The Skin Microbiome: A New Actor in Inflammatory Acne

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REVIEW ARTICLE

The Skin Microbiome: A New Actor in Inflammatory Acne

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Abstract
Our understanding of the role of *Cutibacterium acnes* in the pathophysiology of acne has recently undergone a paradigm shift: rather than *C. acnes* hyperproliferation, it is the loss of balance between the different *C. acnes* phylotypes, together with a dysbiosis of the skin microbiome, which results in acne development. The loss of diversity of *C. acnes* phylotypes acts as a trigger for innate immune system activation, leading to cutaneous inflammation. A predominance of *C. acnes* phylotype IA_1 has been observed, with a more virulent profile in acne than in normal skin. Other bacteria, mainly *Staphylococcus epidermis*, are also implicated in acne. *S. epidermidis* and *C. acnes* interact and are critical for the regulation of skin homeostasis. Recent studies also showed that the gut microbiome is involved in acne, through interactions with the skin microbiome. As commonly used topical and systemic antibiotics induce cutaneous dysbiosis, our new understanding of acne pathophysiology has prompted a change in direction for acne treatment. In the future, the development of individualized acne therapies will allow targeting of the pathogenic strains, leaving the commensal strains intact. Such alternative treatments, involving modifications of the microbiome, will form the next generation of 'ecobiological' anti-inflammatory treatments.

Key Points

Inflammatory acne is related to a loss of the diversity of phylotypes of *Cutibacterium* acnes.

C. acnes and *Staphylococcus epidermidis* play a role in the process of inflammation in the skin.

Treatments other than topical and systemic antibiotics are needed to restore the diversity and balance of bacterial species.

1 Introduction

Acne vulgaris (acne) is a highly prevalent inflammatory skin condition, involving an interplay of several factors. Besides increased sebum production by the sebaceous glands and follicular keratinization of the pilosebaceous ducts [1, 2], a third main actor in acne development has recently been uncovered: the microbiome and its interactions with the innate immune system. The term 'microbiome' refers to microorganisms (bacteria, viruses and fungi) and their environment. Further understanding of the role of the skin microbiome in acne development has been gained by characterizing the skin bacteria, with equal levels of diversity being obtained regardless of whether the sampling method retrieved bacteria located at the skin surface (swabbing) or in the follicle (cyanoacrylate skin surface stripping) [3].

The skin microbiome is divided into 'normal' commensal skin microbes, which live in homeostasis with the host and form the resident microbiome, and pathogen microbes from the environment, which temporarily live on the skin and form the transient microbiome [4]. In acne, the resident microbiome includes *Cutibacterium acnes* (formerly called *Propionibacterium acnes)* and *Staphylococcus epidermidis,* whereas the transient microbiome includes *Staphylococcus aureus* [5]. A microbial imbalance or 'dysbiosis', compared with the normal distribution in healthy tissues, has been

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suggested to be involved in the pathophysiology of inflammatory acne [6].

In this short review, we will first address the recent advances in our understanding of the impact of cutaneous microbiome imbalance on the development of acne lesions, in particular the loss of diversity of *C. acnes* phylotypes. We will then focus on the involvement of particular bacterial strains—including *S. epidermis*—and the interactions between the gut and skin microbiome, and finally, based on this new understanding, we will explore new insights into acne treatments.

2 Dysbiosis in Acne Pathophysiology

2.1 *Cutibacterium acnes* and the Role of Microbiome Dysbiosis in Acne

Although *C. acnes* is a major commensal of the normal skin flora, it also contributes to acne pathogenesis [7]. Present at a low level on the skin surface, C. *acnes* constitutes the dominant resident bacterial species in the sebaceous follicles. Indeed, *C. acnes* is commonly found in sebum-rich areas. However, in contrast with previous thinking, acne is not associated with an over-proliferation of *C. acnes* [8–10]. Indeed, the load of *C. acnes* [11] and the relative abundance of *C. acnes* reported in metagenomics studies has been found to be similar between patients with acne and healthy individuals [7], and slightly higher levels in healthy subjects have even been reported [12]. Instead, a loss of microbial diversity and loss of balance between *C. acnes* phylotypes appears to play a role in the triggering of acne [7].

2.2 Severity of Inflammatory Acne is not Related to the Proliferation of *C. acnes* But to the Loss of Diversity of *C. acnes* Phylotypes (IA_1, CC18, A1)

Several very recent studies have demonstrated that acne severity is associated with a loss of diversity of *C. acnes* strains compared with that in healthy individuals. This loss of diversity has been identified on the face of patients with mild-to-moderate acne, as well as on the back of those with severe acne (Fig. 1) [13]. Acne might be triggered by the selection of a subset of *C. acnes* strains, including the acne-associated phylotype IA_1, which is predominant in facial acne and probably enhanced by a hyperseborrheic environment. Depending on the method of molecular characterization, phylotype IA_1 may also be referred to as the CC18 clonal complex or A1 SLST-type [14].

Advanced metagenomic sequencing revealed that the cutaneous microbiota in acne patients differs from that of acne-free individuals at the virulent-specific lineage level

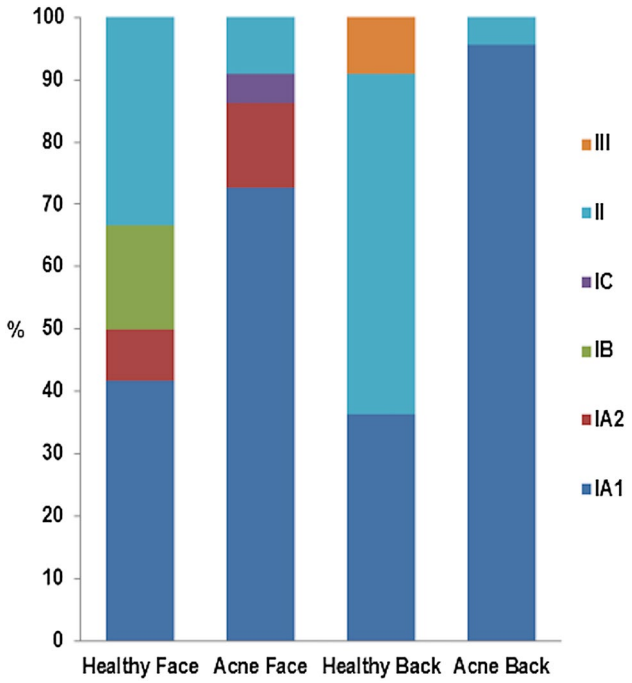

Fig. 1 Dysbiosis is related to the loss of diversity of *C. acnes* phylotypes on the face and back of acne patients [13]. Phylotype IA_1 (in dark blue) is abundant in acne skin. Reproduced from [13], with kind authorization from Acta-Dermato-Venerealogica, under the creative commons licence (Attribution-NonCommercial 4.0 International, CC BY-NC 4.0)

[5, 7]. Acquired DNA sequences and bacterial immune elements may be involved in the virulence of *C. acnes* strains [7].

In contrast, loss of phylotype diversity cannot explain the differences observed between teenage and adult acne, nor those observed between grades of acne severity. According to a very recent study, acne in adult women is not associated with a specific type of *C. acnes* [15]. Moreover, the frequency of *C. acnes* resistance is similar among adult women and teenagers, suggesting that differences in acne between these two groups are more likely related to nonmicrobial factors such as hormonal skin changes, stimulation of innate immunity, or environmental factors [15]. As regards the severity of acne, no significant differences in the distribution of acne strains were found between patients with mild ($n=29$) and severe acne ($n=34$) [16].

2.3 Loss of Diversity of Phylotypes of *C. acnes* Activates Innate Immunity and Cutaneous Inflammation

Loss of microbial diversity can lead to chronic inflammatory skin diseases [17, 18]. Loss of *C. acnes* phylotype diversity has also been shown to act as a trigger for innate

immune system activation and cutaneous inflammation in acne. Indeed, incubation of a skin explant with phylotype IA_1 alone has been shown to lead to up-regulation of innate immune markers (interleukin [IL]-6, IL-8, IL-10, IL-17), compared with incubation with the combination of phylotypes IA_1 + II + III [19]. Conversely, restoration of the microbiome diversity suppressed inflammation via downregulation of innate immunity [19]. In addition, the constitutive release of extracellular vesicles by *C. acnes* can induce an acne-like pattern, as shown in an in vitro reconstituted skin model. Six-day contact with *C. acnes*-derived extracellular vesicles was shown to lead to an increase in the proliferation of keratinocytes and modulation of their differentiation, with dysregulation of the expression of epidermal markers such as the antigen Ki67, keratin 10 (KRT10), desmocollin 1 (DSC1) and filaggrin [20]. Moreover, the vesicles induced a significant rise in inflammatory cytokine IL-8 and granulocyte macrophage colony-stimulating factor (GM-CSF) levels [20]. Indeed, bacterial extracellular vesicles were recently shown to be implicated in intra- and interspecies cell-to-cell communication and to play a pro-inflammatory role in several human diseases, including acne [21]. Consequently, inhibiting the release of *C. acnes* extracellular vesicles or targeting their signaling pathways could represent an alternative way of limiting acne development and severity [20].

Finally, *C. acnes* strains differentially modulate CD4 + T-cell responses, leading to the generation of T helper (Th)-17 cells that may contribute either to homeostasis (IL-17/IL-10-producing) or to acne pathogenesis (IL-17/interferon [IFN]-gamma-producing) [22].

3 Involvement of Particular Strains and Interactions with the Gut Microbiome

3.1 *C. acnes* IA_1 has a More Virulent Profile in Acne than in Normal Skin

Comparative genome analysis has shown that acne-related strains carry extra virulence genes compared with strains of the same phylotype functioning as commensals in skin health [23]. In addition, acne-related strains produce significantly higher levels of the pro-inflammatory metabolites, porphyrins, which generate reactive oxygen species and induce inflammation in keratinocytes [24]. Vitamin B12 supplementation further increases *C. acnes* production of porphyrins [25]. Finally, *C. acnes* types IA and IB were found to induce greater levels of production of the human antimicrobial peptide (AMP), β-defensin 2 (hBD2), from cultured sebocytes, and displayed higher levels of lipase activity than a type II isolate [26].

3.2 Other Bacteria and Fungi Involved in Acne

Recent data show that *S. epidermidis* and *C. acnes* interact [27] and are critical for the regulation of skin homeostasis [28]. *S. epidermidis* can inhibit *C. acnes* growth [28, 29] and *C. acnes*-induced inflammation in the skin [30]. *S. epidermidis* controls the proliferation of *C. acnes* by favoring the fermentation of glycerol produced naturally by the skin, and by releasing succinic acid, a fatty acid fermentation product [31]. The anti-inflammatory effects of *S. epidermidis* are mediated by lipoteichoic acid, which inhibits Toll-like receptor (TLR)-2 production. *S. epidermidis* can thus suppress *C. acnes*-induced IL-6 and tumor necrosis factor (TNF)-alpha production by keratinocytes [30].

Conversely, *C. acnes,* resident in the pilosebaceous follicles, inhibits development of *S. epidermidis* by maintaining the acidic pH of the pilosebaceous follicle, hydrolyzing sebum triglycerides, and secreting propionic acid [4, 29]. As shown by Wang et al., incubation of *C. acnes* in a pH 5.5 buffer did not alter its survival [29].

Finally, Malassezia, the most abundant fungus in the skin, could be involved in refractory acne. Its lipase is 100-fold more active than that of *C. acnes* and it can attract neutrophils and promote the release of pro-inflammatory cytokines from monocytes and keratinocytes. However, its exact role in the pathophysiology of acne remains to be explored [5].

3.3 Interactions Between Bacteria and the Host Cellular Mechanisms

Resident and transient bacteria also interact with skin signaling molecules. Substance P is a major skin neuropeptide that is modulated by pain, stress and infection, and is involved in the pathogenesis of numerous skin diseases with multifactorial origins. Some of the effects of substance P are mediated through interactions with skin microflora [32]. In particular, substance P can increase the virulence of staphylococci: it induces enterotoxin C2 secretion by *S. aureus* and biofilm formation by *S. epidermis*, and promotes the adhesion of both bacteria to the keratinocytes [32].

Finally, bacteria that colonize the skin potentially play a role in the post-inflammatory pigmentation of acne lesions. *C. acnes* and *S. epidermidis* differentially modulate melanocyte survival [33]. Furthermore, strains of the *C. acnes* type III lineage have been shown to be associated with progressive macular hypomelanosis [34].

3.4 The Gut Microbiome Interacts with the Skin Microbiome in Acne

The interactions between the bacteria involved in acne extend beyond the skin itself. Patients with acne also have a gut microbiota that is distinct from that of healthy controls.

A study of 31 acne patients found that Actinobacteria were less abundant and Proteobacteria more abundant in the gut microbiota of individuals with moderate-to-severe acne compared with healthy controls [35]. Another study revealed decreased diversity and an increased ratio of Bacteroidetes to Firmicutes in acne patients, an alteration that has been reported to be the enterotype of the Western diet; thus confirming the impact of the Western diet on the development of acne [36]. The consumption of dairy products, refined carbohydrates, chocolate, and saturated fats has indeed been shown to contribute to the development of acne through the activation of metabolic signals [36]. Moreover, the high ratio of omega-6 to omega-3 fatty acids in Western diets may also be implicated [37]: dietary supplementation with omega-3 fatty acids has been shown to help decrease lesions in patients with mild-to-moderate acne [38].

The connection between gut microbiota and acne development could be related to the fact that bacterial dysbiosis in the gut causes increased intestinal permeability, leading to the release of inflammatory mediators, such as lipopolysaccharide endotoxins, into the circulation [39].

4 New Insights in Acne Treatments

4.1 Systemic and Topical Antibiotics Induce Cutaneous Dysbiosis

Antibiotics and isotretinoin have long been the main treatments for acne. Isotretinoin has been shown to normalize aberrant TLR-2-mediated innate immune responses towards *C. acnes* and this immunomodulatory effect may be involved in the anti-inflammatory response to isotretinoin [40, 41]. However, systemic isotretinoin results in qualitative and quantitative changes in the highly diverse microbiome of the gut and in that of the skin, with marked increases in *S. aureus* [42]. Topical antibiotics induce a 'selective pressure' on the bacteria of the skin microbiome, leading to the selection of resistant *C. acnes, Streptococcus* and *Staphylococcus* strains [8, 43, 44]. The induction of antimicrobial resistance and dysbiosis thus provides a strong argument for limited use of both systemic and topical antibiotics as long term and monotherapy regimens in acne.

As regards alternative treatments to isotretinoin and antibiotics, a study by Ahluwalia et al. in 2019 indicated that the antiseptic benzoyl peroxide (BPO), an over-the-counter acne treatment with bactericidal, anti-inflammatory, and comedolytic properties, did not affect microbial diversity [45]. However, these data need to be confirmed as a smaller-sized study—including only five preadolescent females with acne treated with BPO—found that microflora diversity decreased after treatment [46]. According to a very recent Cochrane review, there may be little to no difference between treatment with long-term BPO and that with clindamycin or adapalene in terms of self-reported treatment success in mild-to-moderate acne management [47].

Thus, we advocate the use of BPO alone, or in association with a cleanser (pH ~ 5) and a moisturizing cream as adjunct treatments, to restore the skin barrier and microbiome. Indeed, intensive washing damages the skin barrier, leads to loss of AMPs and results in impaired innate immunity. Moreover, the pH of the skin is around 5.5. Using cleansers with a higher pH (~ 8) increases kallikrein 5 activity, leading to skin barrier dysfunction [48] and alters the skin and the microbiota (Fig. 2). In particular, Prakash et al. demonstrated that skin pH in patients with mild-to-moderate acne vulgaris in the absence of treatment was significantly higher than that in age- and sex-matched controls [49]. Indeed, the bactericidal activity of antimicrobial peptides is optimal at pH 5.5, and the population size and activity of *C. acnes* and *S. aureus* have been shown to increase as skin pH rises [50].

4.2 Future of Treatments

The objective of treatment in acne is not to kill *C. acnes* but rather to prevent or to treat dysbiosis, thus new ways of equilibrating the dysbiosis in acne have been investigated. One strategy relies on sucrose for selective augmentation of *S. epidermidis* fermentation over that of *C. acnes* [51]. Another way of shifting the balance toward a healthy microbiome involves supplementing the skin microbiota with probiotics [12]. Several clinical trials have shown that topical probiotics can directly alter the skin microbiome and immune response [52]. In addition, modulation of the intestinal microflora via oral probiotics can indirectly influence skin diseases [52]. Bifidobacteria and Lactobacilli, bacteria normally found in the gut, could be used as probiotics for

Fig. 2 Acne lesions after intensive washing of the skin (left cheek) versus mild cleansing (right cheek) in an adult female with mild acne

the treatment of inflammatory skin diseases such as acne [53]. Their effects on acne may be mediated by the ability of oral probiotics to reduce systemic oxidative stress, regulate cytokines, and reduce inflammatory markers [39]. The demonstrated impact of the Western diet on the development of acne also suggests that probiotic-based therapy and dietary management could be used in the prevention and treatment of acne [36].

Essential oils, such as Korean Citrus obovoides and Citrus natsudadai [54], may also be effective acne treatments: they have been shown in vitro to display action against acne-inducing bacteria and have inhibitory effects on *C. acnes*-induced secretion of IL-8 and TNF-α in human monocytic cells, suggesting anti-inflammatory properties. Tea tree oil (TTO), one of the most widely used anti-acne botanical ingredients in the cosmetic industry, has shown comparable efficacy to benzoyl peroxide in several randomized controlled trials. However, skin irritation and late onset of efficacy have been reported [55]. A substance acquired from solid state fermentation of the plant extract *Chamaecyparis obtusa* by *Lactobacillus fermentum* has been shown to be more efficient than TTO in a comparative study in 34 patients [56]. In an 8-week, double-blind, randomized, controlled split-face study comparing topical application of lactobacillus-fermented *C. obtusa* (LFCO) and TTO, inflammatory acne lesions were reduced by 65.3% on the LFCO side and by 38.2% on the TTO side [56].

Alternatively, AMPs could act as new topical antibiotic modulators of cutaneous microbiota and innate immunity [57]. The AMP pheromone, plantaricin A, increases the antioxidant defenses of human keratinocytes and modulates expression of filaggrin, involucrin, β-defensin and TNF-α genes in vitro [58]. Indeed, in addition to their antimicrobial activity, AMPs synthesized by mammals also regulate physiological functions such as inflammation, angiogenesis and wound healing. They are abundant in mammalian skin, and alterations in their levels of synthesis were recently shown to play a role in skin diseases such as psoriasis, atopic dermatitis and rosacea [57].

Finally, another alternative therapy could involve bacteriophages. Both metagenomic analysis and other culture-based studies have shown that naturally occurring *C. acnes* bacteriophages on the skin are more prevalent in healthy individuals compared with acne patients. They are also more abundant in older individuals, which could be related to the decline in acne prevalence with increasing age. Finally, some *C. acnes* strains (from clades IB, II, and III) are resistant to the viral activity of bacteriophages, which could influence *C. acnes* phylotype repartition [59].

These therapeutic approaches could lead to the development of vaccination strategies, through acne immunotherapy. Rather than using killed *C. acnes* [60] or targeting a surface antigen, specifically inhibiting secreted virulence factors should limit the risk of unwanted targeting of non-pathogenic bacteria and overcome the risk of selection of resistant bacteria [61]. For instance, one such target could be Christie-Atkins-Munch-Peterson (CAMP) factor 2, a secreted virulence factor from *C. acnes* that triggers inflammatory responses. Indeed, the anti-inflammatory properties of antibodies to this virulence factor, demonstrated in a murine model and in ex vivo human acne explants, suggest that targeting of CAMP factor 2 in a vaccination approach could inhibit *C. acnes* pathogenicity [62].

5 Conclusion

In conclusion, our improved understanding of the genetic and phenotypic diversity of *C. acnes* strains and of the involvement of other bacterial species in acne physiopathology suggests that it may be feasible to develop individualized acne therapies, targeting only the pathogenic strains and leaving the commensal strains intact. Such alternative treatments, involving modifications of the microbiome, may form the next generation of 'ecobiological' anti-inflammatory treatments.

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Declarations

Conflict of Interest No conflict to be declared on this topic.

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