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Atopic dermatitis: from the genes to skin lesions

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Introduction

Atopic dermatitis (AD) is a common skin disease which has been known from antiquity. According to the Roman biographer Suetonius, the emperor Augustus suffered from this disease (1). The increasing incidence of allergic diseases in general, and especially AD, has recently focused public interest on these diseases. Numerous articles and books by nonmedical professionals, various self-help groups for all kinds of allergic diseases, and even dedicated news groups on the Internet are stressing this phenomenon. The direct cost to treat these disorders, as in the charges of medical professionals and the cost of medication, as well as the indirect socioeconomic cost, e.g., as a result of lost working days, has been calculated to be several hundred million dollars every year in the US and the UK (2, 3), and the annual cost to society was put at 7 billion Deutschmarks in Germany (4). Despite intensive research and significant progress in the field of immunodermatology, a unifying pathogenetic concept of AD has still not been established.

The term "atopy" was coined by Arthur Fernandez Coca and Robert Cooke in a paper, published in 1923, "On the classification of the phenomena of hypersensitivity" (5). In general, the atopic diathesis describes a certain morbid susceptibility to hay fever, asthma, and AD but is not regarded as a disease entity in itself. Since atopic subjects develop their diseases at some particular point during their lifetime, it is widely accepted that

latent atopy derives from a complex genetic background. Unfortunately, we have no exact marker of atopy. Since the term "atopy" is clinically meaningful and useful, it is widely used in clinical medicine throughout the world. However, there is no generally accepted precise definition of atopy (6).

During the last 10 years, some excellent textbooks (7, 8) and review articles (9–12) on the clinical and pathogenetic aspects of this condition have been published. New approaches, which may become important for our understanding of the disease (13, 14), as well as novel therapeutic strategies (15–17), have evolved in the last decade of the 20th century. This review touches on clinical and therapeutic aspects, but focuses on the current knowledge of the genetic background and immunopathogenesis of AD.

Basic clinical aspects

AD is a chronic inflammatory skin disease with a wide variety of clinical manifestations. Regardless of the patient's age, mild to severe erythema, scaling, and excoriations that reflect the severe itch are generally present. The distribution pattern of the skin lesions changes during the patient's lifetime from more generalized eruptions with oozing and crusted lesions to the adult distribution pattern of flexural eczema with lichenification and a scaly, xerotic, dry uninvolved skin. This so called "dryness of skin" actually describes the

reduced softness, smoothness, and water and lipid content of the skin surface (7, 18).

The stigmata of an atopic constitution are features known to be characteristic of atopy. Dry skin (xerosis), hyperlinearity of the palms and soles, an infraorbital fold (Dennie–Morgan’s sign), white dermographism, facial pallor, orbital darkening, thinning of the lateral part of the eyebrows (Hertoghe’s sign), and a low hairline may help the clinician identify atopic patients with a single glance. However, these stigmata are more related to the atopic state and – with the exception of dry skin – are not specific for AD (19). A high serum-IgE level can be considered an immunologic stigma of the atopic constitution (20). Bacterial superinfection, mostly with *Staphylococcus aureus*, is the most common complication of AD. An appropriate antibiotic treatment reduces the amount of topical glucocorticosteroids needed to control this exacerbation of disease. A generalized superinfection with the herpes simplex virus, known as eczema herpeticum, or Kaposi’s varicelliform eruption, is the most severe and feared complication of AD. Immediate antiviral chemotherapy and hospitalization are needed in most such patients. Widespread infection of AD lesions with human papilloma virus or the molluscum contagiosum virus, known as eczema verrucatum, or eczema molluscatum, are seen less frequently, mostly in younger patients.

The diagnosis of AD is easy if the patient presents with lichenified flexural eczema; however, this is not the rule. A thorough history, together with a skillful allergologic workup, should lead to the identification of the individual triggering factors for each patient (21). At present, therapeutic options are based on proper skin care, avoidance of individual triggering factors, and transient anti-inflammatory treatment, depending on the actual skin status of the patient.

Definition and diagnostic criteria of AD: extrinsic as opposed to intrinsic dermatitis

If all disease features are present, AD has a highly characteristic phenotype. Incomplete or minimal disease forms are encountered frequently in clinical practice and lead to a wide gray area of cases that some dermatologists would label as AD and others would not. This may cause a major problem if results are to be compared between different investigators or even different centers. However, the clinical diagnosis of AD is usually much more reliable than the application of diagnostic criteria to an individual patient. Diagnostic criteria for AD have been proposed by several dermatologists. All of these have some major drawbacks, since they are either 1) not widely accepted; 2) too complicated for daily use; 3) too insensitive, because they do not detect mild disease forms; or 4) too

unspecific, because they would, for example, identify nickel contact dermatitis in a patient with hay fever as AD. While highly specific criteria provide a good basis for definition of clinical trial populations, their usually low sensitivity makes them unsuitable for epidemiologic use. Essentially, the classical criteria proposed by Hanifin & Rajka in 1980 are still the most widely used to define AD study populations (22). The diagnostic criteria developed by Diepgen et al. (23) in Erlangen (Germany) seem to have a higher sensitivity and specificity but are not as widely accepted in the medical community.

The UK working party’s diagnostic criteria, established in Nottingham in 1994 (24), have been validated by the proposing authors (25). The attempt to validate these criteria by an independent group from Tehran (Iran) in a population sample of 416 patients revealed the high specificity but low sensitivity of these criteria, making them useful for clinical trials, but not for epidemiologic studies (26). The usefulness of the newly designed “millennium criteria” (27) has still to be confirmed. These criteria raise the issue of the “extrinsic” form, i.e., IgE-associated dermatitis, and the “intrinsic” form, i.e., dermatitis without increased IgE serum level (see below). In conclusion, the choice of the diagnostic criteria used in clinical trials and epidemiologic studies may have a substantial influence on the results.

Approximately 20% of patients suffer from a skin disease which clinically resembles the skin lesions and distribution pattern of AD, but is not associated with elevated total serum IgE levels and does not exhibit sensitization to environmental or food allergens. Therefore, the pathogenesis of this “intrinsic” AD (IAD) (28) seems to be different from that of the disease known as classical, or “extrinsic”, AD (EAD).

Diagnostic criteria for IAD have not formally been proposed, but, according to Wüthrich (personal communication) and our own understanding, these should run as follows:

- 1) a clinical phenotype of AD, fulfilling the diagnostic criteria of Hanifin & Rajka (22)
- 2) low or moderate total serum IgE levels (<200 kU/l) in combination with negative *in vitro* IgE screening for aeroallergens and food allergens (e.g., SX1-RAST and SX-5 RAST), as well as negative prick test results for standard aero- and food allergens
- 3) absence of other atopic diseases such as allergic rhinoconjunctivitis or allergic bronchial asthma.

Hence, patients may initially be suspected to have IAD, but during the allergologic work-up they may need to be reclassified as having EAD.

Recent immunodermatologic investigations show differences in T-cell cytokine secretion, immunohistology, and the immunophenotype of the epidermal dendritic cells between EAD and IAD (29, 30). This

argues strongly against the hypothesis (14) that a mere replacement of aeroallergens by the recently characterized autoantigen Hom s 1 is the basis for IAD.

Epidemiologic studies on AD

Several epidemiologic studies by different groups have clearly shown the increasing incidence of AD (31–34). Furthermore, there is evidence of a higher incidence of AD in second than firstborn children (35). This may be causally linked either to the birth rank or to the age of the mother. There is much discussion of the beneficial effects of breast-feeding, but there is no conclusive evidence of this effect from the epidemiologic data available (36–39).

More recent studies indicate that the most important risk factor for the development of AD is the “Western lifestyle”, although we do not know exactly which factor of our sociocultural behavior is relevant to disease development (40).

Immunohistology of AD lesions

The immunohistology of AD is stage dependent and includes spongiosis, epidermal hyperplasia, thickening of the papillary dermis, and parakeratosis, as well as a superficial perivascular inflammatory infiltrate. An unequivocal diagnosis of AD by histologic means alone is difficult for the following reasons:

- 1) there is already uncertainty about the clinical aspect of the primary lesion
- 2) scratching and prolonged rubbing of the pruritic skin results in various secondary histologic changes
- 3) the histopathology of AD shares certain similarities with contact, nummular, and dyshidrotic dermatitis (41).

Therefore, many authors tend to regard the histologic findings of clinical lesions in AD as nonspecific (42, 43).

However, epidermal dendritic cell phenotyping, a recently standardized technique based on the flow cytometric analysis of epidermal single-cell suspensions from inflammatory skin lesions, has the advantage of high sensitivity and specificity in combination with the potential to analyze individual skin lesions (44, 45). This method is based on the immunophenotype of the two CD1a-positive epidermal cell populations present in inflammatory human skin; namely, Langerhans cells and inflammatory dendritic epidermal cells (IDEC) (46).

The pathophysiologic puzzle of AD (Fig. 1)

Most of the clinical aspects of AD involve components of the skin immune system. This system may be regarded as the interactive network of all cells and

signals that are either resident in the cutaneous environment (static component) or are actively recruited into the skin during inflammatory processes (dynamic component) (47, 48). AD has been shown to occur in a previously nonatopic patient after allogeneic bone-marrow transplantation (49). This key case indicated that a bone-marrow-derived cell plays a pathogenetic role in the formation of AD lesions.

An overview of the different pieces from the pathophysiologic puzzle of AD is given in Fig. 1, and the single components will be discussed in the following subsections.

Ⓐ Gene(s) of AD

There is no doubt of the genetic background in the pathogenesis of AD (50). The many genetic studies on AD published have been recently reviewed (51). These may be classified into two different approaches: linkage analysis studies and candidate gene studies. The former aim to detect an association of the AD phenotype with any of the chromosome regions. To detect associations with polymorphisms of previously unknown genes, such studies need high numbers of investigations.

On the other hand, the candidate gene studies investigate the association of gene polymorphisms of a specific gene with the atopic phenotype (Table 1). They are restricted to the investigation of a single, already known gene locus but are easier to perform in limited numbers of patients. Most of these studies focus on components of the skin immune system, such as cytokines or cell-surface receptors.

As is the case with many other diseases, HLA-type combinations have been identified with increased frequency in either elevated IgE levels or specific atopic disorders (52). However, in subsequent studies, a cosegregation of these markers could not be demonstrated (51). This may have been due to the heterogeneous causes of the atopic diseases.

In 1968, Szentivanyi proposed his “beta adrenergic blockade theory of the atopic abnormality” (53), with reference to a pulmonary atopic disease phenotype with the respective gene located at 5q32–q33. Some reports agree with this hypothesis, but newer data suggest that alteration in the β -adrenergic system is a consequence rather than a cause of respiratory atopic disease (54). The association of a gene locus on 5q, encoding the IL-4 gene cluster, has been reported to be associated with the total serum IgE level (55), but this could not be confirmed by other investigators (56).

The gene locus 11q13, a region encoding for the β chain of the high-affinity IgE receptor $Fc_\epsilon RI\beta$, has been linked to the AD phenotype by the studies of Cookson et al. and other groups (57, 58). However, this association failed to be confirmed by studies in Japan and the UK (59, 60).

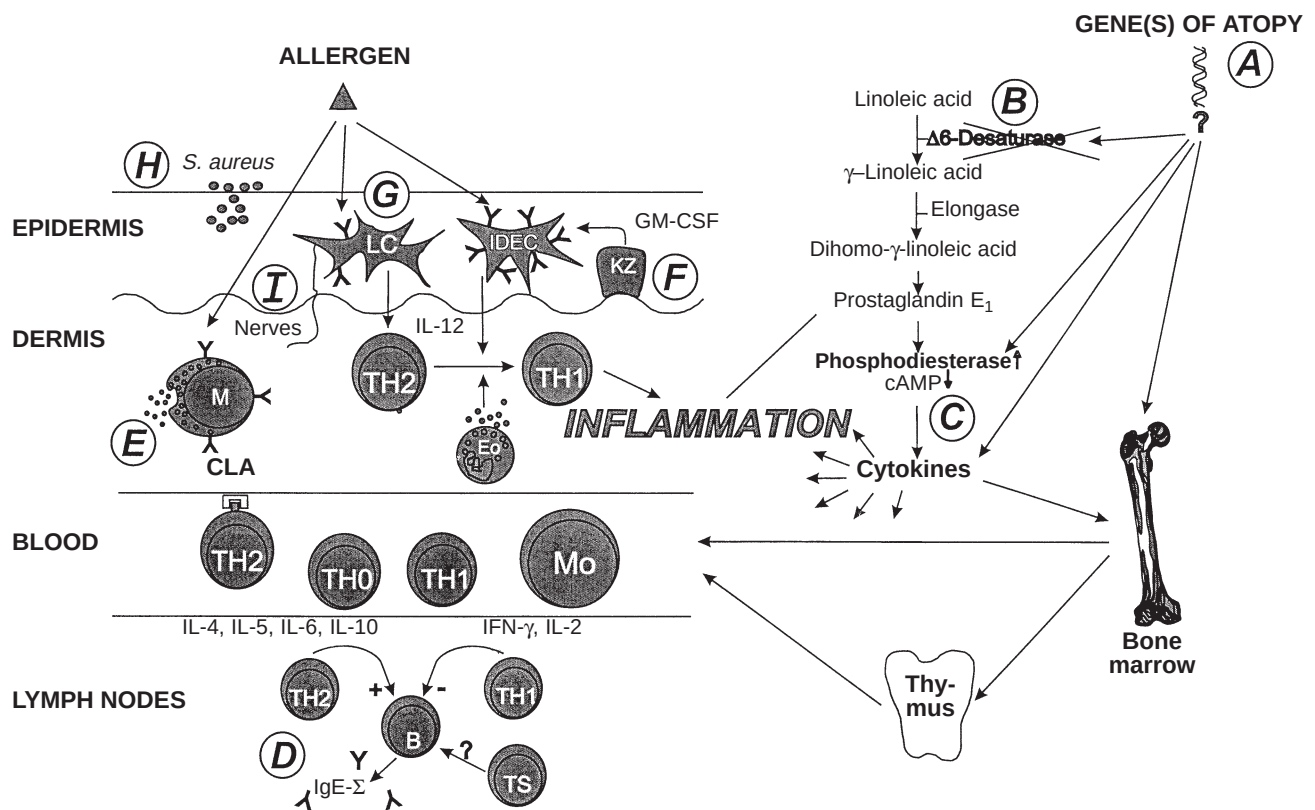


Figure 1. Pathophysiologic puzzle of atopic dermatitis. Circled letters refer to respective pathophysiologic aspects, corresponding to discussion under lettered headings in text.

A gene which has been thought to be specifically linked to AD, but not to other atopic diseases, is that of the mast-cell chymase, encoded at 14q11.2 (61, 62). However, this association could not be confirmed by another Japanese study (63).

In 1998, linkage analysis showed a gene encoded at 16p11.2–12 to be linked to the total serum-IgE level (64). This gene region is the location of the IL-4-receptor gene alpha, which is located at 16p11.2–12.1 (65). Initially, it was suspected that a mutation putatively leading to increased IL-4 receptor activity (Q576R) could be responsible for elevated IgE

secretion (66). However, subsequent analyses have shown that polymorphisms affecting at least four different amino acids in the cytoplasmic domain of IL-4R α may significantly influence the outcome of IL-4 receptor signaling and consequently IgE secretion (67).

In conclusion, there are numerous reports of associations between gene loci and atopic disease, but contradictory results have frequently been published by rival groups shortly after the first claim of a newly identified locus. In addition, these reports are mostly related to IgE levels, and less frequently to respiratory disease, and are rarely specific to the cutaneous manifestations of AD.

Table 1. Gene regions associated with atopy

Region	Candidate gene	Phenotype
2q21–q23	Unknown	Specific IgE
5q31.1	IL-4 cluster	Total IgE
5q32–q33	Glucocorticosteroid receptor	Total IgE
	β_2 -Adrenergic receptor	Bronchial hyperreactivity, asthma
6p21.3	MHC class II	Specific IgE
6p21.3	TNF- α	Total IgE
8p23–p21	Unknown	Specific IgE
11q13	High-affinity IgE receptor beta	Atopy, asthma, total and specific IgE
12q15–q24.1	IGF1, SCF	Atopy, total IgE
14q11.2	T-cell receptor	Specific IgE
	Mast-cell chymase	Atopic dermatitis
14q32	IgG heavy chain	Atopy
16p11.2–12.1	IL-4-receptor alpha	Total IgE

(B) The delta-6 desaturase story

Although it had long been postulated that atopic patients may have a defect in the metabolism of essential fatty acids, only in 1982 were reduced levels of prostaglandin (PG) precursors demonstrated in the blood of atopic patients, and a defective delta-6-desaturase function was proposed as the biochemical basis of atopy (68). Like other studies, a recently published controlled study could not confirm this impaired delta-6-desaturase activity in allergic school-children (69).

Ⓒ Increase phosphodiesterase activity and decrease cAMP

The phosphodiesterase activity of monocytes from AD patients is higher than that found in nonatopic patients, leading to a decreased level of cAMP and consequently a higher formation of the proinflammatory PGE₂ in the affected patients (70, 71). PGE₂ has been shown to inhibit Th1 responses and to increase the IL-4 production of Th2 cells (71). These studies, undertaken in peripheral blood monocytes, are in good accordance with the clinically relevant immune deviation of AD patients but do not explain the eczematous phenotype of cutaneous atopic disease. Furthermore, clinical trials using topical type-4 PDE inhibitors have shown significant, but not dramatic, improvement of skin lesions (72).

Ⓓ The Th1/Th2 concept and the regulation of IgE synthesis

The subdivision of human T cells, based on their cytokine secretion patterns, into the Th1 and Th2 subgroups is generally accepted. After activation, indeterminate T cells (Th0) may be primed to one of the following secretion patterns: Th1 cells produce IL-2 and IFN- γ , and Th2 cells secrete IL-4 and IL-5. On a clinical basis, Th1 secretion patterns are associated with delayed-type hypersensitivity (DTH) reactions such as the tuberculin reaction, whereas the Th2 secretion pattern is associated with IgE-mediated reactions such as exogenous allergic urticaria (73). AD is associated with an immune deviation favoring IgE-mediated immune responses in the presence of a certain susceptibility to skin infections, such as bacterial skin infections, common warts, or molluscum contagiosum. If these Th2-like immune responses were the only basis of AD, the phenotype of the cutaneous atopic disease would be urticarial lesions. However, the phenotype of AD resembles a DTH reaction, corresponding to contact dermatitis lesions; i.e., it rather resembles a Th1-mediated skin disease.

Ⓔ A role for mast cells?

Mitosis of mast cells has been observed in AD lesions (74), suggesting a pathophysiologic role for mast cells in this disease. Furthermore, it has been shown that mast cells may be an initial source of IL-4 in the lesions, a cytokine which may drive the lesional T cells in a Th2 direction (75). An increased number of tryptase-positive mast cells lacking anti-inflammatory chymase activity have been demonstrated in nonlesional skin of AD and nummular eczema (76), and may be linkable to the mast-cell tryptase proposed as a candidate gene for AD.

Ⓕ Do atopic keratinocytes have an intrinsic defect?

During their period of maturation, keratinocytes form the stratum corneum of the epidermis. The function of this epidermal barrier is impaired even in the clinically

uninvolved skin of AD patients, as may be seen in the increased transepidermal water loss. However, it is unclear whether this peculiar weakness of the epidermal barrier function is the cause or the result of the underlying atopic disease (18). Thus, it has remained unclear whether keratinocytes in AD patients have an intrinsic defect that explains these clinically most important features. In this regard, an enhanced production of GM-CSF by keratinocytes from AD patients has been shown in response to IL-1 α , and both gene expression and protein release in both atopic and control keratinocytes could be reduced by hydrocortisone (77). Furthermore, conditioned medium from PMA-treated keratinocytes from AD, together with exogenous IL-4, could support phenotypic and functional maturation of peripheral blood precursors into dendritic cells (77). Enhanced production of GM-CSF by keratinocytes may thus contribute to the establishment and chronicity of AD lesions; in particular, to the increased number and enhanced antigen-presenting function of the dendritic cells.

Ⓖ AD: an IgE-mediated DTH reaction?

IgE-mediated antigen presentation of (aero-) allergens has been considered a key event in the pathogenesis of AD (13). By this mechanism of antigen uptake, antigen-presenting cells may, in the presence of antigen-specific IgE, increase their presenting capacity up to 100-fold. This mechanism, also known as “antigen focusing” or “facilitated antigen presentation”, has been shown to be effective by different research groups in different cell systems (78–80). Thus, IgE receptors are the connecting link between the specificity-gaining IgE molecules and the antigen-presenting cells. Recent research on the identification and characterization of IgE receptors on the cell surface of the antigen-presenting cells has led to the identification of three different IgE receptors on the cell surface of human epidermal Langerhans cells; namely, the low-affinity IgE receptor CD23/Fc ϵ RII (81), the high-affinity IgE-receptor Fc ϵ RI (82–84), and the IgE-binding protein Galectin3/ ϵ BP (85). Therefore, quantitatively, Fc ϵ RI seems to be the most interesting and relevant structure (86).

Following the presentation of allergens to T cells, allergen-specific B cells may be activated to produce high amounts of allergen-specific IgE. This IgE may then in turn bind to the Fc ϵ RI on the antigen-presenting cells, closing a vicious circle of facilitated antigen presentation.

Quantitative flow cytometric examination has demonstrated a significant upregulation of Fc ϵ RI molecules on the CD1a-expressing epidermal dendritic cells isolated from lesional skin in AD (45, 46). Beside the Birbeck's granule-containing Langerhans cells, a second CD1a-expressing cell population lacking this Langerhans cell-specific ultrastructural hallmark could

be demonstrated inside the epidermis by double immunogold labeling and immunoelectron-microscopic examination (46). The immunophenotype and ultra-structure of the latter cell type, the IDEC, have been characterized (45, 46), but its ontogenesis and function are still under investigation. Since a hyperstimulatory function of the *in vivo* mixture of Langerhans cells and IDEC could be demonstrated (87), and both cell types have been shown to express costimulatory molecules on their cell surface (88), a proinflammatory function of IDEC may be assumed. It is tempting to speculate that not only eosinophils (89) but also IDEC, which are the relevant IgE-binding cell type inside the inflamed epidermis, switch the ongoing Th2-like immune response during their invasion of the skin into a Th1-dominated immune response.

The intermittent or continuous flow of aeroallergens or autoantigens (14) into the process of facilitated antigen presentation may define the pathophysiologic basis of the recurrent or self-perpetuating course of AD frequently seen in untreated patients. The successful application of aeroallergens such as cat dander in the recently standardized atopy patch test (90) shows that it is possible to elicit eczematous skin lesions by solely external application of aeroallergens to the skin. Based on the facilitated antigen presentation model of AD, the need for an identification of the individual provocation factors in each patient calls for diagnostic procedures based on the allergen-specific IgE (21). Allergens of cat dander, house-dust mite, and various foods may be successfully avoided after a thorough prick test and *in vitro* IgE diagnostic evaluation.

Ⓜ Staphylococcal superantigens

AD patients frequently are colonized by *S. aureus* in the nasal vestibulum. Upon exacerbation of skin lesions, staphylococci may be cultured from most of these skin lesions, and many of these staphylococcus strains are potent producers of staphylococcal superantigens (91, 92). On one hand, these superantigens are presented as "ordinary" antigens in the peptide-presenting groove of the MHC complex to the respective antigen-specific T cell. On the other hand, the intact proteins bind the MHC complex and are capable of bridging the MHC complex to all T cells with the same V β -chain family irrespectively of their antigen specificity. By these processes, antigen-specific as well as antigen-unspecific T-cell activation mechanisms synergistically lead to proinflammatory signals inside the epidermodermal compartment of the skin immune system, further speeding up the ongoing vicious circle of facilitated antigen presentation. Therapeutic removal of staphylococci from this vicious circle clearly explains the steroid-saving effect seen in an oral antibiotic or topical antiseptic treatment of AD. Since the oozing skin lesions of the staphylococci-infected AD patients

provide ideal culture conditions for these bacteria, this vicious circle may be relevant to the persistence of the AD lesions.

① Neuroimmunologic control of skin inflammation

No clinical dermatologist doubts that psychogenic factors, such as stress, are important cofactors in exacerbation of AD. On the other hand, worsening of the disease has repeatedly been observed in patients shortly after relief from a psychological stress such as a university examination. Experimental dermatologists are seeking to determine the exact nature of interaction between the nervous system and the immune system.

Calcitonin gene-related peptide (CGRP) is a neuro-peptide and vasodilator found within nerve fibers that are intimately associated with Langerhans cells inside the human epidermis. Functional assays have shown that CGRP may inhibit the antigen presentation by Langerhans cells (93). Therefore, CGRP may have immunomodulatory effects *in vivo*, too. Furthermore, it has been shown that keratinocytes, activated under appropriate conditions, produce proopiomelanocortin-derived hormones, i.e., α -MSH, which in turn, seem to promote the secretion of IL-10 (94). These mechanisms may be involved in negative feedback signals down-regulating the inflammatory reactions in the skin.

Other neuropeptides with a putative inflammatory and immunologic role, which have recently been reviewed (95), are vasoactive intestinal peptide, substance P, neurotensin, neuropeptide Y, and somatostatin. However, the exact mechanisms of the so-called "psychoneuroimmunologic network" are still under investigation.

Current therapeutic options in AD

There is no known cure of AD as such. However, its individual skin lesions may be successfully treated by a variety of topical and/or systemic agents. Regular treatment of the dry skin in AD with emollients is time-consuming for the patient but its benefits are frequently underestimated by health-care organizations and the patients themselves. It is of the utmost importance to instruct patients not to stop this applying of emollients once the skin lesions have gone away.

Topical glucocorticosteroid application is still the reference standard of anti-inflammatory treatment. This is due to

- 1) the favorable risk/benefit ratio of topical glucocorticosteroids in AD
- 2) the avoidance of a systemic immunosuppression
- 3) the wide variety in the therapeutic strength of the active ingredient, as well as of the ointment bases, which act as therapeutic agents themselves.

Ultraviolet (UV) light is frequently applied in AD, narrow-band UVB-311 nm being a relatively fast and safe therapeutic adjuvant to the topical glucocorticosteroids. The PUVA bath is effective as monotherapy but should be restricted to the more severe forms in adult patients due to the photocarcinogenic potential of this therapeutic regimen. The therapeutic efficiency of high-dose UV-A is equal to that of potent glucocorticosteroids, but the equipment is expensive and the long-term side-effects are still uncertain.

Extracorporeal photopheresis may be a successful therapy for some patients, but due to the high costs and possible side-effects of long-term treatment, this therapy should be limited to severe cases (96).

High doses of human immunoglobulin (IVIG) have been tried in a series of nine patients and did not show any clear benefit (97).

A highly promising topical treatment of AD are the recently developed topical formulations of immuno-

suppressive macrolides (98). The key substance tacrolimus (FK-506) (15, 17), as well as the ascomycin-derivative ASM-981 (99), has been shown to be effective in the control of AD, and short-term clinical trials with tacrolimus (100) and ASM 981 (16), as well as a long-term safety study with tacrolimus (101), have been successful in this disease.

Conclusion

AD is the clinical basis for a growing number of dermatologic research groups. The results of epidemiologic investigations in both the intrinsic and the extrinsic types of AD will be of special interest. The role of keratinocytes in the initiation and perpetuation of the inflammatory skin lesions is under investigation. Finally, clinically oriented research will be needed to increase our current knowledge of preventive action in this ever challenging disease.

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