

## Etiopathogenesis of Atopic Dermatitis – An Overview

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**SUMMARY** Atopic eczema/dermatitis syndrome is a term that covers different subtypes of atopic dermatitis. The “intrinsic” type of atopic dermatitis is non-IgE-associated, and the “extrinsic” type is IgE-associated atopic eczema/dermatitis syndrome. In the etiopathogenesis of atopic dermatitis there are well known interactions among genetic, environmental, skin barrier, immune factors, and stress. Genetic factors determine the expression of atopic dermatitis as pure or mixed with concomitant respiratory or intestinal allergy, depending on genetic susceptibility. Immunologic abnormalities of type I and type IV reactions have been described in patients with atopic dermatitis. Immunologic triggers are aeroallergens, food allergens, microbial products, autoallergens and contact allergens. Immune reactions determine many features of atopic dermatitis. These immune reactions also include cell mediated or delayed hypersensitivity. The currently accepted model proposes a predominant Th2 cytokine *milieu* in the initiating stages of acute atopic dermatitis lesions, and a mixed Th1 and Th2 pattern in chronic lesions. A two-phase model includes Th2 initiation with attraction of macrophages and eosinophils, which in turn produce interleukin 12 that is the activator of Th1 type response. Atopic dermatitis skin contains an increased number of IgE-bearing Langerhans cells which bind allergens *via* the high-affinity IgE receptor (FcεR1). Langerhans cells play an important role in cutaneous allergen presentation to Th2 cells *via* major histocompatibility molecules. Eosinophilia and IgE production are influenced by type 2 cytokines. Degranulation of eosinophils occurs in the dermis with the release of toxic proteins such as major basic protein and could account for much of the inflammation. Mast cells are increased in number and produce mediators other than histamine that induce pruritus and may have an effect on interferon  $\gamma$  expression. Mast cells produce a number of proinflammatory cytokines. There is an elevated production of prostaglandin E2 by peripheral monocytes. Prostaglandin E2 has at least two potential roles in the initiation of atopic dermatitis. Firstly, it reduces interferon- $\gamma$  production by T helper cells, thereby favoring the initial, dominant Th2 immune response; and secondly, it directly enhances IgE production by B lymphocytes with an increased secretion of interleukin 4, interleukin 5 and interleukin 13. Many lesions of atopic dermatitis result from scratching, thus it is tempting to speculate that immune perturbations in genetically predisposed individuals provoke the release of local pruritogens and keratinocyte-derived cytokines, which then further exacerbate the previously described immune response.

**KEY WORDS:** atopic eczema; dermatitis; atopic syndrome

## INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing, highly pruritic, inflammatory skin disease. AD is associated with a genetic predisposition to immune system dysregulation. AD is often associated with a personal or family history of atopy such as asthma and/or allergic rhinitis, or AD itself (1,2). The "extrinsic" form of AD is associated with IgE-mediated sensitization and involves 70%-80% of patients. The "intrinsic" form of AD does not imply IgE-mediated sensitization and involves 20%-30% of patients (3,4). It is classified under "nonatopic eczema" (5). Eosinophilia is associated with both forms of AD (3). "Intrinsic" AD is associated with less interleukin-4 (IL-4) and IL-13 production than "extrinsic" AD (3). AD may affect 20% or more children in westernized societies, making it one of the most common of all noninfectious childhood ailments (6). Around 85% of affected individuals develop the disease before 5 years of age (1). More than 25% of children in northern Europe are affected (7). There is an especially high prevalence in children and infants (8,9). AD may persist into adulthood in up to 60% of patients (2,10). The prevalence of AD in adults is 1%-3%. Its prevalence has increased two- to threefold during the past three decades in industrialized countries but remains much lower in countries with predominantly rural or agricultural areas, such as former socialist countries like Albania (3,11). The Eczema Area and Severity Index (EASI) is used by dermatologic investigators worldwide to assess the eczema disease severity. The Self-Administered EASI (SA-EASI) was found to be a valid measure of AD severity in old age groups (12). In future studies, SA-EASI will permit relationship analysis of the skin disease severity to measures such as quality of life, disability, patient satisfaction, and the costs of various therapies (12).

Complex interactions among genetic, environmental, skin barrier and immunologic factors, stress and other emotional problems contribute to the pathogenesis of AD. AD is associated with typical clinical features according to Hanifin and Rajka, and significant changes in several important factors of cellular and humoral immunity including increased IgE levels, eosinophil cationic protein (ECP), CD4 depressed CD8, altered peripheral lymphocyte proliferation capacity and phenotype, etc.

## GENETIC FACTORS

AD is a complex polygenic disorder, and several candidate genes have been identified as being associated with AD. Interactions between genes and environmental factors contribute to the genesis of atopy (13,14). A number of these chromosomes contain genes for various interleukins, major histocompatibility complex proteins, and a component for the high-affinity IgE receptor (Fc $\epsilon$ RI) (13). Studies have identified regions of genetic linkage on chromosomes 1,2,3,4,5,6,7,11,12,13,16 and 17 (13,14).

It was demonstrated that the "extrinsic" and "intrinsic" forms of AD differ significantly according to the IL-4 and IL-4 receptor (IL-4R) genes. According to Tanaka *et al.*, polymorphisms in the IL-4 gene and the IL-4 receptor alpha chain gene play no role in the development of AD in patients who have normal IgE productivity (15). The IL-4 gene is located on chromosome 5, and IL-4R alpha chain gene on chromosome 16. Polymorphisms in these genes play a role in the development of AD in patients who have elevated IgE but not in those who have normal IgE (15). The gene for  $\beta$ -2-adrenoreceptor is located on chromosome 5q31-33 in asthma patients (16). The genes for the cluster family of Th2 cytokines, i.e. IL-3, IL-4, IL-5, IL-13 and granulocyte-macrophage colony stimulating factor (GM-CSF) are also located on chromosome 5q31-33 (3,17). The gene for Fc fragment of the IgE high affinity receptor (Fc $\epsilon$ R1B) is located on chromosome 11q12-q13 (18,19). Fc $\epsilon$ R1B is responsible for initiating allergic response on mast and other cells. On chromosome 12q13-q24, the following genes are located: signal transducer and activator of transcription 6 (STAT 6), interferon-gamma (IFN $\gamma$ ), mast cell growth factor (MGF), leukotriene A4 hydrolase (LTA4H), insulin-like growth factor 1 (IGF1), and nuclear transcription factor Y beta chain (NFYB) (19). STAT 6 is involved in IL-4-induced commitment of CD4 $^{+}$  T cells to the Th2 type and IgE isotype switching in B cells. IFN $\gamma$  promotes differentiation of Th1 lymphocytes, and inhibits differentiation and IL-4 production in Th2 cells (19). MGF controls proliferation of hematopoietic stem cells and mature mast cells; LTA4H is involved in prostaglandin metabolism and inflammatory response; IGF1 promotes differentiation of both B and T lymphocytes; and NFYB up-regulates the transcription of IL 4 (19). The gene for costimulatory molecules CD86 and CD80 is located on chromosome 3q21. These molecules may modulate T cell responses (3). Chromosomes 1q21, 17q25, and 20p are also linked to AD

and are known to contain psoriasis susceptibility genes, which suggests common candidate genes involved in the control of skin inflammation (3).

No clear linkage of atopy to HLA has been demonstrated so far. Recently, polymorphisms in the promotor region of RANTES (regulated on activation normal T cell expressed and secreted) and in the gene regulatory region of monocyte chemoattractant protein-1 (MCP-1) have been found to increase the expression of these chemokines. The -40 3A allele of the RANTES promotor region was found to be associated with the atopy eczema/dermatitis syndrome (AEDS) in German children (20).

### SKIN BARRIER

Stratum corneum (SC) is a distinctive two-compartment system consisting of corneocytes and lipid-enriched extracellular matrix. Corneocytes are formed by terminal differentiation of keratinocytes, which includes cross-linking of proteins such as loricrin and involucrin by transglutaminase to form the cornified envelope, as well as the loss of DNA and internal organelles. Corneocytes provide mechanical resistance. The extracellular matrix lipids are organized into lamellar membranes enriched with free fatty acids, cholesterol and ceramides. They are derived from the lamellar body content secretion. The extracellular matrix lipids are responsible for the permeability barrier. There is an intrinsic defect in the keratinocyte barrier function. A decreased skin barrier is associated with reduced ceramide levels, reduced urea content in SC, reduced natural moisturizing factor, reduced level of pyrrolidone carboxylic acid and water soluble amino acids, which reflects as a decreased profilaggrin production and therefore enhanced transepidermal water loss (21-23). In particular, ceramides are the major water-retaining molecules in the extracellular space of the cornified envelope (3). A reduced content of ceramides has been reported in the cornified envelope of both lesional and nonlesional skin in AD patients (3). None the less, this skin barrier function impairment in AD leads to numerous insults which act as triggers of inflammation. These include irritants, allergens, autoallergens, and microbes (3).

The increased susceptibility to irritants in AD may therefore represent a primary defect of epidermal differentiation compounded by the presence of inflammation-induced skin damage (3). Temperature, humidity, and fabrics texture, sweating, and occlusive clothing can modulate the effect

of irritants (16,21). The increased antigen absorption contributes to cutaneous characteristics of AD hyperreactivity (3).

### ALLERGENS

Allergic responses to environmental allergens can develop, and the microbes and yeasts that may contribute to the inflammatory process in AD are *Staphylococci* and *Pityrosporum* (24). Food allergens can induce eczematoid rashes in about 40% of children with moderate to severe AD (3). Studies suggest that food allergies are most likely to be important in a subset of young children, usually under the age of three years, with cow's milk, egg, peanuts, soy, and wheat as most common allergens (11). Food allergy has a role in at least 20% of the cases of AEDS in children younger than four years (25). In patients with cow's milk allergy and AEDS resolution occurs in 90% by the age of four. The presence of cow's milk allergy during infancy increases the risk of development of other food allergies, respiratory atopy, and persistence of AEDS. Adverse reactions to bovine proteins have an important role in AEDS (25). Restriction of antigenic foods during lactation and early life has shown benefit in some prospective studies (26). Although breastfeeding should be recommended for all infants, it does not prevent eczema in children with a genetic risk (27). Parental eczema is the major risk factor for eczema. In a subset of these patients, urticarial reactions or noncutaneous symptoms will ensue that can trigger the itch-scratch cycle that flares this condition. Children with food allergies generally have positive immediate skin tests or serum IgE directed to various foods, particularly eggs, milk, wheat, soy and peanuts, even though they have normal total serum IgE levels (3). There is also a significant increase in plasma histamine levels and eosinophil activation. Food allergen-specific T cells have been cloned from skin lesions of AD patients (3).

Most food allergic children outgrow their food hypersensitivity in the first few years of life, usually till the age of three, so food allergy is not a common trigger factor in older patients with AD. Afterwards, the sensitization to inhalant allergens may begin. Skin lesions can develop after inhalation of aeroallergens (3). Epicutaneous application of aeroallergens by atopy patch test on uninvolved skin of AD patient elicits eczematoid reactions in 30%-50% of patients (3). The degree of IgE sensitization to aeroallergens is directly associated with the severity of AD (3). Human proteins can act as

autoallergens in patients with severe AD, and IgE immune complexes can be detected in AD sera (3). Release of these autoallergens from damaged tissues could trigger IgE or T cell-mediated responses (3). Therefore, environmental allergens can initiate IgE immune response but allergic inflammation can be maintained by the release of human proteins derived from damaged skin of chronic AD patient (3).

Most patients with AD are colonized with *Staphylococcus (S.) aureus* (3,28). *S. aureus* is found in more than 90% of AD skin lesions in contrast to only 5% of normal subjects that harbor this organism. Acute inflammatory lesions have more *S. aureus* than chronic AD skin lesions or normal-looking atopic skin.

As already pointed out, atopic skin is deficient in ceramides, which is related to abnormal metabolism of essential fatty acids. The generation of free fatty acids from phospholipids regulates secretory phospholipase A2, subsequently reflecting on pH, and regulates the activity of at least two enzymes in generating ceramides, acid sphingomyelinase and  $\beta$ -glucocerebrosidase. Fatty acids have mild antiseptic properties; their abnormally low levels in atopic skin may contribute to high levels of *S. aureus* (16,29,30). Bacterial ceramidase causes further ceramide reduction.

As demonstrated in experimental animal models, *S. aureus* binds to a significantly greater extent to skin sites with Th2-mediated skin inflammation due to IL-4 (3). IL-4 appears to induce the synthesis of fibronectin (an important adhesin) and therefore to play a crucial role in the enhancement of *S. aureus* skin binding.

With the overgrowth of *S. aureus*, the inflammation in AD skin is exacerbated or maintained by secreting a group of toxins known to act as superantigens that stimulate marked activation of T cells and macrophages (*S. aureus* can activate up to 20% of all T-cells) (3,28). *S. aureus* can produce other toxins that are likely to contribute to skin inflammation. Scratching due to dryness as a major cause of pruritus probably enhances *S. aureus* binding by disturbing skin barrier and exposing extracellular matrix molecules known to act as adhesin (such as fibronectin, collagen); this is called the "itch-scratch cycle". Specific IgE antibodies directed against staphylococcal superantigens are also produced and correlate with skin severity (31). *S. aureus* exacerbates or maintains skin inflammation in AD by inducing corticosteroid resistance (3). AD skin is also deficient in antimicrobial peptides needed for host defense against

bacteria, fungi, and viruses (32,33). The lack of innate immune system predisposes these patients to viral and fungal infestations (3).

The possible significance of the yeast *Malassezia (Pityrosporum ovale)*, particularly in AD located in the head and neck region, is acting as an allergen inducing maturation of dendritic cells that are incapable of internalizing the yeast and therefore increasing the risk of skin infection (34,35). A study in AD patients revealed a correlation between skin prick test, patch test to *P. ovale*, and family history of atopic diseases, thus proving the role of immediate and contact hypersensitivity to *P. ovale* in the exacerbation of AD (36).

## ENVIRONMENTAL FACTORS

The importance of environmental factors in the development of AD has been ever increasing for several reasons. First of all, the increase in the prevalence of AD cannot be explained by genetic factors, and a wide variation in its prevalence within and between countries suggests that factors associated with "western lifestyle" maybe play a role (11). The "hygiene hypothesis" includes reduction of early childhood infectious diseases through vaccination and increased use of antibiotics. This would prevent the maturation of the immune system and increase the risk of developing atopic diseases (14,37). Furthermore, there is an increase in AD prevalence in people with similar genetic backgrounds from less developed countries who move to industrialized countries (11). The mechanisms of action of environmental factors contributing to AD seem to include immune factors and susceptibility to irritation or sensitization by other agents, and are currently being investigated (11). Whether timing of exposure to environmental factors is also important is still in the phase of research (11).

The major environmental risk factors influence the development of allergy. They include smoking, indoor dampness, poor ventilation that tends to concentrate allergens indoors, ingestion of certain foods, and inadequate clothing (38-40). Several studies showed a greater risk of maternal vs paternal smoking (38,41). Passive smoking in early life is by far the best documented trigger for the development of allergy (38,42). Other environmental risk factors include keeping of pets, floors with carpets (in childrens' bedroom), which may be contaminated with high levels of domestic mite, animal dander, local pollens, mould, etc. Air pollution may exacerbate AD as well (43). Increased concentration of circulating immunocomplexes

was found in 80%, and of total IgE in 50% of AD patients sensitive to nickel (the most common allergen in these patients) (44). The link between house dust mite (HDM) and AD remains less clear than the link between HDM and respiratory allergy. Studies addressing HDM avoidance measures often fail to demonstrate a clinical benefit in AD (11,45).

Western lifestyle includes urbanization, development, changes in diet, body weight, antibiotic use and stress (39,46-48).

## IMMUNOLOGY

Besides early hypersensitivity, delayed hypersensitivity type IV (cell-mediated immunity) is also involved in the pathogenesis of AD. The currently investigated pathogenetic aspects of AD include imbalance of Th1 cells and Th2 cells (Th1/Th2 responses), delayed eosinophil apoptosis, IgE-mediated facilitated antigen presentation by epidermal dendritic cells (DCs), altered prostaglandin metabolism, and intrinsic defects in keratinocyte function (3). The concept of "extrinsic" vs "intrinsic" type of atopic dermatitis is attractive (49). The concept of AD starting with Th2 inflammation, becoming Th1 inflammation in chronicity, and finally progressing to an autoimmune disease with IgE antibodies against autologous epidermal proteins is important. There is evidence for exogenous AD elicitation by contact with aero- or food allergens. Recent investigations show that epidermal LCs bind IgE *via* different receptors, especially the high-affinity receptor, which is more strongly expressed in lesional skin in AD than in other inflammatory skin diseases. The functional expression of costimulatory molecules on antigen-presenting cells (APCs) such as dendritic cells (DCs) may be a key event in the pathogenesis of AD, although their role in the onset and maintenance of AD is not well established. Costimulatory molecules on LCs and inflammatory dendritic epidermal cells (IDECs) might play a role in the pathogenesis of AD (49). Epidermal keratinocytes in AD patients produce and release proinflammatory cytokines and chemokines as a reaction to skin injury by environmental allergens, scratching, or microbial toxins.

As immunologic dysregulation is a possible key defect in AD, the expression of different immunologic parameters and costimulatory molecules such as integrins and selectins has been studied in AD patients (49). The adhesion molecules E-selectin, P-selectin, ICAM-1 and the expression of vascular endothelial cell adhesion molecules

1 (VCAM-1) are preferentially expressed on activated endothelium in the dermis of AD patients (50,51).

Keratinocytes, mast cells and DCs release cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-1 (3). These cytokines bind to receptors on vascular endothelium, and induce the expression of adhesion molecules on VCAM-1 and facilitate the extravasation of inflammatory cells into the skin (3,32,33). LCs produce IL-16 which is a chemoattractant cytokine for Th cells (3). Chemokines play a central role in AEDS. IL-16 has been described as the main cytokine involved in CD4+ cell recruitment during inflammation (52).

Immune responses in AD include a biphasic pattern of T-cell activation. There are different immunologic manifestations in the unaffected skin, acute skin and chronic AD skin. Deep seawater intake improves skin symptoms and mineral imbalance, and decreases serum IgE levels and IgE-inducing cytokines, IL-4, IL-13 and IL-18 in patients with AEDS, whereas distilled water intake fails to do so (53).

## NONLESIONAL AD SKIN

Nonlesional AD skin shows sparse dermal perivascular cellular infiltrate that consists primarily of T lymphocytes. Immunohistologic analysis shows a significantly greater number of Th2 cells expressing IL-4 and IL-13 but not IL-5 and IFN- $\gamma$  messenger ribonucleic acid (mRNA) compared to normal nonatopic skin (3,54,55).

## ACUTE AD SKIN

Acute AD skin shows sparse epidermal infiltrate, which primarily consists of T lymphocytes, and there is marked perivenular inflammatory cell infiltrate in the dermis consisting predominantly of Th lymphocytes and in less number of LCs, IDECs and macrophages (3,56). Immunohistologic analysis of cells shows a significant increase in the number of cells expressing IL-4, IL-5 and IL-13 mRNA but not IFN- $\gamma$  and IL-12 mRNA compared to nonlesional AD skin or normal nonatopic skin (3,54,57). However, acute skin lesions have a predominance of IL-4 and IL-13 expression (3). This is called Th2-type cytokine pattern (54). The authors demonstrated specific regulatory function of CD30+ T cells in acute AD, in accordance with the results reported by Caproni *et al.* (58,59).

Recently, the influx of CD4+ lymphocytes has been related to the upregulation of IL-16 in AEDS

skin lesions. The presence of circulating beta-chemokines (Eotaxin and RANTES) and IL-16, which were investigated in children with AEDS, correlates with the disease severity (52). Soluble CD30 (sCD30) in peripheral blood is a marker of Th2 immune response related to AEDS disease activity (52), and so is the presence of CD30 molecules in the skin (58). Keratinocyte-derived thymic stromal lymphopoietin (TSLP) and epidermal DC derived IL-10 and IL-4 stimulate Th differentiation into Th2 (3). There is also overexpression of IL-16 (3). IL-16 is an LCs cytokine that attracts Th cells in acute lesions and therefore plays a role in the initiation of inflammation (3,54,60). IL-13 and IL-4 elevate IgE levels, induce switching to IgE synthesis, and also induce the expression of vascular adhesion molecule-1 (3,54). Therefore, they may play a role in the migration of eosinophils and mononuclear cells in acute AD skin lesions (3,61). IL-4 also inhibits the production of IFN- $\gamma$ . IL-5 plays an important role in differentiation, vascular adhesion and survival of eosinophils. Eosinophils also intermediate and release cytotoxic granules and contribute to tissue injury but also modulate T cell function by its own cytokines. Th2-type cytokines are involved in the initiation of AD (54).

There is an elevated production of prostaglandin E2 (PGE2) by peripheral monocytes. PGE2 has at least two potential roles in the initiation of AD. Firstly, it reduces IFN- $\gamma$  production by T helper cells, thereby favoring the initial, dominant Th2 immune response. Secondly, it directly enhances IgE production by B lymphocytes with an increased secretion of IL-4, IL-5 and IL-13. Mast cell chymase may induce eosinophil infiltration into AD lesional skin.

## CHRONIC AD SKIN

Chronic AD skin shows IgE-bearing LCs and IDECs in the epidermis. Dermal mononuclear infiltrate is predominated by macrophages, whereas T cells, eosinophils and mast cells are also increased but to a lesser extent. Immunohistologic analysis of cells shows a significant increase in the number of cells expressing a significantly greater number of IL-13, IL-4, IL-5 and IFN- $\gamma$  mRNA cells than in normal or nonlesional skin of AD patients, while there is a greater number of IL-5, IL-12, GM-CSF and IFN- $\gamma$  mRNA cells and fewer IL-13 and IL-4 mRNA compared to acute AD skin lesions (3,54). T cells constitute the majority of IL-5 expressing cells. There is also a significantly greater number of activated IL-5 mRNA-expressing eosinophils

than in acute lesions (3,54). IL-11, a profibrotic cytokine, is also increased with the resulting collagen deposition during chronic AD (3). IL-5 plays an important role in differentiation, vascular adhesion and survival of eosinophils. IL-12 is produced in eosinophils and/or macrophages, and its function is to induce Th cells to differentiate and mature into Th1 cells (54,62). Therefore, IL-12 may account for the termination of the Th2-type cytokine pattern, which is observed in acute lesions, and it also initiates the switch to Th1 cell development in chronic lesions (54,62,63).

GM-CSF, produced by keratinocytes, enhances eosinophil and macrophage survival in chronic lesions (54). Therefore, Th1-type cytokines (IL-2 and IFN- $\gamma$ ) account for the persistence of inflammatory response in AD (54).

In chronic AD lesions LCs are present in increased numbers and have increased amounts of IgE bound to high-affinity surface receptors. LCs have been shown to be hyperstimulatory to T helper cells and can activate T helper cells to Th2 phenotype in the initiating phase of the disease. Antigen-presenting cells, IgE-bearing LCs and IDECs, express the high affinity IgE receptor (3,56). The increased expression of Fc $\epsilon$ RI on DCs in AD skin is due to the enhanced expression of Fc $\epsilon$ RI  $\gamma$  chain and is preserved by increased IgE levels (3,64). LCs and IDECs play an important role in allergen presentation to Th2 and Th1 cells, respectively (3,65). LCs with Fc $\epsilon$ RI-bound IgE enable the capture, processing and antigen presentation of allergens to T cells in atopic skin. They may migrate to lymph nodes and stimulate naive T cells to expand the pool of Th2 cells. Therefore, the immediate (IgE-mediated mast cell type), late (IgE-mediated Th2-type) and delayed (IgE-independent Th1 type) allergic reactions are involved.

## CONCLUSION

Although there is ample new information on the pathogenesis of AD, the basic underlying etiology remains elusive. Despite great progress, the pathogenesis of AD is still incomplete and the clinical importance of various changes in the immune system parameters is still unclear. In the future, we hope the development of new therapeutic AD approaches will be aimed at specific targets. Nowadays, the main directions of current therapy for AD are suppression of inflammation, avoidance and control of trigger factors, and improvement of skin care. Additional studies are needed to elucidate the role of factors involved in the pathogenesis of

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