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Pathogenic Mechanisms of Periodontal Pathogens: Implications for Diagnosis and Therapy

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Abstract. Periodontitis is prevalent chronic inflammation of the oral cavity that significantly affects world oral health and has intimate relationships with systemic diseases, such as cardiovascular illness and diabetes mellitus. Probing and scaling with adjunctive antibiotics are limited by sensitivity, specificity, and long-term success. Increasing evidence proves that periodontopathogenic microbes are centrally involved in disrupting host–microbe homeostasis and perpetuating chronic inflammation. Among the most characterized species, Porphyromonas gingivalis, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans harbor virulence components, such as adhesins, proteases, and leukotoxins, that enable epithelial invasion, modulation of immune responses, and breakdown of the extracellular matrix, leading ultimately to progressive destruction of tissues and alveolar bone resorption. The pathogens also induce host immune signal pathways, such as NF-κB and MAPK cascades, thereby augmenting inflammatory responses and immune escape. Novel advancements of identification of diagnosable biomarkers, molecular detection strategies, and host-modulatory interventions have broadened the horizons of management. Nevertheless, huge challenges persist because of microbial diversity, stability of biofilms, and individual variability. This review aims at fostering mature understanding of interactions of microbes with the host at periodontitis and at outlining modalities of targeted interventions, immunomodulation, and preventive strategies resulting in successful management at the clinic.

Keywords: Periodontitis, Porphyromonas gingivalis, Fusobacterium nucleatum, therapy

1. Introduction

Periodontitis is the most prevalent oral illness that is defined by the chronic inflammation of the periodontium. If neglected, it results in alveolar bone loss, mobility of the teeth, and eventual exfoliation of the teeth. Epidemiological studies indicate that periodontitis has an extremely high prevalence among the global adult population, posing a serious threat to oral health and exhibiting strong associations with systemic chronic diseases such as cardiovascular disease and diabetes [1]. The onset and progression of periodontitis are primarily attributed to pathogenic microbial communities within the oral cavity. In particular, under conditions of microbial dysbiosis, the overgrowth of opportunistic pathogens disrupts the host-microbe homeostasis and triggers inflammatory responses in periodontal tissues [2]. Several key bacterial species are implicated in the

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pathogenesis of periodontitis, including Porphyromonas gingivalis, Fusobacterium nucleatum, Prevotella intermedia, and certain species of Actinomyces. These bacteria can directly damage host cells through the secretion of various enzymes (e.g., gingipains) and exotoxins, disrupt intercellular junctions of gingival epithelial cells, interfere with extracellular matrix synthesis, and induce fibroblast apoptosis, collectively contributing to the structural degradation of periodontal tissues and providing a persistent source of inflammatory stimuli.

Moreover, periodontal pathogens have developed multiple strategies to evade immune detection and enhance their survival within the periodontal pocket. Some species modify their surface antigens or release immunosuppressive factors to inhibit the functions of macrophages, T cells, and other immune cells, thereby impairing local immune defenses. Simultaneously, certain bacteria can activate or suppress host immune signaling pathways, resulting in the continuous release of inflammatory mediators and exacerbating tissue destruction. The most recent literature has indicated that periodontal pathogen interactions with host cell surface receptors are one of the leading mechanisms of inflammation regulation. By interacting with Toll-like receptors (TLRs) or NOD-like receptors (NLRs), such bacteria are able to activate several signaling pathways, such as the NF-κB and MAPK pathways, which induce the production of inflammatory cytokines and recruit and activate immune cells, thereby inducing periodontal tissue inflammation further. This multi-potential communication of microbial components with the host's immune apparatus is one of the primary mechanisms of the chronic progression of periodontitis [3]. This review aims at systematically analyzing mechanisms of communication of periodontitis-associated pathogens with host cells, with special reference to mechanisms of disruption of host cell activity by such pathogens by excreting toxins and enzymes, altering the structure of surfaces, and mechanisms of immune avoidance. Elaborating mechanisms of such microbe-host communication pathways may become one of the theoretical supports and lines of research directed at the establishment of future targeted measures and treatments of periodontitis.

2. Pathogenic mechanisms of periodontitis-associated bacteria

2.1. Porphyromonas gingivalis

The development and progression of periodontitis are closely associated with multiple pathogenic bacteria, among which Porphyromonas gingivalis (P. gingivalis) is considered a representative "keystone pathogen" [4]. Although this Gram-negative, anaerobic short rod may not dominate in abundance, it possesses strong virulence and significantly alters the subgingival microbial community. P. gingivalis exhibits both long and short fimbriae that facilitate adhesion to and invasion of gingival epithelial cells, allowing it to evade immune clearance after intracellular entry. Its lipopolysaccharides (LPS) activate Toll-like receptors (TLR) 2 and 4, inducing monocytes and macrophages to release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, thereby exacerbating local inflammation. Additionally, its cysteine proteases (gingipains) degrade extracellular matrix components like collagen and fibronectin and cleave immunoglobulins and complement proteins, weakening host defense [5]. Immune evasion is further enhanced by LPS structure modification, secretion of IL-8 degrading enzymes that inhibit neutrophil recruitment, and interference with complement activation.

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2.2. Fusobacterium nucleatum

Fusobacterium nucleatum (F. nucleatum), a Gram-negative anaerobic bacillus, acts as a "bridge organism" in the periodontal biofilm, linking early-colonizing Gram-positive bacteria with late, highly pathogenic species. It invades deep tissues via its FadA adhesin, which binds E-cadherin on host epithelial cells, disrupting the epithelial barrier [6]. During biofilm formation, F. nucleatum synergizes with P. gingivalis and others to enhance colonization, antimicrobial resistance, and immune evasion. FadA also activates the β-catenin pathway, altering gene expression and triggering inflammation. Its LPS stimulates excessive IL-8 release, leading to persistent neutrophil infiltration and chronic inflammation. F. nucleatum can also inhibit neutrophil oxidative bursts and reduce bactericidal reactive oxygen species and prolonging its survival in periodontal pockets.

2.3. Aggregatibacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans, a facultative anaerobic Gram-negative coccobacillus, is strongly associated with aggressive periodontitis, particularly juvenile cases. It secretes leukotoxin (LtxA), which selectively kills polymorphonuclear leukocytes and monocytes, leading to local immune cell apoptosis and immunodeficiency [7]. It also stimulates RANKL expression in host cells, promoting osteoclastogenesis and alveolar bone resorption. Its biofilm formation impedes antibiotic and immune cell penetration, while secretion of anti-phagocytic factors suppresses macrophage activity [8]. Its LPS and outer membrane proteins induce inflammatory cytokine production, contributing to tissue destruction.

3. Clinical implications and therapeutic strategies

A thorough understanding of the pathogenic mechanisms of periodontitis is fundamental to advancing clinical diagnosis and treatment. Early detection can be achieved by identifying specific bacterial toxins, such as gingipains and leukotoxin (LtxA), or inflammatory mediators, including IL-1β and TNF-α, which serve as sensitive biomarkers for disease onset and progression. Non-invasive diagnostic platforms, particularly salivary and gingival crevicular fluid assays, are increasingly recognized for their utility in real-time monitoring. Moreover, microbiome-based techniques, such as qPCR, 16S rRNA sequencing, and metagenomic profiling, provide accurate characterization of high-risk pathogens and microbial dysbiosis, thereby supporting personalized risk assessment and treatment planning [9].

Conventional therapies remain centered on mechanical debridement, such as scaling and root planing, aimed at disrupting the biofilm. These approaches are often combined with systemic or locally delivered antibiotics (e.g., doxycycline, metronidazole) to reduce the bacterial load. However, the persistence of biofilms and the emergence of antimicrobial resistance limit the long-term success of such strategies. To address these challenges, host-modulatory interventions have been introduced, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and subantimicrobial-dose doxycycline to inhibit matrix metalloproteinases, thereby attenuating destructive inflammation while maintaining protective immune functions.

Recent advances in targeted molecular therapy have opened promising avenues for precision treatment. Specific inhibitors of gingipains and neutralizing antibodies against LtxA have demonstrated potential in preclinical studies for suppressing key virulence pathways [10]. In parallel, preventive strategies such as peptide- or DNA-based vaccines targeting P. gingivalis antigens (FimA, gingipains) are under active development and may offer long-term protection for

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high-risk populations [11]. Complementary approaches, including the use of probiotics and engineered commensal strains to restore microbial balance, as well as nanotechnology-enabled drug delivery systems capable of penetrating resilient biofilms, further expand the therapeutic landscape [12,13]. Taken together, the integration of microbial biomarkers, molecular diagnostics, host-modulatory therapies, and innovative preventive strategies represents a paradigm shift from conventional broad-spectrum treatment toward precision periodontics. Future clinical translation will benefit from the convergence of molecular biology, immunology, and artificial intelligence, ultimately enabling personalized management and durable disease control.

4. Conclusion

Periodontitis is a long-term inflammatory disease resulting from the long-term coexistence of complex microbial communities with the host immune system. The current review briefly outlines the dominant pathogenic mechanisms of leading periodontal pathogens, such as Porphyromonas gingivalis, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans. These pathogens undermine tissue homeostasis and perpetuate inflammation by several mechanisms, including the production of toxins and enzymes, host cell invasion, and immune clearance escape. The studies have revealed that the pathogens, in addition to injuring periodontal tissues directly, adjust host signal pathways, resulting in immune imbalance and progression of alveolar bone resorption and tooth exfoliation.

At the clinical level, identification of bacterial products and biomarkers of inflammation enables earlier diagnosis, while simultaneous application of antimicrobial treatment and immune modulation opens up new avenues of disease control. New targeted molecular therapies and construction of vaccines hold immense potential for prevention and intervention as well. However, some of the problems, like fluctuations of microbial diversity and host-specificity of efficacy of treatment, and the persistence of durable biofilm-mediated drug resistance, persist, which continue to hamper successful long-term outcome. Future research needs to remain concentrated upon precision medicine and interdisciplinary integration, making optimum utilization of the advancement of molecular biology, immunology, and artificial intelligence, so that personalized approaches of therapy could be implemented. Enhanced understanding of the complexities of interactions among periodontal pathogens and host immune components shall surely provide more efficient and durable solutions of the specific prevention and cure of periodontitis.

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