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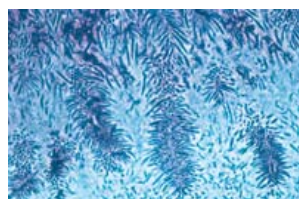
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February/March 2003



Biofilm Basics

Understanding bacterial biofilms is pivotal in the fight against periodontal infection.

By Casey Chen, PhD, DDS, and Sandra K. Rich, RDH, MPH, PhD

Salmonella poisoning at a local restaurant, antibiotic-resistant staph infections in the military and prison systems, flesh-eating bacteria threatening an elderly person—these are all stories in the news today and they can shake public confidence in the capability of modern medicine to overcome bacterial infection. However, recent research has provided insight into bacterial biofilms that may lead to more efficacious strategies for battling bacterial infection.

The most unyielding infections are caused by bacteria that form complex communities—biofilms—that are often resistant to antibiotics.¹⁻³ Research now illustrates that the microorganisms in biofilm rely on their ability to communicate with one another. If this communication can be interrupted, infections may be prevented or weakened.

The Dental Connection

Why is this important to dental hygienists? Dental biofilm is the new term for dental plaque. Bacterial biofilms play an integral role in the etiology of periodontal disease and caries.

The road to understanding dental biofilms has been so long and winding because bacteria behave differently when examined in a laboratory setting than they do in nature. The advancement of certain experimental tools and methods has further opened the study of biofilms in their natural environment. For example, digital imaging devices, such as confocal scanning laser microscopy and the use of various nontoxic fluorescent probes, allow us to observe fully hydrated and viable bacterial biofilms in their native state.⁴ Identifying individual species or molecules that form a biofilm community is now possible.⁵ In the future, we will be able to obtain a detailed microbial or molecular anatomy of naturally occurring biofilms.

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What is a biofilm?

A biofilm is a complex community of bacteria adhering to an inert or living surface.¹⁻³ Biofilms are the predominant mode of bacterial growth in nature. Many microbial species exist as sessile bacteria (attached bacteria in the biofilms), but release small numbers of planktonic cells (free-floating single cell bacteria) for dispersion.

An easy way to conceptualize the formation process of biofilms is to study the single-species biofilms formed by the gram-negative *Pseudomonas aeruginosa* (a major pathogen of cystic fibrosis pneumonia). However, a similar process has been seen in other single-species and mixed species bacterial biofilms.

P. aeruginosa moves using flagella (whip-like appendages for locomotion). At the start of the biofilm formation process, the bacteria “swim” to find an appropriate surface to adhere to. After they attach, the bacteria shed flagella because they no longer need motility and they manifest type IV pili—a type of proteinaceous, hair-like structures.³

P. aeruginosa uses the type IV pili for twitching motility, allowing the bacteria to move on the surface to find other bacteria to form small aggregates. Next the bacteria produce a large amount of matrix and the bacterial groups increase in size and thickness until they form a mature biofilm. After maturation, biofilms may release planktonic cells to begin another cycle of biofilm formation.

The step-by-step gene-regulated biofilm formation process results in a bacterial community with distinct mushroom-like structures that consist of a variable distribution of cells and cell aggregates, the associated matrix, void spaces, and water channels that allow the diffusion of nutrients and waste products.

Cell-to-Cell Communication

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Many bacteria are able to communicate with each other through a process called quorum sensing gene regulation. This process is how the cells in a biofilm know to turn on certain genes.

A number of gram-negative bacteria, including *P. aeruginosa*, use acylated homoserine lactones (AHLs) as signaling molecules. AHL is used as an autoinducer (AI)—a molecule that increases the synthesis of itself through a feedback mechanism.⁶ When enough cells congregate, the concentration of AHL goes up, which then changes gene activity. In *P. aeruginosa*, if the gene for a particular AHL is not present, normal biofilms fail to form.

The AHL-based quorum sensing system above is species-specific (used among bacteria of the same species). There is also a quorum sensing system that permits cell-to-cell communication among bacteria of different species.⁶

Why Do We Study Biofilms?

Understanding biofilm is important because we need to know our adversaries in order to defeat them. Research in biofilms may help identify new strategies to combat bacterial infections. Since quorum-sensing systems play a critical role in biofilm formation, disrupting the systems should diminish the bacteria's ability to cause disease. A proposed therapeutic approach is to use an enzyme that destroys AI molecules to control bacterial infections.

A different approach is to use compounds that interfere with cell-to-cell communication in bacteria. Many higher organisms produce compounds to mount a chemical warfare against pathogens. Some of the compounds work by disrupting the quorum sensing system in bacteria and have the potential to treat bacterial infections.

Biofilm bacteria are several hundred to thousand folds more resistant to antimicrobial agents than planktonic cells of the same species.² This may help explain why some chronic bacterial infections are difficult to treat with antibiotics, even though in vitro antimicrobial susceptibility tests predict that the antibiotic will be effective.

While the mechanism(s) of antimicrobial resistance is currently unknown, a more rational and effective strategy of antimicrobial therapy will be identified once we understand the mechanism(s).



Figure 1. Supragingival plaque of a periodontitis patient. The enamel surface (E) is on the lower half of the photo. A dense layer of bacteria, mostly filamentous, adhere to the enamel. Cornucob formations are visible on the surface of the plaque. x850 magnification.



Figure 2. Subgingival plaque of a periodontitis patient. The cementum surface (C) is toward the top of the photo. Bacteria adhere to the cementum surface appear to be less dense and less filamentous. The test-tube brush formations are found on the surface of the adherent bacterial layer. x600 magnification.

Photos courtesy of Max Listgarten, DDS

Dental Plaque as a Biofilm

Dental plaque is one of the best-studied biofilms, although the term "biofilm" was not originally part of the vocabulary used in dental research.¹

Structural Characteristics

Dental plaque formation is an extremely complex process.⁷ Immediately after removal of bacteria on the tooth surface by prophylaxis, a ubiquitous layer of dental pellicles is formed on the tooth surface. The early bacterial colonizers, made up of harmless bacteria, adhere to the dental pellicles on the tooth surface.

The early colonizers proliferate and provide a variety of niches for the adherence and growth of late bacterial colonizers. The microbial composition of plaque gradually becomes more diversified and, if allowed to grow undisturbed, will eventually include many pathogenic bacteria.

The distinct, orderly feature of dental plaque can be revealed by electron microscopy (EM). With EM, the mature supragingival plaque appears as a layer of dense and predominantly filamentous organisms adhering to the enamel surface (Figure 1).⁸ The filamentous organisms are long and oriented with their longitudinal axis perpendicular to the tooth surface. The surface of the plaque contains distinctive cornucob formations indicative of interbacterial species coaggregation. The subgingival plaque is a natural extension of supragingival plaque (Figure 2).

The adhering layer of the subgingival plaque contains short filamentous bacteria. The surface of the subgingival adherent layer is covered with distinctive bacteria comprising many flagellated bacteria, spirochetes, and bristle brush and test-tube brush formations (Figure 3). Many well-known pathogens like *p. gingivalis* are found in this layer.

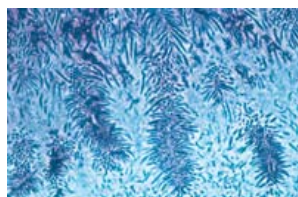


Figure 3. Subgingival plaque of a periodontitis patient. Magnified view of the test-tube brush formations. x1500 magnification.

Cell-to-cell Communication

Bacteria in dental plaque may use certain cell-to-cell communication systems in order to coordinate their behaviors.

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Bloomquist et al⁹ examined the growth of dental plaque on human teeth. Following rapid adherence of oral bacteria onto the enamel surface, there was relatively slow growth. A rapid burst of cell growth occurred when the cell density reached a higher level.

Their growth rate began to decline again when density reached an even higher level. The mechanism was unknown, but it was concluded that the cell density burst of growth was a demonstration of cell-to-cell communication.

Antimicrobial Susceptibility

A limited number of in vitro studies have shown that oral streptococci in biofilms were more resistant to chlorhexidine than planktonic cells.¹⁰ The resistance phenotype of biofilm bacteria may also be inferred from clinical studies of systemic antibiotic therapy for periodontitis.¹¹

Microbial Etiology of Periodontitis

One of the most notable achievements in periodontal research is defining the role of a number of specific bacterial species in periodontitis. However, the causal relationship between periodontal pathogens and periodontitis was assessed based on the modified Koch's postulates.¹² Koch's postulates are based on a model of single-pathogen acute infections, such as primary syphilis. The disease occurs within days of infection by *T. pallidum*. No other bacterial species are involved in the pathogenesis of syphilis, nor does biofilm play a formation role in the infection.

In contrast to single-pathogen acute infections, periodontitis is more similar to bacterial biofilm infections.¹ Interestingly, biofilm infections share some common features.¹³ A critical early step of the disease involves the forming of biofilms on inert surfaces or living tissues. Commensal bacteria are frequently involved in biofilm infections.

Clinically, biofilm infections are slowly progressing and difficult to treat. The bacteria in biofilm infections are frequently resistant to antimicrobial agents that are effective against planktonic bacteria. The bacteria and the infections relapse after the cessation of the drug therapy. The host immune response is ineffective against biofilm infections and may even be harmful to the host. All these characteristics of biofilm infections apply to periodontitis.

Applying Concept to Treatment

Our view of periodontitis as a biofilm infection changes how we interpret and deal with the occurrence of periodontal pathogens in subgingival plaque. The presence of subgingival periodontal pathogens indicates a change from a harmless biofilm to a pathogenic biofilm that contains an abundance of pathogens, which cause tissue inflammation and destruction.

The cause of the microbial change is not the invasion of periodontal pathogens from an exogenous source, but the sequential and orderly development of a pathogenic biofilm arising from residential oral bacteria. An effective approach of periodontal therapy is to change the local environment to suppress the growth of periodontal pathogens. However, a simplistic approach of using antimicrobial agents to treat periodontitis without disruption of biofilms ultimately results in treatment failures.

Following are the key principles for the clinical treatment of periodontitis as biofilm infection.

1. Mechanical debridement is critical in treating periodontitis. An effective biological approach to disrupt biofilm formation may be identified in the near future. However, until that time, mechanical debridement is an effective and reliable method to treat periodontal biofilm infections.
2. Antimicrobial susceptibility, as determined by in vitro systems, may not be relevant to clinical therapy. Many studies of antimicrobial susceptibility were performed with planktonic bacteria. Biofilm bacteria are much more resistant to antimicrobial agents.
3. Removing subgingival calculus remains a key goal of periodontal therapy. While calculus is not an etiology of periodontitis, it is a major contributing factor that allows bacteria to quickly form a mature biofilms. Periodontal therapy will not succeed without first removing calculus.
4. Systemic and local antimicrobial agents are an adjunct therapy and not a substitute for poor mechanical debridement. Without mechanical debridement, systemic or local delivery of antimicrobial agents merely kills off the sensitive planktonic bacteria, while leaving the culprits—biofilms—relatively unharmed.
5. Changing local environment, eg, pocket reduction therapy, may be an effective means to change the composition of biofilms. Pathogenic biofilms (ones dominated by high levels of major periodontal pathogens) are found mainly in deep pockets and do not form in shallow pockets.
6. Meticulous plaque control and regular maintenance visits are needed to prevent the maturation of dental plaque to become pathogenic. Biofilms will recur with time. The strategy is to continuously disrupt the formation of pathogenic biofilms by regular maintenance.

From *Dimensions of Dental Hygiene*. February / March 2003;1(1):22-25.

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