

# 1. Putative mechanisms underlying chronicity in atopic eczema

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Atopic dermatitis (AD) is a chronic inflammatory skin disease which develops on a complex genetic background, the so-called atopic diathesis. AD is in most, but not all, patients characterized by the presence of elevated total serum IgE levels. However, a subgroup of atopic patients exhibits normal IgE levels and mechanisms contributing to the so-called 'intrinsic' or 'non-allergic' form have been the matter of intensive research work in the last years. These forms have been particularly studied in the context of AD, which has also led to a new nomenclature. Moreover, we now have increasing evidence for the putative role of autoimmune phenomena in the complex pathophysiology of AD. Mainly adult patients exhibit specific IgE directed against self proteins of epidermal origin. Therefore, AD may be considered as a continuous disease in which, however, depending on the age, different mutually not exclusive pathomechanisms may be of relevance.

## INTRODUCTION

Atopic dermatitis (AD) is a common disease, the classification of which has caused confusion not only in its treatment, but in any discussion of its pathophysiology. The World Allergy Organisation Nomenclature Committee (WAONC) has recently proposed a new classification system, enabling all those involved with the condition to use the same definitions. This is essential when for example performing genotype studies, which are expensive and time-consuming.

## PROPOSED NEW CLASSIFICATION FOR ECZEMATOUS SKIN DISEASE

Ecematous skin disease is to be split into three different groups: (i) contact dermatitis comprising the allergic and toxic types, (ii) other dermatitis such as seborrhoeic dermatitis and stasis dermatitis, and finally (iii) eczema. Eczema is subdivided into two types, atopic eczema/dermatitis with the IgE-mediated/extrinsic form, and eczema in the non-IgE-mediated/intrinsic form. A theoretical and practical problem with the classification is that patients with eczematous skin disease are seen by different clinicians at different ages; paediatricians, general practitioners and dermatologists. They may each experience the disease differently as the disease develops. A paediatrician will say that around 50% of his patients are not sensitized, whereas among those seen

by dermatologists 80% or more are sensitized. This apparent inconsistency can be explained by the different ages of the patients.

## PROPOSED DISEASE HYPOTHESIS

The hypothesis is that the disease is a continuum of one condition and not two or three different types. The hallmarks of the non-IgE-mediated/intrinsic form of eczema are an impaired skin barrier function and inflammation due to interaction between an 'antigen', the exact nature of which is under investigation, antigen-presenting cells and T cells. There is a typical blood picture of normal IgE levels, absence of FcεRI expression on monocytes, but increased eosinophils. The skin picture involves FcεRI-negative antigen-presenting cells, activated T cells, IL-5, IL-10 and IL-13 and eosinophils. This is the typical pattern of the condition in infancy until the age of 4–8 years.

Psoriasis and AD are pathophysiologically regarded as separate diseases. Psoriasis is considered a disease involving Th1 cells, with a well documented genetic background. AD is associated with genetic variants linked to genes such as CD86, RANTES, FcεR1B and is rather a disease of Th2 than Th1 cells. There are, however, two or three genetic loci shared by the two conditions, which involve the regulation of the inflammation at the level of the skin immune system.

Inflammation is due to both static and dynamic components of the skin immune system. The static components of the skin immune system are keratinocytes, fibroblasts and endothelial cells, which may share common genetic loci and most probably provide pro-inflammatory signals. The dynamic or haemopoietic components are T cells, Langerhans cells, dendritic cells, macrophages and mast cells which produce antigen-specific signals. The static and dynamic components contribute in concert to the inflammation, with an inflammatory microenvironment specific to each individual disease. Genes that are common to AD and psoriasis may involve general aspects of the inflammatory process. The genes relative to sensitization are probably those involving the IgE-specific aspects of inflammation, e.g. IgE receptors. On this basis eczema, which presents in early childhood, involves shared genetic loci. Only in the presence of the AD specific loci the disorder will develop into the sensitized (extrinsic) form of classic atopic eczema. Such patients are also at risk of developing asthma. During early infancy the

sensitization increases and reaches up to 60–80% of the children by the age of 4–8 years, who then present to dermatologists with classic AD. This development concept agrees with recent epidemiological data on the disease presentation.

The pathophysiological puzzle of the inflammatory components of eczematous skin disease is shown schematically in Fig. 1 (1). The effect of Langerhans cells producing inflammation by Th2 cells and of dendritic cells producing inflammation by Th1 cells is apparent. In the early stage of the disease there is a Th2-type response, while in a later phase there is a Th1 response. A by-product of this hypothesis is that we have found that different immunomodulating cells respond differently to immunomodulators such as tacrolimus.

## EFFECT OF *STAPHYLOCCUS AUREUS* ENTEROTOXINS

The inflammatory nature of *S. aureus* enterotoxins is well documented (2). There are decreased defensin levels in such patients, which explains why they are prone to staphylococcal colonization (3). Under normal conditions the enterotoxins should be neutralized by defensins. However, if they are lacking, the inflammatory process can develop.

## PRESENCE OF SPECIFIC ANTIMICROBIAL IgE

The presence of specific antimicrobial IgE in patients with eczema, AD and controls is shown in Table I (4). Sensitization to food allergens and microbial toxins is very apparent in cases of AD. However, in patients with

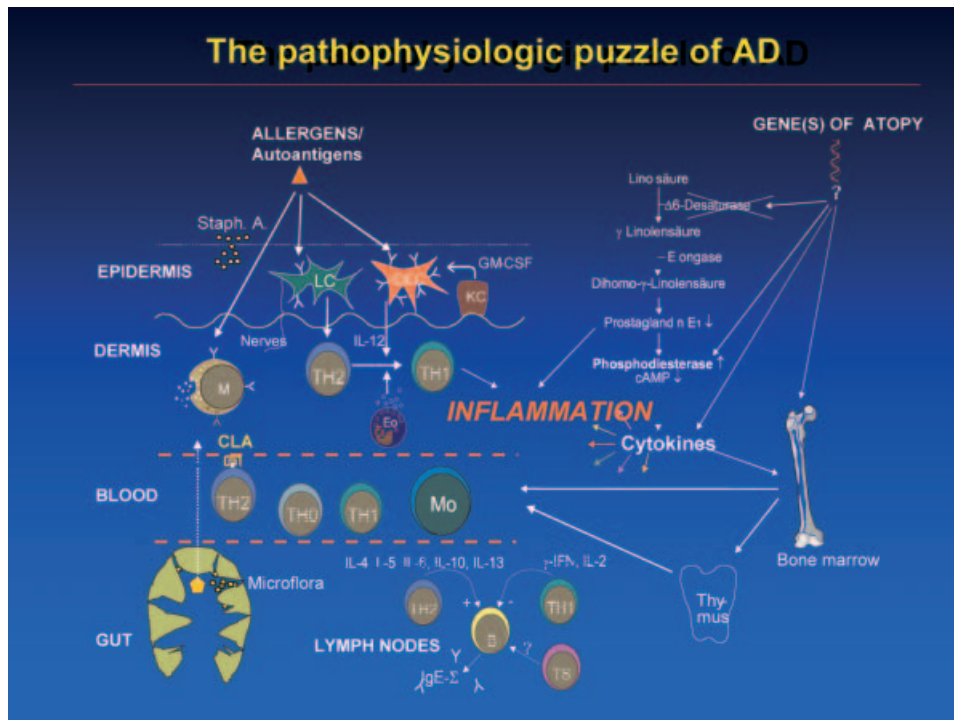


Fig. 1. Pathophysiological component of skin inflammation. Taken from Wollenberg & Bieber (1).

Table I. Presence of IgE against antimicrobials (%)

IgE to	Atopic dermatitis* (n=90)	Eczema† (n=24)	Controls (n=30)
Food/aeroallergens	100	0	0
SEA‡, SEB, SEC, SED, TSSDT, <i>C. albicans</i> , <i>M. sympodialis</i>	85	53	0

\*Atopic dermatitis is here defined as atopic eczema with type I allergies.

†Eczema is defined as atopic eczema, but without type allergies to food or aeroallergens.

‡SEA, staphylococcal enterotoxin A, etc.

Taken from Novak et al. (4).

eczema, according to the new classification, one half produced antimicrobial specific IgE, although they were not allergic to food allergens. These data again show that the very precise separation of the intrinsic and extrinsic forms of eczema may be artificial. It is likely that the more we discover about the mono-sensitized form of the disease, the less likely the intrinsic form will be supportable. It is unlikely that a non-specific IgE exists, but the specific allergen has not been identified. Dendritic cells may have a specific role in the control of IgE synthesis and in widening the IgE spectrum (Fig. 2) (5). Recent evidence has been obtained showing cross reactivity between some enzymes of microbial allergens (*Malassezia sympodialis* mangan-superoxide-dismutase, MnSOD) and human variants of these components (Schmid-Grendelmeier, personal communication). IgE cross-reactivity with protein extracts from keratinocytes has also been found in a substantial proportion of our patients.

#### IS ATOPIC DERMATITIS AN AUTOIMMUNE DISEASE?

The concept of psoriasis as a putative autoimmune disease is gaining acceptance. Could the same apply to AD? The majority of our adult patients have auto-reactive T cells, and IgE against aeroallergens, food allergens, infectious agents *S. aureus* and *M. sympodialis*, but also against autoallergens of which there are three types. Type A: to mangan-superoxide-dismutase, profilin, lipocalin, alfa-NAC, and a 20-kDa

autoantigen. Type B: autoallergens such as atopy-related autoantigens (ARA) Hom S1-S5 and Hom S4 secreted by keratinocytes are found and there could be autoallergy induced during chronic inflammation. Type C: autoallergens to structurally modified proteins are known. There is a need for further investigations to fully determine the role of autoallergens in the context of AD.

#### CONCLUSION

In conclusion this concept of the pathophysiology of eczema should influence our management of the disease. In particular, it is essential to treat the disease as soon as possible and as intensively as possible to minimize its future development. By downgrading the immune response we may prevent the later allergic asthma and the development of autoimmune parameters.

#### DISCUSSION

*Leung*; Do you have any idea on what is common link between psoriasis and AD? A common link is the steroids put out by the body in response to stress. Do patients with dermatitis have a problem with the stress response?

*Thestrup-Pedersen*; If you are treated for long periods with steroids, could this not complicate the picture?

*Leung*; There are data related to asthma which indicate that the disease gets worse at night, when endogenous

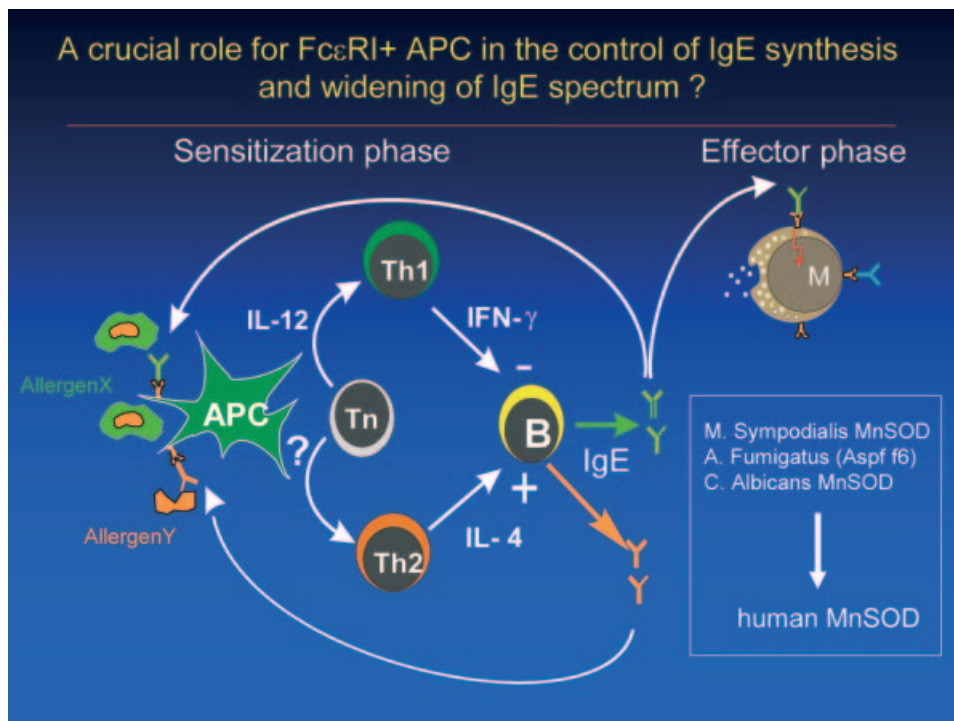


Fig. 2. Role of FcεRI+ve antigen-presenting cells in controlling IgE synthesis (5).

steroid production is low. You can control for this with ACTH or low dose steroid.

*Bieber;* Neurologic control of inflammation is a growing issue. The crucial question is: Does the disease commence with itching or inflammation?

*Leung;* I think it is dangerous to use total IgE to separate patients. In allergic rhinitis there is a normal IgE level, but they are very atopic. Does intrinsic AD have IgE on the high affinity receptor?

*Bieber;* Any inflammation in the skin induces an increase in the IgE receptor and I would expect IgE to be there, but I have no proof.

*Leung;* Do the people who have IgE to superantigens or other microbes already have IgE on their dendritic cell surface?

*Bieber;* We are looking at that. By skin stripping we are looking at cell-bound IgE. We can define the specificity of the IgE in skin cells and compare this to IgE in the blood.

*Thestrup-Pedersen;* I agree with you that the important thing is to treat very early on and keep the inflammation down. Is an IDEC cell (inflammatory dendritic epidermal cell) something important for atopy?

*Bieber;* The IDEC cells are not specific for AD, you can find them in many other skin diseases. The issue is that you only find IDEC cells with tremendous expression of IgE in AD. You can generate the same IDECs from

circulating monocytes in the same patients. This is not possible with monocytes from other patients.

*Leung;* Where do you think the naïve T-cell becomes a Th1-cell, in the lymph nodes or the skin?

*Bieber;* It could be both sites.

*Agner;* We see some patients with food allergy which can disappear, but it does not seem to affect the disease similarly.

*Bieber;* The concept of one disease is still being developed. We have to be careful to use the total IgE. It could be that we may end up with only 2–3% of so-called intrinsic patients.

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