Molecular aspects of allergens in atopic dermatitis

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Purpose of review
Molecular allergology uses pure, mainly recombinant and structurally defined allergen molecules and allergen-derived epitopes to study mechanisms of IgE-associated allergy, to diagnose, and even predict the development of allergic manifestations and to treat and prevent IgE-associated allergies. Atopic dermatitis, a chronic inflammatory skin disease is almost always associated with IgE sensitization to allergens. However, also non-IgE-mediated pathomechanisms seem to be operative in atopic dermatitis and it is often difficult to identify the disease-causing allergens. Here we review recent work showing the usefulness of molecular allergology to study mechanisms of atopic dermatitis, for diagnosis and eventually for treatment and prevention of atopic dermatitis.

Recent findings
IgE sensitization to airborne, food-derived, microbial allergens, and autoallergens has been found to be associated with atopic dermatitis. Using defined allergen molecules and non-IgE-reactive allergen derivatives, evidence could be provided for the existence of IgE- and non-IgE-mediated mechanisms of inflammation in atopic dermatitis. Furthermore, effects of epicutaneous allergen administration on systemic allergen-specific immune responses have been studied. Multi-allergen tests containing micro-arrayed allergen molecules have been shown to be useful for the identification of culprit allergens in atopic dermatitis and may improve the management of atopic dermatitis by allergen-specific immunotherapy, allergen avoidance, and IgE-targeting therapies in a personalized medicine approach.

Summary
Molecular allergology allows for dissection of the pathomechanisms of atopic dermatitis, provides new forms of allergy diagnosis for identification of disease-causing allergens, and opens the door to new forms of management by allergen-specific and T cells-targeting or IgE-targeting interventions in a personalized medicine approach.

Keywords
allergen, allergen-specific immunotherapy, atopic dermatitis, IgE-associated allergy, micro-arrayed allergens, molecular allergology, personalized medicine

INTRODUCTION
Atopic dermatitis is a chronic, eczematous, and itchy skin disease, which is often associated with other symptoms of IgE-associated allergy such as allergic rhinoconjunctivitis, allergic asthma, and IgE-mediated food allergy [1–4].

The longitudinal analysis of the course of IgE-associated allergy in birth cohorts has shown that atopic dermatitis together with food allergy are the first signs and symptoms of allergic sensitization in early childhood which are followed by respiratory forms of allergy [5]. Atopic dermatitis is almost always associated with the presence of IgE antibodies against allergens and patients with atopic dermatitis often show elevated levels of IgE antibodies because of polysensitization to many different allergens. Using traditional forms of allergen-extract-based diagnosis such as skin testing (i.e. skin prick testing, atopy patch testing), it is often challenging and sometimes impossible to identify the disease-triggering allergens. Nevertheless, IgE sensitization to allergens is
Skin allergy

**KEY POINTS**

- Atopic dermatitis, a chronic inflammatory skin disease is a manifestation of IgE-associated allergy and almost always accompanied by allergen-specific IgE sensitization.
- Molecular allergology can be used to investigate IgE-mediated and non-IgE-mediated pathomechanisms of atopic dermatitis and to identify allergen molecules associated with atopic dermatitis.
- Multi-allergen-based tests allow to identify disease causing allergens in atopic dermatitis for allergen-specific forms of atopic dermatitis management in a personalized medicine approach.

present in the majority of patients with atopic dermatitis and there are only few rare forms of atopic dermatitis such as intrinsic atopic dermatitis in which no disease-eliciting exogenous allergens have been identified. Hence, patients with atopic dermatitis are often polysensitized against many different allergens and mount IgE antibodies also against ‘unusual’ allergens such as microbial allergens (e.g. Malassezia, bacteria such *Staphylococcus aureus*, *Escherichia coli*) and also human antigens (i.e., autoallergens) [6–9]. Perturbations of the skin barrier caused by mutations in proteins responsible for the maintenance of the barrier function (e.g. filaggrin) but also by exogenous factors (e.g. climate, irritation, infection, mechanical injury) lead to disease exacerbations and/or promote the disease [3]. Although IgE sensitization to allergens is almost always associated with atopic dermatitis, several findings question the pathogenetic role of IgE in atopic dermatitis. First of all, allergen-induced cross-linking of IgE on mast cells and basophils and subsequent immediate allergic inflammation because of release of mediators, cytokines and proteases from the latter cells is not the major mechanism in atopic dermatitis. By contrast, eczematous inflammation caused by T cells infiltration as it is observed in T cells-mediated type IV hypersensitivity is the hallmark of atopic dermatitis. Although it has been shown by elegant *in vitro* experiments that allergen-specific T cells activation is strongly enhanced when allergens are presented by IgE antibodies present on the surface of antigen presenting cells (APCs) occurring in the skin, it has also been shown *in vivo* by atopy patch testing that non-IgE-reactive allergen fragments/peptides induce eczematous inflammation in sensitized patients with atopic dermatitis [10,11†]. Furthermore, IgE targeting therapies such as the monoclonal anti-IgE antibody Omalizumab which is effective in allergic asthma and chronic urticaria has shown only limited effects in the treatment of atopic dermatitis [12]. Accordingly, T cells-targeting therapies such as cyclosporine, calcineurin inhibitors such as tacrolimus and pimecrolimus, and steroids which are often applied topically are effective. In addition, barrier-enhancing treatments such as emollients and antimicrobial treatment in the case of superinfections are part of the therapeutic armamentarium for atopic dermatitis. Moreover, allergen-specific forms of treatment such as allergen-specific immunotherapy (AIT), dietary avoidance of food allergens and allergen avoidance seem to be very effective if the disease-triggering allergens can be identified. With the isolation of allergen-encoding cDNAs and the deciphering of the molecular structures of disease-causing allergens, defined recombinant allergen molecules became available (Fig. 1). These recombinant allergen molecules allowed to study the mechanisms of allergic diseases, transformed allergy diagnosis towards molecular diagnosis and gave rise to new forms of AIT [13–15]. In this article we review recent data showing the impact of molecular allergology in augmenting our knowledge regarding pathomechanisms in atopic dermatitis, and regarding new forms of molecular allergy diagnosis and recombinant allergen-based forms of AIT which may also be effective for the treatment and prevention of atopic dermatitis.

**ALLERGEN MOLECULES TO STUDY ATOPIC DERMATITIS PATHOMECHANISMS**

*IgE and non-IgE-mediated pathomechanisms revealed with allergen molecules*

After the elegant demonstration that non-IgE-reactive allergen peptides can induce late phase allergic reactions in an major histocompatibility complex-dependent manner in the respiratory tract [16], similar studies have been performed in the skin. In fact it has been shown that epidermal administration of the major respiratory birch pollen allergen, Bet v 1 and of non-IgE-reactive, T cells epitope-containing fragments of Bet v 1 by atopy patch testing to sensitized patients induced eczematous skin inflammation [10,11†]. Thus, testing with the fully IgE-reactive allergen and non-IgE-reactive fragments identified patients exhibiting skin inflammation in an IgE-dependent and/or non-IgE-dependent manner indicating that both IgE-facilitated and non-IgE-mediated antigen presentation mechanisms are involved in allergen-induced skin inflammation in atopic dermatitis. In a controlled experimental setting it was also demonstrated that exposure of grass pollen-sensitized patients with atopic dermatitis to
Airborne grass pollen, induced atopic dermatitis exacerbations demonstrating that exposure to airborne allergens can induce atopic dermatitis [17]. In an earlier study it has been demonstrated that ingestion of food containing allergens which cross-react with the major birch pollen allergen Bet v 1 triggered atopic dermatitis in patients with birch pollen allergy [18]. This study was remarkable because Bet v 1 and Bet v 1-related food allergens are well digested into peptides. The induction of atopic dermatitis by ingestion of the food must thus have originated via an IgE-independent mechanism because Bet v 1-derived peptides lack IgE reactivity. In fact, a recent study showed that children with current atopic dermatitis are frequently sensitized to food allergens [19]. Patients with atopic dermatitis are also frequently sensitized to microbial allergens such as allergens from Malassezia and bacteria including S. aureus and E. coli [6,7,20]. Furthermore, they are frequently sensitized to autoallergens [8,9,21]. A recent study showed that patients with atopic dermatitis have not only autoallergen-specific CD4⁺ but also CD8⁺ cells [22]. In addition, several other studies have demonstrated the presence of allergen-specific CD8⁺ cells in atopic dermatitis [23,24] and experiments performed in mice indicate that allergen-specific CD8⁺ cells may play an important role in skin inflammation in atopic dermatitis [25].

Figure 2 provides an overview of how airborne allergens/allergen peptides and allergens/allergen peptides from skin-colonizing microbes (e.g., S. aureus, Malassezia furfur) can reach the skin via the epicutaneous route [1,2]. This process is facilitated if the skin barrier is disturbed by certain factors (e.g. mutations affecting the function of proteins such as filaggrin, physical factors such as cold and dryness, chemical factors such as proteases derived from various sources for instance allergen sources, and so on) [26]. Autoallergens may originate from the skin and allergens/allergen peptides from food allergens taken up via the gastrointestinal tract may be transported via the blood to the skin as ‘endogenous allergens/peptides’ [9,19]. Using defined IgE-reactive allergens and non-IgE-reactive allergen-derived peptides, it has been shown that eczematous skin inflammation can be induced by IgE-dependent and by IgE-independent mechanisms [11]. Interestingly, there is evidence that in addition to classical APCs such as dendritic cells also B cells may play a role in antigen presentation especially in response to low antigen concentrations [27] and in skin inflammation [28].

Although epicutaneous allergen administration seems to be able to induce systemic allergen-specific antibody production in animals (e.g. mice, guinea pigs) under certain circumstances [29,30], it induces preferentially allergen-specific T cells activation but not allergen-specific antibody responses in humans (Campana and Valenta, unpublished observation). The latter is of relevance for attempts to treat allergy by epicutaneous AIT [31] because the induction of allergen-specific IgG antibodies is important for the efficacy of AIT [32].
Marker allergens associated with atopic dermatitis

The use of recombinant allergens for molecular allergy diagnosis currently revolutionizes diagnosis of IgE-associated allergy. A recently published guide to molecular allergy diagnosis highlights the many advantages of molecular diagnosis [33]. One interesting aspect revealed recently by molecular diagnosis is that sensitization to certain allergen molecules and/or a combination of allergens is more common for certain allergic manifestations than for others. For example, it was found that house dust mite allergens such as Der p 11 [34] and Der p 18 [35], which are associated with mite bodies are more frequently recognized by IgE antibodies from patients with atopic dermatitis, whereas allergens associated with fecal particles such as Der p 1, Der p 2, Der p 5, Der p 23 are more frequently recognized by patients with respiratory allergy [36,37]. This finding may be explained by the fact that there could be different routes of sensitization in atopic dermatitis and respiratory allergy but also by a more polyclonal response in patients with atopic dermatitis which includes otherwise more rarely

FIGURE 2. Possible induction of IgE and non-IgE-mediated skin inflammation in atopic dermatitis by allergens and allergen-derived peptides. Allergens and allergen-derived peptides which often lack IgE binding capacity can induce skin inflammation either via the skin (e.g. environmental allergens such as airborne allergens from pollen, house dust mites, animal dander, certain moulds, allergens from skin-resident microbes such as bacteria and skin-colonizing fungi). Autoallergens may originate directly from the skin whereas food allergens/food allergen peptides may be transported from the gut via the blood to the skin. Intact, IgE-reactive allergens may be presented by antigen-presenting cells (APCs) such as dendritic cells, monocytes, macrophages or B cells via IgE antibodies bound to Fc epsilon receptors (FcεRI, FcεRII) on the surface of the APCs by a process termed IgE-facilitated allergen presentation or by phagocytosis without IgE involvement. The presentation of allergen peptides to allergen-specific T cells may occur via MHC class II (CD4+ T cells) and eventually MHC class I (CD8+ T cells). For the latter event cross-presentation is considered as a possible mechanism. The precise role of allergen-activated CD4+ T cells (e.g., Th2, Th1) and CD8+ T cells in induction of eczematous skin inflammation in atopic dermatitis has not been established. Allergen-specific mast cell activation via cross-linking of FcεRI-bound IgE occurs in atopic dermatitis, but does not seem to directly contribute to eczematous inflammation. Cytokines released from activated T cells and mast cells attract granulocytes, especially eosinophils into the skin which contribute to tissue damage. Allergen contact via the skin (i.e. epicutaneous contact) may induce systemic allergen-specific T cells activation but seems to have little effect on the production of allergen-specific IgE and IgG antibodies in humans. MHC, major histocompatibility complex.
recognized allergens. Allergic dogs which mainly show atopic dermatitis as the most relevant allergic manifestation also mount IgE-reactivity preferentially to house dust mite body-derived allergens [38] but not to allergens which are associated with airborne feces. This would indicate that the body-derived allergen indeed may sensitize via the skin.

A recently conducted extensive survey of the molecular allergen recognition patterns in a large cohort of clinically well characterized patients with atopic dermatitis [20*] has confirmed earlier findings showing that patients with atopic dermatitis are more frequently sensitized to microbial allergens such as allergens from Malassezia, bacterial allergens from S. aureus and E. coli and also to autoallergens [6–8,39]. Although IgE sensitization to S. aureus allergens and Malassezia allergens may be explained by the frequent colonization of the skin of patients with atopic dermatitis by these microbes, the frequent sensitization to E. coli allergens is difficult to explain considering that these antigens are thought to be tolerogenic and mainly occur in the gut. The frequent occurrence of IgE sensitization to autoallergens in patients with atopic dermatitis was considered as a result of tissue damage induced by allergic sensitization to exogenous allergens. However, it was found earlier that IgE auto-sensitization occurs already early in childhood and may precede sensitization to exogenous allergens [40]. Furthermore, it turns out that autoallergens can induce CD4+ Th1 and CD8+ T cells responses which would indicate and confirm that allergen-specific Th1 and CD8+ cells are involved in eczematous skin inflammation in atopic dermatitis [22*,23,24,41]. The detailed analysis of IgE reactivity profiles in patients with atopic dermatitis with allergen molecules thus indicates that atopic dermatitis is associated with characteristic IgE sensitization profiles which are in part distinct from those recognized by patients with respiratory forms of allergy. Moreover, it seems that there could be differences regarding the molecular IgE recognition profiles between patients with moderate and severe forms of atopic dermatitis [20*].

**MOLECULAR DIAGNOSIS OF ATOPIC DERMATITIS**

**The role of multiallergen tests in atopic dermatitis diagnosis**

In the course of the EU-funded research project MeDALL, IgE reactivities towards a large number of micro-arrayed allergen molecules have been determined in several European birth cohorts using the MeDALL allergen chip [42]. This has enabled to determine the evolution of IgE reactivities towards a large number of allergen molecules from early childhood to adolescence [43–46]. Results obtained by multiallergen testing indicate that different allergic phenotypes are associated with monosensitization and oligosensitization versus polysensitization to a large number of allergen molecules [5]. Data obtained in the MeDALL project seem to confirm that patients with atopic dermatitis are often polysensitized towards a large number of different allergen molecules and thus exhibit extremely complex IgE sensitization profiles [47]. Multiallergen tests, mainly chip tests based on micro-arrayed allergen molecules utilizing the ImmunoCAP-ISAC technology have been used for the analysis of IgE reactivity profiles in cohorts of children with atopic dermatitis and adult patients with atopic dermatitis [20*,34*,48,49]. The results of these studies provided insights in sensitization profiles associated with different severity of atopic dermatitis. Importantly, a recently published study demonstrates that based on the in depth analysis of IgE-reactivity profiles in children suffering from severe forms of atopic dermatitis, it was possible to improve the management and treatment individually [50*]. The key findings leading to a personalized treatment for each of the children, which in one case was a highly refined diet and in the other caseAIT for the treatment of house dust mite allergy, were obtained by chip diagnosis identifying the disease-causing allergens. IgE reactivities to clinically irrelevant cross-reactive carbohydrates which in allergen extract-based tests pretended almost infinite allergic sensitization could be discriminated from clinically relevant sensitizations as indicated in Fig. 3. The latter cases may be considered as paradigmatic examples of how the analysis of complex IgE-reactivity profiles by molecular diagnosis can improve disease management following the principle of precision and personalized medicine approaches in allergy [51–53].

**The role of allergen-specific IgE reactivity and T cells reactivity in atopic dermatitis: implications for treatment**

A recent clinical study showed that epicutaneous application of recombinant IgE-reactive birch pollen allergen Bet v 1 and non-IgE-reactive, T cells epitope-containing Bet v 1 fragments induced eczematous skin inflammation [11**]. In this study and in an earlier study [10], it was found that certain patients showed skin reactions mainly to the IgE-reactive allergen but not to the non-IgE-reactive T cells epitope-containing fragments, whereas others reacted strongly to the non-IgE-reactive Bet v 1 derivatives. The results of these studies may be important for two reasons. First, they may explain
why certain patients with atopic dermatitis respond very well to IgE-targeting therapeutic strategies whereas others benefit less from IgE-targeted therapy but from T cells-targeting strategies. Second, the studies indicate that it may be possible to use IgE-reactive allergens and non-IgE-reactive T cells epitope-containing allergen derivatives for atopy patch testing to identify patients who respond either to IgE-targeting or T cells-targeting strategies. If one considers that most of the clinically relevant allergens are available as pure IgE-reactive recombinant molecules and that non-IgE-reactive peptides containing the allergen-specific T cells epitopes can be easily produced by recombinant expression and/or by synthetic peptide chemistry, diagnostic tools for the selection of IgE-targeting or T cells-targeting strategies are available.

Evidence for the clinical efficacy of T cells-targeting strategies in atopic dermatitis and for the importance of purely T cells-mediated pathomechanisms comes from several recent observations and trials. For example, it was found that African patients suffering from AIDS and severe loss of T cells function did not suffer from atopic dermatitis but continued to mount allergen-specific IgE production and IgE-mediated mast cell degranulation [54]. Likewise it was found that high-dose cyclosporine treatment improved atopic dermatitis but had no effects on allergen-specific IgE production [21]. There is also evidence that targeting of certain Th2 cytokines such as IL-4 and IL-13 (e.g. by Dupilumab) can improve atopic dermatitis [55], whereas other Th2 cytokine-targeting strategies (i.e. anti-IL5) do not seem to be effective in atopic dermatitis [56]. Blocking the IL-31 receptor with an anti-IL-31 receptor A antibody was found to reduce itching but the effects on eczematous skin lesions were not significant over placebo [57]. In summary, it seems that targeting T cells and T cells-derived cytokines is partly effective in atopic dermatitis but there seems to be a need for better stratification of patients before treatment [58,59].

However, it has been shown that targeting IgE antibodies by injecting with antihuman IgE such as omalizumab, or by extracorporeal depletion of IgE antibodies [60–62,63] or a combination of IgE depletion and injected anti-IgE [64] may be effective in atopic dermatitis. However, again not all patients with atopic dermatitis seem to respond to the IgE-targeting therapies [12] and one wonders if clinical treatment results could be improved by using diagnostic tests capable of dissecting patients for responsiveness to IgE-targeting or T cells-targeting strategies. In fact, there are different anti-IgE antibodies in clinical trials [65] and new, very well characterized single-use devices for the selective depletion of IgE antibodies by immunoapheresis have become available [66]. Recombinant and synthetic allergen derivatives should be considered as useful future diagnostic tools for selecting patients for suitable therapies.

**ALLERGEN-SPECIFIC FORMS OF TREATMENT FOR ATOPIC DERMATITIS**

Can allergen-specific immunotherapy be used for treatment of atopic dermatitis?

Interestingly it has been suggested that early allergen exposure may have a preventive effect on atopic dermatitis for dog allergy [67]. The beneficial role of allergen avoidance for the prevention and treatment of allergy including atopic dermatitis is therefore a matter of debate but the recently published study by Posa et al. provides very clear evidence that children growing up under conditions of low exposure to house dust mite have a lower likelihood...
of developing house dust mite allergy [46]. Because these results were obtained in a large birth cohort and are based on solid data regarding exposure to house dust mite allergens and detection of allergen-specific IgE to a comprehensive spectrum of house dust mite allergens, it should be considered to recommend at least HDM allergen avoidance for the prevention of allergic sensitization. Other data regarding avoidance for atopic dermatitis prevention are summarized in a recently published review article [68].

Besides allergen avoidance, AIT represents an allergen-specific form of treatment for IgE-associated allergies. AIT is highly effective for respiratory allergies but its role for the treatment of atopic dermatitis is still debated [69–71]. However, the efficacy of AIT has been demonstrated in animals for atopic dermatitis [72–74] and there are studies which demonstrate that AIT is effective for the treatment of atopic dermatitis in humans [75,76]. AIT is therefore considered as a relevant treatment option for atopic dermatitis in a recent position paper [4].

**Novel forms of allergen-specific immunotherapy treatment for atopic dermatitis**

Recently, a new form of AIT based on carrier-bound allergen-specific B-cell epitopes has entered clinical evaluation [14]. This new form of allergy vaccine is based on fusion proteins consisting of hypoallergenic peptides derived from the IgE binding sites of allergens which are fused to a nonallergen-derived carrier protein, the preS protein from hepatitis B [77]. A vaccine for grass pollen allergy consisting of four recombinant fusion proteins named BM32 representing the four major grass pollen allergens has been constructed and was shown to induce allergen-specific IgG antibodies and at the same time has a reduced ability to stimulate allergen-specific T cells [78]. The latter characteristic may be useful for atopic dermatitis treatment because it was found that the application of the recombinant fusion proteins by atopy patch testing did not induce eczematous skin inflammation, whereas natural grass pollen allergens induced APT reactions [79]. In first AIT trials, BM32 was very well tolerated by patients with grass pollen allergy and induced allergen-specific IgG antibodies, which prevented allergen-induced basophil and mast cell activation and also caused a reduction of allergen-specific T cells proliferation by inhibiting IgE-facilitated allergen presentation [80**]. It is thus quite possible that BM32 will become useful for the treatment of grass pollen-induced atopic dermatitis in the future [15].

**Allergen-specific antibodies for treatment of atopic dermatitis?**

As shown in Fig. 2 and summarized in some excellent recent reviews [1–3], T cells activation is crucial in the pathogenesis of atopic dermatitis. According to available data one may speculate that Th2, Th1, and CD8+ T cells play a role in the disease pathogenesis. Data for Th17 cells are mainly derived from mouse models and it is thought that Th17 cells may be more relevant in Asian populations [81]. One possibility of how allergen-specific IgG antibodies can influence allergen-specific T cells activation is the inhibition of IgE-facilitated allergen presentation. It is well established that APCs (dendritic cells, monocytes, B cells) in atopic individuals express receptors for IgE (FceRI, FceRII) [82–84]. Thus, APCs can bind allergen-specific IgE via these receptors and it has been shown in vitro that IgE-facilitated allergen-presentation, activates T cells more strongly than conventional presentation. Interestingly, IgE-facilitated allergen presentation can be inhibited by allergen-specific IgG antibodies, which capture allergens and as a result T cells proliferation and cytokine release is reduced. This happens for example in the course of AIT [85]. Thus, allergen-specific IgG can reduce allergen-specific T cell activation and reduce T cells-mediated inflammation. It is thus not so surprising that a recent paper reports that an allergen-specific IgG antibody when topically applied could reduce allergic skin inflammation in a mouse model [86]. It was also shown that pretreatment of mice with allergen-specific IgG antibodies prevented not only allergen-specific IgE production as has been shown for respiratory and food allergens [87,88], but also reduced allergen-specific T cells responses in a preventive mouse model of allergic sensitization [89]. Allergen-specific human IgG antibodies can in fact be obtained by combinatorial cloning techniques and engineered for therapeutic purposes [90]. Taken together, it seems that the process of IgE-facilitated allergen presentation and subsequent T cells activation can not only be inhibited by IgE-targeting strategies but also by allergen-specific blocking antibodies.

**CONCLUSION**

Recombinant allergens and allergen derivatives are useful for dissecting the pathomechanisms of atopic dermatitis. Molecular testing with defined allergen molecules has proven to be extremely useful in the diagnostic management of patients with atopic dermatitis to guide new forms of personalized treatment. Furthermore, molecular allergology will have an impact on the selection of patients with atopic
Skin allergy

dermatitis for IgE-targeting and T cells-targeting strategies, for allergen avoidance and AIT. Modern and innovative allergy vaccines based on recombinant allergen derivatives will likely be useful for treatment of patients with atopic dermatitis.

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