Cutibacterium acnes

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Cutibacterium acnes is a member of the skin microbiota found predominantly in regions rich in sebaceous glands. It is involved in maintaining healthy skin and has long been considered a commensal bacterium. Its involvement in various infections has led to its emergence as an opportunist pathogen. Interactions between C. acnes and the human host, including the human skin microbiota, promote the selection of C. acnes strains capable of producing several virulence factors that increase inflammatory capability. This pathogenic property may be related to many infectious mechanisms, such as an ability to form biofilms and the expression of putative virulence factors capable of triggering host immune responses or enabling C. acnes to adapt to its environment. During the past decade, many studies have identified and characterized several putative virulence factors potentially involved in the pathogenicity of this bacterium. These virulence factors are involved in bacterial attachment to target cells, polysaccharide-based biofilm synthesis, molecular structures mediating inflammation, and the enzymatic degradation of host tissues. C. acnes, like other skin-associated bacteria, can colonize various ecological niches other than skin. It produces several proteins or glycoproteins that could be considered to be active virulence factors, enabling the bacterium to adapt to the lipophilic environment of the pilosebaceous unit of the skin, but also to the various organs it colonizes.

Keywords: C. acnes ; inflammation ; innate immunity ; virulence factors ; characterization

1. *C. acnes* Characteristics

The genus *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes* or *P. acnes*, see below) is a commensal lipophilic Gram-positive bacterium. *C. acnes* is described as diphtheroid or coryneform because it is rod-shaped and slightly curved with a width of 0.4 to 0.7 µm and length of 3 to 5 µm. Anaerobic bacteria are characterized by their inability to grow on solid media in the presence of atmospheric oxygen. However, *C. acnes* is considered an aerotolerant anaerobe because it possesses enzymatic systems able to detoxify oxygen, allowing it to be sustained on the surface of the skin [1].

Following its isolation [2], *C. acnes* was first included in the genus *Bacillus* as *Bacillus acnes,* and then in the genus *Corynebacterium* as *Corynebacterium acnes* or “anaerobic *corynebacteria*” because of its morphology. Based on its ability to produce propionic acid via its anaerobic catabolism, it was then assigned to the genus *Propionibacterium,* subsequently renamed *Cutibacterium*. Genus *Cutibacterium* belongs to a branch of *Actinobacter* and can be split into two groups, one containing the so-called “classic or dairy” species, bringing together saprophytic species isolated from non-human-pathogenic dairy products, and the other containing commensal “skin” species, most found on the surface of human skin. Classic species, such as *Propionibacterium freundenreichii*, which is essential for the ripening of Swiss cheeses, or *Propionibacterium acidipropionici*, known for its beneficial effects in the bovine rumen, have been studied in considerable detail due to their importance to the agri-food industry. By contrast, the pathophysiology of cutaneous species is less well understood.

Phylogenetic and genome analyses of classic and cutaneous species have highlighted differences in the 16S RNA gene sequences and the core genome between species. This finding led to proposals to reclassify many species into four different genera:

(1)The genus *Propionibacterium*, comprising the species *P. freundenreichii*, *P. cyclohexanicum*, *P. acidifaciens*, and *P. australianse*.

(2)The new genus *Acidipropionibacterium*, comprising the species *A. jensenii*, *A. thoenii*, *A. acidipropionici*, *A. microaerophilum*, *A. damnosum*, and *A. olivae*.

(3)The new genus *Pseudopropionibacterium,* containing a single species: *P. propionicum*.

(4)The new genus *Cutibacterium*, comprising cutaneous *Propionibacterium* bacteria belonging to the species *C. acnes*, *C. avidum*, *C. granulosum*, and *C. humerusii*. *P. acnes* has thus been renamed *C. acnes* [3]. Moreover, the genus *C. acnes* has been further subdivided into subspecies, such as *C. acnes* subsp. *defendens* [4][5], and *C. acnes* subsp. *elongatum* [6] (Figure 1).

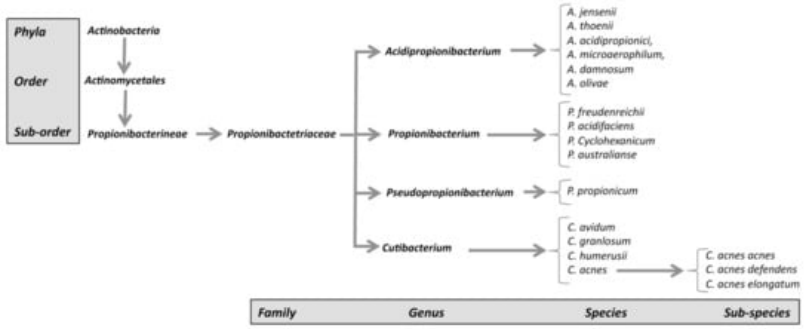

Figure 1. New classification of *C. acnes* strains.

Unlike other Gram-positive bacteria, *C. acnes* has a unique cell wall and envelope, containing phosphatidylinositol, triacylglycerol, and many other common lipids [7]. The cell wall of *C. acnes* consists of peptidoglycan (PNG), but of a type different from that of other Gram-positive bacteria, in that the peptide chain contains the L-acid L-diaminopelic acid and D-alanine. Analyses of *C. acnes* lipoglycans have also revealed the presence of a lipid anchor based on fatty acids and shown that the polysaccharide moiety contains significant amounts of mannose, glucose, and galactose, together with an amino sugar thought to be a diaminohexuronic acid [8]. *C. acnes* has been shown to survive for long periods of time in human tissues with a low oxidative potential. Indeed, *C. acnes* has all of the proteins required for oxidative phosphorylation (NAPDH dehydrogenase/complex I, cytochrome *c* reductase, cytochrome *c* oxidase, and FoF1-type ATP synthase). It also possesses the cytochrome *d* oxidase genes, enabling it to grow in conditions in which limited amounts of oxygen are present and to tolerate oxygen for a few hours. Despite its tolerance of the presence of air, *C. acnes* cannot be reliably detected by culture in aerobic conditions due to its very slow growth (5 to 7 days), associated with a division time of about five hours [9]. A limited number of *C. acnes* strains possess a linear plasmid carrying several genes, including a locus for tight adherence (tad) encoding adhesive Flp (fimbrial low-molecular weight protein) pili [10]. Antibiotics were found to be effective against inflammatory acne, but the selection pressure exerted by antibiotic treatment for this condition has led to the induction of antibiotic resistance in up to 40% of *C. acnes* strains (resistance to erythromycin, clindamycin, and tetracycline), increasing the likelihood of treatment failure [11]. Interestingly, it should be noted that the anaerobic species may have intrinsic resistance due to a lack of molecular mechanisms involved in the uptake of the antibiotic [1]. Therefore, antimicrobial susceptibility testing on *C. acnes* strains should be implemented largely in order to adapt antibiotic treatments and to obtain epidemiological data on *C. acnes* antibiotic resistance. In this review, we summarize current knowledge concerning characterized *C. acnes* virulence factors and their possible implication in the pathogenicity of *C. acnes*, which may interest researchers and clinicians investigating the physiopathology of *C. acnes*.

2. C. acnes Classification

C. acnes strains were previously classified into two main types, I and II, on the basis of their cell wall carbohydrate content and serum lectin responses [12][13]. It was then suggested that *C. acnes* strains could be distinguished on the basis of random amplification of polymorphic DNA (RAPD) analysis [14]. Analyses of the sequences of the non-ribosomal housekeeping genes *RecA* and *tly,* and the use of the QUBPa1 and QUBPa2 mAbs, specific for type I and II strains, respectively, subsequently showed that the two types corresponded to evolutionary lineages of *C. acnes* displaying both genetic and phenotypic differences. An additional phylotype, type III, corresponding to strains with filamentous appendages, was then added to the classification [15][16]. Based on 16S rRNA gene analysis, *C. acnes* strains were divided into ribotypes (RTs), which could be used to differentiate between types I, II, and III, associated with healthy skin or acne [17]. RT4, RT5 and RT8 appeared to be found in acne lesions, whereas RT2 and RT6 were mostly found on healthy skin [18]. Multi-locus sequence typing (MLST) and single-locus sequence typing (SLST) methods have been developed for this species, to increase typing resolution. Depending on the number and nature of the housekeeping genes selected, two schemes for discriminating between *C. acnes* strains have been described. The Belfast scheme, using seven target genes, can differentiate type I into clades IA_1, IA_2, IB, and IC [19][20]. A multiplex touchdown PCR typing method has also been developed that can discriminate between the IA_1, IA_2, IB, IC, type II, and type III phylotypes, providing a rapid overview of the *C. acnes* types present in a population [21]. The other scheme, the Aarhus scheme, uses nine target genes to split type I into clades I-1a, I-1b, and I-2 [22]. This scheme appears to be the most discriminant of these two schemes [23]. SLST and whole-genome sequencing (WGS) methods were subsequently used to develop a new

scheme capable of differentiating *C. acnes* strains into clades IA-1, IA-2, IB-1, IB-2, IB-3, IC, II, and III [24], but some *C. acnes* strains were not identified with this scheme [25] (Table 1). MS-based typing for routine analysis has been evaluated with the MALDI-TOF MS method, to characterize *C. acnes* strains in diverse samples [26]. This method is very useful for rapidly discriminating *C. acnes* phylotypes, although missing some of them [26]. However, this approach was improved using profiling of identified biomarkers, such as ribosomal subunit proteins, and named MALDI-MS prototyping, which allowed discrimination of all of the *C. acnes* phylotypes. Although this method needs to ultrafiltrate bacteria whole pellets in order to analyze the concentrated protein fraction, it is nonetheless compatible with the analysis of a large number of *C. acnes* strains [27]. Another attempt to facilitate *C. acnes* typing involved the use of the MLVA method to analyze the polymorphism of 13 VNTRs; the results of this method were well-correlated with those for the MLST and SLST methods [28]. Nomenclatures highlight the need for standardization. WGS is of potential interest for this purpose because it should provide a higher-resolution phylogeny more rapidly and at lower cost [29][30].

Table 1. *C. acnes* phylotypes.

Phylotypes									
***C. acnes* subspecies**		**WGS/Ribotyping [a]**	**SLST [b]**	**MLST8 [c]**	**CC**	**MLST9 [d]**	**CC**	**MALDI-TOF [e]**	**MLVA13 [f]**
	IA-1	**RT1, RT5**	**A1-A34**	**IA_1**	**CC1**	**I-1a**	**CC18**	**IA**	**IAI**
		RT532	**B1**						
	IA-2	**RT1, RT4**	**C1-C5**	**IA_1**	**CC3**	**I-1a**	**CC3**	**IA**	**IA2**
		RT5							
C. acnes acnes	**IB-1**	**RT8**	**D1-D5**	**IA_1**	**CC4**	**I-1a**	**CC28**	**IB**	**IB**
			E1-E9				**CC31**		
	IB-2	**RT3, RT16**	**F1-F14**	**IA_2**	**CC2**	**I-1b**	**CC28**	**IB**	
	IB-3	**RT1**	**H1-H8**	**IB**	**CC5**	**I-2**	**CC36**	**IB**	
	IC	**RT5**	**G1**	**IC**	**CC107**	**/**	**/**	**IB(IC)**	**/**
		RT2, RT6	**K1-K25**		**CC6**		**CC53**		
C. acnes defendens	**II**	**RT6**		**II**	**CC30**	**II**	**CC60**	**II**	**II**
					CC71				
					CC72				
C. acnes elongatum	**III**	**RT9**	**L1-L10**	**III**	**CC77**	**III**	**CC43**	**III**	**III**

WGS: whole genome sequencing; CC: clonal complex. [a] Ribotyping [17]; [b] SLST [3] [c] Belfast scheme [19][20]; [d] Aarhus scheme [22]; [e] MALDI-TOF analysis [31]; [f] $MLVA_{13}$ analysis [28].

3. Skin Microbiota and Acne

Human skin consists of a stratified, cellular epidermis and an underlying dermis of connective tissue. The epidermis is characterized by a stratified squamous epithelium composed of about 80–90% keratinocytes, which progressively move from the epidermal basement membrane towards the surface of the skin, forming several well-defined layers during this transit. Other cells resident within the epidermis include melanocytes, Langerhans' cells, and Merkel cells. The epidermis has several very important functions in the protection of the body against environmental hazards, and it also acts as an immunological barrier, modulating the microbial population of the skin [32][33][34]. The dermis is characterized by a layer of fibroblast cells that also contains immune cells, such as macrophages, neutrophils, and resident T cells.

Acne vulgaris is a chronic inflammatory skin disease mostly found in the teenage population but also in young adults [35]. In a large majority of cases, acne is not a serious disease but if left untreated, can have serious consequences both

physically and psychologically. However, there are severe forms of acne that cause permanent scarring, which may have severe consequences for personality development in young people, leading to social and economic problems. Adolescents suffering from acne are more anxious, socially inhibited, and aggressive than adolescents without acne. Furthermore, acne is the only skin disease for which outcome has been implicated as a risk factor for suicide, particularly in men [36][37].

Acne vulgaris is a disorder affecting the pilosebaceous unit (PSU), resulting in both inflammatory and non-inflammatory clinical lesions. Most patients have a mixture of non-inflammatory comedones and inflammatory papules, pustules, and nodules. Acne ranges in severity from mild symptoms to rare cases of severe rare fulminant infection, with a small subset of patients displaying a highly destructive inflammatory response that is often associated with scarring [38]. The hair follicle or pilosebaceous unit (PSU) groups together sebaceous glands, a hair, and a follicle duct made up of epithelial cells. The sebaceous glands produce sebum which flows into the infundibulum to be released to the surface of the skin. Sebum contains a wide variety of lipids, such as squalene, wax esters, triglycerides, and free fatty acids. The production of sebum is linked to the interaction between the PSU and the thyroid and androgenic hormones, and is dependent on age [39]. Acne occurs mostly in teenagers, in whom hormonal secretion is often imbalanced, leading to an increase in sebum secretion by the sebaceous glands in the PSU [40]. The accumulation of sebum in the infundibulum induces keratinocyte proliferation in the follicular wall, promoting PSU obstruction and the formation of comedones. PSU obstruction leads to hypoxia, favoring the development of *C. acnes*. By interacting with the cells of the PSU, this bacterium then triggers the expression of pro-inflammatory molecules, resulting in strong inflammation. Acne vulgaris thus appears to be a multifactorial disorder, involving sebaceous hyperplasia, follicular hyperkeratinization, and colonization by *C. acnes*, acting as an opportunistic pathogen. *C. acnes* has also been shown to influence the formation of comedones by secreting propionic acid, which modulates keratinocyte differentiation [41].

However, the long-standing hypothesis that acne results from *C. acnes* proliferation has evolved, because this bacterium is also involved in the maintenance of healthy skin and can act as an opportunistic pathogen in various inflammatory conditions, including acne. Amplification- and sequencing-based methods have shed considerable light on the huge diversity of the skin microbial community. Despite the possible interference of sampling methods with the microbiome profile identified [42][43], it has been demonstrated that healthy skin harbors microorganisms from multiple kingdoms: bacteria, fungi, and viruses. Most skin bacteria belong to four phyla: Actinobacteria (Corynebacterineae, Propionibacterineae), Proteobacteria, Firmicutes (Staphylococcaceae), and Bacteroidetes. The composition of the skin microbiota varies between individuals, but *C. acnes* seems to occur mostly at sebaceous sites (on the face, back, and pre-thoracic region), reflecting its ability to survive in anaerobic and lipid-rich conditions. By contrast, *Staphylococcus* and *Corynebacterium* species are mostly found at humid sites, with a more diverse bacterial population occupying dry sites [17][44][45]. *C. acnes* is, by far, the most abundant bacterium in the skin microbiota, and its load does not seem to differ between healthy skin and skin affected by acne. It has been suggested that inflammatory acne is triggered by an imbalance in the skin microbiota associated with the selection of specific types of *C. acnes* [25][45][46]. It has been shown that phylotypes IA-1 are strongly associated with inflammatory acne and acne fulminans. These phylotypes produce high levels of porphyrins, which can promote inflammation [17][18][20][22][38][47]. The population of cutaneous microorganisms should be considered a dynamic feature. Bacteria can interact with each other (*S. epidermidis*—*C. acnes*) and may also be influenced by changes in host characteristics (hormonal disorders, stress, environmental changes), promoting the selection of pathogenic strains of *C. acnes* capable of producing several virulence factors (biofilm, surface proteins) increasing inflammatory capacity [48][49][50]. The skin also reacts to the commensal microbiota, with effects on the immune response and epidermal development, contributing to skin health and disease [51]. Modulation of the population of *C. acnes* strains on the skin, without inducing a negative reaction, could therefore potentially be used in the treatment of microbiome-related diseases [52].

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