

Review Article

Hypothesis: from epidermal barrier dysfunction to atopic disorders

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The rôle of a genetically-impaired epidermal barrier as the primary cause of the rapid increase in prevalence of atopic dermatitis and respiratory atopy is proposed, based on available clinical and experimental data. The subsequently increased exposure to irritants and allergens postnatally in predisposed individuals would lead in a subset of these to a specific TH₂ cell activation favouring the development of IgE responses to atopens. Other routes of sensitization are probably important, but skin offers a good target to implement prevention strategies, so far completely ignored in the prophylactic recommendations given to high-risk families. Candidate genes for skin-barrier impairment are possibly those associated with ichthyosis vulgaris and X-linked hypohidrotic ectodermal dysplasia.

Key words: atopic dermatitis; epidermal barrier dysfunction; irritants; allergens; atopens; genetic basis; candidate genes; patch testing. © Munksgaard, 1999.

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An increasing prevalence of atopic dermatitis (AD) has been shown in several epidemiological studies worldwide over the last 3 decades. However, a clear link with genetic predisposing factors is still lacking to explain such a trend within a rather short period of time. Better socio-economic status linked to a 'westernized' urban life style is supposed to be involved (1). Such influences may increase environmental hazards, causing increased exposure to irritants and allergens. Most etiologic searches have, however, been focused on immunologic mechanisms, especially since the discovery of immunoglobulin (Ig) E.

Immediate reactions to foods are common in children with AD, and correspond to IgE responsiveness (2). They are however not clearly linked to eczema flares. Overall, if there is a global link between increased IgE production and severity of atopic dermatitis (3), a convincing demonstration of the primary noxious rôle of IgE in promoting eczema/asthma lesions remains to be made. A possible autoimmune rôle for IgE targeting epithelia in AD has been suggested (4). Regulatory influences of IgE on immune responses and the inflammatory cascade at target sites after the intro-

duction of specific allergens are still possible (5). Thus, this important marker, now better understood as the result of a T-cell dysregulation towards the production of TH₂ cytokines, is at best *associated with atopic status*, but not causative of lesions in target tissues/organs when the 2 major atopic phenotypes are considered (AD and asthma).

Atopy, when defined as a genetic trait predisposing to privilege TH₂ responses to common environmental allergens also designated as atopens, can be considered as a latent trait in a substantial proportion of the population. The size of this population is yet to be determined, since most epidemiologic studies indicate constant progression of the epidemic. It is probably dependent on several genes, some of which have already been studied by molecular epidemiologists, and linked to IgE regulatory pathways (6). This trait is probably associated, due to its prevalence, with some unknown benefit to carriers. When and how T-cell immune dysfunction leading to hyper-IgE associated with atopy is turned on, remains elusive. These questions, which have led to some interesting hypotheses concerning fetal environment (7–9), are central to the understanding and prevention of this

group of disorders. Several arguments suggest that we should focus our attention directly on the skin not only as a target of atopy but as a primary step in the initiation of AD (10) and, more generally, atopic disorders.

Relative to body mass, the skin surface is at its maximum at birth, and corresponds to the main interface with the environment after delivery. At the clinical level, skin signs together with those confined to the gastro-intestinal tract, are the earliest related to atopic status. AD is present in most patients in the 1st year of life and it is not rare to see patients with suggestive cutaneous features in the first 2 months of life. Skin is most frequently first involved in air-exposed areas, and well-protected sites like the napkin area are frequently spared (11). Irritant factors have been suspected as causing this pattern, such as contact with detergent-washed materials. However recent studies have shown that sensitizations to aeroallergens occur very early, using the atopy patch test (12) as a model of contact sensitization to unusually large molecules (proteins) which, specifically in patients with AD, induce a TH₂ response mediated by epidermal Langerhans cells (LC) ((13) and review in (14)).

The morphology of the epidermis in non-lesional skin of AD patients is considered as normal by most authors, but subtle microvillous changes have been detected in non-lesional corneocytes using electron microscopy (15). Staphylococcal colonization, a near constant in AD, and subsequent infection may be caused by increased stickiness of staphylococci to such abnormal corneocytes. Several lines of evidence indicate that the barrier function of the epidermis is functionally impaired in AD: lipid constituents, especially ceramides, which act as molecular rivets to consolidate the stratum corneum, are depleted (16); filaggrin, a precursor of hydrophilic molecules important in moisturizing the stratum corneum, is also diminished (17); transepidermal water loss (TEWL), which is a good marker for a "leaking" epidermis, is increased (18).

Hypothesis

A (some) common genetic polymorphism(s) causing a functional impairment of the epidermal barrier in the 1st month of age increase(s) the probability of being sensitized to allergens, and especially to atopens.

A genetic trait influencing epidermal terminal differentiation would allow excessive permeability of the epidermis to irritants allergens and atopens. This mechanism is unlikely to be activated *in utero*, but could explain very early in life a primary sens-

itization via the epidermis in a substantial proportion of the population. More than 9 out of 10 infants with moderate AD tested before 1 year of age react positively and in isolation to the atopy patch test, the earliest atopy marker, with a subsequent decrease with age (19). It is striking to note that the incidence of contact allergy in children with atopic dermatitis follows a similar pattern (20). Furthermore, the recently identified "Lucky Luke" dermatitis (21) due to rubber components of disposable diapers, which seems currently to be the commonest form of contact dermatitis before 2 years of age, is also seen nearly exclusively in children with AD, who usually are spared of AD lesions in this protected location. Thus, large molecules as well as small ones can enter the skin and trigger T-cell cutaneous responses, either TH₁ or TH₂ in infancy, a finding more in favour of a primary barrier problem than a primary immune dysfunction.

What Kind of Link could we Hypothesize between the Abnormal Cutaneous Barrier in AD and IgE Responsiveness?

It could be speculated that, for atopens, the initial cellular response promotes TH₂ patterns individuals with associated predisposing "enhancer" alleles favouring IgE responsiveness. Individuals without such genetic background may just develop a limited contact hypersensitivity response and no switch of B-cells towards IgE production. They would correspond to the so-called "intrinsic" AD with negative prick tests, in the absence of specific IgE, but which may still respond to aeroallergen patch tests, at least in infancy, when the cutaneous barrier is at its most permeable. It is also possible that, in some individuals, repeated encounters with atopens could promote tolerance and clinical improvement (10, 22). In the category of IgE responders, the following steps of TH₂ cells helping to activate B cells would provide subsequent IgE responses and positivity on prick testing with atopens, as already shown in the mouse (23). This dual model is compatible with the data indicating that T-cell cytokine patterning may depend on an idiosyncratic binding strength of antigenic peptides to T-cell receptors, as well as to concentration of antigens (24).

The usual clinical course, with improvement of AD in the 2nd year of life, could be due to improved epidermal differentiation due to normal postnatal maturation, leading to a parallel decrease in prevalence of positivity on aeroallergen patch testing. However, memory cutaneous T-cells remaining in the skin-homing compartment could be stimulated once more if the allergen could reach

this compartment via the skin again (if irritated and more "leaky") or via the mucosal route and the blood (inhaled and ingested allergens for cross-reacting antigens). The common shift towards respiratory manifestations may be linked either to the recirculation of such homing T-cells, which may lose their homing-site-specific receptors under some environmental conditions, as they do in vitro (25), or to the consequences of common viral respiratory illnesses, which favour the entry of aeroallergens via the respiratory epithelium.

For which Genes Involved in Epidermal Barrier Dysfunction should we Look First?

At least 2 genetic epidermal disorders associated with an increased prevalence of AD could be considered as good candidates. Ichthyosis vulgaris is an autosomal dominant disorder linked to filaggrin-defective expression in the epidermis. This condition is common, and associated in at least 4% of cases with AD (26). However, the distinction of this phenotype from AD is so blurred that the rate of association might be higher (27). Another argument for looking at this disorder as a genetic model is that the degradation of filaggrin, a structural protein which packages keratin filaments leads to urocanid acid, a molecule which may serve as an immunomodulator in the epidermis, providing a link between a structural protein basis and immune pathomechanisms in situ (28).

The already-noted maternal effect on the inheritance of AD might be associated with a predisposing gene on the X chromosome (29). X-linked hypohidrotic ectodermal dysplasia is associated with a very high frequency with mild AD and asthma (30). The EDA gene, expressed in keratinocytes, hair follicles and sweat glands, is homologous to the mouse *Tabby* gene which interacts with the EGF receptor pathway (31). This hypothesis is thus easily testable and could provide interesting therapeutic consequences.

Practical Deductions

We should characterize further the skin permeability problem in AD in order to design improved barrier creams (32), both for prevention of disease in at-risk babies and as an associated treatment in affected individuals (33). We also have to address, with epidemiological studies, the issue of what harms the epidermal barrier in the "westernized" at-risk population. In particular, we should probably look more closely at the aggravating changes in probably more aggressive skin care and the quality of water used for skin hygiene (34). Eventually, gene or gene-product delivery in situ,

to compensate for underlying defects, could be a tentative solution in the long term, to avoid repeated local treatment which is difficult in older children and adults.

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