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Review Article

Biofilm formation in periodontitis: A comprehensive review

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Abstract

Periodontitis, a chronic inflammatory condition, remains a significant cause of tooth loss in adults worldwide. Its pathogenesis is deeply rooted in the development and persistence of microbial biofilms, particularly those colonizing subgingival sites. These highly structured and cooperative communities of microorganisms are embedded in an extracellular polymeric matrix, enabling them to resist both host immune responses and conventional therapeutic interventions. This review delves into the mechanisms of biofilm formation, the composition of microbial communities involved, host-pathogen interactions, and modern therapeutic strategies. It also explores emerging diagnostics and novel approaches aimed at mitigating biofilm-associated periodontal destruction.

Keywords: Extracellular polymeric matrix, Polysaccharides, Planktonic cells

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1. Introduction

Periodontitis is a multifactorial, infectious-inflammatory disease affecting the supporting tissues of the teeth, including the periodontal ligament and alveolar bone. It is initiated primarily by dental plaque—structured biofilms formed on tooth surfaces.[1] Globally, severe periodontitis affects 10– 15% of the adult population, making it a leading cause of tooth loss and functional impairment.[2]

In its early stages, periodontitis may be asymptomatic, yet as it progresses, signs such as bleeding gums, recession, tooth mobility, and halitosis become prominent. The transition from gingivitis to periodontitis is not solely microbial-driven but involves dysbiosis—where commensals are replaced by pathogenic species—and an aberrant immune response.[3] Understanding biofilm dynamics is crucial to unraveling the pathogenesis of periodontitis and guiding effective clinical management.[3]

2. Definition and Characteristics of Biofilm

Biofilms are defined as sessile microbial communities irreversibly attached to surfaces and embedded in a self-generated extracellular polymeric substance (EPS) matrix.[4] These biofilms are not mere aggregations of bacteria; they represent a highly organized and functional unit with spatially distributed metabolic activities and communication via quorum sensing.[5]

The EPS matrix, composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA), confers physical protection, nutrient retention, and resistance to antimicrobial agents.[6] This microenvironment facilitates a shift in bacterial behaviour, allowing them to adopt phenotypes that differ markedly from their planktonic counterparts, including reduced growth rates and altered gene expression.[7]

3. Biofilm Development Stages

Biofilm formation on dental surfaces occurs in a sequential, regulated process **(Figure 1).**

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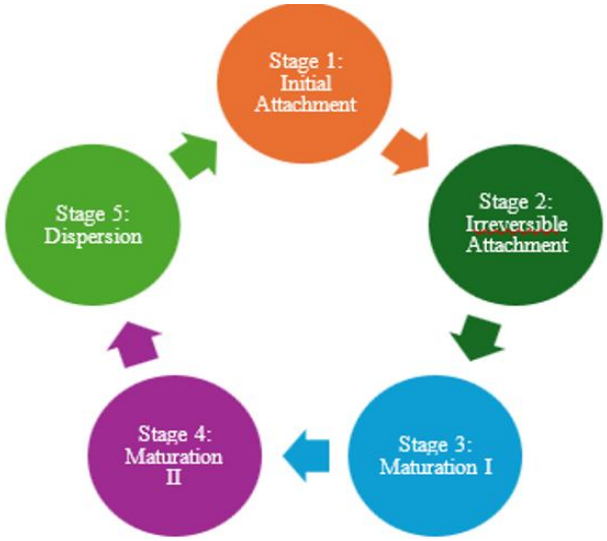

Figure 1: Stages of biofilm formation

1. Initial Attachment

   Salivary pellicle proteins coat tooth surfaces, creating binding sites for early colonizers such as Streptococcus sanguinis and Actinomyces naeslundii.[8] Adhesion is initially reversible, relying on weak physicochemical forces.

2. Irreversible Adhesion and Microcolony Formation

   Attachment becomes stabilized by bacterial adhesins, fimbriae, and glucans. These early colonizers begin proliferating and secreting EPS, forming microcolonies.[9]

3. Biofilm Maturation

   Secondary colonizers like Fusobacterium nucleatum integrate into the biofilm, acting as bridging organisms to late colonizers, such as Porphyromonas gingivalis.[10] Mature biofilms display mushroom-like architecture, nutrient channels, and anaerobic zones.[11]

4. Dispersal

   Biofilm fragments or planktonic cells detach due to environmental signals or nutrient depletion, enabling colonization of new sites and disease progression.[12]

4. Microbiota of Periodontal Biofilms

The microbial complexity of subgingival biofilms increases with disease severity. Healthy sites are dominated by Gram-positive facultative anaerobes, while diseased sites harbor Gram-negative anaerobic pathogens.

1. Early Colonizers

   Species such as Streptococcus mitis, Streptococcus oralis, and Actinomyces viscosus initiate biofilm formaprogressionl

2. Bridging Species

   Fusobacterium nucleatum connects early and late colonizers due to its ability to coaggregate with diverse microbes.[13]

3. Late Colonizers – The Red Complex

   This includes P. gingivalis, Tannerella forsythia, and Treponema denticola, strongly associated with clinical attachment loss and bone resorption.[14]

These pathogens express numerous virulence factors—gingipains, hemagglutinins, and lipopolysaccharides—which contribute to tissue degradation and immune modulation.

5. Host Immune Response

The innate immune system is the first line of defense against biofilm pathogens. Neutrophils infiltrate the gingival sulcus, releasing reactive oxygen species (ROS) and antimicrobial peptides. Dendritic cells and macrophages recognize PAMPs via pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs), triggering cytokine release.

Chronic inflammation leads to persistent activation of T and B cells, increasing levels of IL-1β, TNF-α, and RANKL, which promote osteoclastogenesis and alveolar bone loss. Dysregulated immunity, influenced by systemic conditions like diabetes, exacerbates tissue destruction.

6. Biofilm Resistance Mechanisms

Biofilms exhibit remarkable resistance to antibiotics and host defences due to several mechanisms: EPS Barrier: Limits penetration of antimicrobial agents and immune effectors. The Extracellular Polymeric Substance (EPS) barrier acts as a physical shield. This matrix, composed of polysaccharides, proteins, and DNA, surrounds the biofilm and limits the penetration of antimicrobial agents, such as antibiotics and antiseptics, as well as immune effectors like antibodies and phagocytes. The EPS barrier delays or reduces the exposure of biofilm bacteria to antimicrobial agents, allowing the bacteria to survive and persist despite treatment.

Nutrient Gradients: Create microenvironments where slow-growing or dormant cells are less susceptible to drugs. Within a biofilm, nutrient gradients form due to the uneven distribution of nutrients. This creates microenvironments where bacteria may be slow-growing or dormant. Many antimicrobial agents, such as antibiotics, are most effective against actively growing bacteria. Slow-growing or dormant cells are less susceptible to these agents, making the biofilm more resistant to treatment.

Persister Cells: A small subset of metabolically inactive cells survives lethal conditions and can repopulate biofilms. Persister cells are a small subset of bacteria within the biofilm that are metabolically inactive. These cells are not mutants but rather a transient population that can survive lethal conditions, such as high concentrations of antimicrobial agents. Persister cells act as a "seed" population that can repopulate the biofilm once the

antimicrobial treatment is removed. This makes biofilms resilient and difficult to eradicate.

Efflux Pumps and Enzymes: Biofilm organisms may upregulate resistance genes or produce β- lactamases and proteases. Biofilm organisms may upregulate resistance genes, leading to the production of efflux pumps and enzymes like β-lactamases and proteases. Efflux pumps can expel antimicrobial agents from the bacterial cell, reducing their effectiveness. Enzymes like β- lactamases can degrade antimicrobial agents, further contributing to biofilm resistance.

The combination of these mechanisms – EPS barrier, nutrient gradients, persister cells, and efflux pumps/enzymes – makes biofilms up to 1,000 times more resistant than planktonic cells.

7. Diagnostic Techniques for Biofilm Detection

Traditionally, biofilm presence is inferred through clinical signs and plaque indices. However, advanced methods now offer microbial identification and quantification:

1. Culture-Based Techniques: Useful but limited due to anaerobic organism growth constraints.
2. DNA-DNA Hybridization (Checkerboard): Detects multiple periodontal pathogens simultaneously.
3. PCR and qPCR: Offer sensitive, specific pathogen detection.
4. Next-Generation Sequencing (NGS): Enables comprehensive microbiome profiling, revealing unculturable species.

Microscopy (SEM/CLSM): Visualize biofilm structure and spatial distribution **(Figure 2)**.

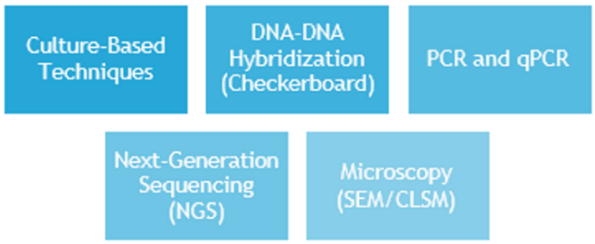

Figure 2: Diagnostic techniques for biofilm detection

8. Therapeutic Approaches

1. Mechanical Debridement: Scaling and root planing (SRP) are the gold standards to disrupt biofilm structure. Ultrasonic devices enhance efficacy in deep pockets.
2. Chemical Control: Adjunctive agents like chlorhexidine, triclosan, and essential oils help suppress microbial regrowth.
3. Systemic and Local Antibiotics: Metronidazole and amoxicillin are often used, though rising resistance is a concern.
4. Host Modulation Therapy: Sub-antimicrobial doxycycline inhibits matrix metalloproteinases (MMPs), reducing collagen breakdown.
5. Emerging Modalities: Photodynamic therapy (PDT), probiotics, antimicrobial peptides (AMPs), and nano-carriers are under investigation for targeting resilient biofilms without systemic toxicity.

9. Future Perspectives

Future periodontal care may be revolutionized by:

1. Quorum Sensing Inhibitors: Block bacterial communication to prevent biofilm maturation.
2. Enzymatic Disruption: Use of dispersin B or DNase to degrade the EPS matrix.
3. Vaccines: Target specific virulence factors of P. gingivalis and others.
4. AI and Big Data: Integration of microbiome data and clinical parameters for personalized treatment planning.
5. Gene Editing Tools: CRISPR-based systems may selectively eliminate pathogenic bacteria.

10. Conclusion

Biofilm formation is central to the onset and progression of periodontitis. Its intricate structure, complex microbial composition, and resistance to treatment underscore the need for multifaceted management strategies. While conventional approaches focus on mechanical removal and antibiotic therapy, emerging innovations offer hope for more targeted and lasting control. A deeper understanding of biofilm biology will continue to shape future diagnostics and therapeutics, ultimately improving periodontal health outcomes.

11. Conflict of Interest

None.

12. Source of Funding

None.

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