

Molecular basis of atopic dermatitis

Sonja Bonness and Thomas Bieber

Purpose of review

Atopic dermatitis is a common chronic inflammatory skin disease and there are numerous publications on this topic. This review will focus on developments in understanding the molecular basis of atopic dermatitis while considering the genetic background, skin barrier impairment, immune system deviation and microbial superinfections.

Recent findings

Atopic dermatitis is a complex genetic disease in which gene–gene and gene–environment interactions play a key role. Surprisingly some genetic regions of interest were found to be overlapping with loci identified to play a role in another very common inflammatory skin disease, psoriasis, while no overlap has so far been observed with asthma. Impairment of the skin barrier followed by antigens trespassing seems to play an important role, favouring sensitization via transepidermal penetration which is the focus of current investigations. Superinfections by pathogens such as *Staphylococcus aureus* due to a weak innate defence seem to be significant in atopic dermatitis as they elicit a strong inflammatory response.

Summary

Atopic dermatitis is a chronic inflammatory skin disease with a high incidence in school children and adults. Disease pathogenesis is complex and the background is multifactorial, making the underlying predispositions elusive. Understanding new pathogenic pathways may lead to the development of new drugs with enhanced benefit for the patient.

Keywords

atopic dermatitis, dendritic cells, epidermal barrier dysfunction, innate immunity

Introduction

Atopic dermatitis is the most common pruritic chronic inflammatory skin disease. Triggered by a multifactorial setting which includes genetic and environmental factors, many attempts have been made to find out the most important causative conditions. There is a strong relationship between atopic dermatitis and other atopic conditions – asthma and allergic rhinitis – but the pathophysiological links are far from being understood. This review will concentrate on the molecular basis of atopic dermatitis.

Genetic background

Children with a parental history of atopic dermatitis are at an elevated risk of developing skin symptoms and it has been observed that this is a more potent risk factor than asthma or allergic rhinitis [1]. There are two traditional approaches to identify genes that relate to disease development. In linkage studies or positional cloning (which have been successfully used for monogenic diseases) genes are mapped to a chromosomal region in families with affected siblings without any knowledge about the pathophysiology. The other approach addresses specific candidate genes which are thought to play a role in atopic dermatitis and these genes are investigated more closely. So far, four linkage analysis have been published [2–5], and surprising, it was found that some of the identified loci overlap with regions known to be linked with psoriasis, for example, 1q21, 3q21, 17q25 and 20p12 [6].

In the exploration of candidate genes, understanding the underlying pathomechanisms is a prerequisite. Here, single nucleotide polymorphisms are analyzed in a case–control setting – that is, in several hundred affected patients and control individuals. To date, a broad number of candidate genes have been described [7••] in approximately 32 publications. One of the gene clusters identified is located on chromosome 5q31–33 and bears the genetic information for T helper type 2 (Th2) cytokines like interleukin (IL)-3, IL-4, IL-5, IL-13 and granulocyte colony stimulating factor (GM-CSF) [8]. Other examples include mutations in the promotor region of RANTES (regulated on activation, normally T-cell expressed and secreted) (17q11), the β -subunit of the Fc ϵ RI (11q12–13), the Filaggrin gene (1q21) (see below), the gene for mast cell chymase (14q11.2) and many more. Since discussing all the suspected genes would be beyond the scope of this review, the reader is referred to the outstanding review article by Morar *et al.* 2006 [7••] and the PRACTALL Consensus Report 2006 [9••]. A

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Correspondence to Thomas Bieber, MD, PhD, Department of Dermatology and Allergy, Rheinische Friedrich-Wilhelms-University Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany
Tel: +49 228 287 1 4388; fax: +49 228 287 1 4881;
e-mail: thomas.bieber@ukb.uni-bonn.de

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Abbreviations

IDEC inflammatory dendritic cell
Th T helper

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third and novel approach to identifying genes of interest is to perform microarray studies, which allow genome expression profiles to be compared. Since this method has only recently been established, the data are limited and need to be expanded upon, especially those relating to control specimens from healthy donors.

Epidermal barrier dysfunction

Epidermal barrier dysfunction seems to be one of the central aspects in the pathophysiology of atopic dermatitis [10^{••}] and is well documented by increased transepidermal water loss. In patients with atopic dermatitis the cornified envelope shows an altered structure and activity of proteases and protease inhibitors compared with those of healthy controls. One gene that has been found to correlate with atopic dermatitis is the *SPINK5* gene, which codes for the protein lymphoepithelial kazal-type 5 serine protease inhibitor (LEKTI). *SPINK5*-deficient mice develop symptoms of the Netherton syndrome [11] and mutations in mice lead to increased transepidermal water loss which results in death by dehydration [12]. Elevating the skin pH by using soap increases protease activity and therefore the breakdown of the cornified envelope. There is evidence that the lipid composition is different compared with healthy skin, in part caused by reduced activity of δ -6-desaturase and lack of linolic acid. One key protein in the epidermis that is crucial for the protective function of the skin barrier is filaggrin, which is responsible for the arrangement of the keratin intermediate filaments into bundles and is located at the cornified envelope. Currently, this protein is the focus of many investigations since reduced expression has been reported. A recent genetic study [13^{••}] showed a strong correlation between atopic dermatitis and mutations of the filaggrin gene. Two mutations (2282del4 and R501X) were found to be common in European populations. There were other mutations of the filaggrin gene found in a Japanese population with atopic dermatitis [14[•]]. Mutation of the filaggrin gene is a predictive marker in terms of atopic dermatitis predisposing and finally leading to asthma – the so-called atopic march [15]. Interestingly, there was no correlation between loss of function of filaggrin and allergic airway disease without atopic dermatitis and there was also a strong correlation between filaggrin mutation and nonatopic eczema.

A number of exogenous proteins have been reported to act as direct proteases and to damage the epidermal skin barrier. Examples are proteins produced by house dust mites [16] and *Staphylococcus aureus* [17]. These proteases have also been shown to cleave intercellular adhesion and therefore increase transepidermal penetration, besides eliciting immune responses with their antigenic properties.

These findings in correlation with atopic dermatitis support the concept that early transepidermal sensitization to

allergens in early childhood is a prerequisite to following specific immunoglobulin E (IgE) production [18^{••}]. Preventing such contact between allergens and the immune system by focusing on the improvement of the skin barrier – for example by consequent skin care – may influence the development of atopic dermatitis and the atopic march.

Immune system deviation

A virtual division into innate and acquired (adaptive) immune systems differentiates between nonspecific highly conserved defence modes and more specific cell and antibody-mediated actions. It should be noted, however, that both immune systems are acting in concert *in vivo* since they are tightly linked.

Innate immunity

Antimicrobial proteins and peptides as well as natural killer cells serve as a first-line defence against the invasion of microbial pathogens and are the major players in the innate immunity. It has been shown that antimicrobial peptides like the cathelicidin hCAP18/LL-37 and defensins are downregulated in the skin of atopic dermatitis lesions. As has been demonstrated for human- β -defensin 3 (HBD3), this downregulation may be a secondary effect of the Th2 cytokine milieu in atopic dermatitis and altering this microenvironment may upregulate defensin expression [19[•]]. Since HBD3 and one cathelicidin (LL-37) have broad-spectrum activity against yeasts (*Candida albicans*), bacteria (Gram-negative and Gram-positive bacteria, including *S. aureus*) and viruses (vaccinia, herpes simplex), reduced levels of these peptides definitely predispose an individual to superinfections.

Although natural killer cells play an important role in airway inflammation in a murine model, this role could not be confirmed for atopic dermatitis [20].

Acquired immunity

In this section we examine T cells, dendritic cells, cytokines and chemokines.

T cells

Atopic dermatitis is often linked to T-helper cell dysfunction and it has to be differentiated between the acute phase, which is dominated by a Th2-cell profile, and the chronic stadium, which is more influenced by Th1/Th0 milieu. Furthermore, regulatory T cells (Tregs), expressing the surface markers CD4/CD25/CD103 and the nuclear transcription factor FOXP3, have been shown to suppress T-cell mediated immune response [21,22]. Loss of Treg function seems to be associated with atopic dermatitis [23[•]]. The extent of a putative defect of Tregs in atopic dermatitis is still unclear.

Recently it has been shown in mice that allergen-primed CD8-positive T cells are required for the development of atopic dermatitis-like skin lesions [24•].

Dendritic cells

Dendritic cells are antigen-presenting cells and are thought to play a major role in the pathogenesis of atopic dermatitis [25••]. They represent a complex family divided into two major cell types: myeloid and plasmacytoid dendritic cells. Inflammatory dendritic cells (IDECs) and Langerhans cells belong to the myeloid dendritic cell group and express FcεRI in high amounts in patients with atopic dermatitis [26,27]. Langerhans cells elicit allergic inflammation by promoting T-cell differentiation into Th2 cells, but in contrast to IDECs, they do not show strong proinflammatory properties by immediate secretion of cytokines. Furthermore, IDECs also promote T-cell switching by production of IL-12 and IL-18 [28].

Plasmacytoid dendritic cells are important in mediating an antiviral immune response by secretion of interferons, namely IFNα and IFNβ. In atopic dermatitis, these cells are absent in skin lesions but are found to be increased in numbers in the blood with high expressions of FcεRI leading to increased apoptosis and decreased secretion of interferons [29]. This may partly explain why viral superinfections can occur in patients with atopic dermatitis (see below).

Cytokines and chemokines

Development of atopic dermatitis is coherent with altered cytokine and chemokine levels which form a complex network [30••]. Depending on the disease phase of atopic dermatitis (acute or subacute/chronic) the cytokine milieu is dominated by either Th2 cell cytokines with high levels of IL-4, IL-5 and IL-13, or Th1/0 cell cytokines like IFN-γ, IL-12 and GM-CSF.

IL-31, which is mostly produced by CD4+ cells, was found to be increased along with IL-13 and IL-4 in lesions of atopic dermatitis and allergic contact dermatitis but not in skin specimens from patients with psoriasis [31•]. Another marker for disease activity next to eosinophilic cationic protein and soluble E-selectin is the level of IL-16 which plays a role in atopic dermatitis inflammation [32•].

Important chemokines are macrophage inflammatory protein-4 (MIP-4)/CCL18, which seems to be responsible for eliciting inflammation, along with thymus and activation-regulated chemokine (TARC)/CCL17, pulmonary and activation-regulated chemokine (PARC)/CCL18, macrophage derived chemokine (MDC)/CCL22 and CCL1. Lack of MIP3α in atopic dermatitis, which also shows antiviral activity, seems to be due to the inflammatory milieu [33••].

Thymic stromal lymphopoietin (TSLP) is expressed by epithelial cells and, in particular, by keratinocytes. Its functions include priming naive T-helper cells to express Th2-cytokines and activation and migration of dendritic cells. The so-stimulated dendritic cells cause T cells to secrete the proallergic cytokines IL-4, IL-5, IL-13 and tumor necrosis factor α (TNFα) and inhibit production of IL-10 and IFNγ. This leads to the suggestion that TSLP plays an important role in allergic inflammation [34].

Finally, one could speculate that skin inflammation has a systemic effect, including on the bone marrow, which impacts on the overall tendency of these individuals to be sensitized.

Neuroimmunological factors

Other mediators also seem to play an important role in atopic dermatitis and one of the central features is strong pruritus. Since histamine does not seem to elicit pruritus in atopic dermatitis, other candidates like neuropeptides and cytokines have been proposed. One of the new hot topics of research in atopic dermatitis is neurotrophins, which have been shown to be a link between the immune and the nervous system. These mediators play a role in vegetative reactions like vasodilatation, oedema, itching sensations, pain and sweat excretion and also show an effect on T cells [35•].

Microbial superinfections

The role of microbial superinfections has not been fully elucidated but there is a general consensus that bacterial superinfections, in parts due to impaired innate immunity (see above), play a critical role in the clinical course of skin lesions [36••]. It is a well known fact that patients with atopic dermatitis run a higher risk of developing severe superinfections with different virus strains, like herpes (eczema herpeticum), molluscum (eczema molluscatum) or vaccinia virus (eczema vaccinatum). Virus infections, however, do not seem to have a causative role in developing atopic dermatitis. In contrast, bacterial products, notably superantigens, have been proposed to be causative agents in the pathophysiology of developing skin lesions.

S. aureus is found very frequently on the skin of atopic dermatitis patients and one of the virulence factors of these bacteria is, aside from the production of proteases which directly cleave corneodesmosomes, the production of enterotoxins, which act as superantigens and elicit a very strong immune response. To date, there are many known enterotoxins with superantigenic properties: toxic shock syndrome toxin (TSST-1), staphylococcal enterotoxin A (SEA), SEB, SEC-E, SEG-S and the enterotoxin-like proteins (e.g. SEIP). The role of most of these bacterial products has not been closely investigated. TSST-1, SEA and SEB seem to alter the cytokines

produced by keratinocytes from lesional atopic dermatitis skin with elevated levels of IL-1 α , IL-1 β and TNF- α [37]. Further, dendritic cells incubated with SEB secrete high levels of IL-2, induce toll-like receptor 2 (TLR2) signalling and promote Th2 cell polarization [38**].

Also yeasts, namely *Malassezia* species, are often isolated from superinfected atopic dermatitis lesions. Sensitization with specific IgE to *Malassezia* antigens and positive skin prick tests and atopy patch tests in numerous cases have been repeatedly been reported. A correlation was found between positive atopy patch tests on *Malassezia sympodialis* and patients with a head and neck type of atopic dermatitis [39].

Autoimmunity in atopic dermatitis

IgE-mediated autoimmune response seems too be another important aspect in atopic dermatitis, but its pathophysiological relevance is still unclear. Due to molecular mimicry, atopic dermatitis patients tend to produce specific IgE to self-proteins with high homology to bacterial allergens. These auto-allergens include the transcription factor LEDGF/DSF70 [40], Hom S1–5 found to be secreted by keratinocytes [41] and the manganese superoxide dismutase (MnSOD) produced by *Malassezia* [42]. Interestingly, the emergence of IgE to such autoallergens is observed during the first years of the disease in up to 80% of children with high serum IgE, but in adults, only 25% display such IgE [43]. Whether this IgE to self proteins has any relevance for further evolution of the disease remains to be studied.

The natural history atopic dermatitis revised

Attempts have been made to subdivide atopic dermatitis in extrinsic/IgE-mediated and intrinsic/nonatopic dermatitis according to the presence or absence of sensitization in these patients. It appears, however, that this binary view has to be challenged when considering recent epidemiological studies which highlight the fact that in more than 50% of infants affected by the disease, sensitization cannot be detected. Instead, sensitization emerges after several months or years following the onset of skin inflammation. Therefore, the course of the disease seems to include three stages:

- (1) In early infancy, the disease starts as a nonatopic dermatitis.
- (2) In 60–80% this is followed by sensitization and production of specific IgE to food or environmental allergens. This state would deserve to be named atopic dermatitis.
- (3) Finally, it is not excluded that IgE to self proteins is the hallmark of a third state of the disease, in which these antibodies may be of pathophysiological relevance and explain why such patients have severe forms and fail to improve to allergen avoidance strategies.

Conclusion

Atopic dermatitis is one of the most important subjects in dermatological research, with many pathogenic pathways to be elucidated. Skin barrier impairment and disturbance in the skin innate immune system seem to be key aspects for sensitization to allergens in early childhood. Systemic immune system deviation, however, is an important prerequisite for sensitization and disease development. Therefore, future research will have to consider the cross talk of the epidermal components and the adaptive immune system. Understanding more of the molecular basis of atopic dermatitis will hopefully lead to the development of new therapeutic strategies with enhanced benefit for the patient.

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