# Features of childhood atopic dermatitis

**Hugo P. S. Van Bever[1] and Genevieve Llanora[1]**

## Summary

Eczema or atopic dermatitis (AD) is the most common skin disease in children, and recent data derived from several studies showed that the prevalence of AD is still increasing in most Asian countries. The role of allergic reactions in AD is still a matter of debate. In some children allergy is not involved, while in others allergic reactions can trigger and maintain the skin lesions. Therefore, AD is now considered as a group of skin diseases with as a common feature the existence of a chronic skin inflammation. The underlying mechanisms of AD are not uniform, but differ from patient to patient, and also differ in one patient in time, suggesting the existence of different subtypes of AD, in a complex interplay. From different studies it is now suggested that at least 4 different players are involved in AD. These 4 players are: congenital skin barrier defects, allergy, auto-immunity (i.e. the production of auto-antibodies against skin cells), and microbial agent colonization, especially colonization with bacteria, mainly *Staphylococcus aureus*. Much more needs to be discovered on the mechanisms of AD and other "players" might be discovered soon, as the current "4-player-model" cannot explain all features of AD. Treatment of AD might change in the near future. Today's cornerstones of treatment are still moisturizers (from a young age to prevent further skin barrier dysfunctions and allergic sensitization), local corticosteroids, and antiseptics, but new future therapeutic approaches become very likely. *(Asian Pac J Allergy Immunol 2011;29:15-24)*

From the [1]Department of Pediatrics, Children's Medical Institute, National University Health System, Singapore.
Corresponding author: Hugo P. S. Van Bever
Email: hugo_van_bever@nuhs.edu.sg

## Introduction

Eczema or atopic dermatitis (AD) is the most common skin disease in children, affecting more than 20% during their early ages[1]. Moreover, recent data derived from the ISAAC studies showed that the prevalence of AD is still increasing in most countries[2]. The reasons for the ongoing increase of AD are linked to the global increase of allergic diseases during the last three decades, but also to an increase in the prevalence of skin barrier defects, induced by increased usage of soap and detergent personal wash products in children[3].

At the moment, it has become clear that AD is not just "an allergic skin disease" as more evidence now became available, pointing to the complexity of AD, suggesting that different "players" are involved, that lead to chronic skin inflammation. Furthermore, it is also clear that underlying mechanisms of AD are not uniform, but differ from patient to patient, and also differ in one patient in time, suggesting different subtypes of AD. Usually, AD is not present at birth, but starts during the first weeks or months of life, especially in children who are born with a dry skin. The initiating factors of AD are totally unknown, but in most infants allergic reactions seem not to be involved at that time. Usually, allergy starts later, after the first AD lesions have occurred. Therefore, it is very unlikely that allergic reactions are responsible for the initiation of AD and it even becomes clearer now that allergy might be a consequence of AD, in a subject with a concomitant underlying atopic constitution.

Taken together the evidence of different studies, it is now suggested that at least 4 different "players" are involved in AD. These 4 players are: 1) skin barrier defects, 2) allergy 3) auto-immunity and 4) microbial agent colonization (Table 1). Other "players" might be discovered soon, as the current "4-player-model" cannot explain all features of AD, especially not the start of AD in newborns[4].

**Table 1.** Identified causal factors in atopic dermatitis

| |
|---|
| **1. Skin barrier defects, such as:** |
|     - Proteases (such as stratum corneum chymotryptic enzyme - SCCE) |
|     - Filaggrin (FLG) |
|     - Loricrin (LOR) |
|     - Involucrin (INV) |
| 2. **Allergic reactions to:** |
|     - Food allergens (hen's egg, cow's milk) |
|     - Inhaled allergens (house dust mites) |
| **3. Auto-immunity** |
|     - Anti-keratinocyte antibodies |
| **4. Microbial agent colonization** |
|     - *Staphylococcus aureus* |
|     - *Malassezia* spp. and *Cryptococcus diffluens* - *Cryptococcus liquefaciens* |

**Table 2.** The two hupotheses of the initiation of AD lesions

| |
|---|
| 1. Inside-outside hypothesis |
|   **INFLAMMATION (allergy)** →   **SKIN BARRIER DEFECTS** |
| 2. Outside-inside hypothesis |
|   **SKIN BARRIER DEFECTS** →   **INFLAMMATION** |

Furthermore, in parallel to asthma, that usually starts as a viral-induced disease in infancy (cfr. bronchiolitis, viral bronchitis, viral-induced wheeze), it is possible that viruses are involved in initiating the first symptoms of AD, and that the role of viruses in AD is totally underestimated. New techniques of viral identification (i.e. DNA microarrays) might give more clues on the mechanisms of initiation of AD in newborns in the near future.

## 1. Skin barrier defects

In a large number of studies, the role of skin barrier defects in children with AD was emphasized[5]. Currently, AD is considered as a multi-factorial, chronic inflammatory skin disorder in which genetic mutations leading to cutaneous hyperreactivity to environmental stimuli (i.e. a defective skin barrier) play a causative role. Genetic mutations alone might not be enough to cause clinical manifestations of AD, and it is merely the interactions of a dysfunctional epidermal barrier in genetically predisposed individuals, with harmful effects of environmental agents that lead to the development of AD. More and more evidence now becomes available showing that specific skin abnormalities, such as an over-expression of stratum corneum chymotryptic enzyme (SCCE) and the malfunctioning of filament aggregating protein (filaggrin - FLG), are involved in the development of AD. However, regulation of skin barrier is complex and under the influence of a large number of cell structure features, enzymes (such as proteases) and other factors. An excellent review of skin barrier features is summarized in the article by Cork *et al.*[5].

Abnormalities in skin barrier have been increasing during the last decades and several environmental factors have been associated with skin barrier defects, including washing with soap and detergents, washing with hard water, and exposure to house dust mites. However, there are few longitudinal studies on the role of environmental changes on the skin barrier, as most of the longitudinal studies in AD were focused on allergy (cfr. the ISAAC studies). An example of these changes is the increased use of soap and detergent personal wash products between 1981 and 2001 in the United Kingdom, where sales increased (inflation adjusted) from £76 million to £453 million while the population only increased from 56.3 million to 59.1 million. The frequency of personal washing has also changed over the past 40 years. In 1961, the average use of water for personal washing was 11L per person per day, increasing to 51L per person per day in 1977/1978[3]. Other environmental changes that have contributed to the increase in skin barrier defects are: changes in heating, ventilation, and insulation systems and floor coverings of houses, which have created an increasingly optimal environment for the house dust mite. All these environmental agents damage the skin barrier directly, and coupled with the increasing prevalence of allergy, this suggests that breakdown of the skin barrier might be a very important event in the development of AD.

At the moment, it is still not clear which event came first: skin barrier defects or inflammation, as no studies have been performed in newborns. Two hypotheses are currently suggested (Table 2). In one it has been suggested that barrier defects in AD are a secondary consequence of the inflammatory responses to irritants and allergens, which is known as **the inside-outside hypothesis**. Alternatively, in the other hypothesis it has been stated that the xerosis and the permeability barrier abnormalities could drive the inflammation in AD, which is known as *the outside-inside hypothesis*. As in most infants xerosis of the skin is usually present before the inflammation (at birth), the outside-inside hypothesis seems to be
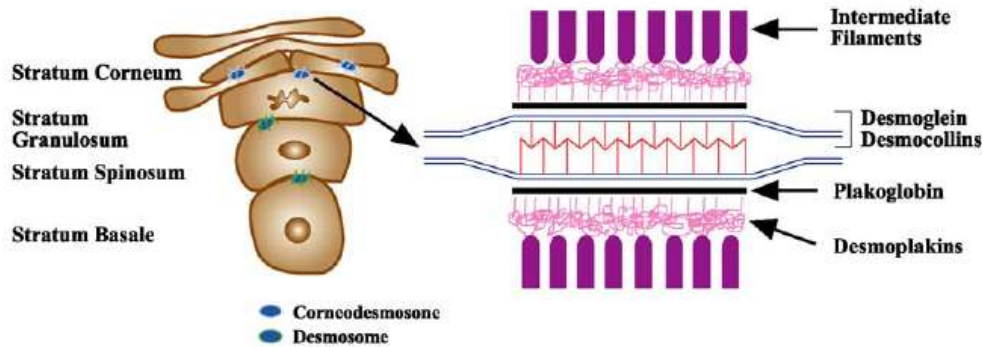
**Figure 1.** The barrier to the penetration of irritants, allergens, and drugs is located in the lower part of the stratum corneum. The structural integrity of the stratum corneum is maintained by modified desmoseomes (corneodesmosomes), which lock together the corneocytes. As the corneocytes move up through the stratum corneum, the corneodesmosomes are gradually broken down by the skin-specific proteases, and unattached corneocytes can then be desquamated from the surface of the skin.

closer to the truth, although exact mechanisms of the initiation of inflammation are totally unknown.

In 1999, it was already proposed that a genetic predisposition to a defective skin barrier was a primary event in the development of AD, allowing allergen penetration and enhanced Th2 responses. Increased penetration of allergens through the epidermis could also promote the initiation of an inflammatory response within the stratum corneum and stratum granulosum by inducing the release of proinflammatory cytokines from keratinocytes[6].

*a. Role of proteases*

The barrier to the penetration of irritants and allergens is located in the lower part of the stratum corneum (Figure 1, *from reference 6 with permission*). The structural integrity of the stratum corneum, which is made up by corneocytes (i.e. flattened cells that represent the final differentiation stages of the outermost keratinocytes) is maintained by the presence of modified desmosomes, called corneodesmosomes.

It has been shown that cleavage of all corneodesmosomes at the skin surface must be completed for normal desquamation to occur. Persistence of peripheral corneodesmosomes has been linked to several ichthyotic, hyperkeratotic, and xerotic diseases, including AD[7]. Regulation of desquamation is performed by a complex network of degradatory proteases regulated by protease inhibitors. Among the proteases involved in the process of desquamation are the SCCE and the stratum corneum tryptic enzyme (SCTE) (Figure 2, *from reference 6 with permission*).

Studies in transgenic mice have shown that overexpression of human SCCE induces changes in their skin similar of those seen in chronic AD[8]. Moreover, genetic variations within the SCCE gene have been associated with deregulation of SCCE activity in human subjects, leading to a thin skin barrier. A high association between a rare variant of the SCCE gene and AD was found in children with non-IgE-mediated AD[9].

**Other proteases:**
- Proteases involved in skin barrier defects can also be produced by cells involved in inflammatory reactions, increasing further damage of the skin barrier. These proteases can be considered as a product of the inflammatory response and their levels will be proportional to the severity of the AD. An example of a secondary protease is mast cell chymase, which was found to be increases in AD lesions[10].
- Other proteases that can affect the skin barrier come from outside. House dust mites are an important source of proteins that can cleave adhesion proteins, thereby increasing permeability of lung and skin. Patch tests have demonstrated that 2 proteins with proteolytic activity derived from house dust mites, Der p 1 and Der p 2, can elicit irritative or immune reactions that are not linked to increased IgE levels, suggesting that these proteins are able to cause skin irritation or immune activation through a direct proteolytic activity[11].
- Staphylococcus aureus, being not a member of the normal skin microflora, has been implicated into the pathogenesis through its
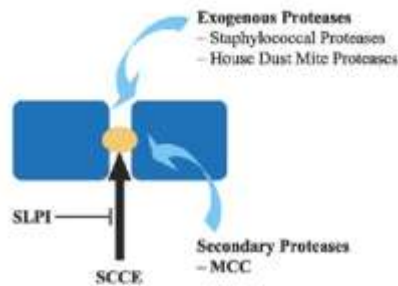
**Figure 2.** Corneodesmosomes are not only broken down by endogenous proteases, such as SCCE. Once a flare of AD has been triggered, cells within the inflammatory infiltrate produce secondary proteases, which can also break down the skin barrier (eg, MCC). The stratum corneum is also exposed to many exogenous proteases from the environment, such as *Staphylococcus aureus* and house dust mites. *SLPI,* serine leukopretease inhibitor.

- release of superantigenic toxins[12]. In addition to their immunologic effects, these toxins might also directly damage the skin barrier. Staphylococci produce proteinases that are able to break down corneodesmosomes through a mechanism similar to that described for SCCE[13].

### b. Role of filaggrin

Filaggrin (FLG) is a key barrier protein that has a role in the compaction of keratin filaments in the stratum corneum and thus contributes to barrier formation and has an additional role in regulating stratum corneum hydration[14]. A possible role of FLG in atopic dermatitis susceptibility is supported by several lines of evidence. Loss-of-function mutations in the FLG gene predispose to ichthyosis, which in its mild form shows many similarities with eczema, such as dryness of the skin and skin hyperlinearity[15]. Furthermore, reduced expressions of FLG in atopic skin lesions have been reported, as well as a genetic association of the FLG gene number polymorphism with a dry skin[16]. The FLG gene is located within the epidermal differentiation complex on human chromosome 1q21. The epidermal differentiation complex is a gene complex composed of more than 30 genes of several structurally and evolutionarily related gene families that are all involved in terminal differentiation of the epidermis. Genetic linkage of childhood atopic dermatitis to this region has previously been reported[17].

Up to 6 loss-of-function mutations and several other family-specific mutations have been described that are linked to atopic dermatitis. In European populations (UK, Germany) it was found that 2 mutations (R501X and 2282del4) are the most commonly found. Moreover, it was demonstrated that these 2 mutations predispose to asthma, allergic rhinitis and allergic sensitization, but only in the presence of eczema. These results lend strong support to the role of FLG in the pathogenesis of eczema and in the subsequent progression along the allergic march. The fact that previous expression of eczema is a prerequisite for the manifestation of allergic airways disease and specific allergic sensitization highlights the importance of the epidermal barrier in the pathogenesis of these disorders[18].

In another recent study it was found that eczema associated with FLG null alleles presents early in life, is more persistent, is associated with early wheezing and persistent asthma and with allergic sensitization. The authors conclude that FLG allele determination help to define the risk profile of children with eczema and help define the "eczema plus early wheeze" and "eczema plus asthma" phenotypes[19].

In contrast, in a study by Donald Leung's group it was found that patients with atopic dermatitis have an acquired defect in FLG expression that is modulated by the atopic inflammatory responses, involving IL-4 and IL-13[20].

Sandilands et al recently analyzed the FLG gene and identified a spectrum of mutations located throughout the entire gene and discovered that at least 47% of individuals from the Irish childhood eczema case series carry one or more of these null FLG mutations[21].

### c. Role of loricrin

Loricrin (LOR) is the major protein component of the cornified cell envelope of the stratum corneum. It is one of the proteins that facilitate the terminal differentiation of the epidermis and formation of the skin barrier. It also functions as a main reinforcement protein for the cornified envelope and is deposited onto a scaffold of other proteins in the epidermis[22]. As this is a skin barrier protein, it plays a role in preserving the integrity of skin. LOR is a single intron of 1188 base pairs in the 6"untransligated region[23]. The chromosome gene is located in 1q21. In electron microscopy, LOR can be seen on the granular

layer of the epidermis and forms composite keratohyalin granules with profilaggrin, but localizes to the cell periphery (cell envelope) of fully differentiated stratum corneum cells[23].

In the study done by Kim et al in 2008, it was postulated that overexpression of Th2 cytokines in patients with atopic dermatitis, down regulates the expression of LOR[22].

### d. Role of involucrin

Involucrin (INV) is a marker of keratinocyte terminal differentiation, expressed in the suprabasal layers of stratified squamous epithelium. Its expression starts in the upper spinous layers of the epidermis, preceding loricrin, which is mainly on the granular layer of the epidermis[24]. It is an 83 kilo-Dalton molecule, consisting of 585 amino acids in the form of 10 amino acid repeats, with high percentages of glutamine and glutamic acid. Together with FLG and LOR, INV is likewise responsible for maintaining the integrity of the skin barrier. In the study done by Kim et al in 2008, overexpression of Th2 cytokines in patients with atopic dermatitis not only down regulates expression of LOR, but also INV[22]. Furthermore, there is a note of decreased expression of INV in lamellar ichtyosis, which could contribute to the altered desquamation process accompanying the disease[25].

### 2. Allergy

The exact link between AD and allergen-specific IgE has still not been elucidated, and remains hotly debated now (4). According to some, allergic reactions can cause AD lesions (cfr. results of DBPCFC), while others believe that both AD and allergy can be present in one patient separately without influencing each other, while others claim that allergy is merely a consequence of the chronic AD, caused by allergen penetration through a defective skin barrier. A large number of studies have been performed on the association of AD and IgE-mediated hypersensitivity[26]. From these studies, the most important findings are:

1. The highest levels of IgE have been detected in patients suffering from both AD and asthma.
2. Increased total serum IgE has been recorded in about 80% of patients. In addition, there is a correlation between total serum IgE and severity of AD.
3. Positive skin prick tests and positive specific IgE to a number of inhaled allergens, especially house dust mite, and food allergens are found in the majority of patients.
4. Positive family antecedents of atopic diseases are found in the majority of patients.
5. Of subjects with AD, 50% - 80% suffer also from asthma and/or rhinoconjunctivitis.

However, most of the studies on which these observations were based were performed in hospital settings, and suffered from selection bias, as conclusions were drawn from data of patients with severe AD, attending hospitals for medical care. Therefore, it seems that the above findings count merely for patients suffering from severe AD. A systematic review revealed that the association with increased IgE levels was much lower in children with mild-to-moderate AD than in children with severe AD[27]. The role of allergens in AD is summarized in Table 3.

### Food Allergy and eczema

IgE-mediated reactions against food allergens are able to elicit urticaria and angioedema, but the relationship of IgE-mediated immunological reactions with atopic dermatitis (AD) is still controversial and not accepted by everyone. However, controlled studies have demonstrated that a low food allergen diet is associated with a significant reduction in the prevalence of AD of infancy, and in several clinical studies it was demonstrated by double-blind placebo-controlled food challenges (DBPCFC), that food is able to induce AD[26]. Especially in young children with severe AD, foods, such as eggs and cow's milk, can be a maintaining factor of AD[28]. In contrast, in older children and in children with mild AD (all ages), food allergy is much less involved in AD.

**Table 3.** Role of allergens according to age and severity of AD

| Severity of AD | Infants | Preschoolers | Older children |
|---|---|---|---|
| **Mild** | No allergy | No allergy | No allergy |
| **Moderate** | Egg | Egg | No allergy (HDM) |
| **Severe** | Egg Cow's milk Soy Wheat | Egg Cow's milk HDM | HDM |

The diagnosis of an underlying food allergy in children with AD is complicated and at the moment the golden standard in the diagnosis of food allergy is the DBPCFC, as both medical history and assessment of underlying allergy, by skin prick testing (SPT) or IgE-determination, can show false positive and false negative results. Studies by Sampson and Hill have focused on the positive predictive value (PPV) of respectively specific IgE and SPT in children with eczema, and cut-off values for specific IgE and wheal reactions of SPT have been published[29,30].

*House dust mites and eczema*

Especially in older children (> 5yrs) with severe AD, a house dust mite (HDM) allergy is frequently detected by skin prick testing or the presence of specific IgE in serum[31]. However, the role HDMs in the pathogenesis of AD is even more controversial than the role of foods. Many researchers claim that a HDM-allergy is mainly an epiphenomenon, and an expression of the underlying atopic constitution, which has no role in maintaining AD. According to others, HDM-allergy is merely a consequence of the impaired skin barrier function, without a causative role in AD. However, in a number of studies a clear association between a HDM allergy and AD has been demonstrated.

**The studies on the role of HDM in AD can be divided in 4 groups:**

1. Epicutaneous application of HDM (atopy patch testing [APT] on non-abraded skin) is able to induce AD lesions, but only in patients with AD and not in healthy controls. Furthermore, positive APTs were associated with longer duration of AD flares[32].
2. Bronchial provocation testing with HDM was able to induce flares of AD, demonstrating that AD can be induced by inhalation of HDM[33].
3. HDM-specific T-cell lines (i.e. lymphoblastic transformation) have been found in patients with AD. Moreover, APT reactions have been found to be significantly associated with allergen specific lymphocyte proliferation, and with a higher number of CD54+ or CD30+ T-cells, after in vitro stimulation[34].
4. In a number of studies the beneficial effect of HDM avoidance on AD was observed, especially in children[35].

Furthermore, the proteases of HDM can be involved in AD by affecting the skin barrier, through non-IgE mediated mechanisms.

## What is new in the association between allergy and atopic dermatitis?

In the past, allergic reactions were considered to be causally involved into the pathogenesis of AD. Recently, however, a number of new findings have been reported, putting a different spotlight on the role of allergy in AD. The most important findings on the role of allergy in AD have been summarized in an article by Sicherer and Leung[36].

### A. Allergy can be a consequence of a defective skin barrier.

It is now clear that skin barrier defects drive allergen sensitization and skin inflammation[5]. Loss-of-function null mutations in the FLG gene are associated with the development of early-onset AD, with allergic sensitization, and with eczema-associated asthma[19]. Because FLG is not found in the lung, these data suggest that allergen absorption through the skin leads to specific IgE production against food and inhalant allergens with progression of the allergic march through systemic allergen sensitization or priming of allergic effector cells. FLG null mutations have also been reported to be associated with increased asthma severity in children and young adults[37]. However, FLG null mutations do not occur in the absence of eczema.

### B. Role of food allergy in AD

A large number of studies, using DBPCFC have shown that food can trigger flare ups of AD. However, in all of these studies AD was assessed by clinical scoring cards, and in none of these studies the flare up of AD was documented by skin biopsies. On the other hand, a large number of patients with AD have positive IgE against a large variety of foods, and it can be expected that intake of these foods may trigger acute allergic reactions, such as urticaria or angioedema. In a very elegant study by Hugh Sampson it was shown that positive DBPCFCs in children with AD that is under control manifest themselves as urticaria and angioedema, and NOT as flare ups of the underlying AD. However, when DBPCFCs were performed when the AD was not under control, flare ups of the existing AD were seen[38].

**Table 4.** Documented routes of food sensitization

| |
|---|
| *1. Eating and drinking* |
| *2. Prenatal (through active placental transport)* |
| *3. Breast milk* |
| *4. Inhaling (airborne sensitization)* |

Therefore, it seems that foods induce AD through urticaria and angioedema that present on top of the AD, and that it is less likely that food is able to induce AD lesions directly. The only way to prove that food is able to induce AD directly is to perform a study using DBPCFCs and to document the clinical results with skin biopsies, which is a study that is ethically not acceptable in children.

### C. Routes of sensitization to food

For long time it was assumed that food sensitization only occurs through eating or drinking of food. A number of recent studies have now shown that there are other routes of food sensitization (Table 4). In a study from Australia, sensitization to hen's egg was found in more than 90% of exclusively breast fed infants with severe AD, suggesting sensitization through breast milk[39]. In older studies the presence of various food allergens, such as lactalbumin, ovalbumine and peanut allergens in breast milk was shown[40]. In other types of studies, looking at the role of prenatal sensitization, an active transport through the placenta of various allergens was found, while house dust mite allergens were identified in amniotic fluid[41,42]. Moreover, in one study the presence of food allergens, such as allergens from hen's egg and cow's milk was detected in dust from kitchens. The authors suggested that sensitization to food can occur through smelling of food[43]. Finally, anecdotic reports of severe allergic reactions to food through kissing have been published[44].

### 3. Auto-immunity

Serum samples of about 25% of patients with severe AD contain IgE antibodies against proteins from keratinocytes and endothelial cells and severity of AD was found to correlate with levels of auto-antibodies[45]. A proposed mechanism was that scratching probably releases intracellular proteins from keratinocytes. In these patients with auto-antibodies early-onset AD, intense pruritus, recurrent bacterial skin infections, and high serum IgE levels are hallmarks of the disease.

In children, only a limited number of studies on auto-immunity have been reported. In one study from Germany, auto-antibodies were found

**Table 5.** Role of Staphylococcus aureus in AD

| |
|---|
| *1. Induce IgE production* |
| *2. Activate naive T-cells by its superantigens* |
| *3. Damage skin by its proteases* |

in infants with AD. These infants had significantly higher total IgE levels, and most of them already developed sensitizations against food allergens[46]. However, the exact role or source (maternal?) role of these auto-antibodies has not been elucidated, and more studies on the subject are needed, especially to get more insights into the initiation of AD in infants.

### 4. Microbial agent colonization

#### *Staphylococcus aureus*

Since long it has been known that most older children (90%) with AD are colonized with Staphylococcus aureus[12]. The high degree of colonization is explained by suppression of the innate immune system of the skin by the inflammatory micro-milieu of AD. Colonization on itself contributes to allergic sensitization and inflammation. S. aureus enterotoxins (SEs) (i.e. a large protein family composed of SEs A to Q and toxic shock syndrome toxin1) act as superantigens, and increase the inflammation in AD and provoke the generation of SE-specific IgE, which correlates with the severity of the disease[47]. Once bound to the T-cell receptor, these superantigens may activate 20% of the naïve T-cell population (whereas conventional antigens stimulate only 0.01%). The enterotoxins interact directly with class II molecules of the major histocompatibility complex and the beta chain of the T-cell receptor to induce an antigen-independent proliferation of T cells. They also up-regulate the expression of the skin-homing receptor cutaneous lymphocyte-associated antigen on T cells and the production of keratinocyte-derived chemokines that recruit T cells. By inducing the competing beta-isoform of the glucocorticoid receptor in mononuclear cells, SEs contributes to the emergence of a resistance to local corticosteroid treatment[48]. A study in infants with AD showed that SE-B is able to stimulate IL-13 production, thereby contributing to Th2-type inflammatory reactions[49].

#### *Yeasts*

The role of yeast colonization has been explored recently, mainly in adults with AD. In one study it was shown that manganese

21

superoxide dismutase (MnSOD) from human and fungal origin acts as an auto-allergen (i.e. superantigens) in adults with AD. Specific auto-antibodies against human MnSOD correlated with disease activity, and MnSOD was able to induce in vitro T-cell reactivity and eczematous lesions by patch testing. Moreover, co-sensitization to structurally related and cross-reacting fungal MnSOD from *Malassezia sympodialis* was observed. The authors conclude that human MnSOD may play a role as an auto-allergen in a subset of patients with AD, and that sensitization might be induced by exposure to environmental fungal MnSOD from *Malassezia sympodialis*[50]. In another study it was found that there were differences in colonization with Malassezia spp. between children and adults. *Malassezia restricta* was the predominant species in the children with AD, while both *M. restricta* and *M. globosa* predominated in the adults. The adults showed increased sensitization in terms of anti-Malassezia-specific IgE responses in the sera to both *M. globosa* and *M. restricta* in comparison with the children[51]. Finally, in a study from Japan it was found that fungal components from *Cryptococcus diffluens* and *Cryptococcus liquefaciens* may act as allergens and play a role in the pathogenesis of AD[52].

## 5. New treatments for AD

There is no real breakthrough in the treatment of AD at the moment, and the classical treatments of AD are still very much in use to control symptoms. These "classical" treatments include: moisturizing (from a young age to prevent skin barrier dysfunctions), local corticosteroids, antiseptics, antibiotics (restrictive use) and systemic treatments for those children with severe AD, which include prednisolone, cyclosporine and azathioprine. Furthermore, mycophenolate showed effectiveness in 2 small uncontrolled studies in adults, but no data on its use in children with AD are available[53].

A number of recent articles have highlighted novel therapies in AD. In one study the use of low-dose anti-IgE therapy, even in patients with high levels of serum IgE, was beneficial[54]. Another interesting approach is the use of sublingual immunotherapy (SLIT) in children with AD who suffer from concomitant allergy to house dust mites. In a study by Pajno et al, it was found that SLIT with house dust mite-extract reduced the severity of AD and the usage of

mediation in children with mild-to-moderate AD. However, SLIT was ineffective in those children suffering from severe AD[55]. This study offers interesting new perspectives in the treatment of AD and the early administration of SLIT to young children with AD is a field that certainly deserves exploration in the future.

Finally, preventive usage of probiotics was not effective in all studies, and much more research on the subject is needed[56,57]. From the data we have it seems that certain strains of probiotics are effective if started prenatally and if given in combination with breast feeding[58]. However, it was also found that probiotics are unable to prevent IgE sensitization, despite being effective on AD. These findings suggest that IgE is not involved in the initiation of AD, and that the preventive effect of probiotics is through other (yet not-identified) mechanisms, such as the initiation of an anti-inflammatory effect or the inhibition of auto-immunity.

## Conclusion

AD remains a complex disease of which many features are still not understood. However, a number of new studies have brought better insights into its underlying mechanisms. It is now clear that AD is not "*just an allergic disease*", but a complex interplay between skin barrier defects, allergic hypersensitivity, auto-immunity and chronic infection. Other underlying mechanisms might be discovered very soon, including the very fascinating "Th17-story in AD"[59]. Furthermore, it is pivotal to get more insights into the mechanisms that initiate AD in newborns. This will allow setting up more appropriate studies on prevention of AD.

## References

1. Tan TN, Lim DL-C, Lee BW, Van Bever HP. Prevalence of allergy-related symptoms in the second year of life. Ped Allergy Immunol. 2005; 16:151-6.
2. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? J Allergy Clin Immunol. 2008; 121: 947 – 54.
3. Cork MJC, Murphy R, Carr J, Buttle D, Ward S, Bavik C, et al. The rising prevalence of atopic eczema and environmental trauma to the skin. Dermatol Pract. 2002; 10: 22 – 6.
4. Rancé F, Boguniewicz M, Lau S. New visions for atopic eczema: An iPAC summary and future trends. Ped Allergy Immunol. 2008;19: (suppl. 19), 17 – 25.
5. Cork MJC, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, Duff GW, Ward SJ, Tazi-Ahnini R. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol. 2006; 118: 3 – 21.
6. Taieb A. Hypothesis: from epidermal barrier dysfunction to atopic disorders. Contact Dermatitis. 1999; 41: 177 – 80.

7. Simon M, Bernard D, Minondo AM, Camus C, Fiat F, Corcuff P, et al. Persistence of both peripheral and non-peripheral corneodesmosomes in the upper stratum corneum of winter xerosis skin versus only peripheral in normal skin. J Invest Dermatol. 2001; 117: 710 – 7.

8. Hansson L, Backman A, Ny A, Edlund M, Eckholm E, Ekstrand Hammarstrom B, et al. Epidermal overexpression of stratum corneum chymotryptic enzyme in mice: a model for chronic itchy dermatitis. J Invest Dermatol. 2002; 118: 444 – 9.

9. Vasilopoulos Y, Cork MJ, Murphy R, Williams HC, Robinson DA, Duff GW, et al. Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. J Invest Dermatol. 2004; 123: 62 – 6.

10. Badertscher K, Bronnimann M, Karlen S, Braathen LR, Yawalkar N. Mast cell chymase is increased in atopic dermatitis but not in psoriasis. Arch Dermatol Res. 2005; 296: 503 – 6.

11. Deleuran M, Ellingsen AR, Paludan K, Schou C, Thestrup-Pedersen K. Purified Der p 1 and p 2 patch tests in patients with atopic dermatitis: evidence for both allergenicity and proteolytic irritancy. Acta Derm Venerol. 1998; 78: 241 – 3.

12. Hon KLE, Lam MCA, Leung TF, Kam WYC. Clinical features associated with nasal Staphylococcus aureus colonization in Chinese children with moderate-to-severe atopic dermatitis. Ann Acad Med Singapore 2005; 34: 602 – 5.

13. Miedzobrodzki J, Kaszycki P, Bialecka A, Kasprowicz A. Proteolytic activity of Staphylococcus aureus strains isolated from the colonized skin of patients with acute-phase atopic dermatitis. Eur J Clin Microbiol Infect Dis. 2002; 21: 269 – 76.

14. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Biol. 2005; 6: 328 – 40.

15. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006; 38: 337 – 42.

16. Ginger RS, Blachford S, Rowland J, Rowson M, Harding CR. Filaggrin repeat number polymorphism is associated with a dry skin phenotype. Arch Dermatol Res. 2005; 297: 235 – 41.

17. Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, et al. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. Nat Genet. 2001; 27: 372 – 3.

18. Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, Gruber C, Lau S, Worm M, Keil T, Kurek M, Zaluga E, Wahn U. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. J Allergy Clin Immunol. 2006; 118: 866 – 71.

19. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, Mukhopadhyay S, Smith GD, Palmer CAN, McLean WHI, Irvine AD. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol. 2008; 121: 872 – 7.

20. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, Schneider L, Beck LA, Barnes KC, Leung DYM. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2007; 120: 150 – 5.

21. Sandilands, Sutherland, Irvine and Mc Lean. Filaggrin in the Frontline: Role in Skin Barrier Function and Disease. Journal of Cell Science. 2009; 122: 1285-94.

22. Kim BE, Leung DYM, Boguniewicz M, Howelll M. Loricrin and Involucrin expression is down-regulated by Th2 cytokines through STAT-6. Clin Immunol. 2008; 126: 332-7.

23. Yoneda K, Hohl D, McBridell W, Wang M, Cehrs KU, Idler WW, Steinert PM. The Human Loricrin Gene. J Biological Chemistry. 1992; 267: 18060 - 6.

24. Hohl D, Huber M, Frenk E. Analysis of the Cornified Envelope in Lamellar Ichthyosis. Arch Dermatol. 1993; 129: 618 – 24.

25. Peña-Penabad C, de Unamuno P, Ludena GSJ, Sarmiento GR, Perez-Arellano JL. Altered expression of immunoreactive Involucrin in lamellar ichthyosis. Eur J Dermatol. 1999; 9: 197-201.

26. Boguniewicz M, Leung DYM. Atopic dermatitis. In: Middleton's Allergy. Principles & Practice, editors. Adkinson NF, Yunginger JW,

27. Busse WW, Bochner BS, Holgate ST, Simons EF. 6th ed. Mosby, Inc: 2003; p. 1559 – 80.

27. Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? J Allergy Clin Immunol. 2004; 114: 150 – 8.

28. Van Bever HP, Docx M, Stevens WJ. Food and food additives in severe atopic dermatitis. Allergy. 1989; 44: 588-94.

29. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001; 107: 891-6.

30. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V; EPAAC Study Group. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. Clin Exp Allergy. 2008; 38: 161-8.

31. Tupker RA, de Monchy JG, Coenraads PJ. House-dust mite hypersensitivity, eczema, and other non-pulmonary manifestations of allergy. Allergy. 1998; 53(48 Suppl): 92-6.

32. Guler N, Kirerleri E, Tamay Z, Ones U. Atopy patch testing in children with asthma and rhinitis symptoms allergic to house dust mite. Pediatr Allergy Immunol. 2006; 17: 346 -50.

33. Brinkman L, Aslander MM, Raaijmakers JAM, Lammers JWJ, Koenderman L, Bruijnzeel-Koomen CAFM. Bronchial and cutaneous responses in atopic dermatitis patients after allergen inhalation technique. Clin Exper Allergy. 1997; 27: 1043 – 51.

34. Kimura M, Yamaide A, Tsuruta S, Okafuji I, Yoshida T. Development of the capacity of peripheral blood mononuclear cells to produce IL-4, IL-5 and IFN-gamma upon stimulation with house dust mite in children with atopic dermatitis. Int Arch Allergy Immunol. 2002; 127: 191-7.

35. Holm L, Bengtsson A, van Hage-Hamsten M, Ohman S, Scheynius A. Effectiveness of occlusive bedding in the treatment of atopic dermatitis--a placebo-controlled trial of 12 months' duration. Allergy. 2001; 56: 152-8.

36. Sicherer SH, Leung DYM. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs and insects in 2007. J Allergy Clin Immunol. 200; 123: 319 – 27.

37. Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. J Allergy Clin Immunol. 2007; 120: 64 – 8.

38. Sampson HA. Food sensitivity and the pathogenesis of atopic dermatitis. J R Soc Med. 1997; 90 suppl 30: 2 – 8.

39. Rennick GJ, Moore E, Orchard DC. Skin prick testing to food allergens in breast-fed young infants with moderate to severe atopic dermatitis. Aust J Dermatol. 2006; 47: 41 – 5.

40. Barau E, Dupont C. Allergy to cow's milk proteins in mother's milk or in hydrolyzed cow's milk infant formulas as assessed by intestinal permeability measurements. Allergy. 1994; 49: 295-8.

41. Szépfalusi Z, Loibichler C, Pichler J, Reisenberger K, Ebner C, Urbanek R. Direct evidence for transplacental allergen transfer. Pediatr Res. 2000; 48: 404-7.

42. Jones CA, Holloway JA, Warner JO. Does atopic disease start in foetal life? Allergy. 2000; 55: 2 – 10.

43. Witteman AM, van Leeuwen J, van der Zee J, Aalberse RC. Food allergens in house dust. Int Arch Allergy Immunol. 1995;107:566-8.

44. Eriksson NE, Möller C, Werner S, Magnusson J, Bengtsson U. The hazards of kissing when you are food allergic. A survey on the occurrence of kiss-induced allergic reactions among 1139 patients with self-reported food hypersensitivity. J Investig Allergol Clin Immunol. 2003; 13: 149 - 54.

45. Mittermann I, Aichberger KJ, Bünder R, Mothes N, Renz H, Valenta R. Autoimmunity and atopic dermatitis. Curr Opin Allergy Clin Immunol. 2004; 4: 367 – 71.

46. Mothes N, Niggemann B, Jenneck C, Hagemann T, Weidinger S, Bieber T, Valenta R, Novak N. The cradle of IgE autoreactivity in atopic eczema lies in early infancy. J Allergy Clin Immunol. 2005; 116: 706 – 8.

47. Bunikowski R, Mielke M, Skarabis H, et al. Prevalence and role of serum IgE antibodies to the Staphylococcus aureus-derived superantigens SEA and SEB in children with atopic dermatitis. J Allergy Clin Immunol. 1999; 103: 119 – 24.

48. Bieber T. Mechanisms of disease: atopic dermatitis. N Engl J Med. 2008; 358: 1483 – 94.

49. Lehmann HS, Heaton T, Mallon D, Holt PG. Staphylococcal enterotoxins-B-mediated stimulation of interleukin-13 production as a potential aetiologic factor in eczema in infants. Int Arch Allergy Immunol. 2004; 135: 306 – 12.

50. Schmid-Grendelmeier P, Flückiger S, Disch R, Trautmann A, Wütrich B, Blaser K, Scheynius A. IgE-mediated and T-cell-mediated auto-immunity against manganese superoxide dismutase in atopic dermatitis. J Allergy Clin Immunol. 2005; 115: 1068 – 75.

51. Takahata Y, Sugita T, Kato H, Nishikawa A, Hiruma M, Muto M. Cutaneous Malassezia flora in atopic dermatitis differs between adults and children. Br J Dermatol. 2007; 157: 1178 - 82.

52. Kato H, Sugita T, Ishibashi Y, Nishikawa A. Evaluation of the levels of specific IgE against Cryptococcus diffluens and Cryptococcus liquefaciens in patients with atopic dermatitis. Microbiol Immunol. 2007; 51: 945-50.

53. Schmitt J, Schäkel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. Acta Derm Venereol. 2007; 87: 100-11.

54. Belloni B, Ziai M, Lim A, Lemercier B, Sbornik M, Weidinger S, et al. Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. J Allergy Clin Immunol. 2007; 120: 1223 – 5.

55. Pajno GB, Caminiti L, Vita D, Barberio G, Salzano G, Lombardo F, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized double-blind, placebo-controlled study. J Allergy Clin Immunol. 2007; 120: 164 – 70.

56. Mah KW, Chin VI, Wong WS, Lay C, Tannock GW, Shek LP, Aw MM, Chua KY, Wong HB, Panchalingham A, Lee BW. Effect of a milk formula containing probiotics on the fecal microbiota of Asian infants at risk of atopic diseases. Pediatr Res. 2007; 62: 674 – 9.

57. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: A randomized controlled trial. J Allergy Clin Immunol. 2007; 119: 184-91.

58. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet. 2001; 357: 1076 – 9.

59. Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol. 2008; 128: 2625 – 30.