoreactive $CD8^+$ T cells to α-NAC (Hom s 2). Lower frequency was found in $CD8^+$ lymphocytes of lesional skin. These cells probably produce IFN-γ, contributing to a Th1 shift. Therefore, α-NAC specific cells may sustain inflammatory response in AD in the absence of an environmental antigen (Hradetzky et al. 2015).

From Bench to Bedside: Autoreactivity and AD Severity, More than an Epiphenomenon

The association between IgE autoreactivity and severity, measured by standardized clinical indices, such as SCOring of Atopic Dermatitis (SCORAD), Investigators Global Assessment (IGA), and Eczema Area and Severity Index (EASI), has been suggested in several studies. Tang et al. (2012) found that 82 % of patients with severe AD had demonstrable IgE autoreactivity compared with 55 % of those with moderate AD, although these results were not statistically significant ($p = 0.052$). IGA and EASI was also significantly higher ($p < 0.001$) in autoreactive

patients than in non-autoreactive ones in the study by Altrichter et al. (2008). Watanabe et al. (2011) showed that the thymus and activation regulated chemokine, a serum biomarker correlated with SCORAD, was significantly higher in patients that tested positive for IgE and IgG4 anti-DFS70/LEDGF autoantibodies.

Schmid-Grendelmeier et al. (2005) showed that SCORAD levels strongly correlated with hMnSOD-specific serum IgE levels ($R = 0.756$; $p < 0.0001$), but not with total IgE levels ($R = 0.213$; $p = 0.246$). In a previous study, Natter et al. (1998) also described moderate to severe AD in autoreactive patients in contrast to moderate to mild disease in patients without autoreactivity. However, these data were not statistically analyzed.

Future Directions and Conclusions

Despite the strong evidence of the occurrence of autoreactivity in AD patients, there is still debate of the clinical implications of these findings or if it just an epiphenomenon (Cipriani et al. 2014; Tang et al. 2012). As stated by Tang et al. (2012), immunologic evidence of autoreactivity does not automatically translate into a clinically relevant autoimmune process. One argument favoring a real implication is that many studies used as controls patients with allergic rhinoconjunctivitis (IgE-mediated atopic disease) as well as patients with psoriasis (non-atopic inflammatory skin disease) and they failed to display IgE autoreactivity (Tang et al. 2012). In addition, the evidence of a correlation between severity of skin lesions and prevalence of autoreactivity, as discussed above, favors the hypothesis (Altrichter et al. 2008; Natter et al. 1998). A recent case report extrapolates this preliminary clinical and laboratory data to our daily clinical practice: the IgE autoreactivity may be reduced by systemic cyclosporine treatment as clinical improvement preceded the reduction of IgE autoreactivity (Kinaciyan et al. 2002). In this scenario, the reduced autoreactive IgE production would be explained by an initial decrease in inflammation and tissue damage leading to a reduction of exposure of self-antigens/proteins to the patient's own autoreactive B cells.

Whether autoreactivity generation is cause or consequence of skin inflammation and exposition of APC to keratinocyte antigens is not completely understood. We encourage researchers and clinicians in generating cohort studies from (ideally) early childhood to monitor the occurrence of autoantibodies and to comprehend its relation to skin inflammation.

Autoreactive patients may define a new variant of AD patients (endophenotype), which likely involves patients with extrinsic AD, but may also include a subset of patients with intrinsic AD that may exclusively produce IgE to cryptic autoallergens that are not tested in clinical allergy panels or only demonstrate cellular autoreactivity. This may become relevant, as a new era of personalized therapy with biologics has begun in allergic diseases in a similar way as it has occurred in autoimmune rheumatologic diseases. It is possible to speculate that AD patients with autoreactivity may benefit more from immunosuppression or from novel treatments with directed biologic therapies, such as rituximab (anti-CD20 antibody) or/and omalizumab (anti-IgE antibody) (Sanchez-Ramon et al. 2013). Further research should focus on a better definition of the clinical and molecular phenotype of AD patients that exhibit autoreactivity and should set the basis for directed therapies for this subgroup of AD. In addition, finding ways of preventing skin injury and autoantigen release, by means of antipruritic therapy, behavioral therapy (avoiding scratching), and skin barrier protection early in the life of AD patients, seems imperative to curb autoantibody production in autoreactivity-prone patients.

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