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REVIEW ARTICLE

Cutibacterium acnes (*Propionibacterium acnes*) and acne vulgaris: a brief look at the latest updates

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Abstract While the commensal bacterium *Propionibacterium acnes* (*P. acnes*) is involved in the maintenance of a healthy skin, it can also act as an opportunistic pathogen in acne vulgaris. The latest findings on *P. acnes* shed light on the critical role of a tight equilibrium between members of its phylotypes and within the skin microbiota in the development of this skin disease. Indeed, contrary to what was previously thought, proliferation of *P. acnes* is not the trigger of acne as patients with acne do not harbour more *P. acnes* in follicles than normal individuals. Instead, the loss of the skin microbial diversity together with the activation of the innate immunity might lead to this chronic inflammatory condition. This review provides results of the most recent biochemical and genomic investigations that led to the new taxonomic classification of *P. acnes* renamed *Cutibacterium acnes* (*C. acnes*), and to the better characterisation of its phylogenetic cluster groups. Moreover, the latest data on the role of *C. acnes* and its different phylotypes in acne are presented, providing an overview of the factors that could participate in the virulence and in the antimicrobial resistance of acne-associated strains. Overall, this emerging key information offers new perspectives in the treatment of acne, with future innovative strategies focusing on *C. acnes* biofilms and/or on its acne-associated phylotypes.
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Introduction

On the skin surface, the microbial community is mostly constituted by bacteria belonging to the three main genera of *Corynebacteria*, *Propionibacteria* and *Staphylococci*.[1] Interplay between members of this cutaneous microbiota is essential for the maintenance of a healthy skin. While the commensal bacterium *Propionibacterium acnes* (*P. acnes*), predominant in sebaceous sites, is critical in the regulation of skin homeostasis[2] and prevents colonisation from other harmful pathogens,[3,4] it can also act as an opportunistic pathogen in acne vulgaris. New findings on *P. acnes* reveal that, contrary to what was previously thought, its proliferation is not the trigger of acne but instead, a tight equilibrium between members of the skin flora and among *P. acnes* phylotypes might play a more critical role in acne onset.[4,5] Loss of microbial diversity can indeed lead to chronic inflammatory skin diseases.[4,6]

Colonisation of the pilosebaceous follicle by *P. acnes* is considered as one of the central factors driving acne by taking part in the inflammatory response of the skin, in addition to the cutaneous microbiota and innate immunity. Two other factors involved in this chronic inflammatory skin disease are the increased sebum production, with a modification of its composition, and hypercornification of the pilosebaceous follicle resulting from hyperproliferation and abnormal differentiation of keratinocytes of the upper part of the follicle.[7,8] There are many other contributing factors that influence the severity as well as the incidence and persistence of acne, such as environmental factors, hormones, family history and stress.[8,9]

Genomic and metagenomic investigations recently led both to changing the denomination of *P. acnes* to *Cutibacterium acnes* (*C. acnes*)[10] accounting for its specific features to colonise the skin, and to starting the characterisation of its different

phylotypes. Considering the potential central role of *P. acnes*/*C. acnes* in acne, emerging key elements related to its genomic and phenotypic heterogeneity open the way to deeply explore the role of its different phylotypes in acne development, and give new insights on the cellular physiology underlying this pathogenesis.

Therefore, this review aims to provide the most recent data re-evaluating the role of *P. acnes*/*C. acnes* and its different phylotypes in acne. The phylogenetically distinct cluster groups of *P. acnes*/*C. acnes*, identified thanks to DNA-based typing methods, are first presented along with their new taxonomic classifications. On these bases, differences in phylotypes between healthy volunteers and individuals with acne are detailed, leading to the description of specific factors that may participate in the virulence and in the antimicrobial resistance of acne-associated strains. Altogether, these data open new perspectives in acne prevention and therapeutic approaches, involving adjunctive treatments, via effects on skin microbiota or biofilm formation.

New data on *C. acnes* taxonomy

Among the multiple commensal microorganisms present in the healthy skin flora, *P. acnes*/*C. acnes* is a ubiquitous gram-positive anaerobic bacterium belonging to the *Actinobacteria* phylum, that predominantly resides deep within the sebaceous follicle in contact with keratinocytes.[3] Conversely, at the skin surface *Propionibacteria* are less represented (<2% of all bacteria), in favour of *Staphylococci*, especially *Staphylococcus epidermidis* (*S. epidermidis*), which dominate with >27% of the total bacteria population.[11] *P. acnes*/*C. acnes* is also found in other tissues such as intestine, stomach, lungs, mouth, conjunctiva, prostate and urinary tract.[3,12–14] Specific metabolic features allow *P. acnes*/*C. acnes* to colonise the hostile lipid-rich sebaceous follicle environment and protect skin from other harmful pathogens to preserve the stability of resident skin microbiota.[3,4] In particular, it can degrade triglycerides present in sebum to generate short-chain fatty acids, including propionic acid, which accumulation participates in the maintenance of an acid skin pH. Despite active research as *P. acnes*/*C. acnes* has been hypothesised as an important pathogenic factor in acne,[15] its contribution to acne pathophysiology is not clearly established while its protective role as a commensal bacterium of healthy skin microbiota has been confirmed.[3] Close examination of the skin microbiome using new genomic and metagenomic approaches is therefore instrumental to appreciate the diversity of the *P. acnes*/*C. acnes* population and begin to explore how this seemingly harmless bacterium might after all have a pathogenic effect contributing to the development of acne lesions.

Reclassification of *Propionibacterium acnes* as *Cutibacterium acnes*

Recently, a high-resolution core genome analysis combining 16S rRNA gene sequences, DNA G+C content, genome size and genes content, clarified the phylogeny of the *Propionibacteriaceae* family, in an attempt to better understand how species relate to each other and unravel adaptive processes behind the transmission and evolutionary adaptation of *P. acnes* to human skin.[10] This work led to the definition of a new genus for cutaneous bacteria, the genus *Cutibacterium* gen. nov., which accommodates the former cutaneous species.[10] Notably, specific genes were identified in these cutaneous species, especially lipase genes encoding for triacylglycerol lipase and lysophospholipase able to specifically degrade sebum lipids, while others disappeared by deletions as part of the evolutionary adaptation of cutaneous *Propionibacterium* to human skin. A taxonomic reclassification was therefore proposed in which *Propionibacterium acnes* was renamed *C. acnes* to account for all those genomic adaptive changes and differentiate it from other environmental *Propionibacteria* species, including those present in dairy products and cattle rumen.[10] This new denomination is used throughout this review regardless of the species name in the original articles referenced.

Refinement of *C. acnes* phylotypes with genomic approaches

At the era of genomic research, various DNA-based methods used for bacterial typing allowed the identification of distinct *C. acnes* phylogenic groups but also yielded diverse nomenclatures that could be confusing. Hence for a better understanding, we have established a summary table (Table 1) of typing methods and correspondences between initially defined phylotypes, clonal complexes (CC), single-locus sequence typing (SLST) types and ribotype denominations, based on the original publications and on the recent reviews of Yu *et al.*[16] and McDowell.[17]

Initial genomic analyses used sequence comparison of either *recA* or *tly* genes (the putative hemolysin gene) to categorise *C. acnes* strains into phylotypes IA, IB, II and III.[18–20] More reliable but time-consuming molecular typing methods, with a better reproducibility and a high discriminatory power, were later used to further discriminate *C. acnes* strains. Multi-locus sequence typing (MLST) approaches, based on nine,[21] then on eight[22] housekeeping genes, similarly identified the 3 divisions (I, II and III) and further divided the type I strain into I-1a, I-1b and I-2[21] or IA_1, IA_2, IB and IC[22] groups, each subtype also consisting of distinct CC or singletons (Table 1). However, these two classifications have created confusion. Afterwards and with the aim to reduce time and cost, McDowell *et al.*[23] described a 4-locus MLST (MLST4) method based on the MLST8 scheme, that correctly predicted the six main phylogroups. An alternative approach was also reported by Fitz-Gibbon *et al.*[24] with the distinction of 10 major ribotypes using 16S rRNA gene ribotyping. This method is cheaper but has a limited resolution and poorly discriminates the major clusters of *C. acnes* (for example, RT1 and RT5 are present across different clades, see Table 1). As a result, it is rarely used in clinical studies. Meanwhile, Nagy

Table 1 Summary of nomenclatures of *C. acnes* phylotypes obtained with the main described typing methods and corresponding clonal complexes, types or ribotypes

Typing based on *tly* and *recA* genes	MLST9† (145 ST)‡‡ Aarhus scheme		eMLST8‡ (138 ST)‡‡ Belfast scheme		SLST§ (113 types)‡‡	Mass spectrometry typing¶	Ribotyping††	
IA1	I-1a	CC18	IA_1	CC-1	A1-34	IA	IA-1	RT5
		Singletons			B1			RT1
								RT532
		CC3		CC-3	C1-5		IA-2	RT4
				Singleton				RT1
		CC28			D1-5			RT5
		CC31		CC-4	E1-9		IB-1	RT8
IA2	I-1b	**CC28**	IA_2	CC-2	F1-14	IA	IB-2	RT3
		Singleton		Singletons				RT16
IB	I-2	CC36	IB	CC-5	H1-8	IB	IB-3	RT1
				Singleton				
NA	NA	Singletons	IC	CC-107	G1	IB/(IC)	IC	RT5
II	II	CC53	II	CC-6	K1-25	II	II	RT2
		CC60		CC-72				RT6
		Singleton		Singletons				RT1
III	NA	CC43	III	CC-77	L1-10	III		RT9
		Singletons		Singleton		III/1		NA

Sources: Yu *et al.*,[16] McDowell *et al.*,[27] McDowell *et al.*[17] and †Lomholt and Kilian,[21] ‡McDowell *et al.*,[22] §Scholz *et al.*,[26] ¶Nagy *et al.*,[25] ††Fitz-Gibbon *et al.*,[24] Tomida *et al.*[31]

‡‡Last update January 15th 2018.

Note that the Aarhus scheme detects CC28 in IA_1 and IA_2 clades.

CC, clonal complex; MLST, multilocus sequence typing; NA, not assessed; RT, ribotype; SLST, single locus sequence typing; ST, sequence type.

et al.[25] designed a rapid mass spectrometry assay to identify the major phylotypes without using PCR. Even though phylotypes IA1 and IA2 cannot be distinguished, this method correctly identifies phylotypes IA, IB, II and III as well as a new III/1 phylotype (Table 1). More recently, a SLST scheme was proposed, that has a resolution comparable to that of existing MLST schemes but, contrary to them it can be used for mapping of multiple strains in a complex microbial environment.[26] In this work, phylogenetic analysis of the 41 distinct SLST types (A1 to L1), identified among 187 strains previously typed with MLST9, demonstrated the overall congruency between both typing methods. These genomic investigations, together with morphological and biochemical approaches, allowed better comparison of *C. acnes* strains belonging to the three main phylotypes (I, II and III), leading to the recent proposal of their reclassification in distinct subspecies: phylotype I as *C. acnes* subsp. *acnes*,[10] phylotype II as *C. acnes* subsp. *defendens*[27] and phylotype III as *C. acnes* subsp. *elongatum*.[28]

Altogether, these studies using various DNA-based techniques assessed the great diversity and complexity of *C. acnes* population and prompted rapid progress in the characterisation of its main phylotypes. As most typing methods are still in use today, despite all of their advantages and drawbacks, they are all presented in Table 1. Nevertheless, to facilitate comprehension, a harmonised denomination of phylotypes based on the initial phylotyping (IA1, IA2, IB, II and III) is used in the rest of the review.

C. acnes phylotypes in acne

Skin with acne does not harbour more *C. acnes* than normal skin

Recent evidence generated by sophisticated genomic techniques and/or new sampling methods allowed it to be proved that, in contrast to what has long been thought, *C. acnes* is by far the most abundant and predominant bacterium in the microbiota of pilosebaceous follicles both in acne patients and in individuals with unaffected skin. Analyses indeed showed that the load of *C. acnes* (this issue) or the relative abundance of *C. acnes* (in metagenomics studies) is similar among patients with acne and healthy individuals (87%–89%),[24] or even slightly higher in healthy subjects (89% vs. 94%).[5] While there was no quantitative difference of *C. acnes* between subjects with and without acne, its phylogenic groups displayed specific genetic (see the following article in this issue) and phenotypic characteristics. Thus, it was hypothesised that some strains may be truly commensal and

contribute to skin health, whereas others may have the potential to act as opportunistic pathogens. To confirm this assumption, distribution patterns of *C. acnes* population have been investigated in acne pathology at the strain and genetic levels, both at the skin surface and in acne lesions.

Specific *C. acnes* strains are associated with acne

In a study of 2010, Lomholt and Kilian[21] observed that among a great number of *C. acnes* isolates ($N = 210$) from skin of healthy individuals, and patients with varying degrees of acne, or other infectious diseases, those from division IA were strongly associated with moderate to severe acne while others, IB, II and III, were associated with healthy skin and opportunistic deep tissue infections. These first observations were further confirmed by another group using the eMLST8 method, showing that phylotype IA1 was predominantly associated with acne, while phylotype IA2, IB and II isolates were less represented in this skin condition.[22,23] Based on PCR using type-specific primers of phylotypes IA, IB and II, Kwon *et al.*[29] found that phylotypes distribution was similar between skin surface and comedones lesions, but papules and pustules were characterised by an increase in phylotype IA and a decrease in phylotypes IB and II. This observation suggested that phylotype IA preferentially proliferate in an inflammatory microenvironment, therefore indicating a shift in the skin microbiota of acne patients. A more comprehensive sampling technique and a metagenomic analysis using ribotyping confirmed that the strain population structures were significantly different between skin microcomedones from acne patients and healthy individuals: phylotype IA1 was more strongly associated with acne, while phylotype II was preferentially present in skin from healthy subjects and other ribotypes belonging to various phylotypes (IA, IB and II), exhibited a uniform dispersion across both cohorts.[24] A recent study provided a more detailed landscape of the clonal complexity and dominant clones in follicles from patients with moderate to severe acne, using the Aarhus scheme (MLST9, Table 1).[30] The *C. acnes* phylotype IA1 was the dominant follicular type in Caucasian patients with acne, while clones from healthy subjects were more heterogeneous with strains from various phylotypes, IA1, IA2, IB and II. However, the phylotype IA1 isolates did not exhibit differences in gene content or genetic elements between healthy controls and acne patients that could explain its association with the disease status.[30] Indeed, the gene synteny is remarkably conserved, indicative of a highly stable C. *acnes* chromosome, the core genome representing 88% of the average genome.[31] Regarding the phylotype III, its possible involvement in *C. acnes* deep tissue infections along with the phylotype IB,[23,32–34] and other pathologies[5,33,35] was recently considered, and it was even detected in patients with severe acne ([36] and this issue). Nevertheless, it was never predominant and not frequently associated with this skin disease.

Unique genomic elements seem to be associated with acne

At the molecular level, lineage-specific genetic elements have been identified among 82 *C. acnes* strains isolated from acne or healthy skin.[31] These specific loci may explain the phenotypic and functional differences of *C. acnes* phylotypes as a commensal in health and as a pathogen in diseases. For instance, three genomic loci, which were unique to phylotype IA1, encode several virulent genes and may thus contribute to virulence of these mainly acne-associated strains. Vice versa, the distinctive genomic characteristic of phylotype II, enriched in healthy skin, is the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas locus considered as an adaptive immune system for bacteria that may allow the elimination of invasive foreign DNA, hence preventing the acquisition of virulent genes. Thus, in the phylotype I strains, mainly involved in acne lesions, the deletion of this CRISPR/cas locus may account for their ability to horizontally acquire fitness or virulence traits.[37] Moreover, deletions in the regulatory regions of a lipase gene in phylotype II strains may potentially explain their decreased lipase activity and their decreased virulence in acne.[31]

In the same way, in-depth metagenomic analysis of the whole skin microbial community, including the comparison of specific *C. acnes* operational gene groups, showed a strong enrichment in a variety of virulence-related genes and reduced abundance in metabolic synthesis genes in patients with acne compared with healthy subjects.[5] Following this work, a robust set of differentially abundant metagenomic elements was identified and could be used as markers for classification of the clinical states of the skin and finally to detect balance shifts towards acne.

C. acnes phylotypes and acne severity

A recent pilot observational study looking at the possible link between acne severity and a specific *C. acnes* subtype or subpopulation in the lesions, found no difference in the distribution of phylotypes between patients with mild acne and those with severe acne, even though phylotype IA1 was the most represented in both populations.[36] A Japanese study, using the same SLST method, also showed that phylotype IA1 was predominant in each acne severity category (with 60%, 57.1% and 63.3% of strains in the severe, moderate and mild acne groups, respectively). In contrast, phylotype IA2, highly resistant to clindamycin, seemed to be more frequently associated with severe and moderate acne, which was hypothesised to aggravate acne severity.[38] Overall, these divergent findings highlighted that the severity of acne might not only be due to a specific *C. acnes* strain but also to host and environmental factors that could potentially yield different level of activation of innate immunity in severe acne.[36] Early and intense inflammatory events in the epidermis have indeed been shown to contribute to the development of scars.[39]

Despite some heterogeneities between studies, regarding population samplings, anatomic sites and typing methods, those results suggest that some *C. acnes* phylotypes IA preferentially colonise skin with acne while others are not or poorly present in acne lesions (IB, II and III). However, quantitative analyses are not always reliable as skin sampling methods are very heterogeneous between studies and not all of them are sensitive and accurate, making result comparison across studies quite difficult.[40,41]

C. acnes phylotypes and virulence

Phylogenic studies also showed that acquired DNA sequences and bacterial immune elements may have roles in determining virulence properties of *C. acnes* strains. Moreover, biochemical, transcriptomic and proteomic analyses demonstrated that *C. acnes* phylotypes exhibit differences in inflammatory potential and expression of various putative virulence factors that may explain their distinct involvement in acne disease.[40,42] These factors include neuraminidase, lipase, polyunsaturated fatty acid isomerase, the iron acquisition protein HtaA (a highly immunoreactive cell surface antigen) and heat shock proteins (HSP20, DnaK, DnaJ, GrpE and GroEL).[3] Host-interacting factors, such as CAMP factors, hemolysins and dermatan sulphate-binding adhesins (DsA1 and DsA2) have also been identified as possible pathogenic factors.[3,40] Some of them might constitute future targets for therapeutic interventions and are thus further described.

CAMP factors

The five CAMP factors, encoded by the genome of all *C. acnes* strains, are membrane pore-forming toxins that act as host tissue degradation enzymes. These secretory proteins are potentially cytotoxic for keratinocytes and macrophages and their activation may result in skin inflammation.[43] Recent *in vitro* findings indicated that CAMP1 may be involved in *C. acnes* virulence by interacting directly with TLR2, thus amplifying the inflammatory response.[44] More specifically, CAMP1-TLR2 binding intensity was stronger in phylotype IB and II strains than in phylotype IA1 and IA2 strains, which was respectively correlated with high and low production levels of the proinflammatory cytokine CXCL8. Consistently, CAMP1 factor genes were found to be most strongly expressed in types IB and II, while CAMP2 factor was detected in greater amounts in IA isolates.[19] However, it should be pointed out that in proteomic analyses, CAMP1, as well as adhesins, are the most abundant proteins of *C. acnes* in sebaceous follicle from both normal and acne skin.[45] Moreover, by disrupting two of the five CAMP genes in a *C. acnes* isolate KPA171202 (IB strain), Sörensen *et al.*[46] demonstrated that the Δ*camp2* but not the Δ*camp4* mutant exhibited reduced haemolytic activity in the CAMP reaction with sheep erythrocytes, indicating that CAMP2 is the major active co-haemolytic factor of *C. acnes*. These experimental researches remain exploratory and cannot yet confirm the relationship between the expression of CAMP factors and the association of specific *C. acnes* strains with acne.

Porphyrins

Porphyrins, which exhibit absorbance properties in ultraviolet and visible light, are produced by *C. acnes* and might contribute to the perifollicular inflammatory reaction during acne development. Indeed, their ability to generate singlet oxygen from oxygen under ultraviolet exposure might enhance the production of cytotoxic substances by oxidation processes, such as squalene peroxide, a proinflammatory lipid.[47] Moreover, they can stimulate the expression of keratinocyte-derived interleukin (IL)-8 and prostaglandin E2 that are mediators of inflammatory and immune responses.[47,48] Interestingly, phylotype IA1 strains isolated from patients with acne were found to produce significantly higher levels of porphyrins than healthy skin-associated phylotype II strains.[49] This finding was correlated with the presence of a repressor gene (*deoR*) of porphyrin biosynthesis in all phylotype II strains, but not in IA1 strains.

Hyaluronate lyase

Recently, another putative virulence factor, the hyaluronate lyase (HYL), has been reported with different gene alleles depending on *C. acnes* phylotypes.[34,50] A genotypic and phenotypic investigation, including the generation of a *C. acnes hyl* knockout mutant, revealed two distinct variants of HYL: one highly active variant (HYL-IB/II), resulting in complete hyaluronic acid degradation and another variant with low activity (HYL-IA), resulting in incomplete hyaluronic acid degradation.[51] Hyaluronate lyase, along with other enzymes capable of destroying components of the dermal and epidermal extracellular matrix, such as proteins, hyaluronic acid and other glycosaminoglycans, may indeed promote the spread of inflammation during acne development.

Other virulence factors

The acne-associated phylotype IA1 also contains a novel plasmid with a tight adhesion locus and two unique genomic islands, that comprise genes supposed to enhance virulence through increased bacterial adhesion and host immune response.[24] In addition, a correlation between the severity of acne and lipase activity has been shown with the *C. acnes* phylotype I that produces higher quantities of propionic and butyric acids than other *C. acnes* biotypes and that predominates in isolates from most severe acne skins.[43,52] These isolates might thus have the greatest influence on skin rash in acne patients. Nevertheless, a recent proteome analysis of human sebaceous follicle infundibula extracted from healthy and acne-affected skin revealed at least 12 putative lipases, but only two (GehA and GehB) possess a signal peptide for secretion.[45] GehB was mainly associated with healthy skin, with more diverse *C. acnes* community population, suggesting a beneficial effect of this lipase. However, it is possible

that other lipases, produced by different *C. acnes* phylotypes, play distinctive roles in regard to health and disease, but this hypothesis needs further investigations.

Overall, these factors may be important in the emerging association of some *C. acnes* strains with acne and participate in the modulation of the cutaneous innate immunity and skin inflammation that may influence the severity of inflammatory acne lesions and scars.[53,54]

C. acnes phylotypes and inflammation

A comparative proteomic analysis of six *C. acnes* isolates belonging to all representative phylotypes (IA1, IA2, IB1, IB2, II and III), revealed a differential expression pattern of proteins between them.[55] The most differently expressed proteins included adhesion proteins, CAMP factors, and one cell surface hydrolase. More specifically, the increased production of inflammatory IFN-γ and IL-17 may be induced by acne-associated phylotypes suggesting that some strains might promote acne by activating both Th1 and Th17 responses.[55] Concordantly, decreased levels of IL-10, that downregulates IFN-γ and IL-17 thereby reducing inflammation, were found with strains related to acne (IA1) and some strains considered as neutral (IB). However, the precise role of some of these newly identified and differently expressed proteins in *C. acnes* phylotypes remains to be clarified in the process of skin inflammation and acne pathogenesis.

These data are however somewhat contradictory with the study of Jasson *et al.*[53] showing that *C. acnes* phylotype III had a high pro-inflammatory potential by up-regulating the expression of PAR-2, TNF-α, MMP-13 and TIMP-2 in skin explants while, the IB phylogenetic cluster produced a minimal effect. These findings allowed the authors to propose a classification of the 5 *C. acnes* phylotypes according to their proinflammatory potential, from the strongest to the mildest: type III, II, IC, IA1 and IB.[53]

Thus, phylogenetic cluster groups of *C. acnes* appear to present various pathogenic characteristics, including distinct abilities to elicit inflammation and secretome profiles that suggest an aetiological role of some particular strains in acne.[24,30,55] Further investigations are needed although to get better insights on these strain-specific factors and their link with the inflammatory response but also with other cellular processes involved in acne progression, as mentioned in a recent review[8] highlighting the interconnection between inflammation, lipid metabolism and innate immunity processes within the pilosebaceous duct.

Biofilm formation

Besides virulence factors, several genes present on the *C. acnes* genome (encoding glycosyltransferase, uridine diphosphate-N-acetylglucosamine 2-epimerase and polysaccharide biosynthesis proteins) are also potentially involved in the formation of biofilm, which participates in the pathophysiology of acne.[43] Additional proteins such as the thrombospondin type 3 and the polycystic kidney disease may participate in *C. acnes* adhesive properties in the biofilm.[56]

A biofilm is an organised conglomerate of bacterial cells attached to a surface and embedded into a self-produced polymeric extracellular matrix composed of polysaccharides. This complex protective shell forms a barrier allowing large clusters of bacteria to survive in harsh environments. The ability of *C. acnes* to form biofilms was originally described in 2007.[57] Sessile *C. acnes* cells that grow in biofilms are more resistant to traditional antimicrobial agents than planktonic (free) cells even if the biofilm consists in antibiotic-sensitive strains[58] and have a greater extracellular lipase activity, implicated in inflammation.[57] In 2012, a case–control pilot study performed on facial skin biopsies reported for the first time that *C. acnes* can grow in macrocolonies producing large biofilms deep within the pilosebaceous follicles. They consisted of at least IA and II phylotypes and contained secreted bacterial proteins with known immunoreactive properties.[59] Biofilm cells were indeed characterised by up-regulated stress-induced genes and up-regulation of genes encoding the potential virulence-associated CAMP factors.[60] It is interesting that the occurrence of *C. acnes* biofilms was significantly higher in patients with acne (37%) than in control subjects (13%).[59] However, whereas phylotype IA strains were shown to be mainly associated with acne in recent metagenomic studies, these large macrocolonies appeared to consist of various *C. acnes* phylogroups (at least IA and II) coexisting within the same follicle.[59] These contradictory observations make it difficult to associate either phylotype individually with the acne aetiology. Furthermore, Holmberg *et al.*[61] found that *C. acnes* isolates from skin are less efficient in forming biofilms than isolates from deep tissues infection. These blurry points warrant clarification in future researches.

C. acnes response to antibiotics

Systemic and topical antibiotics have long been at the core of the acne therapeutic arsenal. As commonly known, *Propionibacterium* species are naturally resistant to 5-nitroimidazole agents (metronidazole, tinidazole and ornidazole), aminoglycosides, sulfonamides and mupirocin and *C. acnes* is generally susceptible to a large variety of widely used antimicrobials. However, resistance of *C. acnes* to antibiotic treatments has gradually emerged over the years to become a worldwide problem, with high rates of resistance reported for erythromycin (macrolides) and clindamycin (lincosamides) (between 21% and 70%) and less frequent resistances to tetracycline (between 4% and 30%), in line with the most frequent use of topical macrolides.[62–64] The most common mechanism of antibiotic resistance in *C. acnes* is chromosomal point mutations, mainly in the 23S rRNA gene for macrolides resistance and 16S rRNA gene for tetracycline resistance.[63,65] The acquired transposon carrying the *erm(X)* gene, which encodes an rRNA methyltransferase, is also

involved in clindamycin, erythromycin and telithromycin resistance.[66] At last, amino acid substitution in the ribosomal S10 protein encoded by *rpsJ* gene also contributes to reduce doxycycline susceptibility in *C. acnes*.[38] Of notice, in Lomholt's study, which examined *C. acnes* resistance in 350 isolates collected from various countries, tetracycline resistance was detected exclusively among isolates from Danish acne patients, who each carried 1–6 clones of *C. acnes*.[67] This observation was correlated with the almost exclusive use of tetracycline for the treatment of acne in Danish primary health care suggesting that the prolonged or inappropriate use of antimicrobial agents can lead to the spread of resistance in *C. acnes* strains as well as among other members of skin microbiota.[63] While the role of previous therapeutic interventions is relevant on *C. acnes* resistance in acne, especially for topical macrolides and lincosamides with more than 70% of patients carrying resistant *C. acnes* strains to erythromycin and clindamycin,[64] many other factors might be implicated. Indeed, for quinolones, no correlation could be identified as no difference was detected in rate of levofloxacin resistance between severe and mild acne, despite orally administered quinolones being more frequently prescribed for severe than mild acne.[38]

Literature regarding an association between strains of *C. acnes* and resistance to antibiotics is scarce. Nevertheless, concordant data demonstrated that phylotype IA1 strains, highly associated with acne, represented most erythromycin- and clindamycin-resistant strains and to a lesser extent tetracycline-resistant strains.[22,67] Moreover, in McDowell's study, all tested phylotype IC isolates ($N = 4$) were resistant to erythromycin and tetracycline.[22] Most of these resistant clones presented mutations in their 23S and 16S rRNA genes.[22,24] The recent description of fluoroquinolone-resistant *C. acnes* strains in acne revealed phylotype IA as the predominant cluster.[68] Focusing on the molecular mechanism involved in this resistance, the authors further demonstrated that most of the clinical strains belonged to phylotype IA1[38]. In a recent case report,[69] bacterial isolates from a slow responder to antimicrobial treatments were found to be phylogenetically heterogeneous and presented variable resistance to clindamycin. In a surprising manner the pathogenic phylotype IA1 displayed clindamycin sensitivity, whereas phylotype IB, associated with commensals, exhibited high clindamycin resistance. After a sensitivity analysis revealing susceptibility of *C. acnes* isolates to tetracycline and nadifloxacin, the authors switched the regimen to a combination of minocycline and nadifloxacin that significantly improved the clinical lesions. This individual characterisation of *C. acnes* isolates in acne lesions demonstrated the relevance of such a personalised approach to choose the best antibiotics but also suggested that the association of certain *C. acnes* phylotypes with acne may be more complex than anticipated. To complicate matters, at the lesion level each follicle behaves independently and may contain a mixture of strains with various levels of resistance that can explain a limited overall response of a patient to conventional antibiotics.[41,67]

In addition to acquired resistance, bacterial biofilms might also play a role in *C. acnes* reduced susceptibility to antibiotherapy and increased resistance to phagocytosis. An intrinsic property of bacteria in biofilms is indeed their increased tolerance to antibiotics, even if the strains forming the biofilm are normally sensitive to antibiotics (see the following article and[58]). Altogether, resistance, virulence factors, restricted access to immune defense cells of the host, poor penetration of antibacterial agents and selection of 'persister' cells are among the mechanisms proposed to explain increased tolerance to antibiotics in *C. acnes* biofilms.[60,63]

Keeping in mind the emergence of acquired resistance of *C. acnes* against the currently approved antibiotics,[41,64] another main concern for using antibiotics is the overall modification of the human skin microbiome, where resistant bacterial species may emerge via selective pressure.[63] These growing threats should thus conduce to a limited use of topical and systemic antibiotics as long term and monotherapy regimens in acne and to the use of alternative treatments, such as benzoyl peroxide alone or combined with topical retinoids [64,70] according to international guidelines for treatment of acne[71,72].

Conclusion and perspectives

To sum up, while *C. acnes* is present on the skin surface at a low level, it is the dominant resident bacterial species in the sebaceous follicles. Contrary to what was previously thought, acne vulgaris is not the result of a greater proliferation of all *C. acnes* strains, as patients with acne do not harbour more *C. acnes* in follicles than normal individuals. Instead, acne might be triggered by the selection of a subset of *C. acnes* strains, including the acne-associated phylotype IA1, probably enhanced by a hyperseborrheic environment. Besides, biofilm formation and differences in virulence and inflammatory potential of *C. acnes* strains might enhance their pathogenicity. Specific operational genomic sequences present in the whole skin microbiota, also support the new paradigm that an equilibrium state exists within the skin microbiota and between the different *C. acnes* subtypes. Recent data show that *S. epidermidis* and *C. acnes* interact together and are critical in the regulation of skin homeostasis.[2,11] In particular, *S. epidermidis* is known to inhibit *C. acnes* growth[11,73,74] and *C. acnes*-induced inflammation[75] in skin. Changes in physiological conditions may lead to an imbalance between the different skin community members, called dysbiosis, and eventually to the selection of more pathogenic *C. acnes* strains.[4,42] Disruption of equilibrium within the skin microbiota and intrinsic properties of *C. acnes* might therefore be conducive to the activation of innate immunity, resulting in cutaneous inflammation.

Overall, this review underscores the importance of *C. acnes* phylotype IA1 in acne and suggests the implication of other

members of the human cutaneous microbiome in this skin condition. As a consequence, improved understanding of the genetic and phenotypic diversity of *C. acnes* strains as well as the involvement of other bacterial species, could be applied in the development of alternative and personalised therapies addressing the pathogenic strains only and leaving the commensal strains intact.

For instance, small molecules, such as levulinic acid, able to inhibit porphyrin biosynthesis in acne-associated *C. acnes* strains without disrupting the growth of health-associated strains, are attractive drug candidates for the treatment of acne.[49] Biofilms can also constitute novel targets to overcome increased resistance to antibiotics and restore a balanced cutaneous microbiome. Interestingly, using anti-biofilm compounds like Myrtacine®, a natural active agent containing myrtucommulones, can help to deconstruct the biofilm and restore antibiotic sensitivity even in resistant strains ([58] and this issue). In the same way, a topical gel containing salicylic acid and designed to address *C. acnes* biofilm exhibited a positive effect on acne lesions.[76] Such products can thus constitute original antimicrobials that could be used as efficient adjunctive agents during the antibiotic course for acne treatment. Recent findings on the balance of the skin microbiota also suggest potential future development of individualised acne therapies and the maintenance of skin health, by supplementing the skin microbiota with probiotics to shift the balance towards a healthy microbiome.[5] Various and novel treatment options, focusing on *C. acnes* biofilms and/or on its acne-associated phylotypes, are hence worthy of further exploration in clinical settings for acne management.

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