

Update review

Innate immune defects in atopic dermatitis

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Atopic dermatitis (AD) is a common, chronic inflammatory skin disease that becomes clinically apparent in the pediatric population. It is well recognized that subjects with AD have an increased susceptibility to cutaneous colonization and infection with bacteria, fungi, and viruses. The notion that subjects with AD have a cutaneous immune defect has received widespread acceptance, and several plausible explanations for this have been proposed. We will review the evidence that this susceptibility to cutaneous infection is at least in part due to a defect in the first line of defense against microbes, namely the innate immune system. (J Allergy Clin Immunol ■■■■;■■■;■■■-■■■.)

Key words: Atopic dermatitis, eczema, innate immunity

Of all the infectious causes found to affect patients with atopic dermatitis (AD), the best characterized is *Staphylococcus aureus*. Approximately 90% of patients with AD are colonized with *S aureus*, whereas in a control or nonatopic population, only 5% to 30% are colonized.¹ In addition to higher colonization rates, up to 50% to 60% of the *S aureus* found on patients with AD is toxin producing.¹ Also, patients with AD can rapidly advance to superinfection with 10⁷ organisms per square centimeter, as opposed to healthy subjects, who have a much lower bacterial burden.¹ Although rare, patients with AD have also been reported to have *S aureus*-induced septicemia and osteomyelitis and have increasingly become reservoirs for antibiotic-resistant strains of *S aureus*. Once present on the skin, *S aureus* can mediate multiple inflammatory cascades. For example, staphylococcal toxins can activate T cells in a superantigen-driven fashion and induce IgE-specific responses.¹ In fact, these IgE levels have been shown to correspond with disease severity.^{2,3} Additionally, bacterial superantigens can induce a state of glucocorticoid resistance, which is due in part to production of the glucocorticoid receptor (GR) β , the GR isoform that competes with GR α 's ability to bind glucocorticoids.⁴

Abbreviations used

AD: Atopic dermatitis
AMP: Antimicrobial peptide
CRTH2: Chemoattractant receptor-homologous molecule expressed on T_H2 cells
GR: Glucocorticoid receptor
HBD: Human β -defensin
HSV: Herpes simplex virus
IL-IR: IL-1 receptor
LL-37: Cathelicidin
LTA: Lipoteichoic acid
MBL: Mannan-binding lectin
NOD: Nucleotide-binding oligomerization domain
PAMP: Pathogen-associated molecular pattern
PGN: Peptidoglycan
PGRP: Peptidoglycan recognition protein
PMN: Polymorphonuclear neutrophil
PRR: Pattern-recognition receptor
SC: Stratum corneum
sCD14: Soluble CD14
TLR: Toll-like receptor
VV: Vaccinia virus

In most studies antistaphylococcal treatments have been shown to improve disease severity.^{5,6} In conclusion, it is clear that *S aureus* is able to induce both nonspecific and specific inflammation in subjects with AD, including that associated with an immediate hypersensitivity reaction. These effects might help initiate and potentiate the disease and might even modify responsiveness to a major therapeutic agent (eg, steroids).

The double-stranded DNA viruses, including herpes simplex virus (HSV), molluscum contagiosum virus, and vaccinia virus (VV; smallpox vaccine), are also capable of causing more severe and generalized infections in patients with AD.⁷ Eczema herpeticum is a disseminated cutaneous form of HSV and is often considered a medical emergency necessitating prompt systemic antiviral therapy. Epidemiologic studies suggest that patients with AD with more clinically severe disease and higher serum total IgE levels are at greater risk for eczema herpeticum.⁷ These data suggest that patients with AD with greater T_H2 polarization might be at greater risk for cutaneous infections that require a robust T_H1 response. Even less is known about the clinical characteristics of subjects with AD who had eczema vaccinatum, the severe disseminated vaccinia infection that develops in subjects with AD exposed to individuals who were recently vaccinated with smallpox or who received the vaccination themselves. We will review

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the recent data that suggest that T_H2 cytokines inhibit the release of antimicrobial peptides (AMPs) important for the immune response to cutaneous infections with HSV or VV.

Lastly, yeast belonging to the genera *Malassezia* and *Candida*, are also thought to be relevant pathogens in AD. In 1983, Clemmensen and Hjorth⁸ found that adult patients with head and neck AD who had positive skin test responses to *Malassezia* species had an improvement in their AD when treated with the antifungal agent ketoconazole. More recently, a Swedish multicenter study of 132 subjects with AD revealed that 60% had a positive skin test response to *Malassezia* species in comparison with no positive test responses in the nonatopic subjects and subjects with seborrheic dermatitis.⁹ Additionally, *Candida* species have been isolated more commonly from the skin of those with AD compared with those with psoriasis and healthy controls subjects.¹⁰

In summary, there is considerable evidence that subjects with AD have an unusual propensity for colonization by certain microbes (*S aureus* and *Candida* species) and aggravated infections with others (HSV and VV). Additionally, these microbes are thought to exacerbate the disease itself. Some of the biologic explanations for these observations have been identified and are highlighted below.

INNATE IMMUNITY

It is now widely accepted that the immune system is comprised of 2 separate branches: innate and adaptive. Adaptive immunity relies on antigen-presenting cells to encounter pathogen and deliver antigen to T and B cells, which take days to mature. In contrast, innate immunity is built on the premise of genetically encoded receptors and antimicrobial proteins that would provide an immediate response to pathogens and thereby provide critical protection while the adaptive response matures. This notion was first introduced in 1989 by Janeway,¹¹ who defined the components of the innate immune system, including pattern-recognition receptors (PRRs), pathogen-associated molecular patterns (PAMPs), and AMPs. PRRs, including Toll-like receptors (TLRs) and the collectin proteins, are engineered to respond to highly conserved structures within common pathogens, otherwise known as PAMPs, which include bacterial cell-wall products, such as LPS, peptidoglycan (PGN), and lipoteichoic acid (LTA); the fungal cell-wall product zymosan; and viral double-stranded RNA. When PRRs bind PAMPs, they initiate a signal transduction cascade that stimulates an immediate cellular response to the challenge.¹² This cellular response includes the release of AMPs, cytokines, and chemokines, which are important for the recruitment of effector leukocytes or have direct antimicrobial effects that are collectively important for the immediate containment of the infection.¹³

During the previous decade, there have been multiple studies evaluating different aspects of the innate immune system in AD and atopy in general. The findings have ranged from genetic polymorphisms in proteins relevant for innate

immunity to defects in AMP production and neutrophil migration. Below we review the components of the cutaneous innate immune system and highlight those that might be relevant for patients with AD (Fig 1).

Stratum corneum/barrier function

The epidermis functions at least in part as a protective barrier, and the majority of the protection occurs at the level of the stratum corneum (SC). The SC is formed by lipid-depleted corneocytes and a lipid-rich extracellular matrix. This creates a barrier that is able to keep water within the body and prevent the entrance of pathogens and allergens.¹⁴ The terminal differentiation of keratinocytes from granular cells to corneocytes is a critical step for maintenance of this barrier. During this differentiation, profilaggrin is cleaved into multiple filaggrin polypeptides, which are cross-linked by transglutaminases and result in the cornified cell envelope. The importance of the SC was highlighted in a recent publication that identified 2 common loss-of-function mutations in the gene encoding filaggrin and found they were associated with an increased risk of AD and asthma associated with AD.¹⁵ This latter association suggests that asthma develops as a consequence of sensitization events that begin in the skin. This work also suggests that the skin barrier defect precedes the development of AD, which was first proposed when it was recognized that subjects with AD had reduced levels of the SC lipids ceramide and sphingosine. The sphingosine reduction correlates with the degree of bacterial colonization, and this is in keeping with the evidence that it has antimicrobial properties.¹⁶ A number of studies have demonstrated reduced ceramide levels, which is thought to be due to the increased expression of sphingomyelin deacylase, an enzyme that competes for glucosylceramide, the precursor to ceramide.^{17,18} Physiologic stress can also disrupt the epidermal barrier through the production of endogenous glucocorticoids, which suppress epidermal lipid production.¹⁴ The SC is also a significant source of antimicrobial cationic peptides in addition to the lipid-rich antimicrobial proteins (sphingosines and ceramides), and this will be discussed later in this review. Lastly, a hallmark of AD is intense pruritus, which inevitably leads to extensive scratching and ultimately further breakdown of the skin barrier. It is clear that an intact and functional SC is required for an effective cutaneous innate immune response.

C-type lectins

Numerous PRRs have been identified and characterized, including the collectin and ficolin families, which are both C-type lectins. The collectin family is composed of mannan-binding lectin (MBL) and surfactant proteins. These PRRs recognize unique sugars present on both gram-positive and gram-negative bacteria, fungi, and viruses. They can act directly as opsonins by coating the pathogen and making them accessible for phagocytosis or they can directly activate the complement pathway.¹⁹ Of the C-type lectins, MBL is the best characterized. MBL is synthesized by the liver and secreted into the serum

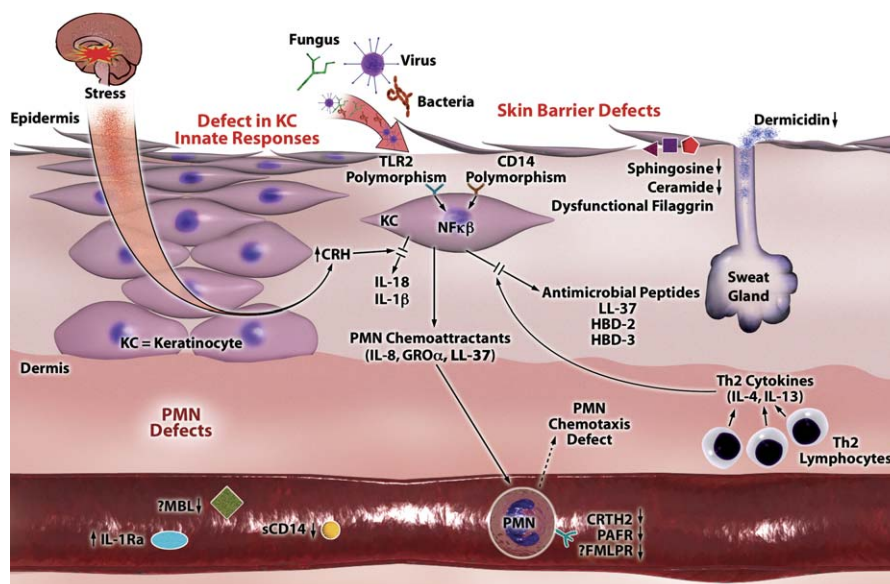


FIG 1. Subjects with AD have defects in innate immunity. The barrier function of the SC is disturbed as a consequence of reduced lipid levels (sphingosine and ceramide); abnormal keratinization, which is caused by dysfunctional filaggrins; and mechanical trauma or scratching. This creates a portal of entry for pathogens (and allergens). AD keratinocytes (KCs) also have an aberrant response to microbes. This might be explained in part by polymorphisms in TLR2 and CD14. Reduced levels of sCD14 have also been observed in subjects with AD. Additionally, increased levels of IL-1 receptor antagonist (*IL-1Ra*) might act as a sponge to dampen IL-1-mediated innate immune responses. Physiologic stress induces corticotropin-releasing hormone (*CRH*) secretion by the hypothalamus, which downregulates IL-1 β and IL-18 release by keratinocytes. IL-1 β is important for a robust innate immune response, and IL-18 functions primarily as an inducer of IFN- γ and a promoter of T_H1 responses. Collectively, this suggests that stress exacerbates AD by compromising the innate immune response to cutaneous pathogens. The production of AMPs (LL-37, HBD2, HBD3, and dermcidin) by the skin of subjects with AD is reduced compared with that seen in the skin of either subjects with psoriasis or healthy control subjects. This is thought to be due in part to the T_H2 cytokines produced by dermal lymphocytes, which have an inhibitory effect on keratinocyte production of these peptides. Lastly, AD PMNs are thought to be defective in chemotaxis, phagocytosis, and superoxide generation. The paucity of tissue PMNs in AD lesions can be explained in part by reduced chemoattractants, such as LL-37, but is likely also due to reduced expression of relevant chemoattractant receptors (CRTH2, platelet-activating factor receptor, and formyl-Met-Leu-Phe receptor [*FMLPR*]) and a defective response to chemoattractants. Finally, there is a case report of reduced MBL levels associated with AD, suggesting that this might be another defect in the innate immune response of subjects with AD. *CRTH2*, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *GRO α* , growth-related oncogene.

and is structurally and functionally similar to C1q, the first component of the complement activation pathway. MBL deficiency has been shown to predispose individuals to bacterial and viral infections, including HSV and *S aureus*.^{20,21}

The role of MBL in asthma and atopy has been debated in the literature, with a few studies finding an association between reduced MBL levels and development of airway hyperresponsiveness or more frequent asthma exacerbations, as well as an association between the MBL2 allele and childhood asthma.²²⁻²⁴ Importantly, undetectable MBL levels were noted in 3 members of a Turkish family who presented with recurrent cutaneous abscesses, pruritus, and AD, suggesting that MBL or other C-type lectins might play a role in the development of AD or in the susceptibility to infection seen in subjects with AD.²⁵

Toll-like receptors

The Toll-like receptors (TLRs) were originally identified and characterized in the fruit fly *Drosophila*

melanogaster.²⁶ In response to the appropriate PAMP, TLRs transduce a signal through the intracellular adapter molecule MyD88, which leads to the nuclear translocation of nuclear factor κ B and transcription of inflammatory mediators (cytokines, chemokines, and AMPs). Human TLRs 1 through 10 have been identified, and each receptor has been characterized on the basis of its specificity for a microbial ligand or ligands.²⁶ Originally recognized for their expression on antigen-presenting cells, TLRs have also been identified on epithelial cells, including keratinocytes. Keratinocytes constitutively express mRNA for TLRs 1, 2, 3, and 5 and potentially 4, 6, 9, and 10 as well.^{26,27} The functions of TLRs 1 through 5 have been implied by the expression of immune response genes after TLR-specific ligand stimulation.^{26,28}

Mice deficient in TLR2 and its downstream effector, MyD88, were found to be highly susceptible to an intravenous inoculation with *S aureus*.²⁹ This is in keeping with the evidence that the purified staphylococcal cell-wall components LTA and PGN are known to signal

through TLR2. Recently, it was reported that a missense mutation in the *TLR2* gene R753Q was found with increased frequency in patients with AD and that it correlated with a more severe phenotype, higher serum total IgE levels, and greater susceptibility to *S aureus* colonization.³⁰ Little is known about the role that keratinocyte-derived TLR3 plays in host defense to viral pathogens, such as HSV and VV, although a recent publication revealed that stimulation of keratinocytes with VV led to induction of cathelicidin (LL-37) through TLR3.²⁸ Nomura et al³¹ looked at mRNA expression for TLRs 1, 2, 3, 5, and 6 and found no significant difference between skin biopsy specimens taken from patients with AD and those from patients with psoriasis. This is in agreement with our studies,³² which demonstrate no difference in TLR2 expression by means of flow cytometry on nonlesional keratinocytes isolated from subjects with AD and subjects with psoriasis.

IL-1 family

The IL-1 receptor (IL-1R) pathway has also been implicated in the host response to *S aureus*. IL-1 α and IL-1 β are known ligands of IL-1R, and IL-1 α levels have been shown to be increased in the skin of mice during *S aureus* infection. Similar to TLRs, IL-1R has been shown to use the adaptor protein MyD88. In a recent publication both IL-1R and MyD88 knockout mice were shown to have impaired neutrophil chemotaxis in response to a cutaneous *S aureus* challenge, whereas a TLR2 knockout mouse did not demonstrate a similar impairment.³³ These findings suggest a greater role for the IL-1R pathway than TLR2 in response and containment of *S aureus* at the skin surface.³³ Inflammatory skin diseases, including AD, have also been shown to have an increased ratio of IL-1R antagonist to IL-1 α in the SC, which would have an inhibitory effect on IL-1-mediated actions.³⁴ Another member of the IL-1 family, IL-18, known to be a mediator of inflammation and innate immunity, has recently been shown to be expressed by keratinocytes and, like IL-1 β , is downregulated by corticotropin-releasing hormone.³⁵ Because inflammatory skin diseases are known to be exacerbated by stress, it can be hypothesized that the stress-induced release of corticotropin-releasing hormone and the ensuing reduction of IL-18 and IL-1 β levels might also play a role in the susceptibility to cutaneous infections in patients with AD.³⁵

Nucleotide-binding oligomerization domain

Nucleotide-binding oligomerization domain (NOD) 1 and NOD2 are cytosolic proteins that respond to the degradation products of PGN.³⁶ Specifically, NOD1 senses diaminopimelic acid-type PGN, which is produced by gram-negative bacteria, and NOD2 senses muramyl dipeptide, a motif found in PGNs from all bacteria, including *S aureus*.³⁶ Recently, keratinocytes were shown to express NOD1 and NOD2, which were presumed to be functional because stimulation with PGN resulted in IL-6 production.³⁷ Furthermore, keratinocytes stimulated

with the NOD2-specific ligand muramyl dipeptide produced the AMP human β -defensin 2.³⁸ An association between NOD1 polymorphisms and AD has been suggested,³⁹ but there are no reports looking at NOD2 expression or function in AD, which would be the PRR more relevant for the response to *S aureus*.

CD14

CD14 is a multifunctional receptor for LPS and other bacterial wall components.⁴⁰ Because CD14 has also been found to induce cellular activation in response to LTA through a TLR2-dependent pathway⁴¹ and has binding affinity for PGN,⁴² it is thought to play a role in host response to *S aureus* as well. Similar to TLR2 signaling, CD14 uses MyD88 to activate nuclear factor κ B. It is also known to produce IL-1 β through a caspase 1-dependent pathway.⁴³ Although it is expressed as a soluble or membrane-bound receptor predominantly on monocytes, it has also been found on a variety of cells, including keratinocytes.⁴⁴

Fueled by the hygiene hypothesis and the epidemiologic data showing that the presence of LPS in house dust is inversely correlated with atopy, numerous genetic studies of atopic populations have been performed looking at specific *CD14* variants.⁴⁰ These studies have shown an association of variants in the *CD14* gene with both the prevention and severity of atopy. However, phenotype definitions and the allele that showed association have differed between studies.⁴⁰ Additionally, children with AD have been shown to have reduced levels of soluble CD14 (sCD14) compared with nonatopic children,⁴⁵ and a small study also found that reduced levels of sCD14 in breast milk were associated with the development of eczema at 6 months of age.⁴⁶ In contrast, exclusively breast-fed children whose mothers had higher levels of sCD14 in their breast milk had a decreased likelihood of having AD.⁴⁷ In summary, the lower levels of sCD14 observed in children with AD or their mothers might be due to genetic differences or a reduced capacity to respond to microbial signals or decreased exposure to microbial signals. Although the reduced serum sCD14 levels might suggest that there is reduced CD14 expression on keratinocytes, we have not observed any differences in the expression of CD14 on keratinocytes derived from the nonlesional skin of subjects with AD, subjects with psoriasis, or nonatopic control subjects.³²

Peptidoglycan recognition proteins

Peptidoglycan recognition proteins (PGRPs) have very recently been recognized for their role in innate immunity. Four different proteins have been identified in human subjects: PGRP-L, S, 1 α , and 1 β .⁴⁸ Only PGRP-1 α and PGRP-1 β are found in epithelial cells, but little else is known about their activity. We have found PGRP-1 α protein in primary human keratinocytes, and stimulation with the staphylococcal-specific PAMP LTA enhanced its expression.³² There is no evidence that there is a deficiency or dysfunction of PGRP-1 α in subjects with AD,

but further studies need to be done because this is an important innate immune receptor for *S aureus* recognition.

AMPs

Another well-described component of the innate immune system is the AMP. Originally discovered in the 1960s as arginine-rich cationic peptides, these small proteins are generally 15 to 45 amino acids in length and are either constitutively expressed or expressed in response to a microbial challenge.⁴⁹ The antimicrobial properties of these peptides arise from their ability to integrate into and disrupt the cellular membrane of the offending organism.⁴⁹ AMPs can also modulate host immune response, including stimulation of neutrophil chemotaxis and activation of PRRs.⁴⁹ Many peptides have been identified in human subjects that have antimicrobial properties, and the most well-characterized AMPs include LL-37, α -defensins, and β -defensins (HBDs) 1 through 4.⁴⁹ Both LL-37 and HBD2 and HBD3 have been shown to have antistaphylococcal activity, although HBD3 is the most potent.^{31,50,51} Human keratinocytes produce LL-37 and HBDs in response to inflammatory stimuli, such as LPS, LTA, IFN- γ , and TNF- α .^{31,52}

Ong et al⁵³ was the first to recognize that subjects with AD had reduced HBD2 epidermal immunoreactivity and mRNA expression compared with that seen in subjects with psoriasis. A follow-up study by Nomura et al³¹ found a reduction in HBD2, as well as HBD3, levels in lesional skin biopsy specimens from subjects with AD compared with those of subjects with psoriasis by using GeneChip microarrays. The reduced AMP expression was due in part to the inhibitory effects of the T_H2 cytokines (IL-4 and IL-13) and the immunomodulatory cytokine IL-10 on keratinocytes.^{31,53,54} Several studies have shown that the AMP LL-37 is necessary for an adequate response to both HSV and VV^{7,50} and that LL-37 levels from skin biopsy specimens are significantly reduced in patients with AD compared with those seen in patients with psoriasis.⁵³ Indeed, an article by Howell et al reports that LL-37-deficient (Cnlp^{-/-}) mouse skin had higher replication of HSV than seen in skin of wild-type mice, suggesting that the lack of this AMP might provide an explanation for the predisposition to eczema herpeticum in patients with AD.⁵⁵ This reduced production of LL-37 might also predispose patients with AD to eczema vaccinatum.²⁸

Other AMPs include dermcidin, which has broad-spectrum activity against *S aureus*, *Escherichia coli*, and *Candida* species.⁵⁶ Unlike the inducible AMPs noted above, dermcidin is constitutively expressed in eccrine sweat glands and with sweating is transported to the epidermal surface, where it reduces cutaneous bacterial burden. A recent study demonstrated that the sweat of subjects with AD was deficient in dermcidin compared with the sweat of healthy subjects.⁵⁶ Additionally, those subjects with AD and a history of viral or bacterial skin infections had reduced dermcidin levels compared with subjects with AD who did not have a history of cutaneous infections.⁵⁶ The deficiency in constitutive production of dermcidin, coupled with the evidence that subjects with

AD perspire significantly less in response to physical exercise or thermal stress, provides a plausible explanation for the high *S aureus* colonization rates.

Neutrophils

A striking finding in the skin biopsy specimens of patients with AD is the absence of polymorphonuclear neutrophils (PMNs), even in the setting of intense scratching or increased *S aureus* colonization and infection. Previous studies have demonstrated various PMN defects in subjects with AD. These include impaired phagocytic function⁵⁷ and a reduced capacity to produce reactive oxygen species.⁵⁸ Rogge and Hanifin⁵⁹ demonstrated that patients with AD had defective PMN chemotactic activity, which correlated with disease severity and the presence of cutaneous infections. Our studies would suggest that the chemotactic defects noted above are due in part to decreased expression of relevant chemoattractant receptors (chemoattractant receptor-homologous molecule expressed on T_H2 cells [CRTH2], platelet-activating factor receptor, and formyl-Met-Leu-Phe receptor), as well as ligand-binding defects, ligand-signaling defects, or both.⁶⁰ It is likely that the defect in cutaneous PMN recruitment observed in patients with AD is also a function of defective tissue signals from the skin (eg, reduced LL-37 production), or otherwise these patients would be susceptible to infections at other mucosal surfaces. Because PMNs are critical cells in the initial response to all pathogens, it is not surprising that patients with AD are susceptible to a wide range of cutaneous microbes.

CURRENT AND FUTURE THERAPIES

Interestingly, treatment with both topical corticosteroids and calcineurin antagonists has been noted to reduce the staphylococcal burden on the skin of subjects with AD. One study revealed that topical administration of a potent corticosteroid could eradicate *S aureus* after a 2-week course.⁶¹ Similarly, the use of 0.1% tacrolimus ointment was shown to reduce cutaneous *S aureus* within the first week of use.⁶² It is believed that the reduction in *S aureus* observed is due to the inhibition of T_H2 cytokines by these therapeutic agents and not due to a direct antimicrobial activity. Interestingly, there is even some suggestion that glucocorticoids might enhance innate immune responses at mucosal surfaces.⁶³

Despite the clinical benefits from topical corticosteroids and calcineurin antagonists, there are many patients with AD who do not achieve adequate relief from these therapies. Pharmaceutical companies have begun to develop therapies aimed at boosting the innate immune system. For example, AMPs have been found in abundant quantities on the skin of amphibians and are currently being evaluated for their use in human disease.⁶⁴ Additionally, there have been efforts to use transfection techniques to increase AMP production by keratinocytes. For example, Carretero et al⁶⁵ transfected keratinocytes with adenoviral vectors containing AMP genes and found increased inhibition of bacterial

growth. Cationic steroid antibiotics have been synthesized by Ceragenix Pharmaceuticals, Inc (Denver, Colo), to mimic the features of naturally occurring AMPs and will likely be marketed as topical broad-spectrum antibacterial agents.⁶⁶

CONCLUSION

It is clear that there are a variety of defects in the innate immune system, ranging from barrier defects to reduced AMP release to genetic polymorphisms in PRRs, that all have the ability to affect the development and severity of AD (Fig 1). Some of these defects precede the development of the disease and others develop as a consequence of the disease process. The reduction in AMPs could certainly be one explanation for the increased susceptibility to pathogens, such as *S aureus*, HSV, and VV. The TLR2 polymorphisms found in subjects with AD could also account for increased fungal and staphylococcal colonization because the mutant TLR2 might not be able to respond appropriately to its PAMPs (zymosan and LTA). We are just beginning to understand the role of the innate immune system in a variety of clinical diseases, and there is certainly much more to learn about its significance in the development and progression of AD.

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