



## REVIEW ARTICLE

# Virulent Acne Biofilms Offer Insight into Novel Therapeutic Options

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**Abstract:** Acne vulgaris is a disease of the pilosebaceous unit that may manifest as either noninflammatory or inflammatory skin lesions. The microcomedone theory suggests that the first step in the pathogenesis of acne vulgaris is the noninflammatory comedone. The comedone is a collection of keratin and sebum that is trapped within the pilosebaceous unit due to hyperproliferation of keratinocytes in the follicular lining. The biofilm produced by *P. acnes* bacteria promotes the formation of a comedone by acting as a biological glue that prevents expulsion of the hyperkeratotic plug. In addition to its adhesive properties, the biofilm has virulence factors contributing to the pathogenicity of *P. acnes* in acne vulgaris. With further investigation and a better understanding of the *P. acnes* biofilm, new therapeutic options for acne vulgaris can be made available. By targeting the *P. acnes* biofilm, treatment can be made more effective and precise, without the concern of side effects seen in currently available acne medications.

**Keywords:** Acne, Comedonal acne, Comedone, *P. acnes* biofilm, Biological glue, Virulence factors.

## 1. INTRODUCTION

Acne vulgaris is a disease of the pilosebaceous unit. The etiology of acne has been studied extensively, and the pathogenesis is considered to be multifactorial, involving increased sebum production secondary to androgens, follicular hyperkeratinization, and colonization of the skin with *Propionibacterium acnes* [1]. Acne vulgaris may manifest as either noninflammatory or inflammatory skin lesions; however, inflammation is believed to occur secondary to an inciting event [2, 3]. The microcomedone theory suggests that the initial phase of acne formation is comedogenesis, which involves androgens, hyperproliferation of keratinocytes in the follicular lining, and buildup of keratin and sebum within the pilosebaceous unit [1, 4].

Androgens, mainly testosterone and 5- $\alpha$ -dihydrotestosterone, bind to nuclear receptors in responsive sebocytes and trigger a cascade of events leading to sebum production within the pilosebaceous unit [5]. Excess sebum can accumulate due to increased levels of androgens and/or due to sebaceous glands with increased sensitivity to the effects of androgens [5]. Simultaneously, hyperproliferation of follicular keratinocytes entraps the sebum within. Given that keratinocytes, like sebocytes, have the machinery to metabolize androgens, hormonal imbalances may contribute to ductal hyperkeratinization as well [6]. Alternatively, follicular keratinocytes may accumulate secondary to abnormal desquamation due to increased proliferation of the deep basal keratinocytes or unregulated differentiation of the keratinocytes [7 - 9]. Other theories explaining the evolution of comedones suggest that keratinocyte proliferation is a response to variations in sebum composition, such as lower levels of linoleic acid [10], or that hyperkeratinization may be a response to the secretion of proinflammatory cytokines such as IL-1 that is induced by the presence of *P. acnes* on the skin [11]. Ultimately, the interaction of these factors and synchronized processes lead to the plugging of sebum and debris within the pilosebaceous unit. Clinically, this presents as a non-inflamed lesion or comedone.

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This report discusses the *P. acnes* biofilm and its role in comedogenesis. We address the virulent properties of the biofilm that contribute to the pathogenesis of acne vulgaris and encourages that this biologically active component be further investigated as a therapeutic target. By targeting the *P. acnes* biofilm, acne vulgaris can be treated in its early phases. Furthermore, the treatment of acne vulgaris can be made more effective and precise, without the concern of side effects seen in currently available acne medications.

## 2. DISCUSSION

The biofilm concept in acne vulgaris offers an alternative explanation to the pathogenesis of the microcomedone [12, 13]. A biofilm is a collection of microorganisms, or microcolonies, encased within a wall of polysaccharides and proteins that are secreted by the organism once it has adhered to a surface [12]. Bacteria within a biofilm are defined as sessile. Compared to the planktonic form, sessile bacteria are in a distinct metabolic state [14] and can change phenotypes related to behavior, gene expression, and protein synthesis [15, 16]. The ability of *P. acnes* to produce biofilms on implant biomaterials was first shown in 2003 [17]. This phenomenon was supported by genome mapping of *P. acnes*, which revealed genetic machinery enabling the organism to synthesize a polysaccharide capsule [18]. It has since been demonstrated that *P. acnes* can adhere to and form an extracellular polymer on various biomaterials *in vitro* [14, 19, 20], as well as *in vivo* [20]. Similarly, immunofluorescence microscopy has revealed that acne-affected skin has an increased frequency of biofilm production [21].

The presence of biofilm within the pilosebaceous unit has been suggested to act as a biological glue that increases the cohesiveness between keratinocytes and provides a medium for *P. acnes* organisms to remain adhered to the follicular epithelium [13]. Thus, after hyperproliferation of keratinocytes from the follicular lining, the biofilm ultimately may be responsible for the formation of the comedone. The strong cohesive forces of the glue-like secretions prevent the hyperkeratotic plug from being expelled through the epidermal surface [1, 13]. Instead, as the comedone expands with debris, its immunogenic contents can be released into the surrounding dermal tissue [13]. This activates Toll-like receptors on keratinocytes and sebocytes and induces the production of proinflammatory cytokines [22, 23], leading to the development of inflamed pustules and papules.

The *P. acnes* biofilm is important not only because it promotes comedogenesis, but also because it increases the pathogenicity of the organism. *P. acnes* is a commensal organism of healthy skin and is considered a resident of the pilosebaceous unit [24]. Though the presence of *P. acnes* is involved in the etiology of acne vulgaris, there is no direct correlation between the number of bacteria and severity of acne [12]. Synthesis of biofilm by *P. acnes* may enable the commensal organism to transition into a pathogen. The ability to form biofilm can differ based on the isolate and *P. acnes* phylotype, designated as types IA, IB, II, and III [21, 25].

In one study, *P. acnes* biofilms in acne-affected sebaceous follicles were composed of *P. acnes* phenotypes IA and II and shown to express Christie-Atkins-Munch-Peterson (CAMP) 1 factor [21]. CAMP factor is toxic to keratinocytes and macrophages and can produce an inflammatory reaction *in vivo* through the binding of Toll-like receptors [26, 27]. Dermatan Sulfate-Binding Protein (DSBP), which recognizes the host proteins human fibrinogen and dermatan sulfate, is also expressed in *P. acnes* biofilms of specific phylotypes on the acne-infected skin [21]. This immunoreactive protein mediates the attachment of *P. acnes* bacteria to host cells and improves the survival capacity of *P. acnes* [28, 29]. Like DSBP, other adhesion proteins may exist within the *P. acnes* biofilm that promote irreversible attachment of the bacteria and cause acne to progress into a chronic disease. Bacterial lipases also are upregulated in *P. acnes* biofilm *in vitro* [19]. Increased levels of free fatty acids, secondary to the hydrolysis of triglycerides, have been shown to enhance the adherence of *P. acnes* bacteria and their ability to colonize the pilosebaceous unit [30]. *In vivo*, free fatty acids are comedogenic and can activate the inflammatory response [31, 32].

Within a biofilm, organisms are equipped with protective strategies that are certainly impressive. Macrocolonies can live in an intimate milieu within a glycocalyx polymer wall that allows organisms to withstand stress. In addition to the physical barrier of the biofilm, bacteria can slow their rate of growth and upregulate proteins like multi-drug resistance pumps to block the effects of antimicrobial agents [16]. Activation of "Quorum sensing," [16] a form of intercellular communication utilizing molecules called autoinducers, enables the coordination of gene expression and promotes adaptation to environmental change [33, 34]. Mature *P. acnes* biofilms *in vitro* have been shown to have levels of autoinducer-2 that are three times higher than those in planktonic bacteria [19]. Though the composition of *P. acnes* biofilms has yet to be fully elucidated, it is reasonable to believe that at least twenty proteins, possibly with virulent properties and protective functions, are secreted extracellularly by *P. acnes* [35]. These findings explain how *P. acnes* can become pathogenic and why sessile *P. acnes* organisms are more resistant to antimicrobials than their planktonic

counterparts [19, 36].

Available therapies for acne can be very effective, however, failed treatments are common and these medications are not entirely harmless. For instance, topical antimicrobials have an associated risk of generating highly resistant strains of bacteria, and so they are not recommended as monotherapy and should be combined with bactericidal agents like benzoyl peroxide. Furthermore, antibiotics lack specificity and can disrupt the microflora of the body by affecting other commensal organisms [37]. Topical retinoids such as adapalene, tretinoin, isotretinoin, and tazarotene are unplugging agents that normalize the hyperproliferation of keratinocytes, increase cell turnover, and enhance the desquamation of follicular keratinocytes. Though these topicals can be potent, reactions such as irritant dermatitis can often become a limitation to its use. Safety also becomes an issue with oral medications such as hormonal therapy and isotretinoin, which are contraindicated in certain populations and have systemic side effects requiring close follow up with extensive workup.

By targeting proteins and molecules within the *P. acnes* biofilm, treatment can be made precise with fewer adverse effects. Currently, few treatment modalities have been suggested to successfully target the *P. acnes* biofilm. CAMP factor, a component of the *P. acnes* biofilm, recently was identified as a therapeutic target. Passive immunization with vaccines neutralized CAMP factor and suppressed the inflammatory response in mice, without affecting the colonization of other harmless organisms [37].

Several agents that are frequently used in acne vulgaris have been shown to prevent the formation of and shrink the *P. acnes* biofilm *in vitro*. Antimicrobials such as 0.5% erythromycin, 2% salicylic acid, 0.1% triclosan, 0.5% minocycline, and combinations of such agents, including 5% benzoyl peroxide and 0.5% erythromycin, and 5% benzoyl peroxide and 1% clindamycin, were observed to cause a significant reduction in biofilm mass [19]. Similarly, the antimicrobial Decanediol led to reductions in mature biofilm mass, and furthermore, also inhibited the formation of biofilm by bacteria in a dose-dependent manner [38].

Additionally, few natural and chemical compounds have been isolated and discovered to have activity against the *P. acnes* biofilm. The combination of ellagic acid (250  $\mu\text{g ml}^{-1}$ ), a polyphenol found in many plants, and tetracycline (0.312  $\mu\text{g ml}^{-1}$ ) inhibited biofilm secretion *in vitro* and *in vivo* in *C. elegans* [39]. Myrtle extract from the plant *M. communis* revealed anti-biofilm properties when used at concentrations between 0.1% and 0.001% *in vitro* [40]. Likewise, icariin, resveratrol, and salidroside, which are active compounds in several plant extracts, also have demonstrated antibiofilm effects against the *P. acnes* biofilm [41]. One study showed that two thiazolidinedione derivatives, (Z)-5-octylidenethiazolidine-2,4-dione (100  $\mu\text{mol l}^{-1}$ ) and (Z)-5-decylidenethiazolidine-2,4-dione (100  $\mu\text{mol l}^{-1}$ ), known to be quorum sensing inhibitors, led to significant reductions in *P. acnes* biofilm mass, likely by mechanisms that affect biofilm development after its initial adherence to surfaces [42]. Another clinical study with 64 patients, tested a topical agent comprised of a chelating agent, buffer, isopropyl alcohol, and surfactant, specifically designed to target the *P. acnes* biofilm. By mechanisms believed to destroy bonds within the extracellular polysaccharides enveloping biofilms, this agent effectively reduced acne lesions and symptoms in patients [43].

## CONCLUSION

We believe that the inciting event for acne vulgaris involves the *P. acnes* biofilm, which is a key player in the virulence of the organism. Inhibition of biofilm synthesis can prevent acne vulgaris at an early stage, prior to the development of comedones and their progression into inflammatory papules and pustules. With a better understanding of the *P. acnes* biofilm structure, composition, and functions, new treatment strategies for acne vulgaris can be established.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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