INVITED REVIEW ARTICLE

Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic and relapsing disease affecting an increasing number of patients. Usually starting in early childhood, AD can be the initial step of the so-called atopic march, i.e. followed by allergic rhinitis and allergic asthma. AD is a paradigmatic genetically complex disease involving gene-gene and gene-environment interactions. Genetic linkage analysis as well as association studies have identified several candidate genes linked to either the epidermal barrier function or to the immune system. Stress, bacterial or viral infections, the exposure to aero- or food-allergens as well as hygienic factors are discussed to aggravate symptoms of AD. Athough generalized Th2-deviated immune response is closely linked to the condition of AD, the skin disease itself is a biphasic inflammation with an initial Th2 phase and while chronic lesions harbour Th0/Th1 cells. Regulatory T cells have been shown to be altered in AD as well as the innate immune system in the skin. The main treatment-goals include the elimination of inflammation and infection, preserving and restoring the barrier function and controlling exacerbating factors. The overall future strategy in AD will be aimed to control skin inflammation by a more proactive management in order to potentially prevent the emergence of sensitization as well as to design customized management based on genetic and pathophysiologic information. **(Ann Dermatol 22(2) 125~137, 2010)**

-Keywords-
Atopic dermatitis, Pathophysiology, Proactive management, Therapy

INTRODUCTION

Among the various chronic inflammatory skin diseases, atopic dermatitis (AD) (also named eczema in some countries) has a singular place since it is considered as the most common, itchy and relapsing inflammatory skin condition. Its increasing prevalence is well documented and represents a major public-health problem, mostly in industrialized countries. Much progress has been made in the understanding of its genetic background and pathophysiology. Recent studies in genetics, epidemiology and immunology have provided new important pieces of the complex puzzle and have dramatically changed our view on the mechanisms, its natural history and the future ways to control the disease in the context of the so-called atopic march.

Definition of atopy and atopic dermatitis

Recently the World Allergy Organization (WAO) has launched a revised terminology for atopy and atopic diseases, defining atopy only in association with IgE-sensitization, i.e. atopic diseases due to IgE-mediated pathophysiology. Hence, the term atopy should be used in combination with documented specific IgE antibodies in serum or with a positive skin prick test[1]. Thus the non-IgE-associated (formerly intrinsic or atopiform dermatitis) form (or eczema or atopic dermatitis strict sensu) has to be distinguished from the IgE-associated (formerly extrinsic) form. However, although some authors propagate the concept of 2 distinct forms, i.e. atopiform dermatitis versus AD, the non-IgE associated form may represent a transitional phase of the IgE-associated form, at least in infancy (see below).

Epidemiology

The lifetime prevalence of AD is estimated to 15~30% in children and 2~10% in adults while the incidence of AD has increased by 2- to 3-fold during the past 3 decades in industrialized countries. The 12-months prevalence in 11-

year-old children has shown to vary from 1% to 20% with the highest prevalence typically found in Northern Europe (International Study of Asthma and Allergies in Childhood, ISAAC)[2]. In children, the onset of AD occurs in 45% during the first 6 months of life, 60% during the first year, and 85% are affected before the age of 5. The prevalence of AD in rural areas and in non affluent countries is significantly lower, emphasizing the importance of life-style and environment in the mechanisms of atopic disease which may be explained by the "hygiene hypothesis"[3], a concept which is however still debated[4].

Histology

Histology of both forms of dermatitis is highly similar to that of allergic contact dermatitis and has no fundamental impact on the diagnosis of AD. Clinically "normal" appearing skin of AD patients contains a sparse perivascular T-cell infiltrate suggesting minimal inflammation[5]. "Acute" papular skin lesions are characterized by marked intercellular edema (spongiosis) of the epidermis. Langerhans cells (LC), in lesional and, to a lesser extent, in nonlesional skin of AD exhibit surface-bound IgE molecules in the IgE-associated form but not in the non-IgE-associated form. In the dermis of the acute lesion, there is a marked perivascular T-cell infiltrate with monocyte-macrophages. The lymphocytic infiltrate consists predominantly of activated memory T cells bearing CD3, CD4, HLA-DR, CD25 and CD45RO. Eosinophils are seen in the acute lesions but basophils and neutrophils are rarely present. Mast cells are present in various stages of degranulation.

"Chronic" lichenified lesions are characterized by a hyperplastic epidermis with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing DC in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells is increased but the cells are generally fully granulated. Although they are hardly seen histologically, increased numbers of eosinophils are suspected in the dermis of chronic AD skin lesions since their products such as eosinophil major basic protein, eosinophil cationic protein and eosinophil-derived neurotoxin can be detected by immunostaining. Thus eosinophils may likely contribute to allergic skin inflammation by the secretion of cytokines and mediators that augment allergic inflammation and induce tissue injury in AD through the production of reactive oxygen intermediates and release of toxic granule proteins.

Pathomechanisms

1) Genetics
The role of genetic factors in AD (OMIM *603165) is

clearly demonstrated by twin studies, which consistently showed a higher concordance rate (0.77) in monozygotic twins compared to dizygotic twins (0.15)[6]. The importance of genetic factors in AD is further underlined by the finding that a positive parental history is the strongest risk factor for AD; the incidence rate is doubled if AD is present in one parent, and tripled if both parents are affected.

In the modern era of genomics, linkage analysis and association studies have greatly contributed to our understanding on the genetic background of AD[7]. The hottest chromosomal region harbouring possibly several important genes is 1q21. This area includes most of the genes regulating the epidermal homeostasis, the epidermal differentiation complex (EDC). The recent demonstration of loss-of-function mutations of the profilaggrin/filaggrin gene, a key protein in terminal differentiation of the epidermis, can be considered as a breakthrough[8-13]. Indeed, these variations may be important risk factors for AD (with IgE) and in combination with sensitization and asthma since they seem to be more associated to IgE-associated form. It is expected that other yet-to-be-defined genetic variants from epidermal structures such as those localized in the EDC on chr. 1q21 such as SCCE[14] may also play a role in these phenomena. These genetic findings provide an important support for the well known impairment of the epidermal barrier observed in AD and could also deliver further clues to the natural history of the disease, i.e. the transition of a non-IgE associated eczema to IgE-associated AD due to a facilitated penetration of and sensitization to aeroallergens during chronic inflammation. Thus, a first kind of genotype-phenotype emerges where patients carrying variations for FLG gene and suffering from an early onset and rather sever form of AD have the highest risk to develop allergic asthma (Fig. 1).

The other set of candidate genes includes the numerous structures related to immunological mechanisms operative in AD. For example, on chromosome 5q31-33, the locus containing genes for the TH2 cytokines interleukin (IL)-3, IL-4, IL-5, IL 13, and granulocyte macrophage colony stimulation factor (GM-CSF)[15] has been suggested. Further studies identified variants of the IL-13 encoding region, functional mutations of the promoter region of the chemokine RANTES (Regulated on Activation, Normal T cell Expressed and Secreted)(17q11) and gain-of function polymorphisms in the alpha subunit of the IL-4 receptor (16q12)[16]. This could be linked to the incidence of non-atopic (formerly intrinsic) eczema, which occurs without any IgE sensitization[17]. The dysbalance between TH_1 und TH_2-immune responses in AD may be elucidated by the detection of polymorphisms of the IL-18-gene, resulting in
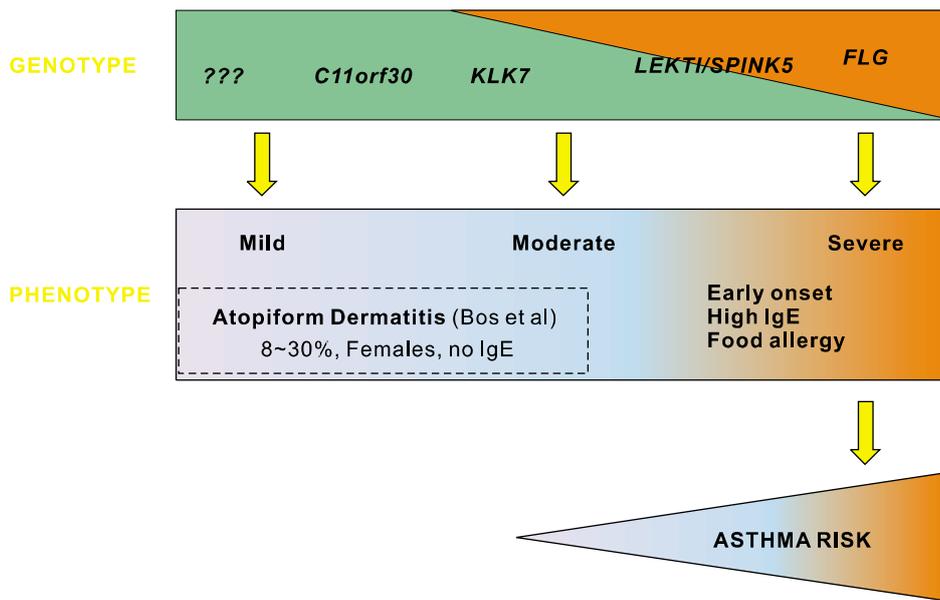
Fig. 1. Genotype-phenotype relation in atopic dermatitis.

TH2 predominance[18]. More recently, the gene encoding for the α-chain of the high affinity receptor for IgE has been identified by GWAS as an interesting candidate gene associated with high IgE synthesis[19]. Finally, besides classical genetics, the role of epigenetic mechanisms in the regulation of the gene expression has not been addressed in AD but will certainly help us to understand a number of so far discrepant epidemiological and genetic studies.

2) Neuroimmunological factors

Neuropeptides and neurotropins mediate different actions such as vasodilatation, oedema, itch and pain or sweat gland secretion and have a minor ability to regulate T-cell activation[20]. They can be detected in blood and within the epidermal nerve fibres in close association with mast cells or epidermal Langerhans cells, suggesting a tight link between the immune system and the nervous system[21]. Recent studies have documented increased levels of nerve growth factor and substance P in plasma of AD patients which correlated positively with disease activity[22]. Brain-derived growth factor, detected recently in sera and plasma of patients with AD, enhances the survival of eosinophils while increasing their chemotactic response in vitro[23].

3) Skin barrier dysfunction

One of the major hallmarks of AD is xerosis which affects lesional and non-lesional skin areas as witnessed by increased transepidermal water loss. It may favour the penetration of high-molecular weight structures such as allergens, bacteria, and viruses[24]. Several mechanisms have been postulated: (i) a decrease in skin ceramides, serving as the major water-retaining molecules in the extracellular space[25], (ii) alterations of the stratum cor-

neum pH[26], (iii) overexpression of the chymotryptic enzyme (chymase), (iv) defect in Filaggrin as well as molecules of the EDC such as SCCE or the S100 protein family (see above).

4) Immunological mechanisms

The immune system has been classified into two branches: innate and adaptive/acquired immunity. Adaptive immunity relies on antigen-presenting cells to capture and present antigen to T and B cells and is therefore the backbone of cellular and humoral immune response. Innate immunity is characterised by an immediate response to pathogens through genetically encoded and evolutionary conserved receptors and antimicrobial proteins.

(1) Innate immunity

The innate immune system of the epidermis presents the first line defense against cutaneous infections. Once the epidermis is invaded by micro-organisms, anti-microbial peptides are activated and form part of the defence system[27]. Up to now, three anti-microbial peptides are known in human skin: the β-defensin HBD-2 and HBD-3, as well as the cathelicidin hCAP18/LL-37. All of them show different spectra of activity: HBD-2 is effective against Gram-negative organisms such as Escherichia coli, Pseudomonas aeruginosa, and yeasts. HBD-3 and cathelicidin are more potent, broad-spectrum antibiotics that kill both Gram-positive and Gram-negative organisms as well as Candida albicans. AD skin is characterized by a significant decrease in expression of anti-microbial peptides, explaining the susceptibility of AD patients for bacterial infections[28-30]. The innate skin defence system of patients with AD may be further reduced by the defi-

ciency of dermcidin-derived antimicrobial peptides in sweat, which correlates with infectious complications[31].

(2) Acquired immunity

① *T cells and the Th1/Th2 concept*: A predominant systemic Th2 dysbalance with increased IgE levels and eosinophilia is widely accepted in the pathogenesis of atopic diseases[32]. The production of Th2 mediated cytokines, notably IL-4, IL-5, and IL-13, can be detected in lesional and non-lesional skin during the acute phase of disease. IL-4 and IL-13 are implicated in the initial phase of tissue inflammation and in upregulating the expression of adhesion molecules on endothelial cells. IL-5 seems to increase the survival of eosinophils. A systemic eosinophilia and an increase of the eosinophilic cationic protein (ECP) are characteristic for a high disease activity of AD.

However, although Th2 mediated cytokines seem to be predominant in the acute phase of AD they are less important during its chronic course. In chronic AD skin lesions an increase of IFN-γ and IL-12, as well as IL-5 and GM-CSF could be detected, being characteristic for a Th1/Th0 dominance. The maintenance of chronic AD involves the production of the Th1 like cytokines IL-12 and IL-18, as well as several remodelling-associated cytokines such as IL-11 and transforming growth factor (TGF) beta 1, expressed preferentially in chronic forms of the disease. Th-1-mediated cells seem to be responsible for apoptosis of cells, although their pathomechanisms are yet not fully understood. Clearly, a generalized Th2-deviated immune response is closely linked to the condition of AD but the skin disease itself is a biphasic inflammation with an initial Th2 phase and while chronic lesions harbour Th0/Th1 cells. This biphasic pattern of T-cell activation has also been demonstrated in studies on allergen patch-test skin reaction sites[33]. Twenty-four hours after allergen application to the skin, increased expression of IL-4 mRNA and protein is observed, after which IL-4 expression declines to baseline levels. In contrast, IFN-γ mRNA expression is not detected in 24-h patch-test lesions, but is strongly overexpressed at the 48~72 h time points. Interestingly, the increased expression of IFN-γ mRNA in atopic patch-test lesions is preceded by a peak of IL-12 expression coinciding with the infiltration of macrophages and eosinophils.

A study using an animal model of AD examined ovalbumin-elicited allergic skin inflammation in mice with targeted deletions of the IL-4, IL-5 and IFN-γ cytokine genes to assess the role of these cytokines[34]. Allergen-sensitized skin from IL-5 knockout mice had no detectable eosinophils and exhibited decreased epidermal and dermal thickening, whereas IL-4 knockout mice displayed normal thickening of the skin layers but had decreased eosinophils. Sensitized skin from IFN-γ knockout mice was characterized by reduced dermal thickening.

Recently regulatory T cells (Tregs) have been in the center of interest in different research areas[35]. Treg comprise diverse and complex family of cells with regulatory activities which became the focus of interest in the field of transplantation or tumour immunology as well as in allergy since they have the ability to suppress T-cells (TH1 and TH2). Special surface markers (CD25＋/CD4＋) as well as mutations of the nuclear factor Foxp3 are characteristic for these cells. It has been shown, that mutations of this nuclear factor results in hyper IgE, food allergy and dermatitis. In addition, staphylococcal super-antigens subvert the function of Tregs and may thereby augment skin inflammation[36].

② *Cytokines and chemokines*: Inflammatory reaction in AD is the result of a distinct microenvironment provided by a series of cytokines and chemokines[37]. A predominant TH$_2$ dysbalance with increased IgE levels and eosinophilia is widely accepted in the pathogenesis of AD[38,39]. The production of TH$_2$ mediated cytokines, notably IL-4, IL-5, and IL-13, can be detected in lesional and non-lesional skin during the acute phase of disease. IL-4 and IL-13 are implicated in the initial phase of tissue inflammation and may mediate an isotype switching to IgE synthesis, and upregulation expression of adhesion molecules on endothelial cells[40]. IL-5 increases the survival of eosinophils and a systemic eosinophilia with an increase of the ECP correlate to disease severity[41,42].

Although TH$_2$ mediated cytokines seem to be predominant in the acute phase of AD they are less important during its chronic course. In chronic AD skin IFN-γ and IL-12 are dominant, as well as IL-5 and GM-CSF, being characteristic for a TH$_{1/0}$ profile[43]. The maintenance of chronic AD involves further on the production of the TH$_1$ like cytokines IL-12 and IL-18, as well as several remodelling-associated cytokines such as IL-11, IL-17 and TGF beta-1[44].

Different chemokines have gained interest in the pathology of AD. Great amounts of chemokines like MIP-4/CCL18, TARC/CCL17, PARC/CCL18, MDC/CCL22, and CCL1 seem instrumental in the development of acute and chronic lesions[37]. C-C chemokines (MCP-4, RANTES, and eotaxin) contribute to the infiltration of macrophages, eosinophils, and T-cells into acute and chronic AD skin lesions. However, MIP-3a which also has some anti-viral activity seems to be deficient in AD due to the particular inflammatory microenvironment[45].

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine[46] expressed primarily by epithelial cells, including keratinocytes. It is associated to the activation and mi-

gration of DC within the dermis of AD. TSLP is thought to prime naive $CD4^+$ T cells to differentiate into Th2 cells which ultimately contribute to the induction of allergic inflammation. TSLP-activated cutaneous DCs prime Th cells to produce the pro-allergic cytokines IL-4, IL-5, IL-13, and TNF-α. However, expression of the anti-inflammatory cytokine IL-10 and the TH1 cytokine IFN-γ are inhibited. These features suggested that TSLP represents a critical mediator in uncontrolled allergic inflammation[47]. Gene profiling experiments using micro-array technology currently provides profound knowledge about the complex cytokine and chemokine microenvironment in AD[29,48] but their exact value in the pathogenesis is still not fully resolved.

③ *Dendritic cells*: Dendritic cells (DC) are highly specialized professional antigen presenting cells and are essential for the allergen uptake and its presentation to T-cells in the context of primary and secondary immune responses. The role DC in AD has been extensively discussed elsewhere[49]. Two types of DC have been found in lesional skin of AD: myeloid (mDC) and to a much lesser extend plasmacytoid dendritic cells (pDC). Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) both belong to the group of mDC and express the high affinity receptor for IgE (FcεRI) in lesional skin suggesting a complex regulatory mechanism related to the atopic status. While LC are present in normal skin, IDEC are detected mainly in inflamed skin. LC and IDEC play a central role in the uptake and presentation of antigens or allergens to Th1/ Th2 cells and most probably also to Tregs. Interestingly, FcεRI-expression is detected on LC from normal skin during an active flares of other atopic diseases such as allergic asthma or rhinitis, while FcεRI+ IDEC are confined to lesional skin. Although it remains to be definitely proven, there is some in vitro evidence that LC play a less dominant role than expected initially in initiating and perpetuating chronic inflammation but could rather be important for the sensitization phase. Nevertheless, they are active in priming naive T-cells into T-cells of Th2 type and produce distinct chemokines such MCP-1 upon receptor ligation. In contrast, the stimulation of FcεRI on IDEC leads to a switch to Th1 response and to the release of high amounts of proinflammatory signals which contribute to the amplification of allergic immune response (Fig. 2). The atopy patch test can be used as an experimental model for AD and skin biopsies thereof have demonstrated the kinetic interplay of DC subtypes and skin migration. 72 hours after allergen challenge, high numbers of IDEC invade the epidermis while alterations of the phenotype of LC and IDEC occur including the up-regulation of FcεRI.
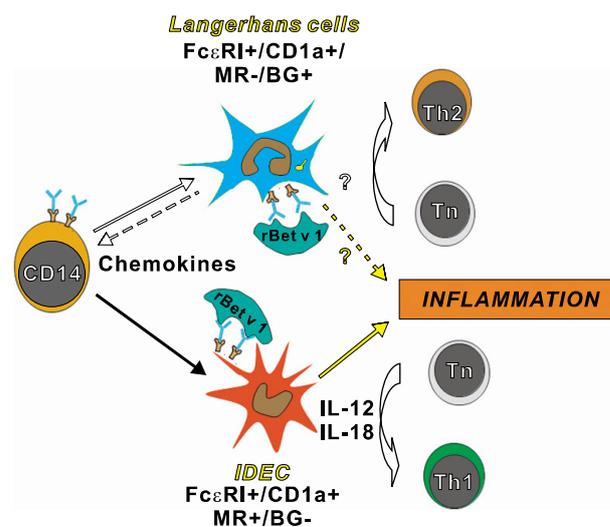

Fig. 2. FcεRI+ Langerhans cells and inflammatory dendritic epidermal cells (IDEC) exhibit distinct functional properties upon activation via the IgE receptor.

Compared to allergic contact dermatitis, the number of pDC is dramatically decreased in the skin of AD-patients. These cells have been shown to play a major role in the defence against viral infections by producing type 1 interferons. A lower density of pDC might contribute to the susceptibility towards viral skin infections such as herpes simplex induced Eczema herpeticum in these patients. In contrast to LC and IDEC, pDC seem to constitutively express FcεRI which is up regulated in AD patients. Activation of this receptor leads to an altered surface expression of major histocompatibility class (MHC) molecules, an enhanced apoptosis of pDC and a decrease in the secretion of type I interferons.

④ *Microbial agents*: Lesional and normal skin of patients with AD is highly colonized with toxins-producing *Staphylococcus aureus* (*S. aureus*)[50]. This colonization is due to the decreased production of anti-microbial peptides which are down- regulated by the particular inflammatory micro-milieu in AD[30,51]. Infections often provoke exacerbation or aggravation of lesional skin, particularly in children. Interestingly, *S. aureus* enterotoxines A (SEA), B (SEB), C (SEC), and D (SED) gained increasing importance in the pathogenesis of AD since they exhibit a large spectrum of biological activities (Fig. 3) including the induction of a specific IgE sensitization, acting as superantigens[52] and altering the function of Treg. Specific IgE antibodies directed against staphylococcal superantigens correlate with their skin disease severity[53]. Additionally it has been shown that binding of *S. aureus* to the skin is significantly enhanced by AD skin inflammation; scratching may enhance *S. aureus* binding by disturbing
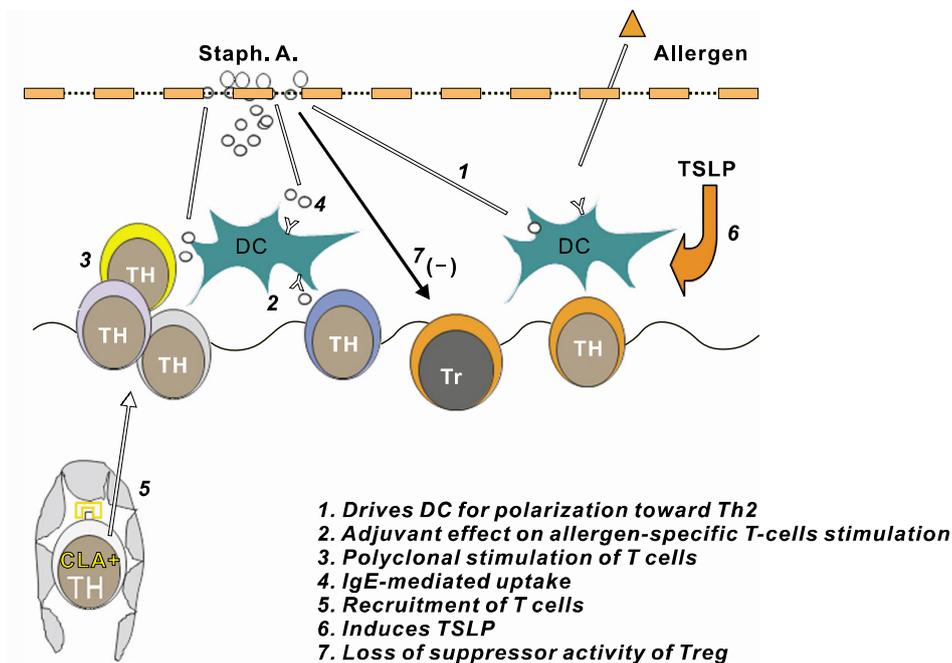
Fig. 3. Staphycoccus aureus exhibits a wide spectrum of biological activities which all can contribute to aggravate sensitization and inflammation in atopic dermatitis.

1. Drives DC for polarization toward Th2
2. Adjuvant effect on allergen-specific T-cells stimulation
3. Polyclonal stimulation of T cells
4. IgE-mediated uptake
5. Recruitment of T cells
6. Induces TSLP
7. Loss of suppressor activity of Treg

the skin barrier and isolated *S. aureus* was detected to possess an increased activity of ceramidase, thereby aggravating the skin barrier dysfunction. Therefore, the overgrowth of these bacteria should be one of the objectives in the management of AD.

Evidence for IgE-mediated autoimmunity in atopic dermatitis

There is some evidence that autoimmune response may play a role in AD. Indeed, patients with severe AD display IgE response to so-called auto-allergens[54]. These structures represent an increasing group of proteins to which the immune systems produces IgE auto-antibodies due to their homology with environmental allergens. Up to now, several auto-allergens have been detected, including the transcription factor LEDGF/DSF70[13], the atopy-related auto-antigens (ARA) Hom S1-S5 produced by keratinocytes[55] and the manganese superoxide dismutase (MnSOD) to which patients with AD produce specific IgE. This sensitization is induced by skin colonization with Malassezia sympodialis which causes, due to its high homology, likewise a sensitization against the human MnSOD[56]. This cross-sensitization is predominantly seen in patients with eczema of the head and neck (head and neck dermatitis). There is good evidence that IgE-related autoimmunity develops during the first years of life[57]. However, their relevance of the clinical course and the natural history of the disease remain unclear.

Clinical features of atopic dermatitis

The clinical phenotype of AD varies with age and may differ during the course of disease[58]. The eczematous lesions may present with acute (oozing, crusted, eroded vesicles or papules on erythematous plaques), subacute (thick and excoriated plaques), and chronic (lichenified, slightly pigmented, excoriated plaques) forms. Furthermore, xerosis and a lowered threshold for itching are usual hallmarks of AD. Pruritus attacks can occur throughout the day and worsen during the night, causing insomnia, exhaustion, and overall substantially impairs quality of life. Three different stages can be distinguished clinically: infancy, childhood and adolescent/adulthood.

1) Clinical features of infants

In the second of third month of life, the first signs of AD usually emerge with eczematous, papulo-vesicular and patchy lesions on the cheeks. Scratching due to itching occurs mostly a few weeks later and leads to crusty erosions. Perioral and para-nasal areas are usually spared in the beginning. The term "milk crust" or "milk scurf" refers to the occurrence of yellowish crusts on the scalp which resemble scaled milk. This stage is clinical quite similar to seborrheic dermatitis. Persisting pruritus leads the infant to become restless and agitated during sleep.

Later on the inner and outer parts of the arms and legs may also be affected while the diaper area is usually spared. In about 20~30% of the cases, lesions heal by the end of the second year of life but the atopic carrier may continue with the first signs of asthma provoked by viral

infection. Interestingly, in about 50% of the AD cases at this age, there is no yet evidence for IgE-mediated sensitization, i.e. these individuals should be classified as non atopic eczema.

2) Clinical features of the childhood

At this stage, eczematous lesions will typically involve flexural areas (ante-cubital fossae, neck, wrists, and ankles) and the nape of the neck, dorsum of the feet, and hands. These lesions can either arise de novo or develop from the preceding phase. Post-inflammatory hypopigmentation (pityriasis alba) may occur when chronic inflammation has resolved. About 60% of the childhood eczema forms will disappear completely but the stigmata may remain, xerosis being the most important one.

3) Clinical features of adolescents and adults

When eczema lesions persist from childhood to adolescence and adulthood or the disease starts de novo at adulthood, flexural areas as well as head (forehead, periorbital and perioral region) and neck will be typically involved with mostly lichenified plaques. Dry skin continues to be a persistent problem, especially in winter months.

4) Complications

The most important complications of AD are due to secondary bacterial and viral infections most probably due to the above mentioned reduced cell-mediated immunity and the deficiency in antimicrobial peptides. Staphylococci frequently provoke an impetiginization of lesions in children leading to yellow, impetigo-like crusting. Patients with AD are at increased risk for fulminant herpes simplex virus infections (eczema herpeticum)[59]. The course of this complication may be severe with high fever and widespread eruptions. Clinically numerous vesicles in the same stage of development are characteristic sign. It is up to now unclear, whether viral warts or mollusca contagiosa are likewise more prevalent in AD. However, large studies have shown that it will be possible to identify patients at risk to develop eczema herpeticum on the basis of clinical, immunological and genetic informations[60,61].

Diagnostic of atopic dermatitis

Diagnosis of AD relies primarily on the patient's and family's history as well as on clinical findings. The clinical diagnosis of AD is based on the clinical phenotype according to the morphology and distribution of the lesions at the different stages (see above). In 1980, Hanifin and Rajka proposed major and minor diagnostic criteria based on clinical symptoms of AD[62]. A revision of the diagnostic criteria was accomplished by Williams[63]. Severity of AD can be evaluated by different scoring systems such as the Score in Atopic Dermatitis (Score in Atopic Dermatitis:

SCORAD)[64] or the Eczema Area and Severity Index (EASI)[65]. These scoring systems can be of help in the daily praxis but are mandatory in clinical trials. The overall atopic status is best appreciated by using the validated Diepgen score[66].

Skin tests and laboratory investigations (specific IgE) are helpful in the search of provocation factors such as food or environmental allergens. Provocation tests are additionally performed to determine the clinical significance of positive laboratory tests since skin tests and in vitro testing should complement one another yet do not always have to be concordant. The atopy patch test (APT)[67] is about to be standardized for the search of AD-relevant allergen. While the sensitivity of APT is rather average, its specificity is high for the individual context of a given patient[68]. Most importantly, laboratory results have always to be interpreted in the context of the patient's history and skin tests.

Management

Beside allergological diagnostics, management of AD remains a clinical challenge where the primary goals are to improve the barrier function, to control microbial colonization and to suppress inflammation. The management of AD should always be adapted to the severity of the condition. Education of the patient or the parents of an affected child is as important as other strategies.

1) Basic therapy

A key feature of AD is xerosis due to the epidermal barrier dysfunction as witnessed by increased transepidermal water loss. Individually adapted emollients containing urea (4% or less in children; up to 10% in adults) should be used to support the skin barrier function and allow hydration of the skin. The patient should be educated adequately to avoid specific provocation factors[69].

2) Control of bacterial colonization

Topical antiseptics such as triclosan or chlorhexidine have a low sensitizing potential and show low resistance rates[70]. They can be used in emollients or syndets or as part of an additional "wet wrap dressing". Short term fusidic acid is preferentially used in the treatment of bacterial infections with S. aureus because of its low minimal inhibitory concentration and good tissue penetration[71]. Intranasal eradication of methicillin-resistant S. aureus, frequently found in AD patients, can be achieved by the topical use of mupirocin. In the case of wide-spread bacterial secondary infection seen mainly in children (primarily S. aureus) systemic antibiotic treatment is indicated. Prophylactic treatment only increases resistant rates and has no benefit on the course of disease. The use of silver-coated textiles and silk fabric with a durable anti-

microbial finish is still under investigation, but seems to be promising, especially for children[72].

3) Anti-inflammatory therapy

Most topical glucocorticosteroids (GCS) present a safe and effective medication when used properly[73]. This is particularly the case for GCS with double esters and favourable therapeutic index, i.e. high efficiency with low side effects. Besides their anti-inflammatory activity, GCS contribute to a reduction of skin colonization with *S. aureus*[74]. Only mild to moderately potent preparations should be used on genital, facial, or intertriginous skin areas. Less potent topical steroids such as hydrocortisone can also be employed to children less than 1 year old. Different therapeutic schemes have been established: initial treatment should be with moderate to high potent steroids followed by a dose reduction or an exchange to a lower potency preparation[75].

The topical calcineurin inhibitors (TCI) Pimecrolimus and Tacrolimus suppress the early phase of T-cell activation, multiple cytokines involved in cellular immunity and affect IDEC but not LC in AD lesions. Their anti-inflammatory potency is similar to GCS of mild to moderate potency and have an important role in the anti-inflammatory management of AD[76,77]. Recent studies have highlighted the importance of the proactive management of AD using TCI[78,79]. Side effects include a transient burning sensation of the skin. While using calcineurin inhibitors, excessive exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) should be avoided. Long-term safety studies analyzing the evidence of a causal link of cancer and calcineurin inhibitors as well as an increased incidence of viral infections are ongoing. Despite the accepted favourable safety profile[80], a black boxed warning has been released by the FDA and a "red-hand letter" from the european agency (EMA), emphazising on the use of these products as second line therapy. However, it seems that these warnings lack substantial scientific background since epidemiological studies have shown that the appearance of cutaneous lymphoma[81] or non-melanoma skin cancers[82] are not linked to the use of these compounds. Long term postmarketing studies are ongoing to further assure the safety of TCI.

4) How to best assure a proactive management with anti-inflammatory compounds (Fig. 4)?

Studies on the compliance of patients with AD have shown that, once the flare has started, these patients begin to treat with anti-inflammatory medication very late, i.e. after an average of 6 to 7 days. Thus the first importance advice to the patients should be not to wait too long before starting the anti-inflammatory therapy of individuals
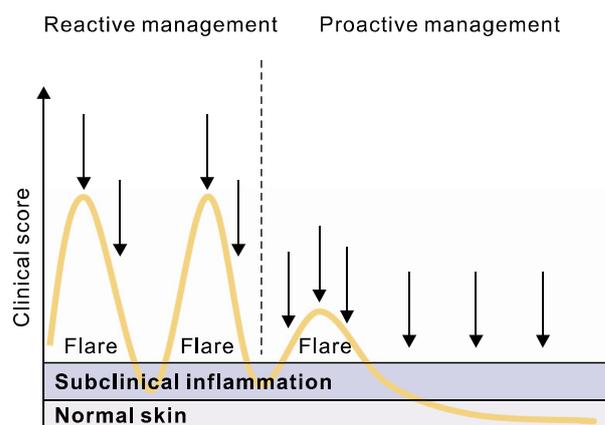

Fig. 4. Schematic view of the reactive and proactive management of atopic dermatitis. The goal of the new approach should be: an early intervention as the flare start, an almost clearance of the lesions and an intermittent application (one or twice/week) of anti-inflammatory compounds.

flares. Secondly, the patients should be educated to continue this anti-inflammatory therapy until the affected areas are almost clear. Third, they should then continue the treatment with an average of once or twice per week (depending on the severity) over a longer period of time. Combined therapy with emollients should be routine during the course of treatment. For mild form, this proactive approache could last for 3 months, while moderate forms would need to be treated proactively for 6 months and more severe forms for about 9~12 months in order to better control the sub-clinical inflammation and the occurrence of flares[83,84].

5) Phototherapy

AD patients usually report a benefit from natural sun exposition. Therefore, different spectrum of UV-light, i.e. UVB (280~320 nm), narrow-band UVB (311~313 nm), UVA (320~400 nm), medium and high-dose UVA$_1$ (340 ~400 nm), PUVA, and Balneo-PUVA have undergone trials for the treatment of AD. Clearly, UVA$_1$ irradiation seems to be superior to conventional UVA-UVB phototherapy in patients with severe AD[85,86]. Narrow-band UVB alone is also effective and its activity seems to be partially due to a decrease in the microbial colonization[87]. In children UV-therapy should be restricted since data about long-term side effects of UV-therapy are still not available.

Systemic treatment

Anti-histamines of the H$_1$-receptor generation (alimemazine and promethazine) are predominantly used for their sedative effect and should be given 1 hour before bedtime. Most studies conclude that non-sedating antihistamines seem to have little or no value in the treatment

of AD[88].

Oral corticosteroids have a limited but definite role in the treatment of severe exacerbations of AD. A brief course may be used to control severe disease, ongoing use of systemic corticosteroids leads to significant adverse effects. After discontinuation of the medication, severe relapses have been noted. Data from randomized clinical trials are lacking.

The ongoing treatment with Cyclosporin A (CyA) should be reserved for very severe cases of disease, not responding to other measures[89,90]. Multiple studies have shown a positive effect for children and adults. Treatment should be started with 5 mg/kg/day and gradually decreased to about 2 mg/kg/day. The lowest dose for minimal side effects should be applied. Despite effectiveness, side effects, especially concerning renal toxicity with hypertension and renal impairment are of particular concern. A close monitoring of creatinine, blood pressure, and CyA serum levels is important. Of note, CyA is rarely effective as monotherapy to completely control AD but topical steroids are usually necessary to reach this goal.

Azathioprine is an immunosuppressant drug which has been reported to be effective in severe AD[91,92]. It affects the purine nucleotide synthesis and metabolism and has anti-inflammatory and antiproliferative effects. Controlled trials are lacking so far; side effects are high, including myelosuppression, hepatotoxicity, gastrointestinal disturbances, increased susceptibility for infections, and possible development of skin cancer. As azathioprine is metabolized by the thiopurine methyl transferase, a deficiency of this enzyme should be excluded before starting an oral immunosuppression with azathioprine.

1) Biologics

Anti-IgE strategy (omalizumab) which is approved for asthma has been tried with variable results in AD[93,94]. Since these patients usually display very high levels of IgE, neutralizing these levels would require extremely high amounts of this biologic. Nevertheless, some recent case reports have suggested the successful use of omalizumab in selected patients. Infliximab (anti-TNF-α) has been also reported to be successful in some reports[95,96]. However, one has to keep in mind that side effects of biologics may be serious and need further evaluation.

2) Immunotherapy

It is well accepted that allergen-specific immunotherapy which has been reported since 1911 in the management of allergic diseases, represents the only causative therapeutic approach. Unfortunately with regard to AD only limited, and often contradictorily information is available. A recently published study, re-examining the efficacy of a subcutaneous immunotherapy (SCIT) in atopic patients sensitized to house dust mites, demonstrated effectiveness in reducing eczema and allergic sensitization to HDM[97]. The improvement of eczema was accompanied by a reduction of topical corticosteroids needed to treat eczema. Interestingly, because of its limited side effects, sublingual immunotherapy (SLIT) may represent an alternative to SCIT. Further studies to verify the benefit of SCIT and SLIT are currently running and we may experience a revival of immunotherapy in AD in the near future[98].

3) Education

As mentioned above, education of especially young patients and their parents emphazising on the knowledge about the disease and its management will lead to a higher compliance as well as psychological stability[99]. Patient's education also significantly contributes to improve its quality of life. Adequate educational programs are of great value when offered in cooperation with dermatologists as well as paediatrics, dieticians, psychologists, and nursing staff interdisciplinary with patients and their families.

Future perspectives

We are currently experiencing a new and fascinating phase in the modern research of AD. Combining data from epidemiology, genetics, skin physiology and immunology and allergy provides new areas of research which will certainly provide us new perspectives and new concepts in the pathophysiology and management of this disease. The role of innate immunity which has been underestimated over years is now the subject of numerous projects and functional genetics will help us to better understand the consequences of so many genetic variants in candidate genes. This will hopefully lead to the development of new biologics but also new antagonist molecules based on small molecular weight compounds against cytokines such as IL-4 or chemokines or there receptors, steroid analogues and many others which are or will be in the pipe line in the next years. Finally, beside these new pharmacological approaches, one of the most important aspects remains the strategy to intervene very early in the carrier of infants and young children by controlling skin inflammation at the earliest time point. This may help us to better control the emergence of sensitization and to provide a rapid and hopefully definitive cure of the disease. Thereby, physicians would be able to provide a convincing disease modifying strategy for AD patients ideally by adapting a more personalized approach in the management of these patients.

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