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The role of skin dysbiosis in atopic dermatitis

The cutaneous microbiota contributes to skin barrier function, ensuring effective protection against pathogens and contributing to the maintenance of epidermal integrity. Dysbiosis is frequently present in atopic dermatitis (AD), a chronic inflammatory disease associated with skin barrier defects. Dysbiosis is associated with reduced bacterial diversity and marked *Staphylococcus aureus* colonization, which is favoured in the case of certain local AD-specific properties such as reduced skin acidity, eased bacterial adhesion and decreased antimicrobial peptide production. Furthermore, *S. aureus*-associated skin dysbiosis, via the production of staphylococcal virulence factors, may also participate in the immunopathology of AD by altering the epidermal barrier and inducing an inflammatory response. However, there are currently no arguments for recommending screening for, and treatment of *S. aureus*-associated dysbiosis outside the setting of cutaneous superinfection. Nonetheless, modulation of the skin microbiota may hold promise for AD management. Here, we describe the relationships that exist between the skin microbiota and AD.

Key words: cutaneous microbiota, skin barrier, dysbiosis, atopic dermatitis, *Staphylococcus aureus*

The microbiome living in the skin is composed of bacteria, viruses, fungi, archaea and skin mites. During homeostasis, human skin contains anywhere between 10^8 to 10^{10} microbes at densities ranging from $10^2/\text{cm}^2$ (fingertips, back) to $10^6/\text{cm}^2$ (forehead, axillae) [1]. Beyond differences in density, the diversity and composition of the microbiota also vary across various skin sites, due to its different physical, chemical and biological characteristics. For example, sebum-rich zones (e.g. glabella) are colonized mainly by *Propionibacteria* and *Staphylococci*, humid zones (e.g. antecubital fossae) by *Corynebacteria*, and dry zones (e.g. the volar forearm) by a more diverse population including predominately *Proteobacteria* and *Flavobacteriales* [1]. The skin microbiota also varies from person to person depending on gender, genetics, the use of cosmetics, personal hygiene practices, physical activity and geographic location.

Bacteria are both the most abundant and the most studied members of the skin microbiota population. Recent advances in sequencing technology have considerably increased current knowledge of microbes. In particular, targeted sequencing of the highly conserved 16S RNA gene (encoding 16S ribosomal RNA) enables taxonomic differentiation of bacterial populations, and high throughput or shotgun metagenomic sequencing is used to analyse bacterial genomes, leading to an accumulation of information on the functional capacities of bacteria [2]. In regard to this, sample collection based on this technology can be performed non-invasively (tape test, swabbing, etc.), which aids skin microbiota assessment during the course of the disease. In the present update, we describe the microbiota's primordial role in skin immunity, illustrate the links between skin microbiota and atopic dermatitis (AD), and finally discuss

perspectives for therapies targeting the skin microbiota of patients with AD.

The dynamics between skin microbiota and immunity

Historically considered as an unwanted invader, the microbiota of the skin is now seen as a functional partner. For example, commensal bacteria participate in the barrier function of the skin, protecting the host from its pathogenic counterparts [3]. The maintenance of skin acidity, the secretion of antimicrobial substances, and interactions with the skin immune system have been identified as protective mechanisms by which commensal bacteria are able to interact synergistically with the skin.

Maintenance of skin acidity

The acidic nature of the skin ($\text{pH} \approx 5$) is necessary for the selective permeability of the stratum corneum and the cohesion of its corneocytes [4]. It also favours the colonization of commensal bacteria and limits growth of potentially pathogenic bacteria such as *Staphylococcus aureus* [5]. Therefore, acidity is an essential factor for cutaneous homeostasis, and numerous mechanisms have been described for its functions [6]. Several commensal facultative anaerobes, such as *Cutibacterium acnes*, ferment glycerol in sebum to liberate short-chain fatty acids [7]. The production of free fatty acids by phospholipase hydrolysis in the stratum corneum is a major contributor to the skin's acidity [6].

Secretion of antimicrobials

The commensal and frequently detected coagulase-negative staphylococci (CoNS), *Staphylococcus epidermidis*, *Staphylococcus lugdunensis* and *Staphylococcus hominis*, secrete antimicrobial peptides themselves, including phenol-soluble modulins (PSMs) that selectively inhibit the growth of certain skin pathogens such as *S. aureus* and Group A *Streptococcus* [8-10]. Additionally, *S. epidermidis* can thwart *S. aureus* biofilms. Biofilms are polymeric matrices englobing a mass of bacteria. They ensure the survival of the bacteria in a hostile environment and provide protection from the immune system [11]. Biofilms thus confer increased pathogenicity for bacteria. This is the case for *S. aureus*, a species found in AD lesions [12]. In healthy subjects, *S. epidermidis* secretes a serine protease that inhibits the production of biofilm by *S. aureus* and lyses existing biofilms [13].

Interactions with the skin immune system

The commensal bacteria of the skin play a role in the regulation of both innate and adaptive skin immunity. Some *S. epidermidis* strains influence innate immunity via toll-like receptors (TLRs) and can thus stimulate keratinocytes to produce antimicrobial peptides. For example, they can increase human β -defensin expression through a mechanism involving TLR-2 [14]. Also, lipoteichoic acid of certain strains inhibits the production of proinflammatory cytokines by keratinocytes through a mechanism involving TLR-3 [15]. *S. epidermidis* also interacts with adaptive immunity. A study performed in a neonatal murine model showed that *S. epidermidis* favours an influx of regulatory T cells [16], which are indispensable for tolerance to other bacterial strains that may colonize the skin. In adult mice, this favours the migration of $\alpha\beta^+$ T cells (which produce interferon- γ (IFN γ) and interleukin-17A (IL-17A) indirectly), and $\gamma\delta$ T cells (which also produce IL-17A), both involved in parasite resistance [17].

Finally, *S. epidermidis* participates in skin healing by recruiting commensal-specific CD8+ T cells, producing IL-17A or IFN γ , and promoting keratinocyte proliferation and cutaneous reepithelialization [18].

The skin microbiota thus interacts with the immune system and plays a role in skin homeostasis. Dysbiosis of the skin microbiota is associated with certain pathologies, including AD.

Atopic dermatitis and *S. aureus* dysbiosis of the skin

Atopic dermatitis: general information

Atopic dermatitis (AD) is a chronic, inflammatory skin disease, characterized clinically by recurrent eczema. It is associated with skin barrier defects (which permit the penetration of environmental molecules, e.g., dust mite proteins, pollen, xenobiotics, pollutants) and type 2 inflammation (Th2 lymphocytes, Group 2 innate lymphoid cells (ILC2), production of IL-4, 5 and 13) [19].

In patients with AD, skin dysbiosis frequently occurs and worsens during flare-ups. It involves a decrease in bacterial

diversity which is favourable to staphylococcal colonization (particularly *S. aureus*) and detrimental to streptococci, *Corynebacterium* and *Propionibacterium* [20]. Effective treatment comprising emollients and topical corticosteroids does restore bacterial diversity [21]. Interestingly, systemic treatment with biologics such as dupilumab is also known to reduce disease severity and improve microbial diversity in the skin [22].

During AD, the cutaneous density of commensal bacteria -and thus their anti-*S. aureus* function- is reduced [10]. In the literature, *S. aureus* colonization is present in 70-100% of acute [23-27] and about 40% of chronic AD lesions [25]. There is also an epidemiological association between AD and *S. aureus*-favourable dysbiosis: first, patients who show *S. aureus* colonization have higher severity scores and more inflammation markers than those who do not [27], and second, in colonized patients, the cutaneous burden of *S. aureus* correlates with AD severity [24, 28]. Interestingly, severe eczema lesions have been shown to be associated with monoclonal *S. aureus* colonization [20]. Considering these observations, *S. aureus* appears to be the principal pathogen involved in AD-associated skin dysbiosis.

Factors favouring *S. aureus* colonization in AD

There are several aspects underlying the high susceptibility of AD patients to *S. aureus* colonization.

The pH of AD-prone skin is higher (less acid) than that of healthy skin and thus less hostile to *S. aureus* proliferation [28]. This aspect is likely due to the reduced amount of free fatty acids produced by AD skin. Furthermore, the degradation products of filaggrin (urocanic acid and pyrrolidone carboxylic acid) participate in the normalization of skin pH. In AD, loss-of-function mutations in the filaggrin gene or the inhibition of its expression (by IL-4 and IL-13) is associated with reduced amounts of those degradation products available to the skin [29, 30].

S. aureus also adheres more effectively to the skin of AD patients (including unaffected skin) than that of healthy people. The *stratum corneum* of people with AD is rich in ligands recognized by *S. aureus*, particularly fibronectin, which is recognized by fibronectin-binding proteins (FnBP) A and B, present on the bacterial surface [31-33]. Additionally, corneocytes of AD patients may present an increase in villi, which further favours *S. aureus* adhesion [34].

Finally, AD-prone skin has fewer antimicrobial peptides than normal skin, which allows for the growth of pathogenic bacteria such as *S. aureus* Type 2 (IL-4 and IL-13), and other (IL-17 and IL-22) cytokines inhibit the production of antimicrobials by keratinocytes, which furthermore raises skin pH, both aspects being advantageous for colonization by *S. aureus* [35]. The latter also leads to the production of proteases that inhibit the production of antimicrobial peptides by keratinocytes [36]. Moreover, in such type of skin, extracellular DNA appears to form complexes with skin antimicrobial peptides, limiting their ability to fight against *S. aureus* [37]. Nonetheless, it remains unclear whether *S. aureus* should be considered as a commensal in AD skin, simply taking advantage of an environment that is favourable for colonization, or whether it actively participates in the immunopathology of the disease.

Role of *S. aureus* in the immunopathology of AD

The idea wherein *S. aureus* is a causal factor for AD flare-ups arising from clinical correlations lacks formal demonstration. Two aspects do, however, lend it credence: first, *S. aureus* can alter the skin barrier, and second, it can induce a skin immune response that may participate in the inflammatory characteristic of AD. These aspects may be associated with a quorum-sensing-dependent production of virulence factors by *S. aureus*. Quorum sensing is a bacterial autoinduction system for the self-regulation of proliferation, toxin production and other processes. Quorum sensing is widespread in bacteria, but differs in specificity according to the species and even the strain.

Skin barrier alteration by *S. aureus*.

S. aureus contributes to the alteration of barrier function of skin it has colonized. Indeed, AD patients with *S. aureus* colonization show more severe barrier defects compared to those without [27]. The mechanisms underlying *S. aureus*-driven barrier defects have been studied mostly in mice and generally involve direct action against the skin. Proteases secreted by *S. aureus* act directly on the epidermal tissue [38]. Deletion of the genes encoding these proteases reduces *S. aureus*'s ability to penetrate the skin, as does inhibition of its quorum sensing (*e.g.*, by other bacteria) [38, 39]. *S. aureus*'s PSMs also cause direct damage to keratinocytes [38, 40], and its production of lipoteichoic acid leads to alterations in keratinocyte differentiation, with reductions in such markers as keratins 1 and 10 and desmocollin 1 [35]. Furthermore, type-2 cytokines, which favour *S. aureus* colonization, also inhibit the synthesis of filaggrin, loricrin and keratins 1 and 10, and thus participate in a pathological vicious circle that leads to barrier defects in AD patients [35]. Of note also, AD patients with *S. aureus* colonization are more likely to be sensitized to environmental proteins (based on multiallergen IgE assay results), which indirectly suggests greater skin permeability compared to AD patients without *S. aureus* colonization [41].

The role of immunity against *S. aureus* in AD inflammation

In addition to its role in barrier defects, *S. aureus* colonization also provokes an immune response, both in murine AD models and in AD patients. The application of *S. aureus* isolated from AD skin to mice with functional skin barriers is associated with the production of IL-13 and IL-17 [20], and its application to mice with disrupted skin barriers is associated with the production of IL-4, IL-13, IL-22, and thymic stromal lymphopoietin (TSLP) in the skin and an increase in total IgE in blood [39, 42]. The mechanisms in this setting are beginning to be elucidated and may involve staphylococcal virulence factors known to play a role in *S. aureus* pathogenicity. These virulence factors may be expressed on the surface of the bacteria (*e.g.*, FnBP), where they contribute to bacterial adhesion, or secreted in the surrounding tissue to induce lesions and ease bacterial proliferation (*e.g.*, proteases). Some virulence factors produced by *S. aureus* interact with the immune system.

In experimental models, δ -toxin has been shown to induce the degranulation of skin mast cells and the development of atopic inflammation [42]. In mouse models, the topical application of *S. aureus* staphylococcal enterotoxins A (SEA) and B (SEB), which are known superantigens, has been shown to provoke cutaneous infiltration of mast cells and eosinophils and cutaneous production of IL-4, IL-5, IFN γ and IL-17 by T lymphocytes and ILCs [41]. In humans, *S. aureus* superantigens also cause type-2 immune responses. The application of SEB to atopic skin induces the infiltration of T lymphocytes expressing β -12 and β -17 chains which specifically interact with it [43]. In a meta-analysis, 33% of 2,369 AD patients showed anti-SEA IgE and 35% of them anti-SEB IgE. The prevalence of these specific antibodies was significantly higher in AD patients compared to healthy controls [44]. The presence of anti-SEA IgE, anti-SEB IgE and anti-FnBP IgE all correlated with AD severity [45-47]. More generally, AD patients with greater *S. aureus* abundance have higher concentrations of serum type 2 inflammation markers (CCL17, periostin and CCL26) compared to AD patients with lower abundance of *S. aureus* [41].

An immune response to *S. aureus* colonization is logically expected. What is less expected, however, is that the immune response can polarize towards type 2 inflammation instead of type 17 inflammation, for example. It remains unknown whether this immune response contributes to skin inflammation (initiation of AD flare-up, symptom aggravation, *etc.*) in AD patients.

Bacterial management in atopic dermatitis

Treatment of bacterial superinfection in AD lesions

Superinfection due to *S. aureus* is the only situation necessitating anti-bacterials in AD. It may be diagnosed clinically based on association with lesion exacerbation and discharge or meliceric crusting. Topical antiseptics and antibiotics are sufficient for localized infections. Systemic antibiotics are indicated only for severe or widespread infections after bacteriological culture [48]. Such therapy, targeting both pathogenic and commensal bacteria and inducing a kind of dysbiosis, is not a treatment for AD itself.

Ineffectiveness of antimicrobials in AD management

Although the role of *S. aureus* in the pathophysiology of atopic eczema remains unclear, antiseptic agents continue to figure in AD treatment guidelines [49]. This state of affairs should, however, be reconsidered in the light of recent studies. For example, the authors of a five-study meta-analysis performed in 2017 assessed 0.005% bleach baths compared to normal water baths for the treatment of AD, and found no differences in effectiveness between them in terms of severity scores at four weeks of treatment. They concluded that any beneficial effect was

more likely attributable quite simply to the water [50]. Indeed, baths with bleach diluted at that level appear to have no effect on *S. aureus* [51]. Furthermore, a systematic review found that antibiotic strategies (oral or topical) provided no benefit in clinically uninfected eczema, despite the observation that they did reduce *S. aureus* burden in that setting [52]. Considering that *S. aureus* rapidly recolonizes lesions, long-term antibiotics might improve effectiveness, but the deployment of such a strategy would have to be weighed against the risk of antimicrobial resistance.

Thus, AD therapy, emollients and topical corticosteroids, as of the time of writing this review, remain the most effective treatments for dysbiosis. Topical corticosteroids can reduce bacterial density -especially of *S. aureus*- on the skin [53, 54] and this does not appear to be increased by bleach baths [53] or phototherapy [54, 55]. The application of emollients has been shown to decrease *S. aureus* penetration in filaggrin-deficient mice [39]. However, whether these treatments modify *S. aureus* colonization in the long term cannot be assessed currently.

Modulating *S. aureus* dysbiosis to treat AD

There are currently a number of studies underway, most in the preclinical modelling stage, to explore therapies specifically targeting *S. aureus* virulence factors, as these may play a role in the immunopathology of AD (see above). These studies are investigating a number of approaches, including vaccines, antibodies against staphylococcal toxins (e.g., alpha toxin) [56] or the ability of certain commensal bacteria (e.g., CoNS) to inhibit *S. aureus* quorum sensing [38, 57].

The application of non-pathogenic living bacteria (probiotics) or their derivatives on AD skin is also garnering an increasing amount of attention. For example, topical application of a *Vitreoscilla filiformis* lysate has shown efficacy as AD treatment, including a reduction in *S. aureus* colonization and improvement of barrier function [58]. Staphfect SA.100, a bacteriophage endolysin, is also currently being evaluated as a topical treatment for AD [59]. Furthermore, a recent Phase I/II study evaluated the efficacy and tolerability of a commensal biotherapeutic approach involving the transplantation of *Roseomonas mucosa* harvested from healthy volunteers to adults and children with AD. The authors of this study reported improved severity scores, reduced use of topical corticosteroids, and reduced *S. aureus* burden [60]. Another team showed that a similar transplantation tactic using CoNS was efficacious on AD lesions [10]. A different approach consisting of bacteriotherapy with autologous CoNS and a randomized double-blind clinical trial showed interesting results [57].

These therapeutic approaches hold great promise for AD management when combined with currently irreplaceable traditional treatments, i.e., emollients and topical corticosteroids. Conversely, another study showed that the application of a CoNS (i.e. *S. hominis* A9) did not modify the severity of eczema lesions. However, efficacy was apparent in certain subgroups, suggesting that bacteriotherapy could be of interest in a targeted way, towards personalized medicine [61].

Conclusion

The dysbiosis of AD worsens during flare-ups, associated with a reduction in diversity of commensal bacteria and a marked increase in *S. aureus* colonization. However, the specific role of *S. aureus* in the immunopathology of AD, involving innate and adaptive inflammatory responses and numerous bacterial mechanisms including virulence factors, remains largely less understood. Novel therapeutic perspectives to improve disease severity and long-lasting efficacy of treatment may, in part, be related to targeting microbial dysbiosis in AD.

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