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REVIEW ARTICLE

New insights into acne pathogenesis: Exploring the role of acne-associated microbial populations

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ABSTRACT

Acne vulgaris, a prevalent disorder of the skin, is found to increase the incidence of suicidal ideation in acne patients (~7.1%). This creates a dilemma in the mind whether acne is a life threatening disease among humans. The main inducer for this multifactorial disease is microbial fluctuation of common resident microbes on the skin with each microbe possessing their own purpose and style in protecting the human body. For acne progression, the microbial population has to get around the defense barriers of the host skin and be able to also resist them in order to survive. These matters have been resolved by their pathogenic lifecycle and associated virulence factors coded within their pathogenic islands in the single circular chromosome. This review addresses the different microbial populations residing in acne lesions and promoting acne by emphasizing their pathogenic mechanisms and the genes associated with virulence factors involved in the development of acne. Model systems such as animal models and cell culture models in studying the pathogenic lifestyle of the microbes are also addressed.

Introduction

Being composed of two primary layers of mammalian skin—epidermis and dermis—the skin organ represents a formidable barrier providing host skin defense by producing molecules like proteases, lysozymes, and antimicrobial peptides. The skin epidermis forms the outermost layer of the skin which resists microbial penetration and potential toxins inside the body. The dermal skin hosts several substructures like hair follicles, sebaceous glands, apocrine, as well as eccrine sweat glands, thus making the skin surface look uneven, with lines, ridges, and invaginations.[1–3] The sebaceous glands present in the thick skin produces sebum that spills into the hair follicle. Apocrine sweat glands excrete a fatty substance, whereas eccrine sweat glands produces salty fluid that helps with the maintenance of thermoregulation inside the body.[4] Thus, the skin is predominated by factors such as pH, temperature, moisture, sweat, and sebum content, making it an intricate habitat for a rich community of microorganisms that outnumbers the human body's own cells.

Being home to a diverse group of microorganisms, the skin represents a complex ecosystem. From the entire complex microbial diversity of the skin, trillions of bacteria, fungi, and small arthropods have been isolated, identified, and studied using culture-based as well as culture-independent methods.[4–6] Bacterial species predominating the skin, mainly belong to four phyla: *Actinobacteria*, *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* out of which over 60% of the bacterial species belong to three genera: *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*.[3,4,7] Microbial fluctuations in the skin ecosystem can contribute to perturbation and consequently causes disease. Although microbes protect the human host, they have also been implicated in the pathogenesis of several skin diseases.[5,8]

The pathogenic life cycle of bacteria is mediated by virulence genes encoding virulence factors within their pathogenic islands. The virulence genes, unlike house-keeping genes, are characterized by the production of toxins, adhesins, invasions, or other types of factors, present preferably in the pathogenic microorganisms.[9,10]

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These products are directly involved in the pathological damage to the host by promoting interaction between the host and organism and also by damaging and degrading the host tissues. For instance, *camp5*, *gehA*, *tly*, *sialidases*, *neuraminidases*, and *endoglycoceramidases* are some of the virulence factors of *Propionibacterium acnes* which causes acne vulgaris.[11] Lipases, fatty acid modifying enzyme, polysaccharide intercellular adhesion (PIA), and polyglutamic acid are the virulence factors in *Staphylococcus epidermidis*.[12,13] Adhesins, fibronectin binding protein (FnBp)-A, FnBP-B, proteases, lipases, and hyaluronidases are the virulence factors in *Staphylococcus aureus*.[14,15] Thus, each pathogen follows its own pathogenic strategy, with a diverse and unique set of genes/factors operating in a concerted manner to cause disease in the host.

This review focuses on the mechanism of the pathogenesis leading the pathogen to cause acne vulgaris. In particular, the pathogenic life cycle of the microorganism and the associated virulence factors encoded within its own genome are discussed. Based on available literature, we have tried to explore how these microbial populations attach themselves and survive within the host skin to promote acne. However, unlike these issues, the availability of appropriate model systems to study acne pathogenesis is poorly understood. In this review, all the possible model systems such as cell culture as well as animal based model systems are also discussed.

Acne vulgaris

Acne vulgaris, a disease affecting the skin's oil glands, is one of the most common skin disorders, making a significant number of the human population prone to acne. Although the disease is not life threatening, it affects the quality of life by creating a psychological burden due to the exhibition of diverse lesions on the face, chest, shoulders, and back.[16] The prevalence of acne vulgaris is around 65–75% of teenagers and youths.[17] Accumulation of sebum and dead skin cells within the sebaceous follicle enhances the microbial load, which disrupts the follicular wall resulting in the inflammation of the skin called acne (Figure 1). Sebum production and hormonal changes are the endogenous factors, whereas the change in the activity of the skin microflora is the most contributing factor in the pathogenesis of acne. The microbial flora isolated from acne patients that seems likely to lead to acne pathogenesis includes: *P. acnes, S. epidermidis, S. aureus, Klebsiella pneumoniae*, *Streptococcus, Enterobacter*, etc, (Tables 1 and 2).[16,18]

Propionibacterium acnes

P. acnes, an opportunistic pathogen that plays an important role in the progression of inflammatory acne vulgaris, are ubiquitously present within the sebaceous follicles of the human skin. These acne-causing bacteria are usually gram positive, nonmotile, fat splitting microorganisms, having the ability to grow under different oxygen tensions. Being an exclusive occupant of the follicular canal, when clogging of hair follicle happens the bacterium aids in the rupturing of the follicular walls, using their secretory enzymes with degradative properties (Figure 1).[19–21] These bacterium also target other skin cells, namely, keratinocytes and phagocytic cells like macrophages, stimulating the cells to produce proinflammatory cytokines, including interleukin (IL)-1β, IL-8, IL-12, and tumor necrosis factor-α, leading in the inflammatory acne disease.[21–24] The genomic information clearly highlights that the products of the *P. acnes* have a major impact on the acne process, but not the invasiveness of the organism. The notable virulence genes involved in the pathogenesis of acne are *camp5*, *gehA*, *tly*, *sialidases*, *neuraminidases*, *endoglycoceramidases*, *lipases*, and *hemolysins* (Tables 1 and 2).[11,20] The lipoglycan-based cell envelope and their extracellular secreted lipase, particularly triacylglycerol lipase, encoded by the *gehA* gene assists in the adherence and the colonization of the bacterium to the sebaceous follicle. The other product which aids in the acne process by destroying the host tissue includes porphyrins, hyaluronate lyase, endoglycoceramidase, sialidases/neuramidase, cardiolipin synthetase, and calcineurin like phosphoesterase (Tables 1 and 2).[10,11] The organism further possesses several proteins associated with cell invasion, which are secreted by genes, namely *PAmce*, *PAp60*, and cell surface antigen, which are produced by htaA and hsp20.[25] These help the pathogen to invade the host cell further and makes it highly immunoreactive, thereby establishing high virulencity. It is logical to think at what point the virulence factors secreted/produced fulfil the functions of the microorganism turn out to be dangerous for the host, which is actually a skin commensal.

Staphylococcus epidermidis

S. epidermidis is a facultative anaerobe of cutaneous microbiota harbored in acne lesions. These microbes which are nonpathogenic resident flora of the human skin at some point of life turns into an infectious agent due to extrinsic factors like an immune system deficiency.[26] The first and foremost virulence factor produced by this organism is fatty acid modifying enzyme which esterifies the fatty acids in the skin to cholesterol, as fatty acids are bactericidal for the organism to survive.[27] The bacterium possesses several adhesion factors for its attachment to the skin surface, like surface anchored proteins, fibrinogen binding protein, autolysin protein, PIA, and poly-N-succinyl-glucosamine, helping as a probable attachment factor.[13,28,29] The potentially virulent *S. epidermidis* also has the ability for biofilm formation and is a reservoir of antibiotic resistance genes, which get horizontally transferred to other organisms.[28,30] In the process of acne development, the lipases (*geh1* gene) and the delta-haemolysin (*hld* gene) are two virulence factors that have an impact in acne inflammation (Tables 1 and 2).[13] Although they have such virulence characteristics, they have been found to rarely damage the keratinocytes in the skin. This has shown that *S. epidermidis* secreted the exopolysaccharide intercellular adhesin (PIA), which is responsible for biofilm formation and protects them against major components of human innate host defence.[28–30] This biofilm provides the favorable anaerobic conditions to grow *P. acne* in an easy manner.

According to Pathak et al.,[31] the population of *S. epidermidis* and *P. acnes* were found to be increased by ~70% and ~82%, respectively, in acne patients compared with controls. The microbial load of these microbes was found to be increased simultaneously in the case of acne, which indicates some important role of these two bacterium in the development and regulation of acne disease. On the basis of above evidence, we can say that *S. epidermidis* plays an important role in acne pathogenesis not in a direct manner but in an indirect manner. Therefore, it might be assumed that *S. epidermidis* strains secrete virulence factors to a certain extent, but the beneficial activity of the microorganism should also be considered. Being found to occur in massive loads in acne patients compared with normal human skin raises a question whether they are the source of disease or defense.[8,31] A potential research including RNA sequencing and quantitative whole-cell proteome analysis of *S. epidermidis* as well as affected tissue at different stages of disease development might help to better understand the role of this bacterium in acne pathogenesis.

Staphylococcus aureus

S. aureus, the most prominent member of the skin microbiota, plays a role as a pathogen in many skin infections such as folliculitis and