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Current concepts in the pathophysiology of atopic dermatitis in human

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Introduction

The skin is much more than just a protective coat and encounters a high number of antigens at the interface between the body and the surrounding environment (1) (2). Atopic dermatitis (AD) is a chronic inflammatory skin disease, clinically and histologically very similar to contact dermatitis. AD can occur at any age and has a high prevalence in children. In the past years, the rising interest in this disease has been forced by its increasing prevalence in the western societies and its contribution to the worsening of health care costs (3). AD offers a wide clinical spectrum ranging from minor forms presented by a few dry eczematous patches to major forms with erythematous rash (4). Cardinal features of AD are erythematous eczematous skin lesions, flexural lichenifications or papules which go along with an intense pruritus and cutaneous hyperreactivity (5;6). Various names, such as atopic eczema, neurodermitis constitutionalis, endogenous eczema, eczema flexurarum, *Besnier's* prurigo, asthma eczema or hay fever eczema have been created for this disease and indicate that still no precise clinical definition of AD exists (7). Additionally, the exact pathophysiological mechanisms leading to AD are still elusive and various studies have tried to unravel the key factors leading to this disease (8).

Since *Prausnitz* and *Kustner* described the existence of a human serum factor that reacts with allergens in 1921, much effort has been made to characterize the effector molecules of human immunity in depth. Today we know that the antibody called immunoglobulin E (IgE) which was discovered in 1967 by *Ishizaka* (9) is composed of two identical heavy and two identical light chains. These chains form the antigen-binding and the constant Fc domain, through which the IgE molecule binds to its cell surface receptors. Most individuals react with an increase of serum IgE levels as a defensive response to parasitic infections. IgE-mediated hypersensitivity reactions are largely regulated by T-lymphocytes and it is generally accepted that the increased prevalence of atopic diseases in recent years is due to a disturbed balance of Th1 cells and Th2 cells with a clear predominance of Th2 cells (10). The latter preferentially

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produce IL-4, IL-5, IL-10 and IL-13, which induce IgE production and activation of eosinophils, thereby facilitating the typical features of allergic diseases. The exact reasons for this disturbance are unknown but are generally attributed to the Western lifestyle (11).

In regard to AD, two types have been identified: the allergic form, which affects about 70-80% of the patients and occurs in the context of sensitisations towards environmental allergens and elevated serum IgE level and the intrinsic, non-allergic form, affecting a minority of 20-30% of the patients, occurring with low IgE serum levels and the absence of any detectable sensitisations (12). This suggests that elevated allergen specific IgE levels are not a prerequisites in the pathogenesis of AD. In recent times the concept of a “pure” type of AD without any previous or actual associated respiratory diseases is distinguished from the “mixed” counterpart associated with sensitisations against aero- or food- allergens, implying that elevated IgE serum levels can be associated with this disease but are not an obligate parameter for defining the disease.

PREDISPOSING FACTORS

The hygiene hypothesis

The generally held belief is that human fetal lymphocytes are skewed towards a Th2 profile as a consequence of intra-uterine priming by placental cytokines, hormones and possibly by transplacental allergen exposure (13). During the post-natal period, in non-atopic individuals the Th2 profile switches into a Th1 profile, probably in consequence of stimulations with different infectious agents. In contrast, in atopic individuals this reversal does not take place during the first month of life and gives rise to immunological reactions of the Th2 type. Additionally, factors of the modern life style, such as the use of antibiotics, the reduction of the family size and the increase of hygienic strategies lead to a reduction of bacterial stimulations and support this development (14).

Other risk factors include low birth weight, maternal smoking, early infection with respiratory syncytial virus, vaccination against *Bordetella pertussis* and early allergen contacts (15).

Recently, an effective prevention of early atopic diseases at children at risk by *Lactobacillus GG* has been described (16). In this study, perinatal administration of probiotics halved the development of AD during the first two years of life.

Other primary prevention strategies constitute in main part of the avoidance of early allergen exposures, i.e. food and inhalation or breast feeding, which is considered as the first choice for atopic infants. As another strategy, it has been found that the administration of antihistamines over a time period of 12-24 month was able to delay / prevent the development of asthma in AD children later in their life (17).

Genetics

The early age of onset, the familial occurrence of the disease and the high concordance rate of 77% in monozygotic twins and 15% in dizygotic twins suggest that AD represents a genetically complex disease, which develops against a background of gene-gene and gene-environment interactions (18). A number of candidate genes have been proposed by several research groups and have sometimes provided contradictory results about numerous linkages to various chromosomal regions. The genetic studies on AD may be classified into two different approaches: Linkage gene analysis studies and the studies of candidate genes. The first strategy is aimed at detecting an association of the AD phenotype with any of the chromosome regions. Meanwhile candidate gene studies investigate the association of

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polymorphisms of a specific gene with the atopic phenotype and are restricted to a single, already known gene locus.

Several chromosomal contain candidate genes, especially on chromosome 5q31-33 containing the Th2 cytokine genes IL-3, IL-4, IL-5, IL-13 and GM-CSF (19). In 1998, linkage analysis showed a gene encoded at 16p11.2-12 to be linked to the total serum IgE level (20). This gene region is the location of the interleukin-4 receptor alpha gene (IL-4R α). It was suspected that mutations leading to an increased IL-4 receptor reactivity such as Q576R could be responsible for elevated IgE secretion (21). Further on, 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 signalling and consequently IgE secretion (12).

Additionally, a linkage of high total IgE with 12q21-1q24.1, where the genes for interferon- γ (IFN- γ) and stem cells factor (KIT-ligand/mast-cell growth factor) are located, was detected (22).

Cookson et al. found that the gene locus 11q13, which represents the region for the β -chain of the high affinity receptor for IgE, has been linked to the AD phenotype and provided the first evidence for an effect of maternal imprinting on atopy (23), as he revealed a significant sharing of maternally inherited alleles in region 11q13 in sib pairs with atopic IgE responsiveness (22). AD has also been associated with a low-producer transforming-growth factor phenotype (24). Similarly, variants of the interleukin-13 coding region (25), functional mutations of the proximal promoter of the RANTES gene and the linkage of AD to chromosome 3q21, a region encoding the costimulatory molecules CD80 and CD86 have been identified as susceptible loci for AD (26).

The disturbance of skin function

Intense pruritus and scratching in combination to a cutaneous hyperreactivity and reduced threshold for pruritus underly the vicious circle of the continuous mechanical stimulation and the dysregulated cytokine release by keratinocytes.

As a basic defect of AD, the altered lipid composition of the stratum corneum is responsible for the xerotic aspect of the skin and determines a higher permeability to allergens and irritants, which could be typically found in AD patients (27). Ceramides serve as the major water-holding molecules in the extracellular space of the cornified envelope, and the barrier function of these complex structures is provided by a matrix of structural proteins bound to ceramides (28). A reduced content of ceramides has been reported in the cornified envelope of healthy and diseased epidermis in AD patients. This abnormal expression of ceramides leads to an abnormal expression of sphingomyelin deacylase-like enzymes. Even non-involved skin of AD patients is characterized by an severe dryness and an impairment of the barrier function of the stratum corneum, indicated by an increased transepidermal water loss. As an additional factor, ceramidase, which breaks down ceramide into sphingosine and fatty acid, is secreted significantly more from the bacterial flora obtained from lesional and non-lesional skin of AD patients. In the active phase of the disease, pH values shift towards alkalinity at both eczematous and uninvolved skin sites (29). Altogether the susceptibility to irritants in AD can be described as a primary, continuous defect of epidermal differentiation and functions in the presence of subclinical inflammation-induced skin damage in combination to a further impairment of the skin barrier during the active phase of the disease.

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PROVOCATION FACTORS

Food and aeroallergens

Food allergies have a pathogenetic role in a subset of AD patients, particularly in infants and contribute to the severity of the disease by the induction of skin lesions. In most of the cases, these food allergens are derived from egg, wheat, milk, soy and peanut and food-allergen specific T-cells have been cloned from the lesional and non-lesional skin of AD patients (30). Intranasal or bronchial inhalation challenge with aeroallergens such as house dust mite or animal dander can lead to the development or worsening of AD skin lesions and the degree of IgE sensitisations to aeroallergens is directly associated with the severity of the disease, while the reduction of exposures to some common allergens such as house dust mite is associated with a significant improvement of AD in some cases (31).

As a proof of concept the successful application of aeroallergens such as cat dander in the atopy patch test (APT) shows that it is possible to elicit eczematous skin lesions solely by external application of aeroallergens to the skin (32). The APT is assumed to evaluate the clinical relevance of IgE-mediated sensitisation in AD patients. The intermittent or continuous flow of aeroallergens and autoantigens in the process of facilitated antigen presentation may define the pathophysiological basis of the recurrent and self-perpetuating course of AD (33).

Microbes

Pityrosporum ovale is a lipophilic yeast commonly found on the head and neck area and is thought to elicit immediate and late-phase reactions in these patients. In over 60% of the AD patients even IgE to *Pityrosporum ovale* can be detected in the peripheral blood supporting the hypothesis of the importance of this organisms in AD (34).

Staphylococcus aureus is found in over 90% of patients with chronic AD skin lesions, reaching a density of approximately 1 million per cm² (35). Acute exsudative skin lesions can contain over 10 million of these organisms per cm² and increased numbers have been found even in normal skin and the nasal vestibula or intertriginous areas of AD patients (36). In contrast, only 5% of normal subjects harbour this organism on their skin surface.

Scratching is an important factor, enhancing the binding of the bacteria by disturbing the skin barrier and exposing extracellular matrix molecules known to act as adhesions to *Staphylococcus aureus* (such as fibronectin, collagens, fibrinogen, elastin, laminin). In addition, bacterial binding seems to be higher at skin sites with Th2 mediated inflammation by the induction of an enhanced production of these adhesins. *Staphylococcus aureus* is capable to secrete toxins, such as enterotoxin A (SEA) and B (SEB) or toxic shock syndrome toxin-1 at the skin surface, which serve as so-called "superantigens" (37).

Staphylococcus aureus superantigens are presented as "ordinary" antigens in the peptide-presenting groove of the major histocompatibility complex MHC to the respective antigen-specific T cell. On the other hand, the intact proteins are capable of bridging the MHC complex to all T cells with the same β -chain family, irrespective of their antigen specificity.

An analysis of the peripheral blood skin homing CLA⁺ T cells from these patients and T cells in their skin lesions shows that they have undergone a T-cell receptor V β expansion consistent with superantigenic stimulation (38). Superantigens augment the synthesis of allergen-specific IgE and induce glucocorticoid resistance in these patients (39). In most of the AD patients specific IgE antibodies against staphylococcal superantigens could be found, which correlate with disease severity. AD skin is also deficient in antimicrobial peptides needed for host defense against bacteria, fungi and viruses. Together, the higher colonisation with microbial hosts in combination with an inadequate host defense might perpetuate the course of disease.

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Autoallergens

Immunglobulin E autoreactivity has been implicated as a immunopathogenetic factor in AD. In addition, molecular analysis of allergens has revealed striking similarities between environmental allergens and human proteins, leading to the hypothesis that autoimmune reactions might play also a role (40). Recently, IgE-reactive autoantigens directed against human proteins have been cloned from human epithelial copy DNA (cDNA) expression libraries and have been found to represent primarily intracellular proteins (41). Autoantigens characterized for AD are *Hom s 1-5* and *DSF70* (42). These autoantigens seem to act as adjuvants to the immunological mechanisms in AD patients with elevated IgE levels, as they have been detected in IgE-immune complexes of AD sera and the release of autoallergens from the damaged tissue, putatively triggered by mechanical factors such as scratching, could trigger responses mediated by mast cells, T-cells and IgE. This notion is supported by the observation that IgE autoallergen levels decrease in consequence of successful treatment. Together these finding imply that immune responses initiated by environmental allergens might be maintained by human endogenous antigens.

Contact allergens

Possible contact allergens, which penetrate can penetrate the epidermal skin barrier in AD patients more easily due to its impairment, include nickel, latex, vehicle of external preparations and fregnances. Furthermore irritative agents such as wool or disinfectants might lead to some exacerbation of the diseases. Therefore, avoidance or even reduction of these factors in the environment, should be one of the basic principles in the management of the disease (18).

Neuroimmunological Factors

One important provocation factor of AD, which can lead to the exacerbation of the disease is stress. Even though the exact mechanisms of the interaction of the skin immune system and the nervous system have not yet been identified, it is believed that this phenomenon might be mediated by neuroimmunological factors such as neuropeptides, which can be found within the epidermal nerve fibres in close association with epidermal Langerhans cells (43). Some of these neuroimmunological mediators, such as calcitonin gene-related peptide (CGRP) are able to exert an inhibitory effect on the antigen presenting capacity of LC. In addition, activated keratinocytes are able to produce the neuropeptide proopiomelanocortin-derived hormones (α -MSH), which in turn seems to promote IL-10 secretion in order to induce negative feedback signals for the down-regulation of the inflammatory reactions in the skin (44). This neuroimmunological network in the skin of AD might provide new therapeutical intervention strategies in the future (45).

IMMUNOPATHOGENIC FACTORS

Monocytes

Increased cyclic adenosine monophosphate (cAMP) hydrolysis by genetically determined overactive phosphodiesterase in monocytes leads to an increased production of mediators such as prostaglandin E and IL-10 (46) . This mechanism turns to inhibit Th2 responses and accentuates IL-4 secretion by Th2 cells and it appears that in addition to prostaglandin E2, IL-10 acts to regulate the balance between Th1 and Th2 functional responses, accounting for many atopic features, including IL-4, IL-5, IL-6 production by T-cells, increased IgE synthesis, decreased interferon- γ production and impaired cell-mediated immune responses

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(47). The question of a defect on the level of monocytes has been an issue for a long time. It has been suggested that monocytes from atopic individuals display enhanced survival and release distinct soluble mediators. Monocytes of patients with allergic AD display enhanced surface expression of the high and low affinity receptor for IgE (FcεRI and FcεRII) and the IL-4Rα chain and in this way can be distinguished from monocytes in patients with non-allergic AD, in which the expression of these surface marker is low (12). Additionally, the composition of different monocyte subsets (48), which have been identified in the peripheral blood recently, is distinct in the acute phase of the disease.

Eosinophils

The common presence of peripheral blood eosinophilia and elevated serum levels of eosinophil granule proteins suggests that eosinophil degranulation plays a major role in AD. Increased serum levels of eosinophils with enhanced survival have been detected and especially on eosinophils from allergic AD patients, the functional CD137 receptor (49), which stimulates T-cell activation and differentiation, could be detected. The granular protein elevations found in the peripheral blood correlate with the disease activity. In the skin, Th2 cytokines together with chemokines such as eotaxin and monocyte chemoattractant protein 4, promote the influx of activated eosinophils into the skin of AD (50). Extensive eosinophil major basic protein deposition has been demonstrated in the lesional skin (51).

Keratinocytes

Dysregulated signal transduction in epithelial cells could favour an exaggerated response to inflammatory stimuli. Altered cytokine synthesis by skin cells is proposed to increase the expression of TNF-α, IL-1β and IL-12 mRNA in the skin of AD after contact with detergents or aeroallergens (52). An intrinsic defect of keratinocytes found in AD leads to an enhanced secretion of GM-CSF, IL-1 and TNF-α and might result in main part from the altered transcriptional control or activation of the signal transduction cascade.

T-cells

One of the most prominent features of AD is the prominent skin infiltration with activated CD4+ T-cell in skin lesions of AD. Immunohistological investigations have shown that the dermal infiltrate in the skin lesions is mainly composed of CD4+ and CD8+ cells with a CD4/CD8 ratio similar to that found in the peripheral blood. It is well known that the human immune system harbours a powerful army of cutaneous T cells, which seem to be highly activated and bear the cutaneous lymphocyte antigen (CLA) on their surface, which enables them to be immediately recruited into the skin on invasion of foreign antigens (53). Homing of T-cells to the skin is determined by the interaction of CLA with vascular cell surface antigens expressed on dermal blood vessels, such as E-selectin. Other important co-factors in this homing process are alpha-6 integrin, VCAM-1, ICAM-1 and IL-8 and are found in higher levels in the peripheral blood of AD patients (54). Following antigen presentation by DC, Th0 precursors are triggered to differentiate into Th1 or Th2 cells. While the Th1 response is associated with delayed-type hypersensitivity reactions (DTH) and the predominance of interferon-γ and IL-2 secretion, the Th2 pattern is associated with an increased secretion of IgE and IgE-mediated reactions as even as the predominance of IL-4, IL-5 and IL-13 (55). In this regard, AD has a particular status, since it is clinically a cell-mediated hypersensitivity reaction. Analyses of biopsy samples from unaffected skin of AD have an increased number of Th2 cells expressing mRNA of IL-4 and IL-13. While acute AD lesions do not contain

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significant numbers of cells expressing mRNA of IL-5, IL-12, GM-CSF or IL-12, the mRNA amount of these cytokines increases in the chronic phase while the mRNA level of IL-4 and IL-13 expressing cells decreases. Together with kinetic studies from lesional skin of atopy patch test reactions a biphasic course of AD is suggested, in which the initial phase is characterized by a Th2 pattern. This phase switches into the chronic phase, predominated by a clear Th1 profile (56). This switch is probably started by local production of IL-12 from infiltrating eosinophils or inflammatory dendritic epidermal cells or both.

Inflammatory cytokines and chemokines in the skin

The paradoxical reduction in cell mediated immunity in AD is a result of the increased production of immunosuppressive cytokines such as IL-10 and TGF- β that have been observed in AD. Further on, the chemoattractant for CD4⁺ T cells, as even as the chemokines T cells expressed and secreted (RANTES), macrophage derived chemokine (MDC) and thymus and activation regulated chemokine (TARC) could be found in AD (57).

Persistent skin inflammation in chronic skin lesions could induced by mediators which enhance the survival of eosinophils, monocytes / macrophages and DC such as IL-5 or GM-CSF, which could be found in high amount in chronic AD skin (58).

The role of Fc ϵ RI-bearing dendritic cells

Since most of the allergens atopic patients react to do not have direct access to B cells in the blood or lymphoid tissue, allergen capture, processing and presentation to T cells must be performed by antigen presenting cells located at the interface between the environment and the body such as the skin . DC in tissues are highly specialised for capturing and processing foreign or autologous antigens or haptens. Uptake of high-molecular weight antigens by DC may occur through macropinocytosis or more specifically through a number of membrane receptors such as Fc γ R2 or Fc ϵ RI, the high affinity receptor for IgE (59). Initially, it was assumed that Fc ϵ RI is exclusively expressed on the effector cells of anaphylaxis, i.e. mast cells and basophils, since the first evidence for an IgE-binding capacity of epidermal LC in the lesional and non-lesional skin of AD has been provided. Later on the presence of specific transcripts for Fc ϵ RI chains as well as the surface expression of Fc ϵ RI on LC and another DC subtype, the so called inflammatory dendritic epidermal cells (IDEC) in the epidermis of AD (60) lesions has been reported and prompted a resurgence of interest in the function of these Fc ϵ RI bearing DC. A characteristic feature of AD is the prominent skin infiltration with hyper-stimulatory cells of the DCc lineage (61). However, it was the combination of immunomorphological and ultrastructural characterizations, which led to the delineation of two different epidermal DC populations in this disease: Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) (62-64). Classical epidermal LC are characterized by their tennis racket shaped cytoplasmic Birbeck granules and their CD1a⁺, Langerin (CD207)⁺ (65) phenotype. In contrast, IDEC lack the typical Birbeck granules but express the mannose receptor (CD206), which mediates the uptake of bacterial components by endocytotic processes, (62;66-72). A hallmark of both, epidermal LC and IDEC in the skin lesions of AD patients is the elevated expression of the high affinity receptor for IgE (Fc ϵ RI) and their putative role in antigen focusing (73)

Indeed the receptor is not constitutively expressed on DC but seems to be regulated by signals of the inflammatory surrounding microenvironment such as local IgE, a reducing microenvironment or TGF- β levels. The highest expression of Fc ϵ RI is displayed on LC and IDEC from lesional skin of AD and correlated positively with the IgE serum level. Recent concepts support the hypothesis that IDEC, which are assumed to be of a rather monocytic origin, are recruited in

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the acute phase of AD into the epidermis by signals mediated from cells of the inflammatory micromilieu. Interestingly, after successful topical treatment of the AD lesions, the number of IDEC in the epidermis decreases below the detecting level, indicating that this cell type is strongly related to the state of inflammation of the skin.

FcεRI- bearing DC play a crucial role in the pathophysiology of AD, since they may represent the missing link between aeroallergens penetrating the epidermis due to the reduced skin barrier and antigen-specific cells infiltrating the skin lesions. This concept is strongly supported by the observation that the presence of FcεRI-expressing, LC bearing IgE molecules is a prerequisite for producing eczematous skin lesions by the application of aeroallergens to the skin of AD patients in the atopy patch test.

Multimeric ligands, which have been shown to be taken up by FcεRI-mediated endocytosis are channelled into MHC class II compartments and peptide loading of newly synthesized MHC class II molecules leads to an optimal antigen presentation to CD4⁺ T cells. DC expressing high receptor densities will display full activation upon FcεRI receptor ligation, most probably inducing the synthesis and release of mediators, which might help to enhance the subsequent antigen presentation.

It is possible, that FcεRI-expressing DC armed with specific IgE can boost the secondary immune response and further trigger the IgE synthesis by recruiting and activating more antigen-specific Th2 cells or IDEC from the peripheral blood into the skin. DC are the most potent stimulators of naïve T cells, i.e. they are committed to initiate primary immune responses. It cannot be excluded that even complex allergenic structures efficiently captured via FcεRI on DC are processed by these cells in a way leading to the unmasking and presentation of cryptic peptides/epitopes, the T cell never met before. This would initiate a primary reaction against these unhidden antigens, thereby helping to increase the variety of the IgE specificities. Antigen uptake and aggregation of FcεRI on DC could lead to the *de novo* synthesis and release of mediators capable of directing T cells toward a defined phenotype and function of Th1 or Th2 cells.

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