Palmieri B, et al., J Clin Immunol Immunother 2021, 7: 069
DOI: 10.24966/CIIT-8844/1000069

HSOA Journal of Clinical Immunology and Immunotherapy

Letter to the Editor

Alive and Inactivated Cutibacterium Acnes: Properties, Functions and Pathogenicity

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Abstract

Cutibacterium acnes (*C.acnes*) is a lipophilic member of the human skin microbiota, usually colonizing the infundibular spaces of the sebaceous glands, lipids particularly rich.

We have tried to summarize in this paper the main biological traits of the alive *C.parvum* strain in a clinical perspective, in order to better clarify and take advantage of the complex interaction between its functional subcellular components and the host cells either into the skin or in the deep organs to achieve or maintain the best healthy conditions.

Introduction

Cutibacterium acnes (*C.acnes*) is a Gram-positive lipophilic member of the human skin microbiota into the lipids filled sebaceous, glands, almost colonizing the infrainfundibular spaces.

More recently, it has also been found in several other organs and tissue sites on epithelial or mucosal linings, such as oral cavity, stomach, lung, urinary tract, and prostate [1-4].

It is thus now debatable whether it is a resident of healthy human skin, or if it can spontaneously saprophytize multiples organs, taking advantage of temporary skin disruption or failure of the host immunosurveillance.

As a matter of fact, *C.parvum* can be a facultative pathogen in the following diseases:

Progressive macular hypolmelanosis (PMH), smooth hypopigmented skin areas rich in sebaceous areas; often the lower back skin is affected, the strains involved belong to phylotype III (SLST type L) of *C. acnes* (*renamed to C. acnes subsp. Elongatum*) [5,6].

Acne fulminans, with heavy ulcerated comedones and spreading infectious symptoms recognizes, but with low evidence the SLST type A (phylotype IA1) in about 60% of patients [7].

Prosthetic infections: more and more studies report the increased detection of *C.acnes* in prosthetic implants in the last years [8-10].

Sonication of periprosthetic granulation tissue to be cultured allowed probably to identify the bacterium with the aid of proper culture techniques acnes, (e.g. cultivation times have often been extended to 14 and even 21 days) [11,12]. Also, the diagnostic mass spectrometry "Matrix Assisted Laser Desorption Ionization-Time of Flight" (MALDI-TOF) as well as the Polymerase chain reaction (PCR) techniques are very much helpful to simplify the identifications o low aggressive strains.

As to the prosthetic joint infections, the 10% find *C.parvum* into the environment, particularly in the shoulder (31-70% of all joint infections) which being contiguous to axillary region rich in sebaceous glands, the men are more exposed to *C.acnes* due to the different anatomic distribution of pilosebaceous units [13,14]. Also spinal instrumentation surgeries bring some more risk of *C.acnes* contamination [15]. The symptoms can be quite weak (mild pain, no fever) and mainly local lasting 2 or more years; mobility of the prosthesis and radiographic signs (osteolytic shadows) are quite late. Prosthetic heart valves and rings, or implantable pacemakers can cause *C.acnes*-associated infective endocarditis (IE) with infectious symptoms and uneasy culture diagnosis.

In breast prosthesis *C.acnes* colonization and biofilm is associated with capsular contracture [16].

Lee et al. [17] confirmed that *C.acnes* was found as the most prevalent microorganism in cases with chronic infection.

In 15% of infections associated with implanted drain cerebrospinal fluid (CSF) tubes to the peritoneum with low fever and inadvertent clinical symptoms [18,19], PCR on CSF (a good, even too much sensitive detection tool) demonstrated *C.parvum* colonization [20].

Generally speaking, only high repeated titres of positive *C.acnes* CFU in a certain number of samples from the infection site state it's causative role, while a single positive culture should be taken with caution.

Native or acquired spine infections, spine surgery, and spine disk degeneration (especially Modic type 1 disc atrophy characterized by fissuring and edema of the endplates) often suggest *C.acnes* as a putative cause, being such infections successfully treated with antibiotic therapy [21].

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Citation: Palmieri B, Manenti A, Vadalà M, Palmieri L (2021) Alive and Inactivated Cutibacterium Acnes: Properties, Functions and Pathogenicity. J Clin Immunol Immunother 7: 069.

Received: November 02, 2021; **Accepted:** November 09, 2021; **Published:** November 16, 2021

Prostate Pathologies

C. acnes has been found in prostate inflammation and prostate cancer [22]. A study from Sweden reported that *C. acnes* was cultured in 60% of the prostate cancer cases (n=100) and in 26% of cancer-free controls (n=50) [4]. The phylotype II (SLST type K) was the most dominant type among *C. acnes* strains obtained from prostatic tissue and 26% of those strains carried an extra chromosomal element [23]. It is debated if they represent contamination/carry-over from the urogenital tract, or if they are colonizers of the tumour tissue (anoxic regions). In contrast a French study has detected only very few *C. acnes* positive samples in their cohort (n=36) [24].

Sarcoidosis

Sarcoidosis is non-necrotizing granulomatous on a systemic background located mainly in the lungs, but also in the skin, lymph nodes, eyes, and other body locations. The most frequent infectious agents of sarcoidosis are primarily *Mycobacterium tuberculosis* and *C.acnes* [25,26].

C.acnes experimentally reproduced sarcoidosis in mice [27,28], hypothetically *C.acnes* trespassed the disrupted skin barrier could colonize intracellularly macrophages like Trojan horses; insoluble immune complexes are then generated, due to a possible genetic individual Th1 cells hypersensitivity against *C. acnes* [26].

Several recent studies have identified *C.acnes* without specific *C. acnes* phylotype in human sarcoidotic granulomas by means of PCR, immunohistochemistry/immunofluorescence staining [29-31].

Epithelioid palisades and giant cells concur to generate the pathologic background of sarcoid nodules which usually remit with different protocols of steroid therapy.

C.acnes Infection and Virulence Factors: Alive Versus Killed *C.parvum*

The virulence factors of *C.acnes*, that will be later presented in details, play a role in the pathogenesis of human diseases, that can be actively or passively secreted, integrated in the cell membrane either attached or embedded: they are Christie–Atkins–Munch-Petersen (CAMP) factors, dermatan-sulfate adhesins (DsAs), lipases, sialidases, hyaluronidases, putative endoglycoceramidases, porphyrins, short-chain fatty acids (SCFAs), cell wall polysaccharide/lipoglycan, and lipoproteins [22,32-38]. We have no evidence from our experience and literature review that subcutaneous injection of the killed *C. acnes* might be involved or promote any bacterium-dependent pathology; on the contrary accordingly with the mice protection experimental study [39], the killed *Corynebacterium* injection, or *C.parvum* sialidase based vaccine is protective against *C. acnes* challenges and it reduces also its inflammatory cytokines burst. In fact, it releases a complex cascade of subcellular components challenging the innate immunity signals and promotes killer lymphocytes and phagocyting cells (monocytes, macrophages dendritic and apc cells) functional enhancement through inflammatory cytokines and interferons release.

This curative approach has effectively been addressed in the past to fight cancer, viral and other pathogenic agents infections and, respectively, it might also prevent infections of the same alive bacterium as successfully previously attempted with *C.parvum* based anti-acnes vaccines.

Morphological Details of *C.parvum (C.acnes)*

Ultrastructurally, it has an unique cell wall made of specific D-alanyne and L-acid diaminopleic rich peptidoglycans and envelope, containing phosphatidylinositol, triacylglycerol, and other common lipids [40].

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, and diaminohexuronic acid [41].

Morphologically, its appearance is somehow rod-shaped and slightly curved measuring 0.4 to 0.7µm x 3 to 5µm, mimicking diphtheroid or coryneform bacteria. It is classified as "aerotolerant anaerobe" because of oxygen detoxifying enzymes [42], oxidative phosphorylation (NAPDH dehydrogenase/complex I, cytochrome *d* oxidase genes, cytochrome *c* reductase, cytochrome *c* oxidase, and FoF1-type ATP synthase), this explains its growth in anaerobic conditions and a much slower growing capacity in aerobiosis [43].

Genetic Details

Genus *Cutibacterium* belongs to a branch of actinobacter that beyond the sin species subgroup encloses also "*Propionibacterium freundenreichii*" a Swiss cheese conditioner producing propionic acids, very much focused in the zootechnical setting because of its bovine rumen functions improving.

The next generation sequencing (NGS) has added a genetic detail about *C.acnes* and the skin microbiome, whose genome was sequenced in its entirety in 2004. It is a single circular chromosome of 2,560,265 base pairs corresponding to 2333 potential genes [32].

During the past decade, several biochemical, transcriptomic, and proteomics analyses have shown that the various phylotypes of *C. acnes* have different inflammatory potentials and express different putative virulence factors.

Summarizing, it has a core genome phylogeny, with 10 lineages (types A-L); the complex phylotype IA1 is further split into five SLST types (A-E) [44]. The other SLST types phylotypes are subdivided as follows: F, IA2; G, IC; H, IB; K, II; L, III (Figure 1).

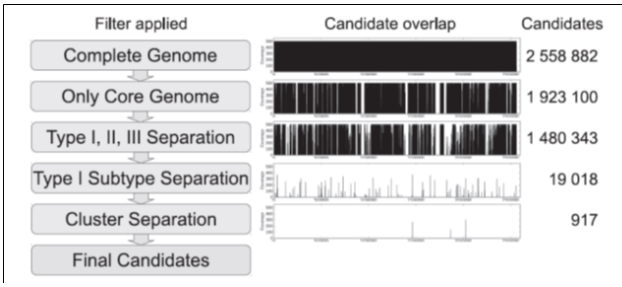

Figure 1: Strategy for the identification of SLST candidates in *C.acnes*. The first column shows the applied filter. The second column indicates the location of the remaining candidate fragments across the genome. The third column gives the number of remaining candidates. Copyright 2014. Published by Plos One, All rights reserved.

The accessory genome of *C.acnes* is not large and encloses a linear and a circular plasmid expressing resistance to macrolides, clindamycin and tetracycline [23,45,46]. 60 other regions outside of the core genome can be identified in the pan-genome of *C.acnes* code

for multiples enzymatic functions [45,47,48], leading to bacteriocins synthesis, resistance to heavy metals and other chemical compounds etc.

C.acnes has been considered a commensal bacterium for a long time, but its implication in various types of infection qualified it as an opportunistic, low pathogenic, pathogen. Several molecular mechanisms enclosed the expression of virulence factors are involved in the adaptation process over the skin or more deeply into the host with facultative damage and triggering innate immune response as well.

C.acnes can release lytic enzymes (metalloproteases, lipases, proteases, hyaluronidases) into its environment, and these enzymes can provide disruption of the follicular epithelium and activation of the immune system [48].

Various putative virulence factor genes have been identified in the *C.acnes* genome. Some may be involved in cell adhesion, whereas others may mediate inflammation, tissue invasion/degradation in the host, and the synthesis of capsule polysaccharides; they are: Lipases sialidases, neuraminidases, endoglycoceramidases, adhesins, thermal shock proteins, CAMP factor, lipases/esterases and porphyrin [32,49]. LIPASES: The genome of *C.acnes* encodes at least 12 putative lipases probably located on the surface of the bacterial membrane [50]. A triacylglycerol lipase, glycerol-ester hydrolase A (GehA), in particular was the first molecule identified as putative *C.acnes* virulence factors, because it produces free fatty acids (FFAs), thereby promoting inflammation.

PUFA: The polyunsaturated fatty acid (PUFA) isomerase from *C. acnes* is a yellow 424-residue monomeric protein that can catalyse the isomerization of conjugated linoleic acid (CLA). CLA and its isomers regulate several functions in humans and are present in low levels in food [51].

Hyaluronate lyase (HYL) degrades hyaluronic acid (HA) and other glycosaminoglycans (GAG), such as chondroitin-4-sulfate, chondroitin-6-sulfate, and dermatan sulfate, present in the extracellular matrix of the epidermis and dermis. It is a virulence factor promoting the spread of inflammation through the extracellular matrix (ECM) depolymerization which facilitates the spread of infectious agents. HA degradation metabolites by HYL are also medium growth factors and proinflammatory compounds as well.

Glycosidase enzymes break down glycolipids and glycoproteins and are subdivided in 2 groups: 1) Exo- and endoglycosidases, responsible for hydrolysing neutral sugars; 2) Sialidases, break down electron negative the neuraminic acid or sialic acid: Sialidases hydrolyses sialic acid from sialo glycoconjugates.

The *C.acnes* genome contains three genes encoding highly immunogenic sialidases/neuraminidases that increase pathogenicity of the *C.parvum* strains.

Sortases are covalent linking proteolytic enzymes degrading adhesion factors, to the cell walls of Gram-positive bacteria.

Porphyrins are fluorescent molecules produced by both eukaryotic and prokaryotic cells. Coproporphyrin III is present in large amounts in acne lesions [52], and type I *C.acnes* strains produce significantly more porphyrins than other phylotypes.

Biofilms are an extracellular matrix melting polysaccharides, proteins, and/or extracellular DNA produced endogenous and exogenously by the bacteria [53].

The *C.acnes* biofilm contains mostly poly-β (1-6)-N-acetylglucos amine (PNAG) polysaccharides, proteins, including the GroEL chaperonin, the elongation factors EF-Tu and EF-G, and many enzymes.

Studies of a polymicrobial biofilm mixing *C.acnes* and *Candida albicans* have shown that the latter has a protective effect on the former, reducing by 40% the lethality of *C.acnes* strains [54].

Sometimes, *C.acnes* colonizes human bone marrow-derived mesenchymal stem cells switching from commensal lifestyle to opportunistic pathogen, by increasing biofilm formation [55].

RoxP, the radical oxygenase of *C.acnes*, reduces free radicals enzymatically. This ROS-scavenging enzyme was purified from *C. acnes* for the first time in 2016. It is present only in *C.acnes* and is secreted into the supernatant culture. RoxP has recently been shown to protect skin cells against oxidative stress [56], RoxP is currently thought to help *C.acnes* to survive in oxygen-rich environments, such as the skin surface [57].

DsA1 Nine putative adhesion protein genes have been identified in the *C.acnes* that codify the molecular microbic surface components recognize adhesive molecules of the matrix (MSCRAMM). These adhesion proteins are truly pathogenic take part in biofilm formation, genome. One of these genes encodes the DsA1 protein, both secreted and cell-wall anchored, which binds dermatan sulphate [58] and has also been characterized as a fibrinogen-binding protein. It appears to be highly glycosylated and contains an N-acetylgalacosamine (GlaNAc) residue.

Fibrinogen adheres to the surface of *C.acnes* and mediates platelet aggregation [59]. DsA1 therefore appears to be an important surface protein expressed by *C.acnes* and further investigations of its role as a virulence factor are required.

CAMP Factors: are toxin proteins secrete or attached to the cell surface that form pores in host membranes, leading to host tissue damage and stimulating the innate immune system through CAMP factors. CAMP1 and CAMP2 are the predominant CAMP factors produced by *C.acnes* strains, the CAMP1-TLR2 interaction is different between phylotypes IA, II, and III (Figure 2). CAMP1 also displays a high degree of genetic polymorphism, with 14 strain-specific amino acid changes inducing strong inflammation and the production of a CAMP1 factor strongly recognized by TLR2 [60].

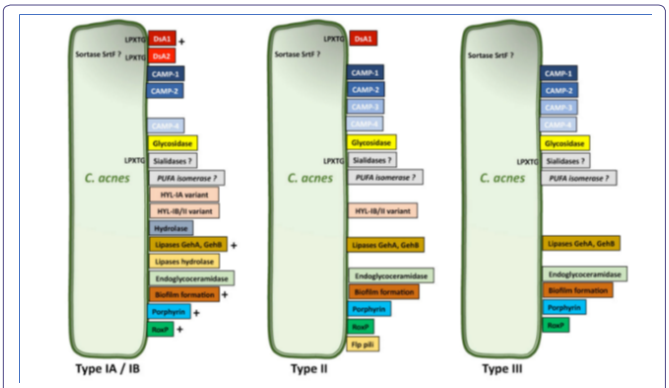

Figure 2: Differential expressions of virulence factor by *C.acnes*. Copyright 2021 MDPI. Published by Microorganisms, All rights reserved.

C.acnes activates the innate immune recognition system mediated via Toll-like receptor (TLR) 2 TLR2 and Toll-like receptor (TLR) 4 and activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) and MAPK signaling pathways, and the NLRP3 inflammasome pathway. The following molecules are *in vitro* and *ex-vivo* (acne lesions) secreted by keratinocytes, sebocytes fibroblasts and mononuclear cells: IL-1α/β, IL-6, CXCL8/IL-8, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, β-defensin-2 (hBD-2), matrix metalloproteases (MMPs). These pro-inflammatory molecules are also produced *ex vivo* in acne lesions [61-64]. Furthermore extracellular proteases of *C. parvum* activate the PAR-2 signalling proinflammatory pathways through IL-1α, CXCL8/IL-8, TNF-α, hBD-2 and MMPs [65].

Also the production of oxygen species (ROS) by keratinocytes due to *C.parvum* stimulation, mediated by the cytoplasmic H2O2, conversion of oxygen radicals out of the cells which is quickly neutralized into water by the GSH/Gpx system; to amplify the inflammation the role of the available scavenger receptor CD36, induces CXCL8/IL-8 production independently of the TLR2-signaling [66].

C.acnes-induced ROS also stimulate the NF-κB and MAPK and macrophage mediated iNOS/NO and Cox2/PGE2 [67] and the type I interferon (IFN-I) pathway production via the cGAS-STING pathway in macrophages [68], due to matrix metalloproteinase (MMP) increased expression on human fibroblasts (MMP2, specifically).

C.parvum takes part to post-phlogistic tissue remodelling and scar induction [69].

Moreover, the presence of activated T helper 1 (Th1) lymphocytes has been shown in early inflamed acne lesions [70], and a Th17-related response mediated by the activation of CD4+ T cells, leading to the generation of Th17 cells and the secretion of IL-17, whose level appears to be higher with acnes-related strains [71,72] (Figure 3).

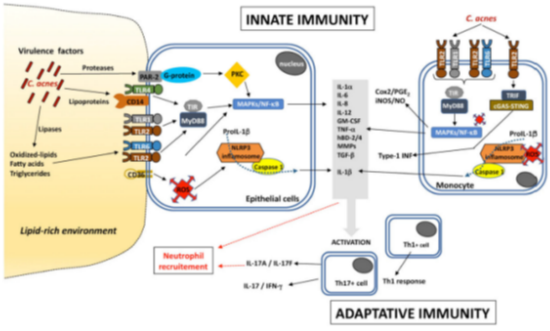

Figure 3: Inflammatory pathways induced by *C.acnes*. Copyright 2021 MDPI. Published by Microorganisms, All rights reserved.

Discussion and Conclusion

We have tried to summarize in this paper the main biological traits of the alive *C.parvum* strain in a clinical perspective, in order to better clarify and take advantage of the complex interaction between its functional subcellular components and the host cells either into the skin or in the deep organs to achieve or maintain the best healthy conditions.

The relatively recent recognized pathology of this commensal, even if facultative, is not infrequent and it is matter of some concern, due to the general impending widespread antibiotic resistance.

The therapeutic approach with inactivated *C.parvum* strain has a long standing history in cancer immunology and infectious diseases; surprisingly many of the innate immunity and phlogogenic *in vivo* properties are preserved even within the killed bacterium, and the complexity of its ultrastructural morphology and biochemistry gives us a strong rationale to follow up using the inactivated *C.parvum* as a whole entity, without separating and exploding each different biochemical components, with selected biologic properties.

The plainly killed *C.acnes* subcutaneous injection in fact differently than vaccines, does not require adjuvants integration to be effective, it has usually a very safe and easy administration and probably it might be a self-limiting approach and treatment to the alive pathogenic strains infections in the clinical setting.

Funding

Funding information is not applicable/No funding was received.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

Data Transparency

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics Approval

Approval was obtained from the local ethics committee.

Author's Contribution

The authors confirm contribution to the paper as follows: study conception and design: MV; data collection: AM, Proof, writing BP.

Consent to Participate

The participant has consented to the submission of the case report to the journal. Each Patient signed informed consent regarding publishing his data and photographs.

Consent for Publication

Each patient given its consent for the publication of identifiable details, which can include photographs and/or case history and/or details within the text ("methods, results") to be published in the above Journal.

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