Review paper

Staphylococcus aureus: an underestimated factor in the pathogenesis of atopic dermatitis?

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Abstract

Atopic dermatitis is a common, recurrent pruritic dermatosis with a complex pathogenesis. It has been associated with disordered patterns of immunological response and impaired epithelial barrier integrity. These features predispose the patients to robust colonization of skin lesions by *Staphylococcus aureus*. Virulence factors of *S. aureus* (e.g. superantigens, α- and δ-toxin, protein A) have been shown to exacerbate and perpetuate the course of atopic dermatitis. Novel therapeutic options with potential for restoring natural microbiome composition are being elaborated and may enter clinical practice in the future.

Key words: atopic dermatitis, pathogenesis, *Staphylococcus aureus*.

Introduction

The pathogenesis of atopic dermatitis (AD) is complex and remains unclear. It develops in subjects with a genetic predisposition under the influence of different environmental factors [1, 2]. The skin microbiome and its fluctuations are directly associated with this disease. This review mainly focuses on the role of *Staphylococcus aureus* in the development and perpetuation of AD (Figure 1).

Microbiome – host interactions

Numerous species of bacteria, viruses and fungi colonize human skin and are collectively defined as its microbiome [3, 4]. To understand the role of the skin microflora in the pathogenesis of AD, it is necessary to explore its qualitative and quantitative composition. The advent of Next Generation Sequencing (NGS) has facilitated the study on human microbiota. Grice *et al.* described the bacterial profile of 20 areas of the human skin thanks to the analysis of 16S ribosomal RNA (16S rRNA) [5]. A total of 19 phyla were distinguished, four of which were dominant: Actinobacteria (59% of total bacterial species, genera of this phylum – *Micrococcus, Propionibacterium, Corynebacteria*), Firmicutes (24%, *Lactobacillus, Streptococcus, Staphylococcus*), Proteobacteria (17%, *Paracoccus, Hematobacter*) and Bacteroidetes (7%, *Prevotella, Porphyromonas*). As expected, each microorganism was isolated from niches where local conditions (moisture level, pH, lipid profile etc.) favoured its growth. Regardless of these differences, it must be pointed out that the healthy skin harbours extremely diverse microflora.

Similarly to gut microbiome, it has been reported that skin commensal bacteria influence many important processes, including the maturation of the immune system [3]. The analysis of prevalence of atopic diseases in children, who were raised in different environments (rural vs. municipal) led to the elaboration of the "hygiene hypothesis" [6, 7], according to which insufficient exposure to antigens of diverse microorganisms may lead to excessive Th2-type immune response. Cytokines produced by Th2 lymphocytes (interleukin (IL)-4, -5, -13) are strategic players in the vicious cycle of atopic diseases. They are also known to aggravate AD through many mechanisms [8–10].

Non-altered microbiome helps in maintaining skin homeostasis. Naik *et al.* have proven that skin commensals provide a specific "training" for the immunological system [11]. Their presence results in increased signalling through IL-1R which inhibits Th2 polarization and ensures correct immunological response to pathogenic microorganisms. Furthermore, specific bacteria are capable of inhibiting the growth of potentially harmful microorganisms e.g. by producing bacteriocins and preventing biofilm formation. These mechanisms will be presented below in more detail.

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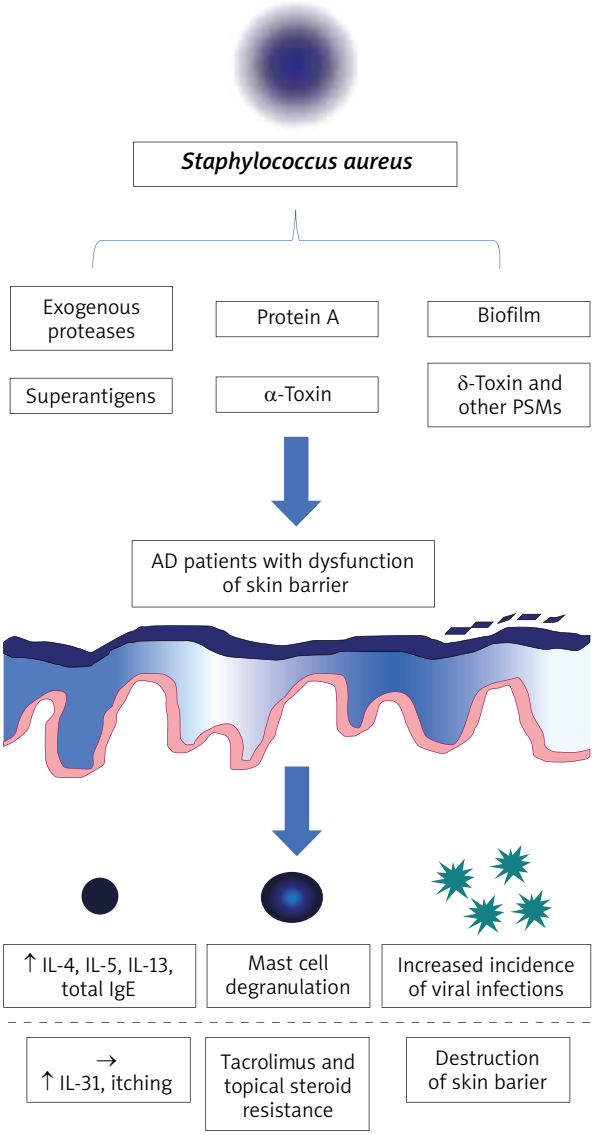

Figure 1. Virulence factors of *Staphylococcus aureus* and their role in the pathogenesis of AD. Colonization by *S. aureus* is facilitated in patients with AD due to dysfunction of the epithelial barrier. Virulence factors of *S. aureus* contribute to the vicious cycle of AD (see the text for reference)

Genetic disorders hampering the control of bacterial pathogens

Pattern recognition receptors (PRR) are a conservative element of the innate immune system. They bind pathogen-associated molecular patterns (PAMP) and danger-associated molecular patterns (DAMP) [12]. PRR-mediated signalling leads to nuclear factor-κB (NF-κB) activation which results in production of pro-inflammatory cytokines and anti-microbial peptides (AMP). Toll-like receptors (TLR) are a PRR subtype, which orchestrate an appropriate immune response. Some reports have shown down-regulation of TLR2 (*S. aureus*-antigen binding receptor) in keratinocytes and monocytes of patients with AD [13, 14]. Reduced TLR2 expression has been associated with decreased production of IL-1B, tumor necrosis factor-α (TNF-α) and IL-8 by monocytes [14]. Additionally, TLR2 seems to be important for maintaining the skin barrier function as *S. aureus* antigens and synthetic TLR2 agonists have been shown to stimulate the production of tight-junction proteins (claudin-1 and claudin-23) [15]. Of note, patients with short-term *S. aureus* colonization tend to have an increased expression of claudin-1 and -4, while prolonged presence of this pathogen on the skin down-regulates their expression and negatively affects the barrier function provided by tight-junctions [16]. Clinical importance of these observations remains unclear.

Destruction of the epithelial barrier and increased skin permeability are another prominent characteristics of AD which predispose to bacterial colonization. The patients with atopic dermatitis show deficiencies in two crucial components of the skin barrier: ceramides and intracellular connections [17–20]. While they are not directly related to negative microbiome fluctuations, they facilitate them for numerous reasons:

1) Epithelium damage leads to the increased expression of adhesive molecules [21–23]. This, on the other hand, favours adherence of pathogenic bacteria to the skin.

2) Increased skin permeability enables local penetration of allergens and irritants. They induce *in-situ* inflammation which further debilitates immune responses and epithelial regeneration [24, 25].

3) Trans-epidermal water loss (TWLE) and skin dryness are increased, which combined with local inflammation causes pruritus and the secondary barrier damage due to scratching [26].

Recent genetic analyses performed by Japanese and German scientists have proven the existence of numerous polymorphisms predisposing to AD, some of which are related to the immune system functioning [27, 28]. Nevertheless, some data suggest that investigation should not be limited to coding sequences of the human genome only. Gene expression may also be deficient because of epigenetic disorders or interference of miRNA in the process of translation. miRNAs have been reported to regulate the expression of TLRs and influence mechanisms of responses to superantigens. These observations may justify the attempts of targeting them to reduce AD symptoms [29–31].

Microbiome characteristics in atopic dermatitis

Many diseases alter natural composition of the microbiome. Two well-known examples include selective expansion of *Clostridium difficile* in antibiotic-associated diarrhoea [32] or excessive development of diverse anaerobic microflora with simultaneous reduction in *Lactobacilli* in bacterial vaginosis [33]. Atopic dermatitis is characterized by specific changes of the microbiome as well.

Classic culture methods have revealed that skin lesions in AD are colonized by *S. aureus* in up to 90% of patients and that this effect is the most prominent in samples collected during disease exacerbation [34, 35]. These observations have been confirmed by the analysis of bacterial 16S rRNA [36]. *Staphylococcus aureus* is associated with the reduction in total microbiome diversity which positively correlates with disease severity. Therapeutic interventions that restore natural skin microflora are known to alleviate the symptoms of AD [37, 38]. Recent investigations in children imply that colonization of the skin by *S. aureus* may not only be an exacerbating factor of AD, but also lead to its development [39]. Nonetheless, infants whose gut was colonized by *S. aureus* strains carrying a specific combination of superantigen and adhesin genes showed a reduced risk of subsequent development of atopic eczema, which suggests that the presence of this pathogen may globally promote appropriate maturation of the immune system [40].

Much effort has also been dedicated to determining the role of *S. epidermidis* in AD. Unlike *S. aureus,* colonization by commensal staphylococci (e.g. *S. epidermidis*) at the age of 2 months was associated with a decreased risk of AD development at the age of one year [41]. Although *S. aureus* expansion tends to inhibit the growth of most skin commensals, *S. epidermidis* remains relatively widespread in AD lesions [42]. Hon *et al.* have shown that aggravation of AD symptoms and increased colonization of the lesional skin by *S. epidermidis* are associated [43]. Nevertheless, they have also reported that *S. epidermidis* inhibits *S. aureus* growth in the lesions. This phenomenon could be explained by the ability of *S. epidermidis* to stimulate AMP production through TLR2 signalling [44] and by secretion of phenol-soluble modulins (PSM) and bacteriocins that act synergically with the aforementioned in controlling pathogens such as *S. aureus* and *S. pyogenes* [45, 46]. Furthermore, *S. epidermidis* can inhibit formation of biofilm by *S. aureus*, while lipoteichoic acid of this specie shows immunomodulatory properties in healing wounds [47–50]. The latter stresses the importance of natural commensals in proper skin recovery and should draw the attention of future research in the context of AD lesions.

Staphylococcus aureus – virulence factors affecting the disease course in atopic dermatitis

Staphylococcus aureus not only causes skin infections, but also influences the course of AD by seemingly asymptomatic colonization. This effect can be explained by its ability to produce virulence factors such as biofilm, superantigens, α-toxin and protein A that are considered as important elements of the vicious cycle of AD.

Biofilm

Some strains of *S. aureus* are capable of biofilm formation. While this process is commonly associated with decreased effectiveness of antibiotic treatment, it may also have other consequences. Biofilm impedes clearance of pathogenic bacteria by shielding them from host immune cells such as neutrophils and macrophages. It is also known to facilitate macrophage cytotoxicity [51]. Furthermore, apoptosis has been observed after exposure of keratinocytes to staphylococcal biofilm *in vitro*, and substances released upon this process (TSLP, IL-4 and IL-13) showed a negative influence on the clearance of pathogenic bacteria and skin regeneration [51]. Chronic skin damage associated with *S. aureus* colonization creates a favourable environment for biofilm development [52].

Exogenous proteases

Epithelial barrier integrity may be impaired by exogenous proteases of *S. aureus* which eases the penetration of environmental antigens into deeper compartments of the skin [53, 54]. It makes the lesions of patients with AD prone to exacerbation in the presence of allergic substances and other irritants. Additionally, recent studies have focused on the ability of *S. aureus* to penetrate into sub-epidermal skin layers. Nakatsuji *et al.* have found that this process depends on the viability of *S. aureus* strains and their ability to produce proteases [55]. Presence of *S. aureus* in the dermis has been correlated with an increased expression of IL-4, IL-13, IL-22 and TSLP as well as with a decreased production of cathelicidin [55]. Another study suggests that SspA/V8 protease is the main substance compromising the epithelial barrier [56]. This process is prevented by IL-1B production and subsequent secretion of human b-defensin 2 (hBD2), giving light to elaborate novel therapies. Moreover, Sonesson *et al.* have discovered that *S. aureus* can produce another protease group, staphopains, which inactivate AMPs (LL-37) responsible for the degradation of bacterial biofilm [52].

Staphylococcal superantigens

Some strains of *S. aureus* produce superantigens. The most important ones include staphylococcal enterotoxin A and B (SEA/B) and the toxic shock syndrome toxin-1 (TSST-1) that are known to affect the course of AD in a negative way [57–65]. These molecules are bound by local antigen presenting cells (APCs) and presented to other elements of the immune system via major histocompatibility complex class 2 (MHC-II) [64]. They cause a chaotic inflammatory response by activating a large percentage of naïve T lymphocytes, which leads to excessive Th2 cytokine release [57, 60]. It has also been demonstrated that despite their regulatory phenotype, CD4+ FOXP3 cells present in the skin of patients with AD can be stimulated to secrete Th2 cytokines after exposure to staphylococcal superantigens [66]. Furthermore, SEB (but also other staphylococcal antigens, such as lipoteichoic acid) has been associated with increased synthesis of IgE [64, 65, 67]. This supports the theory that the presence

of *S. aureus* on the skin can provoke AD flares instead of being just an exacerbating factor. In the study conducted by Hon *et al.* [68], SEB-specific IgE concentration has been positively correlated with disease severity. Another negative function of SEB includes its availability to induce monocyte apoptosis by up-regulating TNF-α [69]. It has also been reported that *S. aureus* superantigens can contribute to the effect of glucocorticoid and tacrolimus resistance, which is especially troubling from the therapeutic point of view [62, 63].

Selected staphylococcal superantigens are also involved in the pathogenesis of itch in AD. IL-31, a molecule whose levels have been correlated with the intensity of pruritus, has been shown to be up-regulated after exposure to staphylococcal superantigens *in vivo* and more particularly to SEB (*in vitro*) [70]. Studies have shown that increased levels of IL-31 negatively affect the production of AMPs, which impedes *S. aureus* clearance [71]. What is more, skin damage and keratinocyte necrosis caused by constant scratching can additionally lead to sensitization to autoantigens, which drives the vicious cycle of AD.

α-Toxin

Staphylococcal α-toxin (also known as α-hemolysin) is highly cytotoxic to keratinocytes by leading to intrinsic caspase activation and cytochrome c release from the mitochondria in experimental studies [72]. It has been demonstrated that keratinocytes exposed to Th2 cytokines are more susceptible to apoptosis through this mechanism [73]. Hong *et al*. have shown that α-toxin induces atopic dermatitis-like skin inflammation and disruption of the skin barrier [74]. α-Toxin production by *S. aureus* positively correlates with disease severity and has been proposed as a potential diagnostic and therapeutic target for the control of AD. Moreover, α-hemolysin is upregulated upon formation of biofilm following neutrophil exposure and causes neutrophil inhibition. Interestingly, it also facilitates viral entry into the cells. It may be one of the reasons why patients with AD are predisposed to infections with pathogens such as *Molluscum contagiosum* or Herpesviridae (increased incidence of eczema herpeticum) [42, 72, 75].

δ-Toxin and other phenol-soluble modulins (PSMs)

Phenol-soluble modulins (PSMs) are a family of short peptides produced by staphylococci [76]. PSMs secreted by *S. aureus* show cytolytic activity in leukocytes and are thought to play an important role in the pathogenesis of AD. δ-Toxin of *S. aureus* is one of the PSMs investigated in this context. The study conducted by Nakamura *et al.* [77] has revealed that exposure of mast cells to δ-toxin leads to their degranulation rather than lysis. Excessive IL-4 and IgE production with simultaneous exacerbation of Th2-mediated inflammation in the skin has been observed as well [77]. The PSMs have also been shown to cause keratinocyte lysis with subsequent release of proinflammatory cytokines such as IL-18 and IL-1β [78].

Staphylococcal protein A

Staphylococcal protein A is constitutively expressed on the surface of *S. aureus* and contributes to evasion of host immune responses [79]. Jun *et al.* have reported that it is highly expressed in membrane vesicles of *S. aureus,* whose application to AD-like skin lesions induces eczematous dermatitis. Based on this observation, the authors suggested that *S. aureus* may be an inducing factor in AD. Another study has revealed that protein A along with toxins of *S. aureus* induce local inflammation mediated by TNF-α [80].

Novel therapeutic methods with the aim of restoring natural composition of the skin microbiome

Increasing knowledge about the significance of disordered skin microbiome in AD is prompting the search for new treatment methods. Routine management of patients with AD with antibiotics would be contraindicated mainly because of the extent and chronic course of disease, cost-effectiveness, selection of drug-resistant strains of pathogenic bacteria [81, 82] and reduction of commensal microflora. In recent years many groundbreaking strategies have been developed. For example, lysate of a recently discovered Gram-thermal spring bacterium called *Vitreoscilla filiformis* has been reported to significantly reduce the symptoms of AD and seborrheic dermatitis [83–85]. Volz *et al.* [86] have revealed that *V. filiformis* antigens induce $IL10^{+}$ dendritic cells. They are a source of stimuli responsible for naïve CD4+ lymphocytes maturation into Treg1 lymphocytes. Treg1 lymphocytes produce IL-10, a cytokine known for its strongly immunosuppressive properties. This process depends on TLR2 signalling, which has already been mentioned in the context of AD-specific disorders of the innate immune system [87]. Another trial has revealed that application of lotion with heat-treated probiotic strain *Lactobacillus johnsonii* for 3 weeks controlled *S. aureus* colonization and reduced disease severity measured with the SCORAD index [88]. Interestingly, a higher concentration of *S. aureus* at baseline was associated with good response to the treatment. Nakatsuji *et al.* [89] have analysed the relation between the presence of commensal coagulase-negative staphylococci (CoNS) *S. epidermidis* and *S. hominis* and skin colonization by *S. aureus*. They have found that CoNS produce lantibiotics, i.e. prokaryotic antimicrobials that along with human AMPs (LL-37) lead to the clearance of *S. aureus* in animal and human models [89]. Favourable results have also

been reported for topical microbiome transplantation with *Roseomonas mucosa* [90].

Other trials have focused on a potential therapeutic effect of synthetic AMPs. In the study conducted by Dawgul *et al.* [91], citropin 1.1 and temporin A appeared to be active against all *S. aureus* strains. Furthermore, unlike conventional antimicrobials, they did not induce resistance and showed anti-biofilm activity. The study of several AMPs introduced in catheter infections caused by biofilm-forming *S. aureus* has revealed high effectiveness of the treatment, especially in case of D-Bac8c2,5Leu [92]. Additionally, some promising data have come from the research over all-D omiganan, which has shown bactericidal activity towards *S. aureus* and satisfactory half-life *in vivo* [93].

Another promising direction of research includes phagolysins, i.e. anti-infectives derived from bacteriophages which have been shown to resensitize bacteria to antibiotics [94, 95]. Totté *et al.* [96] published a case series reporting successful treatment of MRSA infections with Endolysin Staphefekt SA.100. Results of a multi-centre randomized trial designed to evaluate the influence of Staphefekt on the use of corticosteroids, disease severity, quality of life and composition of the microbiome in patients with AD are to be expected shortly [97]. Finally, Baldry *et al.* have managed to block production of α-toxin by inhibiting agr signalling and have subsequently obtained reduction of inflammation in an animal model [98]. Nevertheless, an additional studies to verify the clinical application of these novel therapies in AD is needed.

Conclusions

Despite its complexity, pathogenesis of atopic dermatitis is quite obviously associated with the skin microbiome. The role of *S. aureus* in the vicious cycle of AD seems to be exceptionally pronounced. *S. aureus* eliminates commensal bacteria from the skin, while its virulence factors show a negative effect on the epithelial barrier integrity and immune system functioning. It is possible that *S. aureus* is not only a secondary exacerbating factor but it is also one of the reasons why AD flares occur. Physiologically, the microbiome is responsible for the maintenance of immunological homeostasis and reduction of skin colonization by pathogenic bacteria. Therefore, therapies aimed to restore natural composition of the skin microbiome are being elaborated.

Conflict of interest

The authors declare no conflict of interest.

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