Published in final edited form as:

Immunol Allergy Clin North Am. 2010 August ; 30(3): 309–321. doi:10.1016/j.iac.2010.05.001.

The Infectious Aspects of Atopic Dermatitis

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Synopsis

Atopic dermatitis is characterized by *S. aureus* colonization and recurrent skin infections. In addition to an increased risk of invasive infections by herpes simplex or vaccinia viruses, there is ample evidence that microbial pathogens, particularly *S. aureus* and fungi, contribute to the cutaneous inflammation of atopic dermatitis. We describe recent developments in the pathogenesis of atopic dermatitis in relation to the role of microbial pathogens. Understanding how microbial pathogens interact or evade the cutaneous immunity of atopic dermatitis may be crucial in preventing infections or cutaneous inflammation in this disease.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that causes significant morbidity in affected individuals. The disease is often characterized by chronic inflammation and pruritus interrupted by acute flares and bacterial infection [1]. It results in significant sleep loss, poor school/work performance and disruption of social activities. In addition, severe AD patients are at risk for rare invasive bacterial infections and life-threatening eczema herpeticum [2,3]. Although recent studies have provided strong support for the basis of skin barrier defects in the pathogenesis of AD [4], the cause of AD remains incompletely understood. More recent data have also provided further insights into the important role of immune responses in the pathogenesis of AD (Table 1). Of note, AD patients with increased allergic responses have more severe skin disease as well as a greater tendency to suffer from skin infections. These studies provide evidence for a role of the immune response in the expression of AD. Secondary skin infections have long been known to be associated with AD flare. The most common skin infections in AD are caused by *Staphylococcus aureus* (*S. aureus*) and herpes simplex virus (HSV). In the absence of clinical signs of infections, the majority of AD patients are also colonized with *S. aureus* on

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their skin lesions. This pathogen is known to produce a myriad of pro-inflammatory factors that may trigger the cutaneous immune system [5]. In this review, we will discuss recent developments in the genetic basis of skin barrier, immune phenotypes and the role of microbial pathogens in AD.

Skin Barrier Defects in the Pathogenesis of AD

The stratum corneum (SC) of the skin acts as an important barrier in preventing water loss from the skin as well as in protecting the skin from intrusion by irritants or microbes. Based mainly on trans-epidermal water loss (TEWL) studies, it has long been known that the SC of AD skin is defective. The TEWL in AD lesions is significantly greater, as compared to non-lesional AD skin as well as healthy skin [6,7]. In addition, it has been shown that non-lesional AD skin has greater TEWL as well as significantly thinner SC, as compared to healthy skin (12.2 microns vs. 19.7 microns) [reviewed in reference 8]. Increased TEWL correlates with increased AD severity [9]. Various proteins and lipids responsible for skin barrier function have been found to be deficient in AD skin. These molecules include filaggrin, involucrin, cholesterol, free fatty acids and ceramides [10,11]. More recently, a genetic basis for the skin barrier defect in AD has been demonstrated by the strong association between filaggrin gene mutations and AD [4]. 2 loss-of-function mutations in the filaggrin gene (*FLG*)(R501X and 2282del4) have been linked to childhood-onset AD, particularly in patients who have onset of AD 2 years or younger [12]. 21.3% of patients with onset of AD 2 years or younger had one or more *FLG* mutated alleles, as compared to 15.8% and 9.5% in patients with non-*FLG* related childhood-onset AD and healthy controls, respectively [12]. These results were also replicated in AD patients with rarer *FLG* mutations: R2447X, S3247X, 3702delG and 3673delC [13]. In addition, it has been shown that patients with early-onset AD and *FLG* mutations have a tendency to have persistent disease into adulthood [14]. *FLG* in AD patients was significantly associated with the extrinsic form of the disease (i.e. patients with elevated total serum IgE and/or presence of specific IgE against inhalant or food allergens), and the development of allergic rhinitis and asthma [15–19]. The association of IgE sensitization with *FLG* in AD has recently been supported by a mouse model with homozygous frameshift mutation in filaggrin that is analogous to human *FLG* [20]. This mouse model facilitates cutaneous allergen sensitization that leads to production of specific IgE. Although the association of *FLG* with AD and atopy is clear, the role of *FLG* in modifying immune response in human AD has not been established. Of note, approximately 40% of carriers of *FLG* mutations showed no sign of AD [4]. Indeed, *FLG* mutations were initially found to be the cause of ichthyosis vulgaris, which is a dry skin condition with no apparent inflammation or infection [21]. Therefore, additional factors must be involved in the pathogenesis of AD.

Susceptibility of AD Patients to Infections

Psoriasis is another chronic skin disease with skin barrier defects. Based on TEWL experiments, psoriasis and AD were found to have similar physical barrier dysfunction [6]. However, AD is associated with recurrent bacterial or viral infection, whereas secondary infection in psoriasis is uncommon [22]. A deficiency in host defense molecules may contribute to the increased infections in AD. Sphingosine, a skin lipid with anti-*S. aureus* activity, has been shown to be significantly decreased in AD skin and lesions, as compared to healthy skin [23]. A decrease in dermcidin, an antimicrobial peptide (AMP) produced by eccrine sweat glands, has also been found to be decreased in AD [24]. 2 major classes of AMPs in cutaneous innate immunity, β -defensins and a cathelicidin (LL-37), have also been shown to be decreased in AD, as compared to psoriasis [25,26]. In addition to a deficiency in the first-line defense against microbial pathogens, adaptive immunity may also play a role in perpetuating susceptibility of AD to infections. Cell wall components of *S. aureus* have

been implicated as a trigger for the production of thymic stromal lymphopoietin (TSLP) by epithelial cells including keratinocytes [27]. This cytokine increases the production of Th2-associated chemokines, CCL17 and CCL20, by macrophages or dendritic cells, leading to increased infiltration of Th2 cells, which express increased levels of Th2 cytokines, IL-4 and IL-13. These cytokines favor the attachment of *S. aureus* to in AD skin [28]. IL-4 and IL-13 also suppress filaggrin expression, contributing to further barrier compromise in AD [29]. In addition, IL-4 and IL-13 also suppress AMP expression by keratinocytes [25,26]. These 2 cytokines were shown to suppress the expression of human β defensin-3 (HBD-3), a key *beta*-defensin against *S. aureus*, via the inhibition of mobilization of this AMP in keratinocyte, rather than via the suppression of gene expression [30]. IL-17 is a T cell cytokine that is capable of upregulating the expression of AMPs in keratinocytes [31]. Decreased IL-17 expression in AD lesions, as compared to that in psoriasis, may contribute to the reduced AMP expression in AD [32]. Th2 cytokines may further suppress IL-17 expression in keratinocytes [33], leading to lower expression of AMP in AD, as compared to that in psoriasis.

Environmental factors may also play a role in the increased colonization of *S. aureus* in AD. Patients with more severe AD have a higher level of *S. aureus* found in their home environment [34]. A mechanism for re-colonization of *S. aureus* in AD patients from the environment has been supported by studies that showed that AD patients and their close contacts have the same strains of *S. aureus* based on molecular techniques [35,36]. In addition, topical medications that are contaminated with *S. aureus* may become a source of bacterial re-colonization in AD patients [37].

The Role of *S. aureus* in AD

It is known that over 90% of AD patients are colonized with *S. aureus*, as compared to only 10% in the healthy individuals [38]. The severity of dermatitis correlates with the density of *S. aureus* colonization on AD skin lesions [39]. Anti-*S. aureus* antibiotics have been shown to improve the severity of AD [40]. These observations have provided support for the role of *S. aureus* in the pathogenesis of AD. Deficiency in AMP expression suggests an intrinsic defect in the innate immunity of AD [41]. *S. aureus* is detected by pattern recognition receptors in the innate immune system. Among the best-studied pattern recognition receptors are the toll-like receptors (TLR). TLR2 has been associated with the recognition of the cell wall components (lipoteichoic acid and possibly peptidoglycan) of gram positive bacteria including *S. aureus* [42]. Ahmad-Nejad et al. [43] showed that TLR2 polymorphism R735Q is associated with a subgroup of patients with severe AD. Using human embryonic kidney 293 transfection system, they showed that this TLR2 polymorphism is associated with a significantly decreased expression of NF- κ B, IP-10, and IL-8 [44]. TLR2-mediated production of IL-8 was shown to be significantly decreased in the monocytes of AD patients with TLR2 R735Q polymorphism [44]. On the other hand, the monocytes of these patients express significantly higher levels of IL-6 and IL-12, when compared to AD patients with wild type TLR2 [45]. Hasannejad et al [46] showed that TLR2-mediated production of IL-1 β and TNF- α by monocytes was significantly diminished in AD patients. Dysregulation of cytokine production as a result of TLR defects may lead to inflammation in AD [45]. More recently, another TLR2 polymorphism A-16934T has also been associated with severe AD [47].

In addition to the cell wall components of *S. aureus*, alpha toxin from this bacteria is also capable of inducing immune dysregulation in AD. The prevalence of alpha toxin-producing *S. aureus* strains isolated from AD patients range from 30–60% [48,49], and the presence of alpha toxin-producing *S. aureus* is significantly associated with extrinsic AD [48]. Alpha toxin was found to induce profound keratinocyte cytotoxicity and lymphocyte apoptosis

[49,50]. It also activates T cells to produce IFN- γ , leading to the development of chronic AD [49]. Other staphylococcal products that are frequently implicated in the pathogenesis of AD are their enterotoxins (superantigens).

The Role of Staphylococcal Superantigens in AD

Superantigens are presented on the MHC II molecules of antigen-presenting cells to activate T cells. These antigens bind directly to the common variable β ($v\beta$) chains of T cell receptors, resulting in a polyclonal activation of T cells. Classic staphylococcal enterotoxins include staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin-1 (TSST-1). About 50% of *S. aureus* isolated from AD patients secrete superantigens [51–53]. Direct application of superantigen on normal skin and unaffected AD skin induces erythema and causes flaring of skin disease in AD patients [54]. Increased AD severity correlates with the presence of superantigen-producing *S. aureus* [53,55]. Skin biopsy studies have shown the presence of $v\beta$ T cell clones corresponding to the specific superantigens in the AD lesions [52]. SEB has also been shown to induce lymphocyte expression of IL-31 [56], and this correlates with increased severity of AD [57]. A recent study that included both classical and non-classical staphylococcal superantigens (SEE and SEG-SEQ) showed that at least 80% of *S. aureus* isolated from AD patients are superantigen-producing [58]. Of these patients, a median number of 8 different superantigens were found per *S. aureus* isolate [58,59]. Patients with severe, corticosteroid-insensitive AD have been reported to harbor *S. aureus* strains that produce significantly higher number of superantigens per organism, as compared to that in a general population of AD patients [59]. These *S. aureus* strains that produce multiple superantigens, including SEB, SEC, TSST-1 and SEI-Q, are also associated with methicillin-resistant *S. aureus* (MRSA) [5], which may be a complicating factor in moderate to severe AD [60].

In addition to their ability to directly activate T cells, staphylococcal superantigens also induce the production of superantigen-specific IgE in AD patients [61]. Sensitization to superantigen-specific IgE has been correlated with the severity of AD [62]. The prevalence of superantigen-specific IgE in varying AD severity is as follows: 50–80% in severe AD [51,61], 60% in moderate AD, and 40% in mild AD patients [64], as compared to none in healthy individuals [61]. Binding of superantigen-specific IgE with respective superantigen leads to the activation of basophils [61], which may play a crucial role in the initiation of IgE-mediated inflammation [64].

The Role of Viral Skin Infections in AD

AD patients are also susceptible to viral skin infection [22]. Eczema herpeticum (EH), which is caused by HSV, can present as a life-threatening infection. AD patients with disseminated EH present with fever, malaise and generalized vesicles [65]. EH patients may develop complications including keratoconjunctivitis, viremia, meningitis, encephalitis or secondary bacterial sepsis. Another life-threatening viral infection that may occur in AD is eczema vaccinatum (EV), which is caused by vaccinia virus (VV) in smallpox vaccine. Since the eradication of smallpox virus in the early seventies, routine vaccination with VV had been discontinued in the general population in 1972 and in military personnel in 1990. However, due to bioterrorism threats in recent years, a government program to vaccinate select military personnel and public health workers with smallpox vaccine has been reinstituted. Since then, one case of EV has been reported in the United States. An infant with AD contracted EV through his father who was in the military and had received smallpox vaccine 21 days prior to the onset of the infant's symptoms [66]. The infant needed life-saving measures including the use of investigational drugs via Emergency Investigational New Drug Application. The case illustrates the importance in understanding the mechanisms of

VV infection in AD in order to identify AD patients at high risk for EV and to devise new treatments in AD patients with EV. Due to the rarity of EV and its clinical resemblance to EH [66,67], understanding the mechanism of disease in EH has proven to be fruitful.

Beck et al. [68] in the National Institute of Allergy and Infectious Diseases-funded multicenter Atopic Dermatitis and Vaccinia Network (ADVNI) study has recently shown that a subgroup of AD patients is particularly susceptible to EH. This subgroup of AD patients have more severe disease, higher number of circulating eosinophils, higher levels of serum CCL17, more asthma and specific IgE sensitization to inhaled and food allergens, as compared to AD patients with no history of EH. Patients with history of EH are also more likely to have secondary skin infections with *S. aureus*. The clinical observation that patients with extrinsic AD are more susceptible to viral infection is consistent with laboratory findings that IL-4 and IL-13 suppress keratinocyte expression of the cathelicidin AMP, LL-37, which has potent anti-viral activity against HSV or VV [69,70]. Viral infections in AD further trigger the production of TSLP via TLR3, which increases the Th2 cytokine milieu in AD lesions, thereby leading to further susceptibility to disseminated viral infections [71]. IL-4 and IL-13 have also been found to suppress the expression of S100 calcium-binding protein A11 (S100A11) expression in keratinocytes [72]. Suppression of S100A11 expression leads to the down-regulation of IL-10R2, which is a receptor for IFN- λ , a cytokine with activity against VV [73].

Gao et al. [74] showed that a history of EH in AD patients was significantly associated with *FLG* mutations. The frequency of R501X *FLG* was 3 times higher in AD patients with EH, as compared to those without EH. These findings were seen in both European and African Americans [74]. More recently, microarray analyses were applied to study VV-induced transcriptional changes in unaffected skin explants obtained from AD, psoriatic, and healthy individuals [75]. The skin samples were treated *in vitro* with vehicle or VV and subjected to gene ontology analysis. Wound healing and defense response genes were found to be among the most affected genes in AD-specific responses to VV. Innate immunity genes including leukotriene B4 receptor (LTB4R), orosomucoid 1 (ORM1), coagulation factor II (thrombin) receptor (F2R), complement component 9 (C9), and lipopolysaccharide binding protein (LBP), were found to be significantly down-regulated in VV-treated AD explants, as compared to healthy individuals or psoriasis patients. These observations were confirmed with real-time (RT)-PCR. In addition, the down-regulation of innate immune response gene ORM1, TLR4, and NACHT leucine-rich repeat protein 1 (NLRP1) were found to be associated with AD severity. The latter two genes, TLR4 and NLRP1, are cell surface and intracellular pattern-recognition receptors, respectively, for microbial pathogens.

Compared to chronic AD lesions, acute AD lesions have been shown to have increased expression of IL-17 [76,77]. Patera et al. first noted that IL-17 increased the virulence of VV [78]. In an AD mouse model, increased IL-17 expression was found to be associated with filaggrin-deficient mice [79] and was responsible for the dissemination of VV in AD lesions [80]. This effect of IL-17 may be due to its suppression of NK activity against VV [81].

The Role of Fungi

The role of fungi in AD has been based primarily on observations of colonization by *Malassezia* species in AD patients. There has been controversy whether AD patients have increased colonization with *Malassezia* species, as compared to healthy controls. The controversy stems from differences in sampling methods, culture techniques and identification of different species. Using molecular techniques (nested and real-time RT-PCR), Sugita et al. [82] found that *Malassezia* colonization is common in both AD patients and healthy subjects with detection rates of 100% and 78%, respectively. Among the AD

patients, they found that the head and neck areas are 7 and 10 times more likely to be colonized with *Malassezia* than the limb and trunk areas, respectively [83].

Baroni et al. [84] found that *Malassezia (M.) furfur* may induce AMP and IL-8 expression in keratinocytes via TLR-2. Selender, et al [85] found both TLR2-independent and – dependent pathways in the activation of mast cells by *sympodialis*. They showed that *M. sympodialis* induced the release of cysteinyl leukotrienes from non-IgE-sensitized mast cells. Using knock-out mice for TLR2 and MyD88, an adaptor molecule in most TLR pathways, they showed that IgE-sensitized mast cell degranulation and release of the chemokine MCP-1 was independent of TLR2 and MyD88, whereas IL-6 production was dependent on TLR2/MyD88 pathway [85]. These findings are consistent with a recent study that showed the importance of a non-TLR pattern-recognition receptor, Mincle, in the recognition of *Malassezia* by the host immune system [86]. In that study, *Malassezia* was shown to activate inflammatory responses in macrophages via Mincle [86].

Malassezia species also induce the production of *Malassezia*-specific IgE in AD patients. These specific IgE sensitizations were found exclusively in AD patients, but not in patients with allergic rhinitis, urticaria or allergic contact dermatitis [87]. *Malassezia*-specific IgE molecules are significantly more prevalent in AD patients with head and neck dermatitis, as compared to AD patients with lesions in other locations (100 vs. 14%)[88]. The prevalence and degree of IgE sensitization to *Malassezia* in AD patients are also age- and severity-dependent. Adult AD patients were found to have a higher specific IgE levels to *Malassezia*, as compared to children with AD [89]. Among young children with AD, the prevalence of IgE-sensitization to *Malassezia* were also significantly higher in the older age group than infants [90]. However, infants with severe AD and repeated oozing lesions are particularly at risk for developing specific IgE against *Malassezia* [91].

Malassezia may also contribute to AD inflammation via cell-mediated immunity and IgE-mediated autoimmunity. Patients with intrinsic AD were also found to have a significantly higher prevalence of positive atopy patch tests to *M. sympodialis*, as compared to healthy controls (38 vs. 0%)[87,92]. IgE-binding epitopes from *M. sympodialis* may cross-react with the human IgE autoantigen, manganese superoxide dismutase [93]. This may explain the ability of human manganese superoxide dismutase in inducing eczematous reactions in *M. sympodialis*-sensitized patients [94].

The Role of Other Microbial Pathogens in AD

Group A beta hemolytic *Streptococcus* can also cause skin infections in AD [95]. Streptococcal infection is associated with severe AD [96] and may result in complications including acute poststreptococcal glomerulonephritis, hypertension and posterior reversible encephalopathy syndrome [97]. Molluscum contagiosum (MC) virus belongs to the family of poxviruses. It causes skin lesions characterized by flesh-colored papules. AD patients are at increased risk for having higher number of MC lesions [98]. In addition, these lesions may lead to disfiguring scars in AD patients [99]. Patients with EH are also at increased risk for MC [68].

Clinical Implications

The discovery of *FLG* mutations as a predisposing factor for AD may lead to new molecular classification of eczema. Although it has been shown that *FLG* facilitates the production of IgE in a mouse model of *FLG* mutation, whether *FLG* plays a role in modifying the immune response of AD in human remains to be proven. Further understanding of *FLG* function may result in the development of targeted therapy in AD e.g. by increasing the expression of filaggrin [100]. Not only will this approach help AD patients with their skin disease, it may

prevent the development of asthma in these patients since multiple studies have now confirmed the association of asthma with *FLG* mutations in these patients. Genetic polymorphisms in the immune system remain an important area of research in the pathogenesis of AD. Increasing evidence suggests that innate immunity is the primary driver of adaptive immunity. Genetic polymorphisms in TLR2, which is the chief extra-cellular pattern-recognition receptor for *S. aureus*, illustrates the potential role of innate immunity in defining the phenotypes of AD. These findings are crucial as *S. aureus* cell wall products have now been shown to be capable of enhancing the production of TSLP, a key molecule in subsequent Th2 immune responses, which include the production of IL-4 and IL-13. The roles of these two cytokines in AD have been well-characterized. They have been shown to suppress the expression of AMPs, filaggrin and S100A11, all of which contribute to the pathogenesis of AD. Therefore, IL-4 and IL-13 remain important targets in the therapy of AD. The pathogenic roles of *S. aureus* in AD are numerous, including the production of superantigens, alpha toxin, stimulation of host TLR and superantigen-specific IgE. As chronic use of antibiotics leads to the development of resistant bacteria such as MRSA, which has an emerging role in AD, new therapeutic approaches against *S. aureus* in AD are needed [1]. A recent study showed that bleach baths lead to significant improvement of AD in children although patients remain colonized by *S. aureus* [101]. Useful information on the role of viral infections in AD has been generated by ADVN studies. The identification of the subgroup of AD patients with increased susceptibility to EV i.e. those with more severe disease, early age of onset, increased Th2 response and allergic sensitization to common allergens, may help identify those AD patients who are at highest risk for EV. These observations may help clinicians in weighing the risks and benefits of smallpox vaccine in AD patients, in the event that the threat of bioterrorism with smallpox becomes imminent. Direct studies of VV infection in *in vitro* or mouse models have also helped to elucidate the mechanisms of VV infection in AD. The studies by Bin et al [74] and Grigoryev et al [75] provide further insight on the genes that are critical for the innate immune responses against VV. These in turn may lead to novel approaches in treating or preventing VV infection in AD e.g. upregulation of S100A11, IL-10R2, ORM1, TLR4 or NLRP1 to increase innate immune response against VV. Increased expression of IL-17 in acute AD lesions may be an important predisposing factor in AD patients' susceptibility to VV. Thus, IL-17 may be a therapeutic target in limiting VV dissemination in AD patients. As *Malassezia* species play an important pathogenic role in a subgroup of AD patients, the identification of Mincle as the host pattern-recognition receptor for *Malassezia* may lead to novel therapies against this pathogen in AD.

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Table 1

Recent developments in the infectious aspects of atopic dermatitis

1	Filaggrin gene mutations facilitate IgE expression in a mouse model [ref. 20].
2	Toll-like receptor genetic polymorphisms may lead to cytokine dysregulation and inflammation in AD [refs. 45,46,47].
3	Emerging roles of non-classical staphylococcal superantigens (SEE and SEG-SEQ) and methicillin-resistant <i>S. aureus</i> in the pathogenesis of AD [refs. 5,58,59].
4	AD patients with specific IgE sensitization or other atopic diseases including asthma and food allergy are at increased risk for viral skin infections [ref. 68].
5	Innate immune response genes including leukotriene B4 receptor (LTB4R), orosomucoid 1 (ORM1), coagulation factor II (thrombin) receptor (F2R), complement component 9 (C9), lipopolysaccharide binding protein (LBP), and leucine-rich repeat protein 1 (NLRP1) may be involved in the pathogenesis of vaccinia virus infection in AD [ref. 75])