Role of Immune Response and Some Microbial Agents in Atopic Dermatitis Pathogenicity and Management

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Article Information

Received 29 Sept 2020

Received in revised form 21 Nov 2020

Accepted 24 Nov 2020

Keywords:

Atopic Dermatitis,
Immune Response,
Pathogenicity,
Management

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DOI: [10.20510/ukjpb/8/i6/1606485484](https://doi.org/10.20510/ukjpb/8/i6/1606485484)

Abstract

Atopic dermatitis is a disease characterized by chronic inflammation, exhibiting its effects on a large number of children and adults. This disease results from many factors like defects in skin barrier, immunological, genetic and environmental factors. In addition to these factors, the presence of microorganisms on the skin surface of the patients, like *Staphylococcus aureus*, play important role in exacerbating the chronic inflammation. Atopic dermatitis patients exhibit defects in immune responses, which in turn increase the susceptibility to infections (bacterial, fungal and viral), so the presence of bacterium or its toxin lead to exacerbate the activity of the disease by stimulating the immune cells like Th-2 cells and eosinophils, in addition to activate the production of toxin-specific IgE. The relationship among atopic dermatitis, immune response and microbial infection, especially *S. aureus*, is incompletely understood. The current review aims to help the researchers within immunologic and dermatologic fields through shedding a light on the role of immune response and some microbial agents on the pathogenicity of atopic dermatitis.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease persisting predominantly in the pediatric population¹. Its frequency increases during childhood but usually resolves by the age of 30. Atopic dermatitis is divided into three categories: Infantile (from birth to 2 years), Childhood (from 2 to 11 years), and Adults².

In all stages, pruritus is the hallmark of AD. Itching often precedes the appearance of lesions³. This disease is variable in distribution and it's related with age, with a distribution that corresponds to areas of the body that are accessible to scratching and rubbing. There is no objective laboratory test that exist for AD, the diagnosis depend mainly on clinical manifestation and family history of skin abnormalities⁴.

Several triggers are involved to exacerbate AD. Common triggers include: irritants, dry skin (xerosis), infections (microbes), allergens, sweating, changes in temperature, and emotional stress⁵.

2 Epidemiology

Atopic dermatitis is recorded as the most common skin inflammatory disease affecting about 20% of children and adolescents worldwide¹. This disease represent a major public health problem worldwide, especially in industrial countries where it can be as high as 20-37% of the population⁶.

The prevalence of AD in adults is 1-3%. It is important to mention that the lower prevalence of AD was recorded in agricultural countries (Eastern Europe and China) and rural regions (Central Asia and Africa). The preponderance of AD in females is greater than males, with an overall ratio of 1.3:1.0, respectively⁷. The increased prevalence basis of this disorder is not well understood, it is suggested that environmental factors may be critical in determining disease expression⁸.

In contrast to respiratory atopic disease which develops more frequently in males than females (1.5:1.0), nearly 80% of children with AD eventually develop allergic rhinitis or asthma (Arshad, 2005), some risk factors had been associated with the rise in

atopic diseases including: small family size, migration from rural to urban environments and increased use of antibiotics, this called "western life style"⁹ and resulted in the hygienic hypothesis, where infection may prevent allergic disorders in childhood period¹⁰.

3 Clinical findings

AD presents similarly across racial and ethnic groups as chronic or relapsing pruritic eczematous skin lesions; however, some features may be more or less prominent in patients with darker skin¹¹.

There are no specific skin signs, distinctive histological features, or even laboratory findings through which AD can be diagnosed. Each patient has his own unique sets of features. The diagnosis of AD depends on the collection of clinical features, as illustrated in table 1. Its typically start during childhood, 50% of patients develop AD during the first year of life and approximately 30% of patients between 1 and 5 years. Many AD patients (50 - 80%) develop asthma or allergic rhinitis (AR) later in childhood, many of these patients develop their AD when they developed respiratory allergy¹².

Table 1: Atopic dermatitis clinical features¹⁴

Essential features	Important features	Associated features
Pruritus	Start at early age	Atypical vascular responses (e.g., facial pallor, white dermatographism, delayed blanch response)
Eczema (acute, subacute, chronic)	Atopy	Keratosis pilaris, hyper linear palms, and ichthyoses
Specific morphological patterns which is age dependent (i.e., facial, neck, and extensor involvement in children; current or previous flexural lesions in any age group; sparing of groin and axillary regions).	Personal or family history	Ocular or periorbital changes
	Immunoglobulin E reactivity	Other regional findings (e.g., perioral changes, periauricular lesions)
	Xerosis	Perifollicular accentuation, lichenification, and prurigo lesions.
Chronic or relapsing history		

The important features of AD are intense cutaneous reactivity and pruritus, which may be intermitted throughout the day, but it's usually increase in early evening and night, leading to consequences of lichenification, papules, scratching, and eczematous skin lesions¹³.

4 Pathogenesis

Atopic dermatitis pathogenesis is multifactorial, and can originates from the effects of many factors like: immunologic, genetic, environmental factors, infections that cause skin barrier dysfunctions, and inflammation¹⁵.

Skin barrier function may decrease as a result of cornified envelope genes (filaggrin and loricin) down regulation, increased of proteolytic enzymes levels and reduced ceramide levels¹⁶. This predispose children to develop respiratory allergy later in life¹⁷.

The epidermis intracellular edema (spongiosis) represent the characteristic of acute eczematous skin lesions. Antigen presenting cells in AD skin lesion exhibit immunoglobulin E molecules which are surface-bounded, T-lymphocytes epidermal infiltration is also observed¹⁸. In the acute lesion dermis, there is an influx of monocyte-macrophages and T-cells. The lymphatic infiltrations contains mainly an activated memory T- cells that carry CD3, CD4 & CD45RO¹⁹.

Chronic lichenified lesions are characterized by a hyperplastic epidermis with prominent hyperkeratosis, and minimal spongiosis²⁰. There is an increased number of IgE bearing LCs in the epidermis. In AD skin, fully granulated mast cells are increased in number, neutrophils are absent, while large number of eosinophils release granule-protein contents as a result of cytolysis²¹.

An IgE-inducing lymphokine called IL-4 is responsible for the production of IgE which binds to its receptors on the lymphocytes that are presented in the dermis. So, when an allergen is captured by the cell, it will elicit IL-4, this increase of IgE levels is closely associated with AD²².

The defect in cell-mediated immunity, which may appear in most AD patients, is reflected by increased susceptibility of the skin to severe infections with viruses (herpes simplex, vaccinia, coxsackie virus) as a result of low numbers of dendritic cells (DCs) in skin lesions of AD patients, in contrast to other inflammatory skin diseases²³.

High percentage of AD patients have CD3+ T-cells and CD8+ suppressor T-cells with decreased proportion²⁴. In contrary, patients suffered asthma, allergic rhinitis, or skin disorders other than atopy, like psoriasis or contact dermatitis, not exhibit a reduction of circulating suppressor/cytotoxic T-cells²⁵.

5 Immune responses in AD skin

Analysis of biopsies from clinically unaffected skin of AD patients compared with normal non atopic, demonstrate an increased number of Th₂ cells expressing IL-4 and IL-13 (figure 1), but not IFN- γ mRNA²⁶. Acute eczematous skin lesions is intensely

pruritic, erythematous papules association with excoriation and serous exudation. There is marked infiltration of CD⁴⁺ activated memory T-cells, with great numbers of IL-4, IL-5, and IL-13 mRNA expressing cells, but few IFN- γ or IL-12 mRNA expressing cells²⁷.

Fig 1: Major cellular and molecular components that are involved in AD skin immune response²⁸

Chronic lichenified lesions suffered a structural remodeling by chronic inflammation and can diagnosed by thickened plaques with high markings and dry fibrotic papules, these dermal lesions have low IL-4 and IL-13 mRNA-expressing cells, while huge number of IL-5, GM-CSF, IL-12 and IFN- γ mRNA expressing cells compared with acute AD²⁹.

6 Defective innate immunity

6.1 skin barrier dysfunction

Atopic dermatitis characterized by dry skin and increased transepidermal water loss, which lead to high extent of antigen absorption shared with cutaneous hyperactivity specific to AD³⁰.

The epidermis represent the first line of defense against invasive micro-organisms, which can enter when skin is damaged³¹. Antimicrobial substances form part of this defense system which should be naturally occurred (e.g., β -defensin 2, 3 and Cathelicidin) and required for host defense against bacteria, fungi and viruses³².

Ceramide is a water retaining molecule present in the extracellular spaces of the cornified envelope, and the complex-structured barrier is due to a matrix of proteins that bound to ceramides. In AD cornified envelope skin, the content of ceramides has been reported to be low³³.

Dermadin, a peptide with broad spectrum antimicrobial activity, is expressed in skin dermis of sweat glands, transported to the surface of epidermal after secreted into sweat³⁴.

In healthy persons, bacterial cells on the skin surface are reduced significantly after sweating, but this doesn't happen in AD patients³⁵. The permeability barrier abnormality in AD is the driver of disease activity (i.e., the reverse outside-inside view of disease pathogenesis). For a number of reasons, the extent of the permeability barrier abnormality parallels the severity of disease phenotype in AD³⁶, both clinically uninvolved skin sites and skin cleared of inflammation for as long as 5 years continue to display significant barrier abnormalities³⁷.

Specific replacement therapy, which targets the prominent lipid abnormalities that account for the barrier abnormality in AD corrects both the permeability barrier abnormality and comprises effective anti-inflammatory therapy for AD³⁸.

6.2 Toll-like receptors and AD

Toll-like receptor 2 (TLR2) and 4 (TLR4) are members of pattern recognition receptors (PRR) that recognize various conserved microbial components. The pathogen recognition by dendritic cells depending on PRR is important in stimulating the correct balance between Th₁ and Th₂ responses. TLR2 recognizes G⁺ bacteria and yeast components, like lipotechoic acid and

peptidoglycan³⁹, while TLR4 recognizes G-ve components, like LPS⁴⁰.

The receptors have two single nucleotide polymorphism (SNPs) that lead to change in amino acid sequences, one of the these polymorphisms (TLR2: Arg 753 Glu) that present in AD patients with high frequency located within the intracellular part of the receptor which associated with *S.aureus* infection⁴¹, these AD patients had increased disease severity, elevated IgE antibodies to *S.aureus* super-antigens. Two of the TLR4 polymorphisms (Asp 299 Gly and Thr 399 Ile) has been expressed with a high frequency in AD patients compared to controls⁴².

7 Immunological pathway in AD

Epidermal dendritic cells express FcεRI, and incoming allergens are taken up as allergen-IgE complexes and passed to the MHC class II processing pathway for presentation to Th₂ cells, Th₂ cells circulating in the peripheral blood of AD patients result in elevated serum IgE and eosinophils. These T-cells express the skin homing receptor, cutaneous lymphocyte associated antigen (CLA), and recycled via intact AD dermis where they can conjugates allergen-triggered IgE+ (LCs) and mast cells (MCs) that shared to Th₂ cell development⁴³.

Skin may undergo injury due to environmental microbial toxins, scratching or allergens. The injury can stimulate production of chemokines and proinflammatory cytokines from keratinocytes and induce the vascular endothelium production of adhesion molecules that facilitate the attraction of inflammatory cells into the skin⁴⁴.

Keratinocyte-derived thymic stromal lymphopoitin (TSLP) and DC-derived IL-10 also enhance Th₂ cell differentiation. The acute skin lesions of AD characterized by increased Th₂ cell, but chronic AD associate with inflammatory infiltration of dendritic epidermal cells (IDECs), eosinophils, and macrophage. Production of IL-12 cause switch to a Th₁-type cytokine and stimulate the expression of IFN-γ⁴⁵.

8 Cytokines and chemokines role in AD

The T-helper cells (native CD⁴⁺ T-cells) (Th₀), are the major source of cytokines. In AD, there is often an imbalance in the differentiation of Th₀ into Th₂ or Th₁ cells with far more Th₂ cells and their associated cytokines⁴⁶.

Atopic skin inflammation is orchestrated by the local expression of proinflammatory cytokines and chemokines⁴⁷. TNF-α and IL-1 from DCs, MCs and keratinocytes bind to the receptors on the vascular endothelial cells and stimulate cellular signaling pathways that lead to the stimulation of VCAM⁴⁸. In acute AD, IL-4 and IL-13 are produced that stimulate immunoglobulin class switching which lead to synthesis of IgE, and induce expression of endothelial cells adhesion molecules. In contrast, with chronic AD, the eosinophilic development, survival and predominant are stimulated by the activity of IL-5⁴⁹.

In AD, production of GM-CSF is recorded to inhibit monocyte apoptosis, that contributing to the AD persistence⁵⁰. Also, IL-18 and Th₁-cytokines like IL-12 may contribute to the maintenance of chronic AD⁵¹, as well as other cytokines including TGF-β and IL-11⁵². Acute inflammation in AD and elevated IgE may be contributed by decreased IL-15⁵³.

Interleukin-16 play an important role in AD through a cutaneous inflammatory response. It induces chemotactic responses in CD⁴⁺ T-cells, eosinophils and DCs⁵⁴. Lesions of AD contain abundant expression of IL-10 which acts as a regulatory cytokine, responsible for inhibition of Th₁ activity and its cytokines. It is believed to be an important factor in the pathogenesis of AD. Studies showed that IL-10 may play a role in enhancing IgG₄ antibody while suppressing production of IgE⁵⁵.

Interleukin-21 is strongly expressed by mononuclear leukocytes⁵⁶, and is identified as a critical regulator of the processes that lead to sensitization and allergic inflammation of the skin⁵⁷. The expression of IL-21 is elevated in acute AD lesions, compared with normal control subjects.

Interleukin-31 is a novel Th₂ cytokine that plays an important role in allergic skin inflammation and AD⁵⁸. Human IL-31 is significantly up regulated in pruritic forms of skin inflammation as AD but not in non-pruritic forms as in psoriasis⁵⁹, circulating CLA+ memory T-cells of patients with AD produce higher levels of IL-31 than the T-cells of patients with psoriasis⁶⁰. IL-31 expression is not only increased in AD patients but also those with allergic contact dermatitis (ACD), in both types of eczema, expression of IL-31 is associated with the expression of the Th₂ cytokines IL-4 and IL-13^{61,62}.

Chemokines play important role in AD, psoriasis, melanoma, viral infections, infectious diseases and others⁶³. The skin specific chemokine, like cutaneous T-cell attracting chemokine (CTACK), is highly up regulated in AD and preferentially attracts skin homing (CLA) + CC chemokine receptor 10 (CCR10) T-cells into the skin⁶⁴.

In AD, the aggregation of CCR4-expressing Th₂ cells induced by chemokine derived from macrophage-derived and thymus activation-regulated cytokine (TARC), both of which are increased⁶⁵. Fractalkine, another chemokine and IFN-γ inducible protein 10, is regulated by keratinocytes and cause migration of Th1-cell toward epidermis, especially in chronic AD⁶⁶.

In acute and chronic AD skin lesions, the macrophage-chemoattractant protein 4, eotaxin, CC chemokines, and RANTES are increased and participate to infiltration of eosinophils, T-cells and macrophages⁶⁷. The chemokine CCL18 was shown to be expressed by DCs in the dermis and LCs and IDECs in the epidermis of patients with AD but not in normal or psoriatic skin⁶⁸. CCL18 was also shown to bind CLA+T-cells in peripheral blood suggesting a role in homing of T-cells to the skin. Expression of CCL18 appears to be induced by exposure to

allergens and *S.aureus* enterotoxin B⁶⁹. CCL1 has also been shown to be selectively upregulated in AD compared with other inflammatory skin diseases in response to allergens and staphylococcal products⁷⁰.

Both cutaneous T-cell attracting chemokine (CTACK) and thymus activation-regulated cytokine (TARC) levels have been shown to be specific for AD, increasing with disease severity and decreasing with successful treatment⁷¹. If these observations are confirmed, these two chemokines could serve as biochemical markers for clinical management of this disease.

Interleukin-8 is a chemokine (CXCL8), where in the skin it can stimulate attraction of PMN leukocytes to start phagocytosis and kill bacteria, IL-8 and inducible nitric oxide synthase (iNOS) is decreased in AD compared to psoriatic skin. The ability of NOS to kill viruses, bacteria and fungi depend on nitric oxide production. Th2 cytokines play important role in inhibit the production of IL-8 and iNOS. The T cell functions are changed during AD, so certain biotherapies targeting this alterations gave encouraging results, as with etanercept, infliximab and ustekinumab. Also, an increment in IgE titer were reported in AD. Therefore, several studies regarding "omalizumab" as anti-IgE monoclonal antibody had been mentioned in literature for controlling AD⁷².

9 Microbial colonization of AD skin

Patients with AD often exhibit high incidence to bacterial, fungal or viral attacks. They usually unprotected against severe viral infections like herpes simplex type1 (eczema herpeticum)⁷³, vaccinia (eczema vaccinatum), coxsacki-A or *molluscum contagiosum* viruses⁷⁴. They also susceptible to infection with human papilloma virus (warts) and to infections with cutaneous fungi such as *Trichophyton rubrum*⁷⁵.

Malassezia (Pityrosporum orbiculare/ovale) is a normal flora of human skin and it colonize the stratum corneum, it is most abundant at the chest, scalp and back⁷⁶. Healthy individuals develop *Malassezia* IgG antibodies, but AD patients (30-80%) can develop reactivity to the organism by IgE and/or T-cell⁷⁷.

In both lesional and non-lesional AD, the colonization by *S. aureus* represent the most common cause of skin infection. Many factors contribute in the alteration of skin colonization by this bacteria, including changes of epidermal barrier, increased adhesion of bacteria, problem in clearance, and insufficient innate immune response⁷⁸.

The incidence of *S. aureus* on the skin of AD patients is usually higher than controls⁷⁹. About 80-100% of patients with AD are colonized with *S. aureus*. In contrast, *S. aureus* can be found on the skin of only 5-30% of normal individuals⁸⁰, several reason related to colonization atopic skin with *S. aureus*, first, the presence of receptors (adhesions) specific for epidermal and dermal laminin and fibronectin on the cell walls of *S. aureus*. The

lacks of an intact stratum corneum in AD patients skin, make the dermal fibronectin receptors to be uncovered and increase the susceptibility of the skin to adhere with *S. aureus*⁸¹.

Skin surface lipids such as free fatty acids and polar lipids have been shown in patients with AD, it will facilitate *S. aureus* penetration into intracellular spaces of the epidermis⁸²

Staphylococcus aureus has important implications for the pathogenesis of AD, patients with AD differ in the ability to clear *S. aureus* from the skin during anti-inflammatory treatment, which appear to be related to the abnormalities in immunological parameters⁸³. Several extracutaneous factors that may cause *S. aureus* re-colonization specially in adult AD patients, extracutaneous mechanisms by which *S. aureus* can re-colonize the skin, including antibiotic resistance and nasal carriage⁸⁴.

It has been reported that incidence of MRSA accounting for *S. aureus* was 31% in skin lesions of adult patients with AD⁸⁵. *S. aureus* is strongly attached to the corneocytes, and through the intracellular spaces can penetrate the epidermis, may be resulted from the deficiencies of lipid in AD skin. Skin pH in AD is alkaline and both lesional and non-lesional stratum corneum have decreased levels of sphingosine⁸⁶. Bacterial colonization may be facilitated by the dryness and cracking of AD skin, which resulted from transepidermal water loss as a result of alteration in lipid content. The adhesion of *S. aureus* to stratum corneum in AD skin induced by cytokines produced by Th₂ like IL-4 which stimulate the expression of fibrinogen receptors⁸⁷. Persistent of *S. aureus* correlated with the level of total IgE that mean IgE may participate to susceptibility of skin to infection, especially in AD patients who respond poorly to anti-inflammatory treatment. In addition to that, IgE inhibit phagocytosis, neutrophil adhesion and respiratory burst, and as a result inhibit skin microbial clearance.

Staphylococcus aureus has the ability to maintain the inflammation in AD skin, this ability related to the production of toxins which act as superantigens that stimulate T-cells and macrophages⁸⁸. Cutaneous inflammation caused by Staphylococcal exotoxins can induced by different pathways: First, exotoxins act as superantigens, stimulating polyclonal activation of T-cells; Second pathways, they induce the generation of exotoxin specific T-cells able to promote the generation of exotoxin-specific IgE antibodies in their function as conventional allergens (Figure-2)⁸⁹.

Although patients with AD have significantly increased numbers of peripheral blood T-reg cells with normal immunosuppressive activity, after superantigen stimulation, T-reg cells lose the CLA+, CD4+, and CD25+ which are increased in AD patients⁹¹.

Staphylococcal superantigens stimulates the production of IL-12 that induce T-cell expression of the skin homing receptor CLA, IL-12 can be secreted by LCs and T-cells⁹². The activation of T-cells by superantigens stimulate apoptosis after a distinct number of cell divisions⁹³. Superantigens have effects on other cell types

such as macrophages, keratinocytes, LCs and eosinophils. Inflammation and tissue damage during AD flares result from the

recruited eosinophils which stimulated by RANTES and eotaxin that promote degranulation⁹⁴.

Fig 2: Function of staphylococcal exotoxins as super-antigens or as allergens⁹⁰

Reports show that staphylococcal enterotoxin B (SEB) in AD skin lesions is localized predominantly to eosinophils, LCs, and IgE-bearing cells in the dermis⁹⁵. Superantigens can alter the course of AD by inhibiting eosinophil apoptosis, increase the expression of activation surface antigens and stimulate its oxidative burst⁹⁶, they also stimulate LCs and macrophages to produce IL-1, TNF- α and/or IL-12, thus stimulate CLA+ memory T-cells recruitment to the skin⁹⁷. Keratinocytes type HLA-DR can also display superantigens to T-cells, as they cannot secrete IL-12, resulting in the stimulation of Th₂ rather than Th₁ cells⁹⁸.

In AD patients, staphylococcal exotoxins may act as allergens. Approximately, half of AD patients produce IgE against the toxins of staphylococcal, particularly TSST-1, SEB and SEA in their sera⁹⁹, whereas the levels of those antibodies are rare in healthy controls or psoriatic patients, although the skin of these individuals is also colonized with *S.aureus* which have the ability to produce superantigen¹⁰⁰.

Staphylococcus aureus superantigens have the ability to penetrate the epidermis and dermis and interact with different immune system cells¹⁰¹, therefore local superantigens production could enhance IgE production and stimulate histamine release that trigger itching and scratching which can exacerbate AD¹⁰².

Atopic dermatitis patients who exhibit high positive rates of SEA/SEB-specific IgE antibodies were found to be severe cases, with high serum concentrations of total IgE and cases with exacerbation particularly in summer because such weather

promotes bacterial proliferation especially *S.aureus* on the skin¹⁰³.

The correlation between the presence of staphylococcal superantigens IgE antibodies and both the AD severity and the level of total serum IgE were recorded, also IgG₂ production deficiency, but not IgG₁ or IgG₄ antibodies against SEC, is associated with disease phenotype severe in a subgroup of AD patients. Most updated guidelines encourage prescribing antibiotics for severe pathogenic bacteria, like cloxacillin and cephalixin, as some microbes can worsen a flare of dermatitis. In those subjects, antimicrobial agents must be added to protect against acute attack¹⁰⁴.

10 Future perspective aspects

From the available guidelines, physicians can control so many cases of AD successfully, in spite, a lot of patients stay suffer. It's expected that the advance in immunology, biotechnology and biologic therapies will significantly help to relieve these restrictions and obstacles and minimizing adverse effects of drug therapies.

11 Conclusion

From this review, it becomes clear that the atopic dermatitis result from the defects in innate and adaptive immune responses, also the presence of microorganism increase the severity of the disease. The susceptibility to microbial infection result from the defect in the innate immune system and the infection, in turn,

stimulate the inflammatory process and increase the severity of the disease.

12 Acknowledgments

Special thanks to Mustansiriyah University (www.uomustansiriyah.edu.iq), Baghdad- Iraq for its support in the present work.

13 Conflict of interests

None.

14 Author's contributions

SYJ, MEA and BARM carried out the literature review and draft the manuscript. SYJ participated in the articles collection. All authors read and approved the final manuscript.

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