

REVIEW ARTICLE

Atopic dermatitis – from new pathophysiologic insights to individualized therapy

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Abstract

Recently, important novel insights into the complex pathophysiology of atopic dermatitis (AD) have been gained. However, in most cases the therapy of AD is limited to base line therapy with emollients combined with symptomatic, rather general immunosuppressive treatment approaches of the flare-ups. Latest research findings together with experiences from daily clinical practice, which support the concept that a combination of general disease features together with specific trigger factors in the individual patients drive the disease, might be helpful for a subclassification of patients with AD based on the most relevant pathophysiologic modifications. Subclassification of patients with AD seems indispensable to introduce rationale-based, individualized treatment approaches of AD, which target specific modified pathways. In this review, we provide an overview about a selection of pathophysiologic pathways, which hold promise to represent targets of such therapeutic approaches in the near future.

Atopic dermatitis (AD) is one of the most frequent chronic inflammatory skin diseases, affecting up to 25% of children and 1–3% of adults worldwide. Pathophysiology of AD is complex and regulated by a multitude of genetic and environmental factors. In contrast to the multifaceted trigger factors of AD, the clinical picture is rather homogenous and dominated by chronic eczematous skin lesions in typical localizations (1). This implies shared common disease-related factors on the one hand, supplemented by individual triggers on the other hand as a disease model for AD. However, treatment of AD is often frustrating in the clinical practice, because most of the approaches are mainly limited

to symptomatic, unspecific anti-inflammatory or immunosuppressive treatment of the flare-ups and the disturbed skin barrier in general (2). Within recent years, much research efforts have been focused on the identification of main trigger factors and have elucidated stepwise different aspects and facets of this fascinating disease (3). Thus, it became more and more clear that AD might be based on very heterogeneous and different aspects, which act in the foreground as triggers in the single patient. Therefore, a first step toward an individualized, rationale-based therapy of AD would be to carefully classify subgroups of patients with AD, such as AD patients with genetically predetermined skin barrier defects, deficiencies on the level of innate or adaptive immunity or autoreactivity reactions, which initiate or perpetuate the disease. As a second step, individualized therapeutic approaches targeting specific pathways of relevance for the different subgroups should be conducted. In this review, we provide an overview of selected pathophysiologic aspects identified recently in AD (Fig. 1), which might hold promise to serve as targets for

Abbreviations

AD, atopic dermatitis; AMP, antimicrobial peptides; DCs, dendritic cells; EH, eczema herpeticum; FcεRI, high-affinity receptor for IgE; FLG, filaggrin; hBD, human beta defensin; IL, interleukin; IgE, immunoglobulin E; MnSOD, manganese superoxide dismutase; *M. sympodialis*, *Malassezia sympodialis*; *S. aureus*, *Staphylococcus aureus*; SIT, specific immunotherapy; TLR, toll-like receptor.

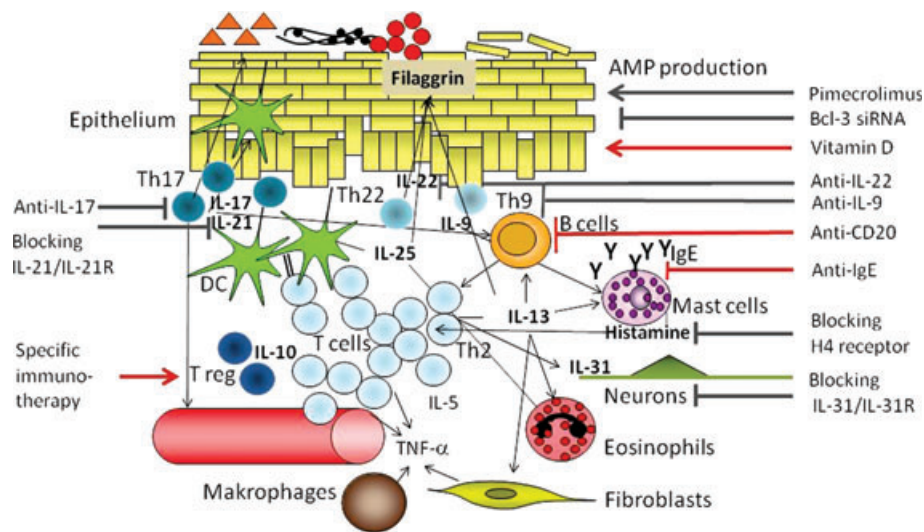


Figure 1 Summary of target cells and pathways for individualized therapeutic approaches. Red arrows indicate therapeutic strategies evaluated in clinical studies and gray arrows show potential targets.

AMP, antimicrobial peptide; DC, dendritic cell; T reg, regulatory T cells.

rationale-based therapeutic approaches of defined subgroups of patients with AD in the future (Fig. 2).

Loss-of-function mutations in the filaggrin gene

With the discovery of associations of loss-of-function mutations in the filaggrin (*FLG*) gene with AD, the model of AD as a disease based on a primary genetic epithelial barrier defect with consecutive, secondary modified immune responses has revised our understanding of the pathogenesis of AD and the atopic diathesis in general. In the Caucasian population, loss-of-function mutations in the *FLG* gene are detectable in about one-third of patients with AD (4). Filaggrin is released from the keratohyalin F granules as an inactive precursor protein and is converted into FLG later on after proteolysis and dephosphorylation (5). Its main function is to bundle the keratin cytoskeleton and to form macrofibrils (6). Modification of the degradation of FLG into short peptides and free amino acids leads to the lack of hygroscopic amino acids, resulting in decreased epidermal water retention. Besides that, FLG seems to be involved also in the regulation of the transcription of other proteins of the epidermal differentiation complex. Considering the important role of FLG for the maintenance of the skin barrier, it is obvious that *FLG* haplo-insufficiency might contribute to the impairment of the skin barrier in AD and increase the risk for severe courses of AD and concomitant development of asthma (5). Moreover, first data evaluated in murine-model systems together with data available on genetic associations in humans provide evidence for a link between low FLG expression in the skin and increased risk for the development of sensitizations to allergens as well as haptens such as nickel via the cutaneous route (7–10). In addition, distinct environmental co-factors, such as exposure to cat allergens at early

time points of life seems to increase the risk for eczema development in particular in the subgroup of *FLG*-loss-of-function mutation carriers (11, 12).

Besides a genetic predisposition, factors from the characteristic microenvironment in AD skin lesions, such as high levels of Th2 cytokines seem to reduce secondarily the expression of FLG in the skin (13, 14). Based on the insights gained into the regulation of the FLG expression in the skin as well as its function, therapeutic approaches aimed at the reversion of low FLG expression by different pharmacological substances and drugs as well as at the reduction in the overexpression of soluble factors such as interleukin (IL)-4 and IL-13, which have been demonstrated to downregulate FLG expression in the skin, might represent novel therapeutic approaches to counteract this deficiency. Just recently, IL-25 that is produced by activated eosinophils, basophils and dendritic cells and has been detected in AD skin was reported to decrease FLG mRNA expression by keratinocytes, so that reduction in IL-25 should be considered as well (15, 16).

Besides that, preventive measures, such as avoidance of frequent exposure to environmental factors that increase the risk for eczema development, including cat allergens or nickel, might be conducted in *FLG*-mutation carriers (9, 11).

Patient selection

Because routine genotyping of multiple but rare *FLG* mutations might be difficult in daily clinical practice, identification of specific Raman signatures with Raman spectroscopy as a noninvasive method (17, 18) might represent an alternative, helpful tool to identify of *FLG*-mutation carriers among patients with AD or children at risk for atopic diseases at earliest time points of life possible, such as immediately after birth.

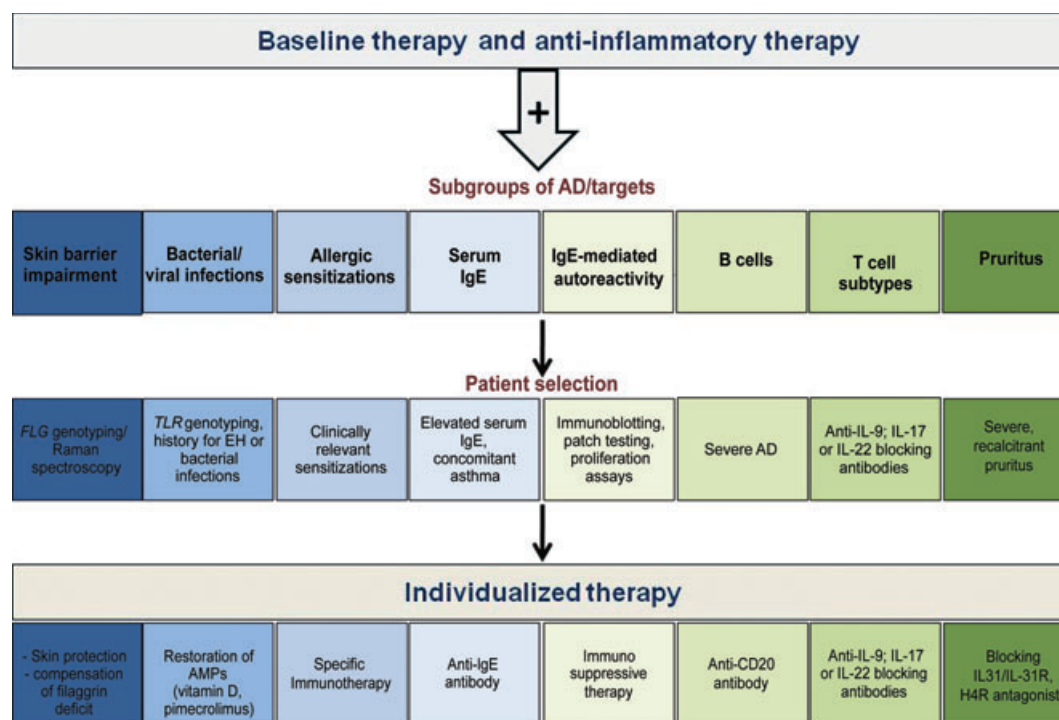


Figure 2 Schematic diagram of potential subgroups of patients with AD based on frequent and important pathogenic factors and related individualized therapeutic approaches.

Targeting antimicrobial peptide expression

The innate immune system consists of a billion years proved and tested composition of mechanisms, which work hand in hand together to sense danger signals from the environment by pattern recognition receptors and to rapidly react with sophisticated defensive immune responses. Several lines of evidence indicate abnormalities on the level of the innate immune system as a cause for increased susceptibility to bacterial and viral infections, which aggravate the course of the diseases in a subgroup of patients with AD. In this context, antimicrobial peptides such as human beta defensins (hBD) as well as cathelicidins, which are expressed by skin cells and exhibit antimicrobial activities to avoid uncontrolled growth of microbes, have been supposed to play a role (19).

In terms of antimicrobial peptide expression, only hBD-1 is constitutively expressed in the epidermis and sweat glands, while hBD-2, hBD-3 and hBD-4 production is induced by cytokines, bacterial infection, differentiation or other stimuli (20). Antimicrobial peptides (AMP) including cathelicidins such as LL-37 display direct antimicrobial activity on the one hand and induce a host response characterized by cytokine release, chemotaxis, inflammation, angiogenesis and re-epithelialization on the other hand (21). When compared to other chronic inflammatory skin diseases such as psoriasis, deficiency of LL-37 and hBD-2 (22) as well as hBD-3 and dermicidin has been observed in AD (23, 24). Lower expression of those peptides has been linked to higher propensity to

Staphylococcus aureus (*S. aureus*) infections, which is a characteristic feature of a subgroup of patients with AD (25). Moreover, anti-viral activity of LL-37 and hBD-3 was detected *in vitro* (26, 27). Therefore, lower LL-37 expression in the skin of AD patients with a history of one or more episodes of eczema herpeticum (EH), a severe, disseminated infection of the skin caused by herpes simplex virus, has been interpreted as a putative risk factor for this complication (28).

With regard to AMP regulation, it has been demonstrated that 1-25-dihydroxyvitamin D3 upregulates the expression of both, the toll-like receptor (TLR) coreceptor CD14 and AMPs by human keratinocytes, resulting in an enhanced antimicrobial function against *S. aureus in vitro* (29, 30). The reason for the inducibility of AMPs by vitamin D3 is that promoters of the human cathelicidin and defensin beta2 gene contain consensus vitamin D response elements (29, 31).

As a consequence, AMP deficiency in AD skin should be compensated as therapeutic approach in the future. Addition of vitamin D(3)-1,25-dihydroxyvitamin D(3) to *in vitro*-cultured human keratinocytes increased their cathelicidine expression (30). In line with these *in vitro* observations, oral administration of vitamin D was reported to induce the cathelicidin production in the skin of patients with AD. In addition, supplementation of vitamin D3 went along with an improvement in the disease (32–35). Furthermore, pimecrolimus enhanced the expression of cathelicidin, hBD-2 and hBD-3 in human keratinocytes stimulated with a TLR2/6

ligand and thus their capacity of bacterial killing of *S. aureus* (36) *in vitro* (34). This could represent another way to actively enforce antimicrobial defense by topical treatment in patients with AD. Because innate immune signaling in keratinocytes is in part regulated by B-cell leukemia (Bcl)-3, silencing of Bcl-3 by small interfering RNA (siRNA) has been shown to enhance vitamin D3-induced AMP expression of keratinocytes *in vitro* (37). Whether such an approach could be transferred to *in vivo* application has to be tested in future clinical studies.

As an alternative to the induction of endogenous AMP production, synthetic antimicrobial compounds, which mimic the structure and function of antimicrobial peptides, the so-called ceragenins, have been developed. Topical application of exogenous antimicrobial compounds to the skin is supposed to be helpful in AD patients with active disseminated virus infections. As a first step toward such treatment approaches, topical application of ceragenin CSA-13 was shown to exhibit direct antiviral effects and induce endogenous LL-37 and hBD-3 expression and thus inhibited vaccinia virus replication in infected keratinocytes *in vitro* (38).

Taken together, direct supplementation of AMPs expressed in reduced levels in the skin as well as topical treatment of skin with pimecrolimus and oral supplementation of vitamin D3 represent putative novel approaches to compensate AMPs deficiency in the skin of a subgroup of patients with AD at risk for bacterial and/or virus infections.

Patient selection

Selection of applicable patients could be achieved by subdividing patients into patients with active, severe bacterial or viral infection and patients with frequent episodes of severe bacterial or viral skin infections in their history. Furthermore, prophylactic treatment could be conducted in patients with known risk factors for bacterial or viral infections, such as single nucleotide polymorphisms in the *TLR2* gene, which have been shown to be associated with AD complicated by severe bacterial infections (39). As another group, patients with high total immunoglobulin E (IgE) and thymus and activation-regulated chemokine and cutaneous T-cell-attracting chemokine (TARC) levels, multiple sensitizations, eosinophilia and frequent infections with *S. aureus* and Molluscum contagiosum virus could be selected as it has been demonstrated that those patients are at higher risk for EH (Fig. 1) (28, 40).

Targeting allergen sensitizations

Allergen sensitizations play an important role as triggers of AD. While food allergens such as cow's milk or hen's egg aggravate AD in particular in children, aeroallergens such as house dust mites, birch or grass pollen allergens might be of relevance in both children and adults. However, allergen avoidance including encasing strategies is of limited success in controlling allergen-dependent flare-ups of the disease. Specific immunotherapy (SIT) represents a well-established treatment for patients with allergic rhinitis or mild asthma

(41). For a long time, AD has been excluded from the list of indications for SIT because of putative side effects and unwanted exacerbations of symptoms under therapy as well as lack of a substantial number of controlled studies (42). Nevertheless, a recent study conducted in adult patients sensitized against house dust mites revealed promising results in terms of efficacy of SIT in AD (43). Moreover, in parallel with a decrease in AD severity of and reduction in concomitant medications, the quality of life improved upon SIT in patients with AD sensitized to birch pollen allergen (44). In addition to allergen-specific tolerance, a reduction in allergen-specific IgE and increase in allergen-specific IgG4 as well as decrease in serum factors correlating with the severity of AD such as IL-16, CCL18 or CCL22 has been observed (45, 46).

Because in most of the adult patients with AD, specific IgE to distinct allergens is elevated in the blood and the patients have multiple positive skin-prick test results, selection of the allergens as main triggers of the disease is strongly dependent on the clinical symptoms and correlates with flare-ups of AD upon allergen exposure. However, in view of the satisfactory results of SIT with a single allergen in patients with AD, which are most often sensitized against a plethora of different allergens, an allergen-specific effect combined with a general positive modulation of the immune system of patients with AD as a result of SIT is very likely. Most of the studies available have been conducted using subcutaneous route of immunotherapy, while less data on allergen application via the sublingual route exist (42).

Concerning sensitizations to food allergens (47), approaches using oral immunotherapy with selected food of relevance in AD, such as cow's milk, hen's egg or peanuts, are still under clinical investigation. First results of small double-blind placebo controlled food challenge studies revealed some positive results, mirrored in the threshold of the amount of food tolerated without the development of symptoms (48, 49). However, studies are still ongoing but might result in for rationale-based treatment approaches in food-sensitized individuals in the near future.

Patient selection

Patients with clinically relevant sensitizations to house dust mite, birch or grass pollen allergen or in terms of children sensitizations to hen's egg or cow's milk have to be identified. Before starting immunotherapy, the relevance of allergen sensitizations for eczema development should be evaluated by atopy patch testing, skin-prick testing and evaluation of the level of allergen-specific serum IgE or double-blind placebo-controlled food challenges, respectively.

Targeting IL-31 and H4 receptor

Puritus is a key symptom of AD that together with subsequent sleeplessness and restlessness profoundly impairs the quality of life of the patients. Treatment of pruritus in AD is difficult and often frustrating. Histamine receptor 1 antagonists are of limited value. Novel insights into the pathogenesis of pruritus in AD have been gained with the

discovery of IL-31, which is expressed in enhanced amounts in the skin of patients with AD. IL-31 production is induced upon stimulation of cutaneous lymphocyte antigen + T cells with *S. aureus* enterotoxin. IL-31 induced together with *S. aureus* enterotoxins proinflammatory cytokine production of monocytes and macrophages *in vitro* (50). Furthermore, IL-31 is involved in the scratching behavior of NC/Nga mice with atopic-like dermatitis (51–54). IL-31 binds to the IL-31 receptor A (IL-31RA) and the oncostatin M receptor. IL-31RA transcripts are expressed in dorsal root ganglia, where the cell bodies of the primary sensory neurons reside (51). Interestingly, it has been observed that Th2 cells of patients with AD stimulated by histamine receptor 4 (H4R) agonists release significantly higher amounts of IL-31 compared with Th2 cells isolated from healthy control donors (55). Moreover, H4R stimulation-increased release of inflammatory cytokines by distinct DC subtypes in the skin (56). This links for the first time IL-31/IL-31R signaling to the histamine/histamine receptor pathway, unraveling potential novel therapeutic targets in AD including inhibition of IL-31 by direct inhibitors (57) or indirectly by histamine receptor interaction (58, 59).

Patient selection

All patients suffering from pruritus that usually is recalcitrant to treatment with H1R antihistamines might be selected for this kind of treatment approach.

Targeting IgE-mediated autoreactivity

The observation that not only exogenous components from the environment but also endogenous factors apparently aggravate the course of AD in a subgroup of patients has drawn the attention to the phenomenon of IgE autoreactivity in AD. In this context, it is supposed that IgE autoantibodies to human proteins, which are exposed in the skin because of chronic inflammation and/or mechanical damage, perpetuate endogenously the course of the disease (60). This phenomenon is assumed to be based on a molecular mimicry between common B-cell epitopes of foreign, exogenous antigens and endogenous proteins (61), leading to misrouted IgE autoreactivity to self-antigens. One example is the homology of the stress-inducible enzyme human manganese superoxide dismutase (MnSOD) with the allergen Mala s 11 of the exogenous yeast *Malassezia sympodialis*, which is part of the normal cutaneous flora (62, 63). Specific IgE antibodies against *M. sympodialis* cross-reactive to MnSOD were detectable in the sera of a subgroup of patients with AD and correlated with disease severity. Moreover, MnSOD was shown to induce eczematous reactions in patch tests conducted in sensitized patients as well as increase T-cell proliferation *in vitro* (62). A subgroup of AD patients with severe course of the diseases display autoreactive IgE antibodies (64, 65). Even in children between 1 and 6 years with elevated IgE serum levels and sensitizations to food and/or aeroallergens, a development of IgE autoreactivity is detectable. This implies that early allergen contact and related tissue inflammation at

mucosal surfaces might trigger IgE autoreactivity and increase the risk for severe, chronic courses of AD, perpetuated by autoreactive immune reactions starting at very early time points of life. In terms of therapeutic consequences, allergen avoidance should be conducted as early as possible to reduce the degree of allergen-induced inflammation and tissue damage causing the exposure of self-antigens. Furthermore, decrease in IgE autoreactivity was observed upon systemic treatment with cyclosporine A (64). Based on the hypothesis that autoreactivity might perpetuate the disease in a subgroup of patients, immunosuppressive therapy might be a rationale-based approach to counteract and attenuate autoimmune reactions in AD for the benefit of the patients.

Patient selection

To select patients with IgE autoreactivity, immunoblotting assays with patients' sera T-cell proliferation assays or atopy patch tests with selected autoallergens e.g. MnSOD could be applied.

Targeting B cells and IgE

Variable numbers of B cells have been detected among infiltrating cells in AD skin (66, 67). In about 80% of adult patients with AD, elevated total IgE levels and specific IgE to environmental allergens can be detected (68). Langerhans cells of AD skin bearing the high-affinity IgE receptor FcεRI on their surface provide a link between environmental allergen exposure and T-cell activation (69). Furthermore, B cells act as antigen-presenting cells, activators of T cells and DCs, and structural cells producing cytokines/chemokines (70, 71). The high expression of CD86 on B cells in AD (72) might provide costimulatory signals via CD28 on T cells, resulting in the production of large amounts of IL-5 and IL-13 in AD (73). Moreover, activated B cells produce the chemokines CCL17 (TARC), CCL22 (MDC) and IL-16 and thus may recruit other immune cells into the skin (74, 75). The depletion of B cells with rituximab, an anti-CD20 antibody, resulted in a rapid reduction in skin inflammation in all patients with a sustained effect over 5 months in five of six patients (76). Another report on two cases of severe AD receiving rituximab showed a temporary improvement (77). Interestingly, the allergen-specific IgE levels were not affected by rituximab (76). The depletion of B cells in the peripheral blood and to a lesser extent in the skin was followed by a reduction in T-cell activation including reduced production of cytokines, in particular IL-5 and IL-13 in the skin (76).

A further treatment approach is the neutralization of IgE. The anti-IgE antibody omalizumab was shown to exhibit dual effects by removing free IgE and thus downregulating the surface expression of FcεRI on basophils, mast cells and DCs (78–80). *In vitro* experiments showed that IgE/omalizumab immune complexes trapped allergens resulting in a decreased antigen-induced activation of FcεRI+ cells (81). A recent study investigating the effects of omalizumab in AD confirmed that omalizumab reduced free serum IgE, as well as the expression and saturation of FcεRI on the surface of

blood and skin cells in AD (82). In addition, the numbers of IgE + DCs in the skin decreased (82). Upon low-dose anti-IgE therapy with 10 cycles of 150 mg omalizumab, six of 11 AD patients with serum IgE levels >1000 kU/l before therapy responded as shown by a decrease in SCORAD by more than 50% in 2 and between 25 and 50% in four patients (83). Several studies reported that accompanying AD significantly improved in patients receiving omalizumab because of severe bronchial asthma (84–86). Nevertheless, the reports on the effects of omalizumab in AD are still controversial. In patients with AD receiving omalizumab dosed according to body weight and IgE levels over 16 weeks, no significant improvement in skin symptoms and pruritus was achieved (82).

However, targeting B cells of IgE might represent a rationale-based treatment approach for a small subgroup of patients with AD.

Patient selection

According to recent studies, patients with elevated IgE serum levels and severe AD with concomitant asthma should be selected for this type of treatment. Furthermore, a decreased sensitivity to allergens in the skin-prick test and atopy patch test was observed, suggesting (82) that omalizumab might be helpful in acute rather than in chronic AD (82).

Targeting Th9, Th17 and Th22 cells

In addition to Th1 and Th2 cells, new T-cell subsets have been identified recently and named according to their predominant cytokine expression: Th9, Th17 and Th22 cells. IL-9, which is regarded as Th2 cytokine, was shown to enhance inflammation, eosinophil and mast cell infiltration as well as subepithelial fibrosis (87). Increased IL-9 mRNA expression in the AD skin has been observed upon allergen challenge correlating with the number of eosinophils (88).

Th17 cells are a source of IL-17, IL-21 and IL-22 (89). A role for Th17 cells has been implicated in host defense, autoimmunity and allergy (89). In patients with AD, Th17 cells have been detected in the papillary dermis of lesional skin and in the peripheral blood correlating with disease severity (90). Allergen-induced IL-17 expression in acute AD lesions was shown to be enhanced upon additional exposure to *S. aureus* enterotoxin B (91). Furthermore, autoallergen-specific T-cell clones isolated from AD skin were found to produce IL-17 (92). According to animal and *in vitro* experiments, Th17 cells might contribute to skin barrier dysfunction as well as to epicutaneous sensitization and asthma development. In FLG-deficient mice that developed AD-like lesions, the inflammation was dominated by Th17 cells permitting epicutaneous sensitization to ovalbumin (93). Moreover, epicutaneous immunization with ovalbumin in Balb/c mice was shown to induce local and systemic Th17 responses (94). Subsequent airway allergen challenge resulted in strong inflammation with influx of Th17 cells in the lung (94). The observation that IL-17-induced upregulation of HBD-2 by keratinocytes was abolished by IL-4, and IL-13 might explain

the failure to clear *S. aureus* in AD (95). IL-17 was reported to promote IgE production in B cells (96). These observations point to an important role of Th17 cells in the pathogenesis of AD.

IL-21 exerts its effects on both immune cells and resident cells such as epithelial cells (97). IL-21 was shown to be essential for the maturation of B cells into antibody-secreting plasma cells, to influenced antigen-specific T-cell responses and drive Th17 cell differentiation (97). IL-21 and IL-21 receptor (IL-21R) expression were detected in acute skin lesions of patients with AD, in infiltrating cells and the epidermis, respectively (98). Upon mechanical injury, the expression of both IL-21 and IL-21R was upregulated (98). In mice epicutaneously sensitized with ovalbumin, IL-21 signaling was shown to be critical for CCR7 upregulation on DCs and their migration from the skin to the draining lymph nodes, where they initiate an immune response (98). IL-21 is assumed to contribute to the pathogenesis of AD in so far as skin inflammation and scratching increase the expression of IL-21 and its receptor followed by an enhanced migration of DCs carrying antigens from the injured skin to the lymph nodes resulting in further sensitization to environmental allergens in AD (98). Thus, blocking of IL-21/IL-21R interaction could prevent cutaneous sensitization in patients with AD.

A new subset of skin-homing memory T cells that are distinct from Th17 cells as they produce IL-22 but no IL-17 or IFN- γ have recently been identified (99). Th22 cells were shown to promote proinflammatory responses by producing IL-22 and TNF- α , as well as remodeling and wound healing (100). In AD, serum IL-22 levels were found to correlate with disease severity (101). *S. aureus* exotoxins significantly enhanced the production of IL-22 by T cells from patients with AD (102). Investigating the effects of IL-22 on keratinocytes revealed a downregulation of genes coding for proteins of the epidermal terminal differentiation pathway including FLG (103) and an induction of epidermal hyperplasia (104).

According to these recent observations, Th9, Th17 and Th22 cells as well as their cytokines play an important role in the pathogenesis of AD and might be considered as therapeutic targets (Fig. 2). Because these T-cell subsets are also involved in host defense, functional neutralization might potentially increase the risk of infections (105–107). Currently, anti-IL-17, anti-IL-22 and anti-IL-9 antibodies are under clinical investigation in autoimmune diseases and asthma. A further interesting target for AD therapy would be transforming growth factor- β , which regulates the differentiation of proinflammatory Th9, Th17 and Th22 cells, but also regulatory T cells (108).

Patient selection

Because research on the putative functional relevance of those T-cell subsets is still ongoing, it is quite too early to define clear criteria for patient selection. However, it is conceivable that a subgroup of patients with AD for example with specific microbial infections, high number of sensitizations or concomitant asthma might benefit from treatment approaches, which target the pathways described earlier.

Conclusion

Recent active and ambitious research activities provided new information on the complex pathophysiology of AD. These new insights into the function and interaction between inflammatory cells, resident cells, their cytokines and mediators might pave the way to more rationale-based treatment approaches. New therapeutic approaches aim to specifically target dysregulated structural or immune functions and/or disease triggers. As there are interindividual variations between AD patients in terms of underlying endogenous and exogenous disease mechanisms and triggers, subgroups have to be identified to create an individualized and effective treatment. Such individualized treatment approaches might substantially amend current symptomatic therapies, which target more general pathways of inflammation and skin barrier function. On a long-time perspective, the introduction of individualized treatment approaches will reduce the risk for severe and chronic AD and improve the quality of life of patients with AD.

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Authors contributions

N.N. and D.S. have written the manuscript.

Conflict of interest

N.N. has received research grants from Alk Abello and is speaker for Alk Abello, Bencard Allergy Therapeutics, Phadia and Novartis/LetiPharma. D.S. was supported by a research grant from Roche Pharma Switzerland.

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