

REVIEW

New treatments for atopic dermatitis

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Introduction

Atopic dermatitis (AD) is a highly pruritic, chronic, relapsing inflammatory dermatosis frequently seen in families with a history of atopic diseases [1]. Its prevalence has increased in recent years and is currently estimated to be as high as 20% in children of western countries [2]. The pathogenesis is still not fully understood, particularly, it is a matter of debate as to whether AD is an allergic disease or is instead an inflammatory skin disease frequently associated with other forms of atopy. Regardless of the exact origin, inflammatory, haematopoietic cells definitely play a major role in the pathogenesis of the disease. In addition to antiseptic/antibiotic regimens, current therapies that suppress the immune system are useful to treat and eventually prevent acute exacerbations. However, there is almost a complete lack of effective strategies to achieve long-term control of the disease, which could result in a significant increase in the quality of life. The wide use of modern glucocorticoids, which are highly effective and generally safe, has definitely improved the quality of life of patients. However, glucocorticoids are used less and less for AD due to the fear of severe side-effects arising from long-term treatment [3]. Therefore, there is the need to develop new steroid-free strategies to manage the disease under acute, as well as under chronic conditions. A causal therapy would be desirable, but is not yet available. Based on the current knowledge of the skin immune system in AD [4], rational approaches to interfere with components of the inflammatory cascade can be conceived and have encouraged researchers and pharmaceutical companies to explore new treatment possibilities. Based on the four important components of the immune response in AD (Fig. 1), this review will focus on the progress of new experimental therapies designed to interfere with: (1) the stimulus, which is required to activate dendritic cells, (2) the immunization of naïve T cells in the draining lymph node, (3) the recruitment of inflammatory cells into the skin, and (4) effector functions of skin infiltrating cells.

Can the initial stimuli triggering an immune response in AD be avoided?

IgE overproduction is a hallmark of AD. The overall level of IgE correlates with disease severity and specific IgE directed

against common aeroallergens, like house dust mite antigen, is frequently observed in AD patients. The role of IgE in the pathomechanism of the disease is, however, not clear. Regarding typical skin symptoms, AD is characterized by eczema resulting from infiltrating mononuclear cells rather than by weals which are typical for IgE-mediated type I hypersensitivities and extremely rare in AD. High-affinity IgE receptors are overexpressed on epidermal Langerhans cells and monocytes from AD patients. It has been proposed that specific IgE bound to these receptors might facilitate allergen uptake and presentation resulting in a sustained T cell response [5]. The observation that aeroallergens can induce eczema in AD patients after epicutaneous application supports this hypothesis. This so-called atopy patch test is assumed to reflect the relationship between aeroallergen sensitization and subsequent development of eczema [6] in AD patients. However, only 52% of patients reacted positively in a patch test with *Dermatophagoides Pteronyssinus*, while specific IgE against this aeroallergen was found in 75% of the patients tested. Consequently, the avoidance of house dust mite at patients homes may [7,8] or may not [9] lead to clinical improvement, probably dependent on the selection criteria of patients. Surprisingly, the frequency of positive patch tests in AD patients to house dust mite antigen was inversely correlated with the house dust mite concentration in patients homes [10], suggesting a poorly understood mechanism of tolerance following exposure to high levels of allergens. In summary, at present it is not possible to predict precisely which AD patient might benefit from allergen avoidance.

In addition to aeroallergens, also autoantigens may induce an IgE-mediated immune response in AD [11]. IgE autoantibodies are often directed against cytoplasmic proteins sharing similarities with aeroantigens, suggesting a high degree of cross-reactivity. IgE-mediated autoantigen presentation would ultimately lead to autoreactive memory T cells, ready to react, once the antigen is presented again. Keratinocytes, even from non-inflamed, healthy-appearing skin, from AD patients produce pro-inflammatory cytokines like IL-1 and TNF- α following activation [12]. These cytokines can stimulate neighbouring epidermal and dermal dendritic cells (DCs) to pinocytose antigen and migrate out of the skin. In addition to a basal level of keratinocyte activity in AD, scratching, due to intense pruritus, ultimately leads to cell damage and unspecific production of pro-inflammatory cytokines by keratinocytes. Consequently, the threshold to present antigens in AD skin is remarkably low, indicating that any antigen, including intracellular autoantigens accessible after cell damage, can be presented to T cells triggering an autoimmune response.

Therefore, it is not surprising that superantigens produced by skin colonizing *S. aureus* can induce an IgE response in AD

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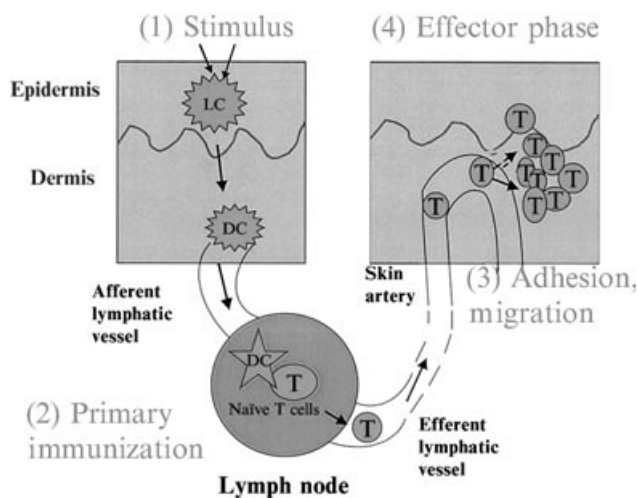


Fig. 1. Schematic description of the four important compartments in the pathogenesis of AD, where new therapies can be expected.

patients [13]. Moreover, they activate T cells directly by bridging the T cell receptor β -chain with MHC II molecules on antigen-presenting cells [14]. The colonization of superantigen-producing *S. aureus* on AD skin is a very frequent phenomenon and pathogenetically relevant since the eradication of the bacteria improves the disease and supports anti-inflammatory therapies [15]. Thus, if (a) autoantigens or microbial antigens can be presented by DCs following unspecific activation via keratinocytes, and (b) this mechanism feeds into a pool of pathogenetically relevant T cells, then attempts to avoid antigens, which are in these cases almost impossible to achieve, are questionable for the long-term treatment of AD patients.

Very recently, new insights into the biology of DCs and regulatory T cells provided evidence that tolerance induction might be a promising approach for the development of novel therapies [16]. Depending on their state of activation, DCs are able to down-regulate a T cell response. This effect is longlasting and antigen-specific [17]. In addition, there appears to exist a subset of regulatory T cells within the pool of $CD4^+ CD25^+$ T cells that can inhibit the proliferation of $CD4^+ CD25^-$ T cells [18]. The precise molecular mechanisms of this suppressor effect are not known yet. We can, however, expect that further investigations will ultimately lead to the development of new therapeutic strategies, which might overcome the problem that stimulus avoidance is difficult to achieve and often not at all reachable.

How to modify primary immunization of naïve T cells?

Once DCs have migrated to the draining lymph node, they are capable of activating naïve T cells. The decision whether a naïve T cell matures after activation to a T helper type 1 (Th1) or type 2 (Th2) cell depends on a number of factors like the composition of costimulatory molecules on DCs and the cytokine milieu present at priming [19].

Inhibition of the CD28 costimulatory pathway on T cells by infusion of CTLA4Ig, which blocks the ligands CD80 and CD86 on DCs, has recently been shown to be effective in

psoriasis [20]. High expression of CD86 on B cells correlated with IgE synthesis in AD patients [21], suggesting that also in AD, the CD28/CD86 pathway might be a promising target. However, data from clinical trials is not yet available. High IgE levels inducing the expression of the high-affinity Fc receptor for IgE on antigen-presenting cells may play a role in antigen presentation and T cell activation as outlined above [22]. Therefore, it will be interesting to see whether the humanized anti-IgE antibody E25, currently in development for allergic asthma [23], will also be therapeutically effective in AD.

The cytokine milieu and its role for the developing cytokine response has been extensively studied during the last few years [19]. It has been convincingly shown that the development of Th2 cells requires a source of IL-4, whereas Th1 cells develop under IL-12-rich and IL-4-poor conditions. T cells from AD patients activated by aeroallergens develop predominantly into Th2 cells producing high levels of IL-4, IL-5 and IL-13. These cytokines are important for triggering systemic immune reactions typically seen in AD, such as IgE synthesis in B cells, as well as growth and survival of eosinophils [4]. The predominance of Th2 cells is associated with an impaired Th1 response characterized by low IFN- γ production. Impaired IFN- γ production seems to be a hallmark of atopy, since low levels of IFN- γ in cord blood samples from high-risk children were associated with the subsequent development of AD [24,25]. Short-, as well as long-term treatment for up to 24 months with IFN- γ has been shown to be safe and efficacious in patients with AD [26–29], which argues that low endogenous IFN- γ production is indeed pathogenetically relevant in AD. IFN- γ treatment normalized eosinophil counts, but, surprisingly, not IgE levels in sera. Thus, supplementation with IFN- γ , although rather expensive and requiring daily subcutaneous injections, appears to antagonize at least some Th2-mediated effects and should be considered as an effective treatment for AD.

A therapy based on enhancement of the endogenous IFN- γ production, thus circumventing the need for supplementation, would, however, be preferable. IFN- γ production by purified mature peripheral T cells from AD patients cannot be completely restored *in vitro*, even in the presence of IL-12 [30]. In contrast, naïve T cells can be stimulated to produce high levels of IFN- γ by culturing *in vitro* in the presence of IL-12 or IL-2 [31]. This suggests that the ability to produce IFN- γ can only be restored at the level of naïve T cells. This observation is in accordance with a previous finding showing that naïve, but not memory T cells, are susceptible to immunoregulatory effects of cytokines [32]. As shown in Fig. 2, activated naïve T cells ($CD45RA^+$) mature into IL-4-producing cells after long-term culture *in vitro*. While exogenous IL-4 enhanced, IL-12 almost completely inhibited the IL-4 production. In contrast, memory/effector T cells ($CD45RO^+$) were not at all susceptible to exogenous IL-4 or IL-12. Consequently, therapeutic approaches to redirect an imbalanced cytokine response will target the naïve T cell rather than an established memory/effector cell. Attempts to interfere with the immunization process aiming to correct the Th1/Th2 cytokine imbalance should therefore start early in life. Vaccines inducing a predominant Th1 response are promising agents. Indeed, the benefit of early BCG vaccination in preventing atopic diseases in childhood was demonstrated [33]. This result could, however, not be confirmed in subsequent studies [34,35]. A very recent study where *Lactobacillus GG* was given to pregnant women with a family

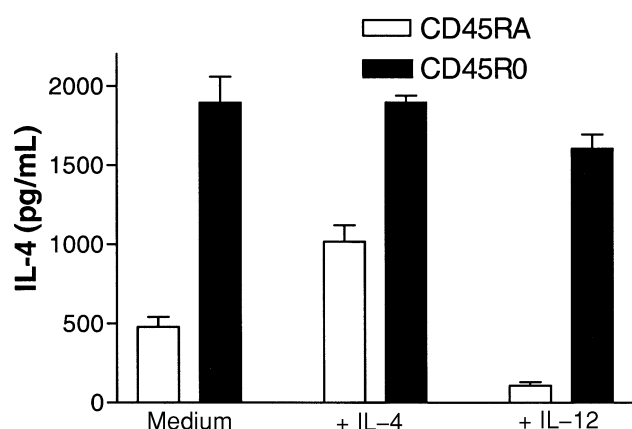


Fig. 2. Naïve T cells are susceptible to the modulatory effects of IL-4 and IL-12. CD4⁺ CD45RA⁺ naïve and CD4⁺ CD45R0⁺ T cells were purified from the peripheral blood of a healthy volunteer and activated with anti-CD3 plus anti-CD28 antibodies. IL-4 or IL-12 was added from the beginning of the culture at 10 ng/mL each. After 2 days, IL-2 was added to expand the cells. After 7 days of culture, cells were restimulated with anti-CD3 plus anti-CD28 mAbs in the absence of IL-4 or IL-12, but in the presence of IL-2. After another 7 days, cells were restimulated with PMA + ionomycin for 24 h and cell supernatants were then analysed for IL-4 production by ELISA as described [50]. The results are representative for a total of seven experiments.

history of atopy 4 weeks pre- and up to 6 months postnatally (to breastfeeding mothers or to the newborns) demonstrated a 50% reduction in the frequency of AD at the age of 2 years [36]. This remarkable result strongly argues for the logic of this concept and for an early intervention to induce a Th1 response. Moreover, elevated house dust mite endotoxin concentrations in the homes of children younger than 2 years positively correlated with increased IFN- γ production and were inversely correlated with the frequency of sensitizations to at least one aero- or food-allergen [37]. This data further implies a protective role of early IFN- γ production in AD. A recent study showed that a single intradermal injection of killed *Mycobacterium vaccae* was able to significantly improve the severity of AD in children aged 5–18 years [38], suggesting that even later in life, a strong induction of Th1 responses can improve an already existing AD.

Alternatively, instead of promoting Th1 responses, inhibition of Th2-immune responses might also be promising. It is not yet clear, however, which of the cytokines produced by Th2 cells is the best candidate for this approach. Antagonizing IL-4 by IL-4 receptor (IL-4R) antagonists prevented airway inflammation and hyper-responsiveness in murine models of allergic inflammation [39]. When IL-4 signalling was suppressed, exogenous IL-5 could restore bronchial hyper-reactivity [40], indicating that both IL-4 and IL-5 are important for the development of an allergic inflammatory response. At least in mice, IL-13 seems to be required to mount strong Th2 responses [41] and its over-expression facilitates lung inflammation [42]. The expression of IL-13 in human bronchoalveolar lavage samples after allergen challenge suggests that it might also be involved in the pathomechanisms of atopic asthma [43]. Furthermore, the neutralization of the Th2-specific transcription factor GATA-3 inhibited airway inflammation and bronchial hyper-responsiveness in mice [44]. A role of Th2 cytokines in murine models of allergic dermatitis has been described. In NC/Nga mice, skin inflammation was found to be associated with Th2 immune responses including high IL-4 and IgE production [45]. In a recently

described model of food-induced AD-like lesions, eosinophilia and high IgE sera levels, as well as overexpression of IL-5 and IL-13 in skin samples, were noted [46]. Using knockout mice it could be demonstrated that IL-4-deficient mice, like wild-type mice, displayed thickening of the skin associated with an influx of infiltrating T cells after antigen challenge [47]. In contrast, IL-5-deficient mice showed a reduced dermal thickening. Thus, Th2 cytokines also seem to play a role in these dermatitis models. However, the relevance of a single cytokine is not ultimately clear.

Theoretically, neutralizing humanized antibodies directed against IL-4, IL-5, or IL-13 could be new therapeutic agents. In addition, cytokine mutants that are able to compete with the natural cytokine for binding to its receptor but lack signal transduction properties or soluble cytokine receptors might be promising candidates. Finally, low molecular weight compounds interfering with the binding of cytokines to their cell surface receptors or with other, specific components of the signalling pathway could be developed. Yet, no data have been published from clinical trials aiming to inhibit Th2 responses in AD. Phase I/II studies investigating the effect of the soluble IL-4 receptor (sIL-4R) in patients with moderate atopic asthma have been published [48,49]. Nebulized sIL-4R was shown to be safe and well tolerated at doses up to 3 mg once weekly for 3 months. Forced expiratory volume (FEV₁) was improved and the exhalation of nitric oxide was reduced. These first promising results need confirmation in larger cohorts of patients with longer treatment times. Based on the aforementioned considerations, attempts to inhibit IL-4 with the aim of reducing the frequency of IL-4-producing cells will target mainly naïve, but not memory/effector T cells. This would imply that the efficacy of the therapy is presumably detectable only after long-term treatment when new memory/effector T cells have matured from naïve T cells under the neutralization of IL-4. It must, however, be noted that soluble cytokine receptors can also act as agonists and may enhance the cytokine activity. This could be shown for IL-4 *in vitro* with human cells [50] and *in vivo* in murine models [51] and is most likely a result of protection from proteolysis by binding to the sIL-4R.

Is inhibition of the migration of inflammatory cells a future therapeutic concept in AD?

Once memory/effector T cells have emerged from the immunization process in draining lymph nodes, they express adhesion and homing molecules enabling them to migrate into non-lymphoid tissues. The process of migration is tightly controlled by a number of factors: activation of endothelial cells at the sites of inflammation, expression levels of receptors on T cells able to interact with activated endothelial cells, chemokines produced by resident skin cells and chemokine receptors expressed on circulating T cells. The relative importance of these factors for the inflammatory response in AD patients is not completely clear.

Much has been learned and can be extrapolated from a primary immunodeficiency, the leucocyte adhesion deficiency (LAD) [52]. The first form of this disease (LAD I) is caused by mutations in the CD18 gene coding for the beta subunit of the β_2 -integrin family. This mutation results in a complete loss or marked reduction of LFA-1 (CD11a) and Mac-1 (CD11b)

expression on haematopoietic cells which prevents them from interaction with ICAM molecules on tissue endothelial cells. The disease manifests in severe skin infections and patients die from uncontrollable sepsis. Neutrophils and monocytes are unable to migrate into the skin. Lymphocyte function is severely impaired due to the lack of LFA-1 as an important costimulatory molecule and migratory activity is severely depressed. Surprisingly, other organs including the lung are less affected or even unaffected by the disease, indicating that β_2 -integrins are particularly important for an intact skin immunity. The ligands for LFA-1 are not only expressed on endothelial, but also on atopic dermal and epidermal cells [53], even in healthy-appearing skin from AD donors [54]. Thus, attempts to block the interaction between LFA-1 and ICAM molecules are highly promising to inhibit not only the migration, but also the activation of skin-infiltrating T cells by neutralizing an important second signal. Indeed, neutralizing anti-LFA-1 antibodies have been successfully used to inhibit skin inflammatory responses in murine acute contact dermatitis models [55,56]. A humanized anti-LFA-1 antibody is currently under development for the indication psoriasis. It could be shown that a single dose of the antibody reduced the Psoriasis Area and Severity Index (PASI) score and dermal thickening due to a decrease of skin infiltrating T cells [57]. Administration of the antibody at weekly intervals for 8 weeks resulted in significant clinical improvement and was well tolerated [58].

A second form of the disease (LAD II) is caused by defective fucosylation resulting in the absence of sialylated Lewis X molecules which prevents leucocytes from binding to selectins and thus eliminates rolling on endothelial cells [59]. The clinical phenotype is milder than in LAD I and also qualitatively distinct. There is no obvious sepsis due to uncontrollable skin infections. T cell and B cell responses are virtually normal. The skin homing receptor cutaneous lymphocyte antigen (CLA) [60] belongs to the family of sialylated Lewis X molecules. LADII patients therefore provide the possibility to evaluate the role of CLA in skin homing [61]. Immunization of one patient with keyhole limpet hemocyanin (KLH) resulted in normal T and B cell responses and during a delayed type hypersensitivity (DTH) reaction normal migration of T cells into the skin. However, the inflammatory response as the clinical manifestation of the DTH reaction, was reduced, at present for unknown reasons. Thus, CLA appears not to be essentially required for T cell recruitment into the skin, a conclusion which is further supported by the observation that, following atopy patch testing, the majority of infiltrating T cells were CLA-negative [62]. CCL27 (CTACK), a recently discovered chemokine produced by keratinocytes [63] is chemotactic for CLA⁺ T cells expressing CCR10, a receptor for CCL27 [64]. However, neither CCL27, nor CCR10 were found to be overexpressed in inflamed skin specimens, including AD skin. This suggests again that CLA might be required for the physiological homeostasis of T cell homing, but not for the recruitment of T cells during an acute inflammatory response.

The expression of the chemokine receptor CCR4 on memory CLA⁺ T cells was found to be associated with skin homing properties [65]. Its ligand, thymus and activation-related chemokine (TARC/CCL17), induced integrin-dependent adhesion to ICAM-1 and was found to be overexpressed in various inflamed skin samples. CCR4 expression was increased on peripheral CD4⁺ T cells from AD and correlated with serum IgE

levels and eosinophil numbers [66]. In addition, the frequency of CCR4⁺ T cells in AD lesions was higher compared to psoriatic lesions. Serum TARC levels were higher in AD patients than in healthy control subjects and TARC immunoreactivity was found in keratinocytes and infiltrating T cells in AD patients [67]. Moreover, high levels of CCR4 on bronchial mucosa-infiltrating T cells and TARC on airway epithelial cells were detected following allergen challenge in atopic asthmatics, while T cells in chronic obstructive pulmonary disease or pulmonary sarcoidosis failed to express CCR4 [68]. Taken together, this data strongly suggests that CCR4 is a relevant therapeutic target for the infiltration of T cells in atopy, including AD and asthma. It is conceivable that, due to the accumulating knowledge of chemokines and chemokine receptors, other candidates might also become interesting therapeutic targets for AD. For example, lack of CCR8 was associated with a defective Th2 response in a murine model of antigen-induced airway inflammation [69], but no dermatitis has been described. Furthermore, CCR3 also seems to be a relevant target for atopic asthma [70,71], however, its relevance for AD has not yet been assessed.

How to control the effector phase of skin-infiltrating T cells?

The control of an inflammatory immune response at the last stage is the most obvious and promising strategy to mitigate patients suffering. Glucocorticoids are the best example of this strategy. However, as outlined in the introduction, there is an urgent need to control the disease in a steroid-free manner. Undoubtedly, UV irradiation is an established therapy and will have its place in the treatment of AD. In particular, high-dose UV-A₁ treatment has been shown to be efficacious in the treatment of AD [72]. However, the treatment is often not convenient for the patient and, at least in the case of the classical combination of UV-A and UV-B, it is clearly less efficient than immunosuppressants like cyclosporin A (CsA) [73]. Experimental therapies such as high-dose intravenous immunoglobulin therapy [74], photopheresis [75] and anti-CD4 therapy [76] for selected patients with severe and refractory forms of AD will continue to have their legitimation in the future. Low molecular weight compounds targeting phosphodiesterases [77], leukotrienes [78] and platelet activating factor [79] have been shown to improve AD with low to moderate efficacies. Recent case reports and open label studies indicate that mycophenolate mofetil might be efficacious in severe AD [80–82]. However, it remains to be determined where mycophenolate mofetil should be ranked in the treatment of AD, since it might have severe side-effects such as *S. aureus* septicaemia [83].

Immunosuppressants or immunomodulators are the most efficacious and best proven therapies for AD so far. In this category, most of the clinical experience is with CsA. Undoubtedly, the introduction of CsA into the therapy of AD has opened a new area and has set new standards in the treatment of severe AD. CsA has been shown to be extremely efficient in relieving pruritus and inflammation in a number of studies in adults, as well as children, with AD [84–89]. Even at doses as low as 150 mg/day it seems to be beneficial for AD patients, allowing for a body weight-independent dosing regime [90]. Despite the fact that CsA is potentially associated with renal and other side-effects, doses used in dermatology (<5 mg/kg body weight) were

shown to be generally safe with a low frequency of side-effects. Initial reports emphasized a long-term remittance of the disease after discontinuing the treatment, however, newer studies show that approximately 50% of the patients relapse after 2 weeks [91]. Nevertheless, the overall severity of the disease has been reported to be lower compared to the starting point of the treatment, indicating that patients may still profit from the therapy even 2 years after the therapy [92].

A major drawback of CsA is that it is not effective when applied topically [93]. This hinderance has been overcome with the two new compounds FK 506 (Tacrolimus) and SDZ ASM 981 (Pimecrolimus). Although structurally different, both compounds, like CsA, target the phosphatase calcineurin and subsequently inhibit the activation-driven nuclear import of the cytosolic subunit of the transcription factor NFAT. Consequently, T cell proliferation and cytokine production is inhibited by both drugs in the low, or even subnanomolar range *in vitro*, which is up to 100-fold more potent than CsA [94,95]. In addition, tacrolimus and pimecrolimus inhibit the release and production of preformed and soluble mediators in mast cells [96,97]. Although none of the three compounds inhibits selectively Th1 or Th2 cytokines *in vitro*, a reskewing of the imbalanced cytokine response has been demonstrated in AD patients after treatment with CsA [98,99]. This might be associated with the ability of calcineurin inhibitors to inhibit preferentially the differentiation of naïve T cells to Th2 rather than to Th1 cells [100]. The first evidence that tacrolimus, originally developed for transplantation, might be effective in the topical treatment of inflammatory skin disorders was reported in 1992 [101]. Since then, its efficacy and safety in the topical treatment of adults and children with AD has been shown in a number of studies [102–107]. 0.1% tacrolimus ointment was effective in long-term treatment (up to 12 months) with only minor and transient side-effects like skin burning [106]. Unlike potent glucocorticoids, tacrolimus does not induce skin atrophy [108], and is able to inhibit superantigen-mediated T cell proliferation [109], which might help to eradicate superantigen-driven worsening of AD.

The ascomycin macrolactam derivative pimecrolimus was recently developed for the treatment of inflammatory skin diseases [95,110]. Like tacrolimus, it effectively inhibits skin inflammation in various animal models by systemic or topical treatment [110,111]. Importantly, pimecrolimus does not have atrophogenic activity [110,112]. Although sharing with tacrolimus and CsA the same molecular mode of action, it has a different, unique and skin-specific pharmacological profile [113]. While pimecrolimus potently inhibits the inflammation in animal models of T cell-mediated dermatitis, it only weakly affects systemic immune responses like graft rejection in transplantation models. In particular, it should be noted that pimecrolimus inhibits the elicitation phase in an acute contact dermatitis model, but, unlike CsA or tacrolimus, does not impair the sensitization phase [114]. Finally, pimecrolimus permeates through the skin slower than tacrolimus, suggesting that there is a very low risk of percutaneous resorption after topical application. Treatment with pimecrolimus cream 1% was shown to be well tolerated, safe and effective in adults [115,116], adolescents, children, and infants (>3 month age) with AD [117]. Low blood concentrations were consistently observed, regardless of age, severity of disease and body surface treated. Only minor side-effects such as transient burning were reported.

Conclusions

A better understanding of the skin immune network has opened new rational strategies to interfere with inflammatory responses in AD. Current knowledge of antigen presentation and subsequent T cell responses will ultimately lead to experimental therapies aimed at modifying the capacity of DCs to present antigen. It could be shown that strong inducers of Th1 responses, given early in life, are able to normalize T cell responses and are therapeutically beneficial for the clinical outcome of the patients. In addition, approaches are being explored to inhibit the undesirable increased Th2 response. Together, these activities will lead to a better control of the imbalanced T cell responses at the level of antigen presentation and primary immunization. The ongoing process of discovering new molecules involved in the migration of inflammatory cells into the skin will ultimately provide a better understanding of how to inhibit tissue-specific migration. Only a few adhesion molecules and chemokines/chemokine receptors seem to be essential for homing to the skin. Therefore, it is tempting to speculate that in the near future we will have the first therapeutics blocking skin-specific migration. The clinical efficacy of CsA in patients with AD and psoriasis has proven that the activation of T cells plays a key role in these inflammatory skin disorders. Due to the lack of topical efficacy, the use of CsA is restricted to the oral therapy of severe cases of AD. Tacrolimus and pimecrolimus have shown impressive results in the topical treatment of AD and will undoubtedly enrich the therapeutic options to treat AD patients. In particular, if it turns out that both drugs improve the long-term management and the quality of life in AD, there is no doubt that the goal of treating AD patients safely, more effectively, and without steroids will be reached in the near future.

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