

What is the role of *Staphylococcus aureus* and herpes virus infections in the pathogenesis of atopic dermatitis?

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Atopic dermatitis (AD) is a chronic, relapsing disease. Genetic, environmental and immunological factors are involved in its pathophysiology. Individuals with AD have an increased predisposition to colonization and/or infection of the skin by various pathogens, especially *Staphylococcus aureus* and herpes simplex virus. The composition of their skin microbiome is also different, and changes during flares. The disease severity can be related to the degree of colonization by *S. aureus*. In addition, the presence of this bacterial species can predispose the host to more severe and disseminated viral infections. This article reviews the role of *S. aureus* and herpes virus infections and the skin microbiome in the pathogenesis of AD and their importance in the treatment and prevention strategies of this dermatosis.

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Atopic dermatitis (AD) is the most common form of dermatitis in childhood. In the United States, the prevalence in school-age children is around 17%, with similar numbers for most developed countries [1]. The prevalence of AD in developing countries has grown in recent decades, especially in Africa, Asia and Latin America [2,3]. The clinical characteristics of AD vary with age and may change during the course of the disease. The eczematous lesions may be acute, subacute or chronic [4]. The presence of xeroderma and a low threshold for pruritus are characteristic of AD. The intense itching causes sleep disorders, irritability, fatigue and significantly impacts the quality of life of affected children and their families [5]. AD manifestations are different for different age brackets. In infants, eczema predominates in the face and extensor surfaces, while in older children eczema appears more in the flexural regions. In adolescents and adults, eczema appears not only in the flexural regions but it also frequently affects palms, soles and perioral and periorbital regions [6].

AD is a complex disease with many factors that can contribute to its pathophysiology. It is a genetic skin disease influenced by changes of the innate and adaptive immunity, as well as exposure to environmental factors, in which the dysfunction of the skin barrier (SB) has a key role [7]. A dysfunctional SB has been reported to facilitate sensitization to allergens and increase the risk of infections [8].

There are two hypotheses to explain the mechanisms of AD: one that maintains the initial cause is an immunological defect that generates sensitization to antigens mediated by IgE with the dysfunction of the SB emerging as a result of local inflammation. The second hypothesis considers that a change in the SB is the primary cause leading to the absorption of allergens by the skin, with a consequent sensitization and inflammatory response. The immunological cause would be an epiphenomenon [8,9]. However, once AD has installed itself in the host, the distinction between these two hypotheses seems unnecessary, as these two mechanisms come to coexist [9].

Skin barrier

The protective functions of epidermis are organized in four elements which act in synergy: the first is the physical barrier of cells and protein layers of cornea and the granulos of the epidermis. The second is the chemical barrier, which includes several families of peptides such as the antimicrobial peptides, the S100 proteins and degradation products of filaggrin. The immunological barrier, formed by immediate and nonspecific response (innate immunity) and the specific and long-term response (acquired or adaptive immunity) is the third element to form the SB, and the fourth element is the microbiota of the skin formed by a large number of microorganisms that protect the skin from pathogens and play an important role in the cutaneous inflammatory response [7,8,10,11]. Over the last few decades, studies have shown that defects in the SB are involved in the start-up and maintenance of skin inflammations in AD patients [12,13]. The magnitude of the SB dysfunction is correlated directly with the severity of the disease [14]. Consequently, the SB in AD patients is altered, as can be seen by the increase in transepidermal water loss and defects in the differentiation of keratinocytes that cause a reduction in protein concentrations such as ceramides, filaggrin and antimicrobial peptides [13,15]. Also contributing to damage the SB are the increased protease activities and release of proinflammatory cytokines by keratinocytes, mast cells, as well as mites and bacteria [16]. These changes in the SB of AD patients are found both in the cutaneous lesions and in normal skin, which also demonstrates transepidermal water loss, reduction of sebum secretion and the presence of a minimal inflammatory infiltrate [17]. These features facilitate the penetration of allergens and bioactive substances causing subsequent sensitization in AD patients [18].

Staphylococcus aureus & atopic dermatitis

The skin of AD patients is normally colonized and may be infected by various microorganisms, including bacteria, fungi and viruses. Although there are defects in the SB, other skin diseases, such as psoriasis, rarely coexist with secondary infections [19]. This tendency was initially attributed to changes in the adaptive immune response of the disease itself; however, more recently defects in innate immunity have been reported to contribute to a higher incidence of colonization/infection, such as SB damage, reduction of antimicrobial peptide concentrations, decreased recruitment of immune cells into the skin and defects in toll-like receptors (TLR), among others [9,20].

TLR-2 recognizes different components of the cell wall of *S. aureus* and due to the importance of this bacterium, it is the most studied in AD. Several studies have shown a reduced expression of this receptor in circulating monocytes and keratinocytes from patients with AD [21,22], while other studies have indicated mutations in TLR-2 of patients with AD; however, the clinical significance of these findings is unclear [7]. TLR-2 appears to be less immunoreactive in the AD lesion sites in relation to healthy skin [7]. Apparently inflammatory mediators in the skin of AD patients, where the standard Th2 response predominates, could reduce the TLR-2 expression in contrast with psoriasis, in which the Th1/Th17 standard predominates and the expression of TLRs is increased [23]. Another factor still being studied is the epigenetic alterations induced by pathogens in epithelial cells, which affects the function and expression of TLR-2, but there are no specific studies relating to AD in this field yet [15].

Keratinocytes express small amounts of cathelicidin (LL-37) in the skin of healthy individuals, and when damage or viral or bacterial infection affects the SB, the expression of this antimicrobial peptide (AMP) is strongly induced; however, in AD patients, the induction process of both cathelicidin and defensins is defective due to the presence of cytokines, such as IL-4 and IL-13 that characterize the Th2 microenvironment [24]. These cytokines are capable of suppressing the expression of defensins and the proteins of the S-100 family, contributing to a defective response to a skin infection [7]. The expression of dermcidin, an AMP secreted by the eccrine sweat glands, is also reduced in AD patient's sweat compared with healthy controls, and this decrease is more evident in patients with a history of viral and bacterial infections [25].

Mutations in the gene encoding filaggrin (*FLG*) found in patients with AD is related to an increased risk of skin infections [26]. Filaggrin plays an important role in maintaining the integrity of the SB, as well as an acidic skin pH, which contributes to decrease the expression of *S. aureus* binding proteins, such as the clumping factor B and the fibronectin binding proteins. Furthermore, filaggrin degradation products, such as urocanic acid, are capable of inhibiting the growth of *S. aureus* [27].

S. aureus can be present in the skin and mucous membranes of humans, especially in the nasal fossae, which are the most common sites of colonization [28]. Nasal colonization by *S. aureus* has been shown to be related to the worsening of AD, in addition to being a risk factor for the development of cutaneous infections caused by this pathogen [29]. Up to 90% of AD patients are colonized by *S. aureus*, while in healthy subjects this rate is from 20 to 40% [24]. About 50% of AD patients who are colonized by *S. aureus* present infections that require systemic

antibiotic treatment [9]. The severity of AD is proportional to the degree of *S. aureus* colonization of the skin lesions and improves with adequate management of inflammation and infections [30].

Cutaneous colonization or infection by *S. aureus* is also able to contribute to the worsening of AD through various mechanisms, such as the production of toxins that induce changes in immune regulation, leading to the development of chronic AD [31].

The α -toxin produced by *S. aureus* is cytotoxic against lymphocytes and keratinocytes, and the presence of IL-4 and IL-13, as well as filaggrin deficiency, are capable of increasing the action of this toxin against keratinocytes [32,33]. Superantigens produced by more than 80% of the *S. aureus* isolates from AD patients, interfere in the pathogenesis of AD by polyclonal activation of T-cells, causing massive release of cytokines and amplification of the inflammatory reaction. They also act in the induction of IgE, which is present in 50–80% of severe cases of AD, 60% in moderate cases and 40% in mild cases. Staphylococcal enterotoxin B has been shown to induce IL-31 expression, one of the main mediators of pruritus, and to be linked to increasing severity of AD [34]. The superantigens of *S. aureus* have also been shown to be capable of inducing *in vitro* resistance to corticosteroids, the most used drugs in the disease control, which would contribute to the difficulty in managing AD patients when colonized by this pathogen [35]. Some authors suggest that methicillin-resistant *S. aureus* produces more superantigens than methicillin-sensitive *S. aureus* isolates, justifying the association of methicillin-resistant *S. aureus* colonization with increased severity of AD [36,37].

Herpes virus & atopic dermatitis

The clinical course of AD may be altered by viral infections; mainly those caused by the herpes virus, human papillomavirus or by the molluscum contagiosum virus. Among these, herpes simplex virus (HSV) seems to be the most associated to AD. About 3% of AD patients are susceptible to severe and disseminated viral infections, including eczema herpeticum (EH) and the eczema vaccinatum, a complication that occurs after immunization for smallpox [38,39]. A recent review reported the correlation between several viruses and the development and worsening of AD [40].

EH is a widespread and potentially serious cutaneous infection caused by HSV-1 or less commonly by HSV-2, which occurs in about 3% of AD patients; however, it is extremely rare in individuals without AD [41]. EH symptoms include fever, malaise and widespread distribution of vesicles and it may develop complications such as keratoconjunctivitis, viremia, meningitis, encephalitis and secondary bacterial sepsis [42].

Risk factors for EH include: early onset of AD, severe AD, untreated patients, as well as eczema on the face and neck, previous history of EH or HSV infection, increased levels of total and specific IgE, and for airborne allergens from food or fungi such as *Malassezia sympodialis* [38,43].

Patients with AD and a history of EH have a higher Th2 bias. Th2 cytokines reduce various processes of the innate and adaptive immune systems required for effective antiviral defense, and reduce the expression of epidermal proteins such as filaggrin, and proteins necessary for the differentiation of keratinocytes, such as S100 and A11 [44]. Also the risk of developing EH has been shown to be associated with a reduced production of β -defensins and claudins, characteristic of AD patients [45]. AD patients with a history of EH exhibit variations in several genes, such as those of *FLG*, *IFNAR1*, *IRF2*, *IFNGR1* and of *TSLP* [46,47].

In a more recent study, Bin *et al.* in 2014 demonstrated that circulating mononuclear cells from AD subjects with a history of EH are deficient in their antiviral immune response when stimulated with HSV-1, unlike AD patients without a history of EH. Other changes found in this group of patients were decreased interferon production of types I and III, which play a central role in antiviral defense, and the suppression of the regulatory factors of IFN, IRF3 and IRF7, two of the main regulators of innate immunity [41]. These changes cause AD individuals that have EH to have *S. aureus* infections more often compared with those without a history of EH. In 2009, in a multicenter study in the USA, Beck *et al.* demonstrated that a history of *S. aureus* infection was the one predisposing factor for the development of EH in patients with AD. About 78% of the subjects who developed EH had a history of staphylococcal infection, against a total of 29% among those who did not develop EH [43].

Based on this fact, Bin *et al.* in 2012, demonstrated both *in vitro* and *in vivo* that the α -toxin of *S. aureus*, even at sublytic doses, was able to induce the penetration of herpes virus in keratinocyte through structural changes in the cellular membrane, making it more permeable to HSV; consequently, predisposing the host to more severe and disseminated viral infections [48]. ADAM-10, a functional receptor for *S. aureus* α -toxin in epithelial cells, also seems to be involved in the virus entry into keratinocytes. The proteolytic action of ADAM-10 is activated by the

toxin, inducing cleavage of cadherins, protein components of the 'tight junctions', with reduced cohesion between the keratinocytes and subsequent exposure of the receptors for binding the virus to epidermal cells [49].

Another virus able to cause a worsening of AD is Coxsackie, from the enterovirus group. In 2013, Mathes *et al.* described patients with AD who presented oral ulcers and papules on the palms and soles, as well as vesicular and erosion lesions in extensor, flexor and gluteal areas. The presence of the virus was confirmed in these regions and these authors named this condition as 'eczema coxsackium' [50].

Skin microbiome & atopic dermatitis

Metagenomic studies are able to identify and quantify different microorganisms on human skin [51]. The composition of the skin microbiome varies according to the characteristics of the site under study, such as temperature, pH, humidity, concentration of hair follicles and glands, as well as factors relating to the host, such as age or disease, and these may be influenced by genetic and environmental elements [52]. These microorganisms interact with each other and with the host and the host's immune system, and they are implicated in the maintenance of the skin integrity as well as in the pathogenesis of several skin diseases [53].

Habitats with similar characteristics also have similar microbiomes. In areas with higher concentrations of sebaceous glands, *Propionibacterium* species predominate, while in wetter areas such as armpits and inguinal folds, *Staphylococcus* and *Corynebacterium* predominate. In dry areas, such as limbs, Gram-negative bacteria are found [54]. In addition to the variation related to the studied area, there is a temporal variation of the microbiome composition. More occluded areas have less variation than exposed areas such as the palms of the hand, for example, as discussed in [53].

Some studies of the skin microbiome have demonstrated that the antimicrobial peptide expression increases in the presence of *Propionibacterium* species and other Gram-positive bacteria [55], as well as the hydrolysis of cutaneous triglycerides by *Propionibacterium acnes* and *Staphylococcus epidermidis*, which can produce free fatty acids with antimicrobial activity [56]. Some Gram-positive commensals, such as *Lactococcus*, *Streptococcus* and *Staphylococcus* produce bactericidal factors, thus indicating the role of the microbiome in innate immunity [57]. Based on evidence that the intestinal microbiota can influence acquired immunity through the activation of T cells and the induction of interleukin synthesis, some authors have questioned whether this influence also exists in the skin microbiota [53].

Different methods have been used to identify skin virome in healthy human individuals such as papillomaviruses, polyomaviruses and circoviruses [58]. This has been demonstrated previously in one study showing the presence of β - and γ -papillomaviruses in the skin of healthy individuals [59].

Sites of disease predilection in AD, like the antecubital fossa and the popliteal fossa, for example, have similar microbiomes [54]. This similarity leads to speculation that the microbial community could be a key factor in the predominant location of AD lesions in this topography [52].

When using culture methods, both colonization and infection of the skin are commonly seen in individuals with AD, and are related to a worsening of the clinical condition. Metagenomic studies have confirmed this trend. *Staphylococcus* species increase their participation from 35 to 90% in the microbiome skin of AD patients during exacerbations of the disease, with increasing populations of both *S. aureus* and *S. epidermidis*. Increases in *Propionibacterium*, *Corynebacterium* and *Streptococcus* species can be observed after flare control [60]. The interaction between the different *Staphylococcus* species on the skin has not been fully clarified, although there is evidence that *S. epidermidis* can produce molecules which selectively inhibit *S. aureus* [61].

Intestinal microbiota & atopic dermatitis

There is speculation that the intestinal microbiota plays a role in AD. Some authors have reported differences in the prevalence of *Escherichia coli*, *Clostridium difficile*, *S. aureus* and *Bacteroides* in the intestines of AD patients when compared with healthy children [62,63]. Also, changes in intestinal microbiota with the development of AD in the first years of life have been reported. These changes demonstrate, for example, that the presence of *Clostridia* in the intestines of infants with few weeks of life is considered a risk factor for the development of AD in the subsequent 6 months [64,65]. There are studies that have reported a decrease of the intestinal bacterial diversity in children with an increased risk for AD [64], and an increase in the disease severity [66] while others have demonstrated that allergic infants were colonized with a lower frequency of *Bacteroides* and *Bifidobacteria* species and a greater frequency of *S. aureus* [62].

Conclusion

S. aureus and viruses, especially the herpes virus, play an important role in the pathogenesis of AD. Changes in SB and innate and acquired immunity of AD itself facilitate the infection of patients by some microorganisms, in particular *S. aureus* and HSV, and these changes modify the cutaneous and intestinal microbiota. Infection or colonization by *S. aureus* is able to alter the inflammatory response and increase the severity of the disease, while the presence of certain bacteria such as *S. epidermidis* have a protective effect. Other microorganisms such as HSV cause severe and potentially lethal conditions to AD patients. Understanding the role of microorganisms in AD is essential for the management and appropriate prevention of this disease.

Future perspective

In recent years, the relationship between defects of AD immunity and *S. aureus* and viral infections has been made clearer, paving the way for studies involving new strategies for the treatment and prevention of AD. However, potential interventions involving drugs that act on the characteristic immunological mechanisms of the disease, such as the Th2 shift, agents that restore or preserve the skin and intestinal microbiota as well as studies that characterize the risk factors more clearly for bacterial colonization and development of serious infectious conditions, such as EH, and strategies to control colonization and infection by *S. aureus*, are future goals for a better management of AD.

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Executive summary

- Atopic dermatitis (AD) is a multifactorial disease caused by a combination of genetic, environmental and immunologic factors that are associated with an increased predisposition to colonization and infection by various microorganisms, particularly *Staphylococcus aureus* and herpes simplex virus.
- In AD, the prevalence of cytokines such as IL-4 and IL-13 predominant in the Th2 reaction, as well as changes in the expression of toll-like receptors, AMPs, and defects in the skin barrier, among other alterations of the disease itself, are all responsible for the predisposition to viral and bacterial infections, as well as more severe and invasive infections, such as eczema herpeticum.
- Colonization or infection by *S. aureus* is able to enhance the inflammatory response in patients with AD by producing superantigens and toxins, and therefore is an aggravating factor of the disease.
- Future strategies for the prevention and treatment of AD take into account the role of *S. aureus* and viral infections in the pathophysiology of this disease.

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