

Review article

New insights into the mechanism and management of allergic diseases: atopic dermatitis

Rapidly increasing knowledge on the complex background of atopic dermatitis (AD) on the genetic, immunological and environmental level in combination with the continuous improvement in our diagnostic options has initiated an ongoing discussion on factors, which primarily promote the disease on one hand and mechanisms which emerge rather secondarily as a consequence of disease-specific modifications, on the other hand. Beside a sustained search for reliable and meaningful diagnostic tools for elicitors of the disease, novel therapeutic approaches are required, as most of the treatments of AD are limited to symptomatic therapies. In contrast, therapeutic approaches selectively regulating aberrant pathophysiological mechanisms in AD itself would be much more effective and promising.

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Atopic disorders such as allergic rhino-conjunctivitis, allergic asthma, atopic dermatitis (AD) and food or insect allergy are increasing. As a result, about one-third of the population suffers from one or more of these diseases (1, 2), which impact significantly on both, the burden of healthcare costs and the quality of life of affected patients. This new trend 'to be allergic' is interpreted as a kind of a 'side-effect' of modern lifestyle with epidemiological and environmental factors influencing the manifestation of atopic diseases (3). Atopic dermatitis represents an eczematous disorder of the skin, which affects up to 20% of children and 1–3% of adults (4). Atopic dermatitis is characterized by chronic eczematous lesions, typically involving the flexural folds which are impaired by recurrent severe flare ups of AD (5). Rapidly increasing knowledge about the complex background on the genetic, immunological and environmental level combined with continuous improvement in our diagnostic options has initiated an ongoing discussion about an appropriate nomenclature for AD, which should ideally comprehend as much of the different aspects of the complex nature of AD as possible (6, 7). Furthermore, the important question which factors primarily promote the diseases as opposed to factors which emerge rather secondarily as a consequence of these modifications remains largely unanswered. In terms of diagnostic tools, it became clear that total immunoglobulin E (IgE) and

allergen specific IgE is profoundly elevated in the sera of most of the AD patients. Nevertheless, a subgroup of children and adult patients with AD exists in which IgE-mediated mechanisms seem to play rather an inferior role (8). On the other hand, even though several types of allergen-specific IgE are detectable, they are not always linked to clinically relevant sensitizations, so that increased total or allergen specific IgE alone or even positive prick test results do not serve as useful diagnostic tools or reliable markers to estimate the severity of the disease (9). Atopy patch tests (APT), performed by application of aero allergens or food allergens in patch test chambers to the skin of AD patients leading to eczematous skin reactions in the area of exposure after 24–72 h have been established a few years ago (10). Atopy patch tests are primarily useful in patients with suspected sensitizations against aero allergens or food allergens, in particular in cases in which allergen specific IgE is missing or other available diagnostic tests do not lead to satisfactory results (9, 11, 12). However, sensitivity and specificity of APT vary and depend on the type of allergen tested and various other factors which are difficult to standardize, so that further studies are required to optimize APT as standard diagnostic tools in the clinical practice (12). Besides the search for reliable and meaningful diagnostic tools for trigger factors in the individual AD patients, novel therapeutic approaches are

required, as most of the treatments of AD are limited to symptomatic therapies such as anti-inflammatory or anti-pruritic therapy only (13, 14). Obviously, therapeutic approaches which selectively regulate aberrant pathophysiological mechanisms in AD would be much more effective and promising.

Atopic dermatitis is a genetically complex disease

Genetic risk in terms of skin barrier function

Most patients with AD have a positive family history for atopic diseases, which documents the strong genetic background of AD (15, 16). Atopic dermatitis is not a monogenic disease. Instead, several genetic factors contribute to the complex pathophysiology of AD (17, 18). Through different approaches aimed at finding universally valid candidate genes for AD, which provided quite heterogeneous results, it came to the assumption that AD might be directed not only by an abundance of different genes but also that different subtypes of AD, such as AD with early onset, childhood AD *vs* adulthood AD or AD with IgE-mediated allergic reactions in the foreground might be based on distinct genetic constellations (19–23). This genetically complex situation profoundly aggravates efforts to define gene regions characteristic for AD or to predict the severity and the course of AD based on the genetic repertoire. At present, one reasonable attempt to sort this complexity is to subdivide genetic predilections according to the different pieces of the pathophysiological puzzle of AD. These pieces include factors leading to improved skin barrier as well as deficiencies on the level of innate *vs* adaptive immunity (Fig. 1) (19). The impaired skin barrier in AD patients is mirrored by dry

skin induced partially by increased transepidermal water loss and reduced levels of natural moisturizing factors (24, 25). An important protein which is essential to maintain the formation of the stratum corneum barrier is filaggrin (26). Within the recent 2 years, loss-of-function mutations in the filaggrin gene have been shown to be strongly associated with AD, a finding which was replicated and confirmed by a series of independent studies (27, 28). In particular, specific clinical features and subforms of AD have been described to be highly associated with these mutations, including AD with early onset and a high number of sensitizations (29, 30). Furthermore, specific interactions of a genetic predisposition and environmental factors such as cat exposure at the time of birth seem to increase the risk for the manifestation of eczema during the first year of life, in particular, in filaggrin mutation carriers (31). In addition, in the context of a genetically determined disturbed skin barrier in AD, reports about associations of polymorphisms in the *SPINK5* gene, which encodes the lympho-epithelial kazal-type related inhibitor, an inhibitor of serine proteases exist (32). Furthermore, studies reported about associations of genetic modifications in the gene region encoding the stratum corneum chymotryptic enzyme with AD, leading to impaired stratum corneum integrity and function (33). In addition to the already identified factors, it is more than likely that other modifications of components of the epidermal differentiation complex contribute to the skin barrier defect in AD (17). Besides these genetically predetermined factors, other aspects such as higher serine protease activity induced by a shift in the pH from pH 5.0 to 5.5 as well as increased transepidermal water loss and lower skin hydration act in concert and impair the skin barrier in AD (34).

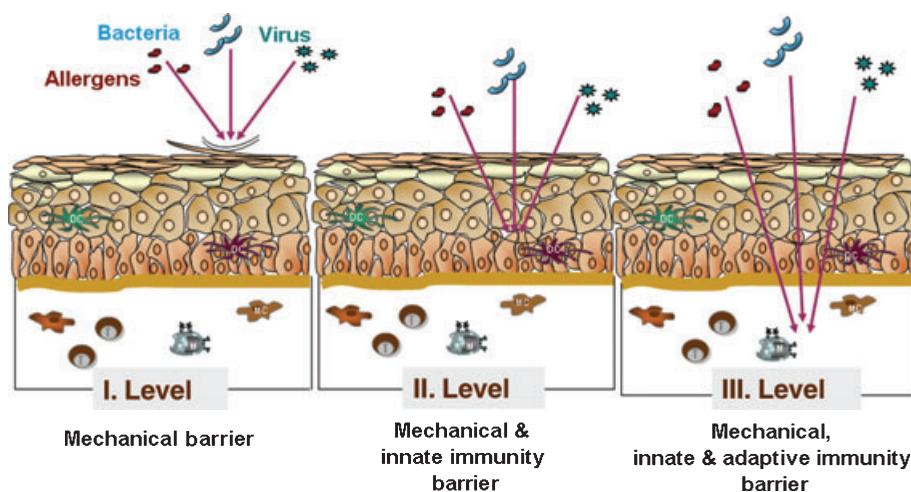


Figure 1. Deficiencies on the level of the skin barrier function as well as the innate and adaptive immune system contribute to the pathophysiological puzzle of atopic dermatitis (AD). The first level of the barrier is the mechanical skin barrier represented by the stratum corneum and the upper part of the skin. The second level of the skin barrier is represented by structures of the innate immune system such as pattern recognition receptors expressed by skin cells or antimicrobial peptides. The third level of the skin barrier is represented by the cellular defense of components of the adaptive immune system. DC, dendritic cell; M, mast cell; MC, macrophage; T, T cell.

Genetics of innate immunity

Once invading antigens have passed the epidermal skin barrier, pattern-recognition receptors (PRR) expressed by different skin cells play a pivotal role in the induction of first-line defence mechanisms of the innate immune system and trigger immune responses to a wide range of microbial pathogens (35, 36). To discriminate between diverse pathogen associated molecular patterns, our innate immune system uses a variety of PRR such as toll-like receptors (TLR), intracellular nucleotide-binding oligomerization domain (NOD) proteins or the lipopolysaccharide (LPS) receptor CD14 (37, 38). Deficiencies on the level of immunity receptors are suspected to affect the maturation of our immune system and to avail thereby the high prevalence of atopic diseases and susceptibility of atopic patients to microbial infections (3). In this regard, it represents a plausible hypothesis that genetic modifications leading to functional changes of PRR might alter the supposed protective effect of ligands to PRRs as it has already been shown for asthma (39). Several studies have investigated a putative association between genetic variations within the gene regions encoding components of the innate immune system and AD. A polymorphism within the *TLR2* gene has been shown to be associated with severe forms of AD with recurrent bacterial infections (40) and has been linked to functional modifications of TLR2 protein, which depend on the allelic variant at the respective gene region (41). In contrast, no association of polymorphisms in the *TLR4* and *TLR6* gene with AD could be shown (42, 43), while a polymorphism in the *TLR9* gene was associated with pure AD (44). In addition, polymorphisms in the *NOD1* gene, encoding a cytosolic sensor for bacterial host defense showed strong association with AD (45).

As an addendum to the genetic predisposition, several factors on the level of the innate immune system are secondarily modified by the AD-specific microenvironment in the blood and peripheral organs (46). One example for such a counterregulation is the amount of antimicrobial peptides in the skin, which have synergistic and specific antimicrobial functions. While small amounts of antimicrobial peptides are detectable in noninflamed skin, inflammatory mediators induce the release of human beta-defensin-2, -3 and cathelicidin (LL-37) by epithelial cells and keratinocytes (47). Reduced levels of antimicrobial peptides have been detected in acute and chronic skin lesions of AD compared with lesions of other inflammatory skin disease, such as psoriasis or contact dermatitis (48). This downregulation was most likely induced by high levels of interleukin (IL)-10 and T helper 2 (Th2) cytokines in the skin microenvironment of AD (49). As a proof of this concept, a downregulation of these antimicrobial peptides was observed in *in vitro* studies using epidermal cells incubated with IL-10 or with typical Th2 cytokines (50, 51). Together, genetically predetermined as well as secondarily modified changes on the level of the

innate immune system are supposed to contribute to a higher susceptibility to bacterial as well as viral infections in AD (52).

Genetic modifications on the level of the adaptive immune system

After allergens and microbial pathogens have passed the epidermal skin barrier and the defense machinery of the innate immune system, activation of the adaptive immune system takes place by the induction of different receptors on effector cells, dendritic cells (DC) or other cells in the skin. Numerous genes suspected to predispose to AD have been observed in gene regions encoding components of the adaptive immune response (18, 53, 54). As cytokines and chemokines, which play a crucial role as soluble mediators of the adaptive immune system, show profound variations in AD, it is more than likely that some of these deviations are already genetically encoded (55). For instance, genetic variations on chromosome 5q31–33 containing genes of the Th2 cytokine cluster such as IL-3, IL-4, IL-5, IL-13 and granulocyte-macrophage colony stimulating factor have been shown to be associated with subtypes of AD (18, 19). Other studies could demonstrate associations of AD with variants of the IL-13 coding region, functional mutations of the promoter region of *RANTES* (17q11) and gain-of-function polymorphisms in the *IL4RA* gene (16q12) (18, 19, 56, 57). Furthermore, polymorphisms in the *IL4RA* region were associated with a variant of AD which had been formerly signified as intrinsic AD, going along with low IgE serum levels and without any sensitizations (56). Polymorphisms in the *IL18* gene have been shown to go along with differences in the IL-12/IL-18 production of immune cells of AD patients after stimulation with bacterial stimuli *in vitro* and might contribute partly to the modified immune reactions in response to microbial components in AD patients *in vivo* (58).

Structures mediating allergic reactions on antigen presenting cells

The sensitization phase precedes allergic reactions. Typically, B cells start to produce allergen-specific IgE and IgG molecules after contact with different allergens during this phase (59). In case these IgE molecules bind to IgE receptors on effector cells of allergic reactions, such as mast cells or basophils, allergic reactions of the immediate type are induced (60, 61).

The high affinity Fc receptor for IgE, FcεRI is the initial structure commencing the allergic signal transduction cascade. In the human immune system as well as in the rodent immune system, the tetrameric form of FcεRI is expressed on allergic effector cells including mast cells and basophils and consists of the α-chain, the β-chain and the γ-chain dimer (Fig. 2A) (62, 63). The trimeric FcεRI variant can be detected on human

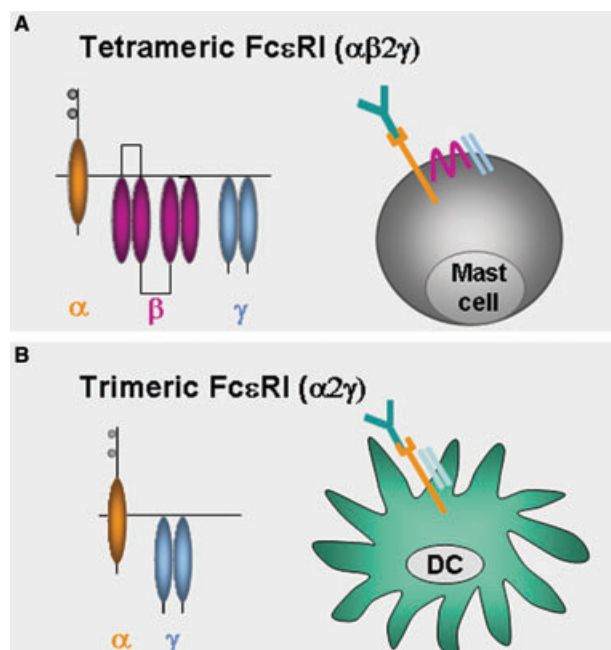


Figure 2. Tetrameric structure of FcεRI on mast cells and basophils as opposed to trimeric structure of FcεRI on antigen presenting cells is shown. DC, dendritic cell.

antigen presenting cells (APC) and consists of the α-chain and the γ-chain dimer in the absence of the β-chain (Fig. 2B) (64, 65). FcεRI can be subdivided into an IgE binding part represented by the FcεRIα subunit and a signal transducing part represented by the γ-subunits. It is assumed that allergens which invade the skin are taken up by IgE molecules bound to FcεRI expressing DC. Structural factors influencing the expression of the FcεRI variants are complex and have gained considerable interest within recent years. The concen-

tration of transforming growth factor (TGF)-β (66) as well as the presence or absence of IgE (67) and the oxidative state of the microenvironment (68) determine and regulate the FcεRI surface expression on APCs *in vivo* and *in vitro*. FcεRI expression is regulated distinctly in DC of atopic and nonatopic donors. Both the mature form of the FcεRI-α chain and the presence of sufficient amounts of the FcεRI-γ chain determine the contingent of FcεRI expressed on the cell surface (Fig. 3) (67). In the epidermis of the skin, FcεRI expression on DC is related to the atopic state of the individual with higher expression in AD lesions compared with nonlesional skin of AD patients or epidermal skin of nonatopic individuals (69). Correlation of FcεRI expression on skin DC with serum IgE levels and increased expression after application of allergens during APT has been reported as well (70).

IgE-receptor bearing dendritic cell subtypes

Several FcεRI bearing subtypes have been identified in human skin of AD patients so far. Concerning myeloid DC, both, CD207⁺/CD1a⁺, i.e. Langerhans cells (LC) as well as CD207⁻/CD1a⁺/FcεRI⁺ DC are located in the epidermis (71). While low numbers of CD207⁺/FcεRI⁺/CD1a⁺ DC occur in the dermis, CD1c⁺/FcεRI⁺ DC represent the major DC subpopulation of the dermal compartment (72).

A closer look at the DC subtypes expressing FcεRI in the skin and blood of AD patients revealed IgE receptor bearing epidermal LC, which predominate in nonlesional AD. Furthermore, a subtype of DC, which, in contrast to LC, does not have any Birbeck granules, the so-called inflammatory dendritic epidermal cells (IDEC) invades the skin in the acute phase and persists

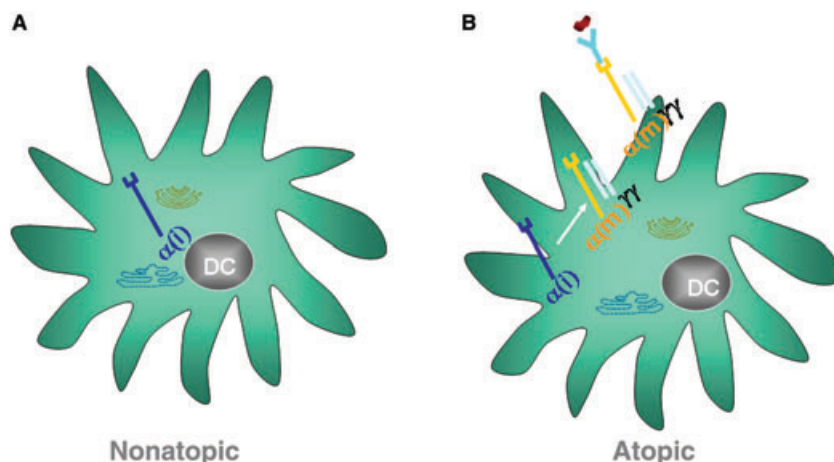


Figure 3. Distinct regulation of FcεRI expression on human antigen presenting cells (APC). Immature form of FcεRIα (i) can be detected in the intracellular space of APCs in nonatopics, while in APCs of atopics immature FcεRIα as well as mature FcεRIα variant (m) are present. Mature FcεRIα variant colocalizes with FcεRIγ-chain dimers, which promotes the transportation of the complete trimeric FcεRI complex to the cell surface of APCs of atopic individuals.

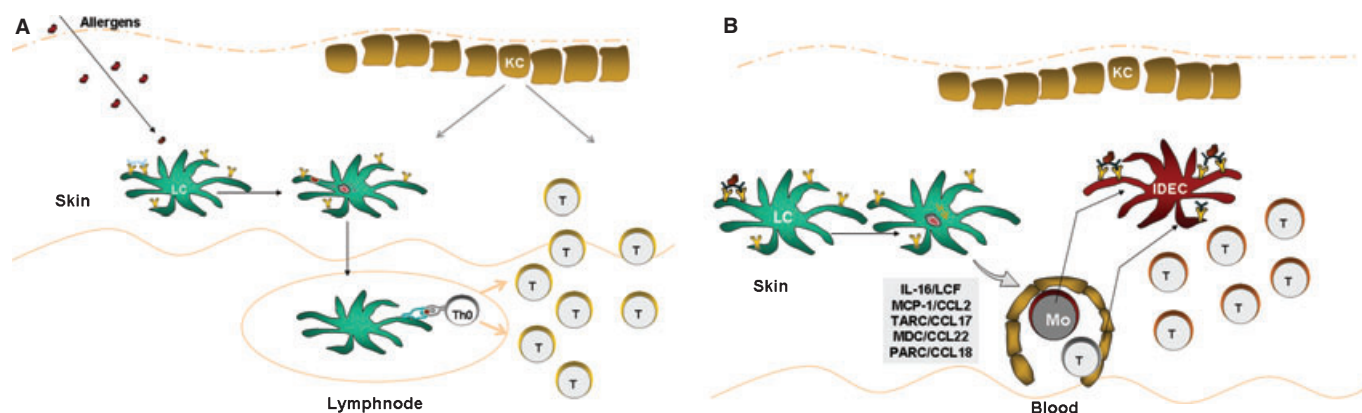


Figure 4. Langerhans cells (LC) predominate in healthy and nonlesional epidermis (A), while inflammatory dendritic epidermal cells (IDEC) are rapidly recruited to the skin at the exacerbation phase of atopic dermatitis (AD) (B). KC, keratinocyte; MCP, macrophage chemoattractant protein; MDC, macrophage-derived chemokine, thymus and activation-regulated chemokine; PARC, pulmonary and activation-regulated chemokine; LCF, lymphocyte chemoattractant factor.

during the chronic phase of AD (69). Most likely, IgE receptor bearing monocytes in the peripheral blood and dermal DC represent precursors of IDEC (Fig. 4A,B) (73). This hypothesis is supported by the observation that the amount of Fc ϵ RI bearing monocyte subtypes decreases during the flare up of AD as a sign for increased recruitment of these cells to the skin, while it decreases again after successful therapy and clinical improvement of the lesions (73). Vice versa, sequential biopsies taken before and after application of allergens to the skin of sensitized AD patients during APT revealed increase in chemotactic signals in the skin (74–76) and invasion of IDEC and other proinflammatory cell subtypes within 24–48 h after allergen application and disappearance of IDEC from the epidermis after topical treatment with tacrolimus (77, 78). Studies with *in vitro* generated LC-like DC and IDEC-like DC in combination with LC and IDEC isolated *ex vivo* assessed distinct tasks of LC and IDEC (79). An important role of LC can be allocated to the initial phase. Langerhans cell most likely take up allergens via Fc ϵ RI, migrate to the lymph nodes and prime predominantly T cells of the Th2 type *in vitro* (80). Furthermore, Fc ϵ RI-cross linking of LC *in vitro* leads to the release of chemotactic signals which might, together with chemotactic mediators released by other skin cells contribute to the recruitment of inflammatory cell subtypes, including IDEC to the skin (80). Inflammatory dendritic epidermal cell have been uncovered as important amplifiers of the allergic inflammatory reaction in the skin, mirrored by the release of numerous proinflammatory cytokines and chemokines in response to microbial components and allergens *in vitro*. Furthermore, IDEC have a high stimulatory capacity towards T cells and might be involved in the switch from Th2 predominated initial AD to chronic AD. In addition to epidermal DC, Fc ϵ RI expressing DC without any Birbeck granules are located in the dermis (72).

Plasmacytoid dendritic cells (PDC), which are characterized by the expression of the blood-derived DC antigen-2 are also equipped with Fc ϵ RI and the expression level of this structure correlates with the IgE serum level (81). The function of Fc ϵ RI on PDC is unclear, but a counterregulation between Fc ϵ RI and TLR9 has been observed, implying an interaction of allergens with their capability to develop an effective response against microbial antigens (82). Plasmacytoid dendritic cells link innate and adaptive immunity and play a pivotal role in the defence against viral infections (83). Fc ϵ RI–IgE bearing PDC are detectable in the dermis of AD patients only, while the amount of PDC in the epidermis is significantly reduced in comparison with other chronic inflammatory skin diseases, such as psoriasis or contact dermatitis (84).

Aggregation of Fc ϵ RI on PDC induces the release of IL-10 and increases in an endogenous-loop IL-10 mediated apoptosis of PDC *in vitro*. Furthermore, the preactivation of PDC via allergen challenge significantly reduces the capacity of PDC to produce interferon- α (IFN- α) and IFN- β in response to subsequent stimulation with viral DNA motifs *in vitro* (81). The reduced capacity of PDC to produce type I IFN after allergen challenge together with decreased number of PDC in the epidermal skin might be one of the reasons for the high susceptibility of AD patients to viral infections. Reduced amount of PDC in the epidermis of AD patients in comparison with other chronic inflammatory skin diseases such as psoriasis, allergic contact dermatitis or lupus erythematoses (84) may be based on a lower recruitment of these cells into the skin because of reduced expression of skin homing molecules on PDC of atopic donors or a higher rate of apoptosis of PDC in the Th2 prone microenvironment of AD skin (84). Furthermore, overbalance of Th2 cytokines and high rate of sensitizations seems to predispose a particular subgroup of AD patients to higher susceptibility to viral infections caused by herpes simplex virus, leading to one or more episodes of eczema herpeticum (85, 86).

IgE autoreactivity

Repetitive allergen challenge and activation of the immune system is a typical feature of AD. Reactivity against self antigens with structural homology to environmental allergens is partly a result of a molecular mimicry between different B-cell epitopes (87). In the past, it was observed that patients with chronic AD showed IgE autoreactivity to a variety of human antigens. This IgE autoreactivity has been shown to be more frequently present in AD patients with an early onset of AD and a wide spectrum of sensitizations (88). One example in this context is the stress-inducible enzyme manganese superoxide dismutase (MnSOD), which has been shown to play a role as an autoallergen in AD (89). Specific IgE antibodies against this antigen have been shown to correlate with the activity of the disease (89). Furthermore, eczematous reactions and T-cell responses were inducible by exposure to the antigen in sensitized patients (89), indicating that these antigens might aggravate the course of the diseases in a subgroup of patients. This is of particular relevance for cosensitization to fungal MnSOD and MnSOD of lipophilic yeast *Malassezia sympodialis*, which frequently colonizes the skin of AD patients (89). Another intracellular autoantigen, which has been identified in AD, is the alpha-chain of the nascent polypeptide-associated complex *Hom s 2* (90). Induction of Th1 prone T-cell immune responses (91) as well as IFN- γ mediated damage of epithelial cells and keratinocytes mirrored by apoptosis induced by *Hom s 2* has been shown in *in vitro* studies (90). However, specific IgE autoantibodies against human proteins are detectable not only in the sera of adult, but most interestingly also in those of children with AD, which developed sensitizations (88). This might indicate that chronic tissue damage in the gut, respiratory airways and skin at very early periods of life might predispose a subgroup of AD patients to severe courses of AD, which might persist in some of these cases until adulthood (88). However, it is unclear, how this IgE autoreactivity exactly emerges and which prophylactic measures might help to avoid this process. Reduction in IgE autoantibody serum levels in an AD patient treated with the immunosuppressive drug cyclosporine has been reported in the literature so far (92).

New approaches to treat AD

As the pathophysiology of AD is quite complex and different trigger factors are in the foreground in each individual patient, anti-inflammatory treatment should be supplemented by specific and individually adapted therapeutic approaches. Such an attempt would presume detailed clinical, genetic and immunological evaluation of

each patient to ensure that all relevant aspects are taken into consideration.

At present, besides sufficient and regular base line therapy, topical glucocorticosteroids are still the first line therapy for AD in cases in which anti-inflammatory treatment is required. Calcineurin inhibitors (CNI), such as the macrolactone tacrolimus (FK506) or pimecrolimus were introduced as alternatives for topical treatment of AD some years ago. Efficacy of topical treatment with CNI has been shown convincingly in clinical trials (93–95).

Besides symptomatic treatment with CNIs, preventive approaches with regular intermittent treatment to reduce the number of flare ups and to prolong remission phases so called pro-active treatment approaches have been established in recent times (96–98).

On the cellular level, T cells are the primary target cells of CNI, which induce the suppression of T-cell activation and proliferation as well as changes in cytokine secretion (99, 100). Furthermore, CNI inhibit the release of mediators by basophils and mast cells and impact on keratinocyte function and apoptosis (99, 101–104).

Particular attention has to be focused on the effect of CNI on APCs: pimecrolimus has been reported to lead to the depletion of IDEC and dermal PDC (100, 105) without affecting LC. Tacrolimus downregulates the expression of the IL-2 receptor CD25, the co-stimulatory molecules CD80 and CD40 and the major histocompatibility class I and II molecules on LC from AD patients *in vitro* (106). Phenotypical analyses of LC and IDEC isolated from lesional skin of AD patients before and after topical treatment with tacrolimus ointment, revealed a significant downregulation of the high-affinity receptor for IgE on the surface of these cells and a decrease in the cellular pool of IDEC as well (77, 78).

In addition, the amount of IL-12 detectable in the epidermis decreases after tacrolimus treatment and the monocyte-derived DC incubated with tacrolimus released significantly reduced amounts of TNF- α and IL-12 in response to proinflammatory stimuli, such as LPS or *Staphylococcal enterotoxin B* (107, 108).

Interestingly, tacrolimus and TGF- β 1 act synergistically on the generation of LC-like DC *in vitro*, lowering the stimulatory capacity of LC-like DC towards T cells and inhibiting LC maturation (109). Supporting the hypothesis of a consolidated generation of LC induced by tacrolimus, the number of CD1a⁺ LC increases in the epidermis of AD patients after treatment with tacrolimus, while the number of IDEC decreases (109). Therefore, shifting the balance of differentiating DC to LC might be of major importance for the therapeutic effect of tacrolimus and represents an attractive strategy for the treatment of AD (Fig. 5) (109).

Another, novel approach to treat a subgroup of patients with AD not only symptomatically but also specifically is represented by allergen-specific immunotherapy (110). In

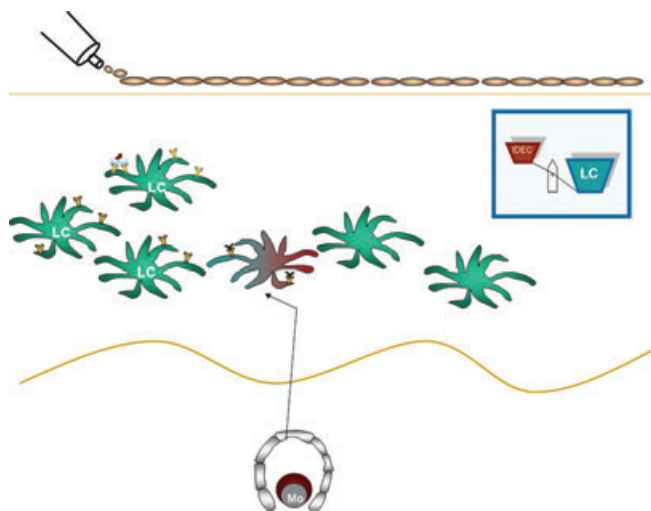


Figure 5. As a mode of action, topical treatment with tacrolimus might shift the balance of differentiating inflammatory dendritic epidermal cells (IDEC) to the generation of Langerhans cells (LC) with rather suppressive and disease regulating properties.

a majority of AD patients, the course of their diseases is aggravated by exposure to aeroallergens leading to severe flare ups of the disease. So far both, inhalation of allergens and contact of these allergens with the skin induce exacerbations of AD. Allergen-specific immunotherapy has been proven to represent the only long-time therapy of sensitization in patients with allergic rhinitis and mild asthma so far. However, there are several uncontrolled as well as a few controlled studies (111), which have been conducted to address the question, whether allergen-specific immunotherapy might represent a therapeutic option for AD patients as well. In fact, reduction in serum markers, which correlate with the severity of the disease such as CCL17 or IL-16 and decrease in allergen-specific IgE and increase in allergen-specific IgG in the sera of treated patients have been observed in addition to profound clinical improvement of the skin lesions (112). Other approaches to treat AD include therapy with anti-IgE antibodies, which have been shown to lead to clinical improvement and increase in the IgG/IgE ratios in a subgroup of AD patients (113, 114). Moreover, first reports about successful use of biologicals, such as anti-CD20 (115) antibodies or anti-CD11a antibodies (116) as a treatment of severe AD cases exist. Interestingly, treatment with anti-CD20 antibodies profoundly reduced the number of B cells in the blood and also partially in the skin. Although IgE serum levels remained mainly unchanged, anti-CD20 treatment went along with a significant improvement of the skin lesions, implying that B cells themselves play an important role in AD (115). In contrast, treatment with anti-CD11a antibodies has been shown to act in main part by the blockage of the extravasation of T cells into tissues (117). Together with controlled studies necessary to evaluate reliable specific

therapeutic alternatives in AD, these approaches hold promise that we will be able to expand our repertoire and therapeutic measures for AD in the near future.

Plans for future research and concluding remarks

Atopic dermatitis is one of the most complex diseases of the skin. Therefore, research work all over the world has been conducted to elucidate stepwise, the different aspects and facets of this fascinating disease. Without any doubt, all the new insights gained have profoundly improved our knowledge about AD so far. However, there are still numerous questions unaddressed and new questions about the pathophysiology of AD arise continuously. Furthermore, treatment of severe, recalcitrant cases of AD, persisting until adulthood still remains quite frustrating and challenging. Therefore, much attention should be focused on the development of diagnostic tools to identify AD patients at risk for severe courses, to be able to conduct preventive measures as soon as possible in these risk groups. One example for such preventive measures based on insights from gene-environment interactions might be the avoidance of contact with cat allergens during early periods of life by carriers of loss-of-functions mutations in the filaggrin gene, as a recent study showed that cat exposure at birth might impact on the risk of developing eczema in this subgroup of genetically predisposed children (31). In addition, therapeutic replacement of components important for the maintenance of the skin barrier functions such as ceramides (118) or other components of the epidermal differentiation complex and enzymes (119) might represent specific therapeutic approaches in the future. In addition, one of the most important aspects we learned about AD in the past is that we need to keep in mind that despite the very homogenous clinical picture most AD patients present in the clinical practice, AD might be based on very heterogeneous and different aspects in the single patient. Therefore, it appears much more promising to develop novel diagnostic tools, such as genetic or immunological read-outs to be capable of carefully classifying subgroups of AD patients, such as AD patients with genetically predetermined skin barrier defect, deficiencies on the level of innate or adaptive immunity or autoreactivity. This would be crucial to enable us to use the upcoming specific treatment forms such as different biologicals, small molecules or variants of immunotherapeutic approaches to treat AD directly, more specifically and successfully.

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