doi:10.36849/JDD.9313R1e

 BRIEF COMMUNICATION Journal of Drugs in Dermatology

A Review of the Relationship Between *Cutibacterium acnes*, Biofilms, and Keratosis Pilaris

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INTRODUCTION

Keratosis pilaris (KP) is a very common, benign dermatological disorder with characteristic small keratotic papules in a folliculocentric pattern.[1] This paper aims to explore the relationship between KP and *Cutibacterium acnes* (*C Acnes*). It will also explore the role of *C Acnes*'s biofilm in the formation of the biological glue that sticks keratin together in KP.

Overview of Keratosis Pilaris

KP includes a group of follicular disorders, with KP simplex being the most common.[2] KP affects approximately 40% of the population and typically begins during childhood and is most severe during adolescence. KP more commonly affects females. In fact, approximately 80% of adolescent females are affected.[2]

KP is a benign dermatologic condition in which there are multiple hyperkeratotic, folliculocentric papules. The papules are primarily on the extensor surface of the arms, thighs, and buttocks. The first noticeable symptom of KP is the development of rough, folliculocentric keratotic papules that are light pink or flesh colored and contain a finely oiled brittle hair. They typically measure 1–2 mm in diameter. The papules are said to resemble goosebumps. Patients also describe the papules as resembling the texture of sandpaper.[2]

Erythema is sometimes also associated with KP, but when present, it is typically mild and localized to the perifollicular skin. KP can also occasionally be associated with pruritus, which usually worsens in the winter and improves in the summer. Additionally, KP can be associated with ichthyosis vulgaris, palmar hyperlinearity, and atopic dermatitis.[2]

Histologically, KP demonstrates a keratin plug that fills the infundibulum of the hair follicle and extends above the skin surface. These plugs can lead to atrophy of the follicular wall, sebaceous gland, and arrector pilorum atrophy.[2]

The basis of KP is excess keratin production. This excess keratin builds up and surrounds hair follicles, trapping the hair beneath the keratin debris. This leads to the formation of follicular papules. While the cause of this is not entirely understood, inherited mutations in the FLG gene and ABCA12 gene have been linked to the pathogenesis of KP.[2] Filaggrin is an epidermal structural protein that allows for aggregation of keratin filaments into keratocytes. This protein can be hydrolyzed into osmotically active amino acids. These amino acids can then provide the skin with moisture, photoprotection, and acidification. Therefore, variations in the filaggrin protein, caused by mutations in the FLG gene, lead to abnormal keratinization, reduced moisture, and alkalinization of the skin. This mutation can also lead to xerosis cutis, dysfunction in the epithelial barrier, bacterial growth, and inflammation.[2]

Another genetic mutation implicated in KP is the ABCA12 mutation.[2] The ABCA12 gene expresses an ATP-binding cassette (ABC) that allows for lipid transfer between the lamellar granules and the granular layer keratinocytes. A mutation in this gene can disrupt the lipid transport and desquamation, which can lead to the dry and solid lesions associated with KP.[2]

Additionally, sebaceous gland abnormalities, hyperandrogenism, obesity, decreased insulin or IGF-1 have also been implicated in KP pathogenesis.[2]

Overview of Keratin Structure and Function

Keratin is a fibrous protein and makes up 90–95% of cells in the epidermis.[3] Keratins are the intermediate filament proteins of the epithelium and show a great degree of molecular diversity. In the human genome, there are 54 functional keratin genes. Keratin plays a role in the mechanical stability and integrity of epithelial cells and tissues. Keratin can also play a role in regulatory pathways, intracellular signaling, wound healing, and apoptosis.[4] The main purpose of keratin, however, is to maintain the architecture of the cell by providing support for the cytoskeleton of cells and tissues, especially when they incur mechanical stress.[3]

Keratin can be distinguished from other fibrous proteins by its high cysteine residue content. These cysteine residues form disulfide bonds and contribute to mechanical, thermal, chemical, and water stability.[3]

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C Acnes and Its Biofilm

C Acnes is a gram positive, lipophilic, rod-shaped, non-spore-forming, facultative anaerobe[5] implicated in many diseases of the skin as well as post-surgical infections.[6] *C Acnes* is found in areas rich in sebaceous glands, most notably the sebaceous glands of the skin. The bacterium also contains lipoglycans, which have a lipid anchor of fatty acids and possess significant concentrations of mannose, glucose, and galactose.[5]

One key virulence factor of *C Acnes* is its production of a biofilm. A bacterial biofilm is an extracellular matrix that is composed of polysaccharides, extracellular DNA, and proteins. The biofilm produced by *C Acnes* forms in the pilosebaceous unit.[5] *C Acnes* possesses UDP-N-acetylglucosamine 2 epimerase as well as glycosyl transferases. These are both adhesive proteins used in the production of *C. Acens*'s biofilm and act as the biological glue.[7] This biofilm allows the keratinocytes to stick to one another via a biological glue.[5]

Interaction Between _C Acnes_, Biofilms, and Keratosis Pilaris

In our previously published article "A Review of the Role of *C Acnes* and its Biofilm in Dandruff Pathogenesis", we related the bacterial biofilm's ability to stick together and form a glue to acne pathogenesis. Now, we hypothesize that the biofilm production by *C Acnes* creates a biological glue that also plays a role in keratin sticking together in KP. This is in part supported by the role of ammonia-oxidizing bacteria (AOB) in KP treatment.

Nitrosomonas eutropha is an AOB[6] and is commonly found in soil.[8] Modern-day hygiene, particularly the use of antibacterial soap, has resulted in the depletion of *Nitrosomonas eutropha* from the skin.[9] This bacteria facilitates the oxidation of ammonia to nitrite, nitrates, and nitric oxide (NO).8 Nitrates synthesize the nitro lipids and activate the human immune system. At the same time,[9] NO plays a key role in the regulation of biofilm function at epithelial surfaces.[8] In vitro findings have shown that NO can aid in the dispersal of bacterial biofilms. This has been confirmed via a double-blind controlled trial with cystic fibrosis patients who are administered a low dose of gaseous NO, and after which they demonstrated significant decreases in their level of *P. aeruginosa*, a biofilm-producing bacterium, aggregates.[10]

It has been found that the inhibition of this nitrification process can lead to enhanced biofilm formation by other microbial species, and increased AOB concentrations have been associated with biofilm disruption.[11] NO has also been found to aid in antimicrobial and anti-inflammatory processes, and these properties have been maintained evolutionarily in part by AOBs. When there are healthy physiologic levels of NO on the skin, it results in decreased keratinocyte proliferation.[12]

Treatment of KP is largely limited to topical emollients, exfoliants, and retinoids, which have proven to be only minimally effective. However, due to the role AOB plays in decreasing keratinocyte proliferation and in dispersing bacterial biofilms, AOB has started to prove effective in treating KP.[12] In fact, studies of topical Nitrosomonas eutropha spray showed greater than 45% reduction compared to placebo.[13] Because AOB disrupts biofilm formation by other microbes, and AOB has proven efficacy in KP treatment, it supports the hypothesis that biofilms are implicated in KP pathophysiology.

The similarities between KP and acne vulgaris are another way in which we support the hypothesis that biofilm production by *C Acnes* creates a biological glue that plays a role in keratin sticking together in KP. Acne vulgaris is associated with increased sebum production and follicular hyperkeratinization. Keratin accumulates, and the sebum converts a microcomedo into a closed comedo. The follicle continues to expand, leading to an open comedo.[14] The follicles eventually rupture and release bacteria, keratin, and proinflammatory lipids into the surrounding dermis. The increased sebum provides *C Acnes* with triglycerides that the bacteria can hydrolyze into free fatty acids and glycerol. Additionally, increased androgen is associated with acne vulgaris. Androgens act to stimulate the sebaceous glands to grow and increase secretions, contributing to the development of increased sebum and acne.[14]

C Acnes produces a biological glue that aids in the formation of its biofilm. *C Acnes* possesses UDP-N-acetylglucosamine 2 epimerase as well as glycosyl transferases. These are both adhesive proteins used in the production of *C Acnes*'s biofilm. This biological glue has been implicated in acne vulgaris.[7] The biofilm of *C Acnes* may provide the biological glue that allows corneocytes to adhere to the infundibulum, leading to comedonal acne.[15]

In KP, keratin builds up and creates a keratin plug that fills the infundibulum of the hair follicle and extends above the skin surface. This leads to the formation of the follicular papules that are characteristic of KP.[2] Because the keratin is clumping together, something has to be acting as the glue. We hypothesize that the biofilm produced by *C Acnes* plays a role in this glue. While this has been explored somewhat in relation to acne vulgaris, it has not been studied in regard to KP to our knowledge.[15] However, because of the similarities between the pathophysiology of acne vulgaris and KP, it is reasonable to hypothesize a similar mechanism for KP. KP and acne vulgaris are both dermatological conditions that affect the pilosebaceous follicles and alter follicular keratinization. Both are most severe at puberty and are associated with increased androgen concentration. The local skin microbiome has been implicated in both acne vulgaris and KP as well. The similarities between these two dermatologic conditions lay the groundwork for the role of the *C Acnes* biofilm in the sticking together of keratin clumps in KP.[16]

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Clinical Implications and Therapeutic Considerations

C Acnes is a common cutaneous bacteria implicated in many dermatologic diseases. While *C Acnes*, like most other bacteria, is gaining increasing antimicrobial resistance, antibiotic therapy is still effective in many *C Acnes* infections.[5] By demonstrating the link between *C Acnes* and KP, it provides another treatment avenue for KP. This is especially beneficial for patients whose KP has been resistant to more traditional treatment modalities for those whose KP is particularly pruritic and bothersome.

CONCLUSION

In conclusion, KP is a very common condition affecting nearly 40% of the population. Its pathogenesis is based on keratin accumulation and clumping together to form a keratin plug. This leads to the formation of the follicular papules that are characteristic of KP.[2]

We hypothesize that the biofilm produced by *C Acnes* plays a role in creating the glue that allows the keratin to stick together. This is supported by evidence that KP has been effectively treated by AOB, which disrupts biofilm production and keratin proliferation. Additionally, this biofilm glue theory has been previously studied and supported regarding acne vulgaris. Because of the similarities between KP and acne vulgaris, we further support our hypothesis.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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