

Dual role of *Cutibacterium acnes* in acne vulgaris pathophysiology



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ABSTRACT

Acne vulgaris (AV) is the most common and multifactorial skin disease in adolescents affecting the pilosebaceous unit that involves hormonal imbalance, increased sebum production, and bacterial colonization, which causes both physical and psychological disorders. *Cutibacterium acnes* is considered one of the key contributing factors even though many *Cutibacterium acnes* colonies are on healthy skin. *Cutibacterium acnes* induces lipogenesis and production of sebum. Through its production of porphyrins, it may act as a catalytic agent in squalene oxidation that is comedogenic, thus aggravating comedogenesis. We review the dual role of *Cutibacterium acnes* to provide an understanding of the pathophysiology of acne vulgaris.

Keywords: acne vulgaris, *Cutibacterium acnes*, comedogenesis, inflammatory and non-inflammatory process

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INTRODUCTION

Acne vulgaris (AV) is a multifactorial disorder of the pilosebaceous unit involving some main processes like hormonal imbalance, increased sebum production, and bacterial colonization, which causes physical and psychological disorders. It is the most common skin disease as it is ubiquitous.^{1,2} Acne vulgaris affects more than 85% of adolescents, which about 90% of young boys and 80 % of young girls in all ethnic groups affect AV.^{3,4} Early-onset acne is more common in women than men since puberty is more apt to occur in women than in men.⁵ Acne vulgaris affects female persons through all decades of their adult life.⁶ Although the exact pathogenesis of acne is still unknown, *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) is considered one of the key contributing factors. Classically, it is known that four main factors contribute to the development of acne, namely increased sebum production, follicle hyperkeratinization, skin bacterial colonization, and inflammation.^{7,8} Micro-comedones formation is an early subclinical sign of AV due to hyperproliferation of the follicular epithelium. These lesions then develop into non-inflammatory

comedonal lesions or inflammatory comedones, which have two specific types: closed or opened comedones.⁹ The objective of this review is to conceive the pathophysiology of AV by focussing on the dual role of *Cutibacterium acnes*.

ANATOMY AND PHYSIOLOGY OF SEBACEOUS GLAND

Anatomically, the sebaceous glands are formed from multi-lobular structures originating from the epithelium which are directly connected to the common excretory tract known as the sebaceous duct. Sebocytes are the differentiated epithelial cells that produce lipids. At the same time, the sebaceous ducts are covered by undifferentiated keratinocytes. They are associated with hair follicles lined with complex squamous epithelium, where there is a basal cell layer consisting of small nucleated cuboid-shaped sebocytes on edge and has a high level of mitosis.¹⁰ The sebaceous glands emit lipids through the disintegration of whole cells, a process known as holocrine secretion. The holocrine secretion carried out by sebaceous gland cells does not occur mechanically through increased cell volume, as considered previously.

However, instead of the lysosomal DNase2 mode mediated by specific cells, programmed cell death differs from apoptosis, necroptosis, and cornification.¹¹ The process of sebocyte maturation is accompanied by a certain cell death process called holocrine secretion of sebum, consisting of various mixtures of lipids. This occurs due to the complete sebocytes disintegration into the follicular duct in the pilosebaceous unit.¹² Increased sebum secretion is a significant factor in the pathophysiology of acne vulgaris. In general, AV patients have a higher sebum level than normal individuals, which is closely related to the degree of AV severity. Excess sebum production, as well as sebum modification qualitatively and quantitatively, can occur in AV patients. The ingredients of human sebum mostly triglycerides, wax esters, and squalene. The wax ester is formed from the synthesis and metabolism of fatty acids. These lipid types are composed of long-chain fatty acid and long-chain fatty alcohol due to the reduction of fatty acid due to the chemical processes of various esters. The process of wax ester biosynthesis is generally applicable to all sebaceous glands and is a biomarker of functional and differentiation of sebocytes.^{12,13} Meanwhile, the formation

of a smooth acidic acid mantle (between pH 4.5 and pH 6.0) by the sebaceous glands and is a chemical barrier system found on the skin's surface against various pathogenic microorganisms such as bacteria or viruses to prevent them from penetrating the skin layers. The presence of lipids produced by the sebaceous glands also plays an essential role in maintaining skin integrity. Sebaceous glands lipids collaborate with epidermal lipids so that the epidermis becomes the first line skin barrier.¹⁴ In addition, the lipid compounds produced by the mixture of keratinocytes and sebum membrane lipids are called skin surface lipids. Squalene produced from cholesterol metabolism secreted by the sebaceous gland and α -tocopherol (vitamin E) will function as an antioxidant on the skin surface.^{15,16} Another essential role of the sebaceous glands is in the regulation of the innate immune system. Various chemical compounds produced by the sebaceous glands such as various peptides, neuropeptides, sapienic acid function as antibacterial or antimicrobial. As mentioned earlier, the sebaceous glands function like an endocrine organ, so it can be understood that there is a relationship between stress and AV severity due to the induction of the release of hormone corticotropin.¹⁷

MICROBIOME ENVIRONMENTAL

In the past few decades, the role of the microbiome has become the focus of studies in various skin disorders, including AV. The microbiome is a collection of microorganisms and their genetic material content. A microbiome provides genetic diversity, modulates the symptom and signs of disease, and influences the metabolic processes and immunomodulatory competence, which are dynamic. On the skin, the microbiome is an easy target for intervention both diagnostically and therapeutically.¹⁸ Skin is the largest organ in the human body. Various beneficial microorganisms, both bacteria, fungi, or viruses, have a role as a physical barrier in preventing the invasion of pathogenic microorganisms.¹⁹ The most dominant skin microbiome is bacteria, more than 40 genera have been identified, and it is the most researched. Four phyla can be identified as the bacterial microbiome

on the skin: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes.^{7,20} A study conducted by Grice et al. found that more than 62% of microorganisms could be isolated from the skin microbiome: Corynebacteria (22.5%; Actinobacteria), Propionibacteria (23.0% Actinobacteria), and Staphylococci (16.8%; Firmicutes).²¹ The physiology of the cutaneous sites affects the microbial community so that microbial colonization will be different in the skin with a moist, dry, and oily or sebaceous microenvironment. Propionibacterium dominates the sebaceous microenvironment because of its lipophilic nature. Meanwhile, Staphylococcus and Corynebacterium are more commonly found in moist areas of the skin, such as the folds of the elbows and feet. The microorganism composition differs from one individual to another individual and varies depending on the body site.²²

THE BIOLOGICAL ASPECT OF *Cutibacterium acnes*

Orla-Jensen first described the genus Propionibacterium in 1909. This bacterium produces propionate acid as the final product of fermentation. One of the Propionibacterium species called Propionibacterium acne can cause common skin disease, namely acne vulgaris, and can contaminate human samples.^{23,24} Taxonomic changes of the reclassification of the genus Propionibacterium to Cutibacterium are based on genomic evidence. This proposal is consistent with the 16S rRNA gene sequence tree and allows new species to be assigned by 16S rRNA gene sequence homology. The proposed changes are consistent with species habitat, genome topology, DNA G + C content, and peptidoglycan composition.²⁴ *Cutibacterium acnes* (formerly known as Propionibacterium acnes) is a rod-shaped, pleomorphic, gram-positive, anaerobic, non-spore-forming bacteria belonging to the phylum of Actinobacteria. Some of these bacterial species are normal flora on the skin, oral cavity, gastrointestinal tract and are usually non-pathogenic. *Cutibacterium acnes* can be isolated using culture media such as blood agar, brucella, chocolate, or brain heart infusion under

aerobic, to microaerophilic environment.²⁵ *Cutibacterium acnes* density is high on the face and upper trunk area. Body site with fewer sebaceous glands indicates low *Cutibacterium acnes* density as well. On the scalp and face, the density of *Cutibacterium acnes* is estimated to be 10^5 organisms per cm.²⁶ As normal flora, *Cutibacterium acnes* is rarely associated with invasive skin infection, soft tissue, and cardiovascular system. In certain conditions, *Cutibacterium acnes* can be pathogenic.²⁷ For some communities, acne vulgaris, is generally caused by *Cutibacterium acnes* bacteria. Various media promotion of cosmetic products related to acne vulgaris and prescription of antibiotics by doctors have confirmed this theory. There is still an inaccurate understanding of acne vulgaris with *Cutibacterium acnes* infection, even though many *Cutibacterium acnes* colonies are on healthy skin.^{28,29} Based on the phylotype, *Cutibacterium acnes* is divided into six strains: IA1, IA2, IB, IC, II, and III. Each phylotype has a different role in the manifestation of skin disorders. *Cutibacterium acnes* type IA1 predominantly causes AV.^{30,31}

Microcomedones formation is an early sign of acne vulgaris, a subclinical lesion accompanied by hyperproliferation of the follicular epithelium. Sebum production facilitates microcomedones during desquamation to maintain the homeostasis between new keratinocyte cells and the desquamation process. However, there is an imbalance that causes excessive accumulation of keratinocytes in the pilosebaceous duct.⁹ The formation of microcomedones by sebaceous follicles cause *Cutibacterium acnes* (formerly *Propionibacterium acnes*) to thrive due to a lipid-rich anaerobic microenvironment. The presence of *Cutibacterium acnes* induces lipogenesis.³² *Cutibacterium acnes* colonization in the face area triggers the production of sebum as well.³³ As a physical skin barrier, sebocytes produce skin surface lipids, while innate immune cells enable recognizing patterns and enhancing the immune response. *Cutibacterium acnes*, through its production of porphyrins, may act as a catalytic agent in squalene oxidation. Oxidized squalene has been comedogenic in the rabbit ear

model, which may be another possible mechanism by which the organism can be involved in comedogenesis. It has also been proposed that *Cutibacterium acnes* biofilm may act as a biological glue causing adhesiveness of keratinocytes, thus aggravating comedogenesis.³⁴ Several studies have found evidence that the collaboration of the *Cutibacterium acnes* triggers the expression of HBD2 and pro-inflammatory cytokines TNF- α , IL-1 α and chemokine CXCL-8 in the human sebocyte cell line.^{35,36}

The skin's immune system consists of innate and adaptive immune components. The innate immune system has certain motives such as proteins, lipids, nucleotides, and other metabolites, with a vast spectrum of pathogens. The adaptive immune system is based on the formation of antigen receptors or antibody diversity, which in principle provides immunological memory through differentiation, expansion of antigens, and persistence of a long life span antigen-specific lymphocytes.³⁷ Many studies have shown the mechanism of action of *Cutibacterium acnes* in immune system regulation related to the pathophysiology of AV inflammation. This immune response triggers the inflammation process in AV. The primary activation of the innate immune system by *Cutibacterium acnes* goes through three mechanisms: activation of complement both classical

and alternative pathways, cytokine-induced, and Toll-like Receptor.³⁸

The epidermal layer is a frequent route for foreign intruders, antigens, and pathogens. Meanwhile, the complement system is a fundamental part of the innate immune system, which plays a crucial role in host defense against various pathogens, such as bacteria, viruses, and fungi.^{39,40} The involvement of complement in AV pathophysiology is indicated by the accumulation of C3 in AV lesions. The most frequent finding is perivascular granular or linear pilosebaceous basement membrane zone deposition of C3b in both non- and inflammatory acne lesions. In early non-inflamed acne lesions, C3b deposition preceded the influx of mononuclear cells, while inflamed lesions showed both C3b deposition and mononuclear inflammation.⁴¹ In addition, the carbohydrate antigen in the cell walls of *Cutibacterium acnes* will stimulate the antibody. The antipropiobacterium antibodies increase the inflammatory response by activating the complement and initiate the inflammatory process.⁴²

As previously described, microcomedones are the first subclinical AV lesions developing from the pilosebaceous unit, which can evolve into the blackhead and white head comedones and subsequently become inflammatory lesions such as papules, pustules, nodules, and cysts. The IL-1

cytokine release triggered by keratinocyte damage due to an imbalance of the sebaceous gland precedes AV lesions. IL-1 is mainly produced and released by non-inflammatory keratinocytes.⁴³ Although the formation of microcomedones is not accompanied by the accumulation of pro-inflammatory cytokines. It does not mean that there is no inflammatory process in the initial AV lesions. The study conducted by Do et al. showed that at the time of microcomedones formation, the inflammatory process in AV has already begun.⁴⁴ Several studies have shown that IL-1 is found in vivo in various comedones and sebaceous follicles' walls. Conversely, an increase in IL-1 expression can trigger the formation of microcomedones and comedones.⁴⁵ Study by Cappel et al. (2005) demonstrated a relationship between serum IGF-1 level and the number of acne lesions in young female patients.⁴⁶ *Cutibacterium acnes* also contributes to the inflammatory nature of acne by inducing monocytes to secrete pro-inflammatory cytokines including TNF- α , IL-1 α , and IL-8.⁴⁷

Toll receptors were first identified in *Drosophila* as an integral part of the innate immune system and have been shown to play a significant role in antimicrobial defense in adult flies.⁴⁸ Toll-like receptors (TLR) are crucial players in the innate immune response to microbial invaders.^{49,50} These receptors are expressed on immune cells, such as monocytes, macrophages, dendritic cells, and granulocytes. *Cutibacterium acnes* induces inflammatory cytokines in monocytes, provides evidence of innate immune response through a TLR2-dependent pathway. The expression of TLR2 in acne lesions indicates that activation of TLR2 contributes to inflammation at the site of disease activity. Toll-like Receptor involvement in acne vulgaris goes through three mechanisms: 1. *Cutibacterium acnes* induces the IL-12 p40 promoter 2. *Cutibacterium acnes* triggers monocyte cells to express IL-12 and IL-8, and 3. Expression of TLR 2 due to induction release IL-6 in pilosebaceous follicles.⁴⁷

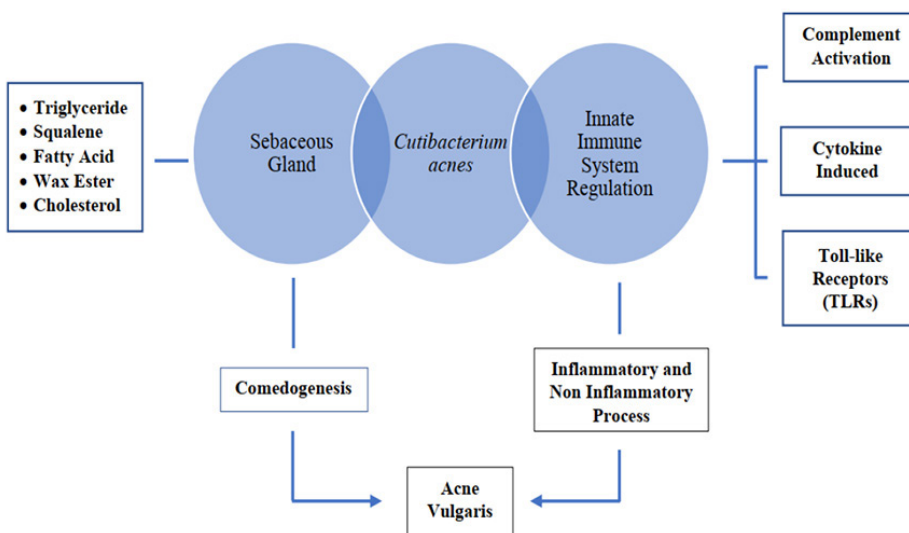


Figure 1. Dual role of *Cutibacterium acnes* in acne vulgaris with comedogenesis and Inflammatory and non-inflammatory process.

CONCLUSION

Cutibacterium acnes has a dual role in the pathophysiology of acne vulgaris, namely

triggering comedogenesis by activation of the sebaceous glands through the action of lipogenesis on sebum products and the innate immune system mechanism, either complement activation, the release of various cytokines produced by keratinocytes, or activation of other cytokines from immune cells such as monocytes, macrophages, granulocytes via Toll-like receptors.

DISCLOSURE

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All authors contributed to drafting, designing, and preparing the manuscript.

Ethical Statement

Not applicable

Conflict of Interest

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