Reassessing Biofilm Dysbiosis as the Primary Etiological Driver in Chronic Periodontitis: Beyond the Keystone Pathogen Hypothesis

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Abstract. The keystone pathogen hypothesis has dominated periodontal etiopathogenesis discourse for over a decade, positioning Porphyromonas gingivalis as the principal orchestrator of polymicrobial synergy and dysbiosis. However, accumulating metagenomic and transcriptomic evidence challenges the sufficiency of this model in explaining the full spectrum of chronic periodontitis progression. This study performed a systematic meta-analysis of 47 clinical cohort datasets (n = 6,312 subjects), integrating 16S rRNA amplicon sequencing, host immunogenomic profiling, and subgingival metabolomics. Findings demonstrate that polymicrobial community restructuring—driven by shifts in Treponema denticola, Tannerella forsythia, and Filifactor alocis abundance ratios—predicts clinical attachment loss with greater fidelity than P. gingivalis load alone. These results necessitate a fundamental re-evaluation of treatment paradigms targeting single-species virulence and advocate for community-level antimicrobial intervention strategies.

Keywords: chronic periodontitis, keystone pathogen hypothesis, polymicrobial dysbiosis, subgingival microbiome, Porphyromonas gingivalis, clinical attachment loss, periodontal immunopathology, metagenomic profiling, antimicrobial periodontal therapy

Introduction

Chronic periodontitis remains one of the most prevalent infectious inflammatory diseases globally, affecting an estimated 1.1 billion individuals as of 2024 and constituting a significant burden on systemic health, quality of life, and healthcare infrastructure. The disease is characterized by irreversible destruction of the periodontium—encompassing the alveolar bone, periodontal ligament, and root cementum—driven by a dysregulated host immune response to subgingival polymicrobial biofilm accumulation. Despite decades of clinical research and substantial advances in microbiological characterization, the mechanistic framework governing the transition from a commensal subgingival ecology to a pathogenic dysbiotic state remains incompletely resolved. The keystone pathogen hypothesis, first formally articulated by Hajishengallis and Lamont in 2012, proposed that P. gingivalis, even at low abundance, could subvert innate immune complement signaling—specifically through C5a receptor manipulation—to orchestrate community-wide virulence amplification within the subgingival sulcus. This model offered an elegant mechanistic explanation for the disproportionate pathogenic influence exerted by a numerically minor species and rapidly became the dominant conceptual framework in periodontal etiopathogenesis. Consequently, much of the subsequent therapeutic development has been skewed toward targeting P. gingivalis-specific virulence determinants, including gingipains, fimbriae, and outer membrane vesicles, as singular intervention points. However, the translational yield of this pathocentric focus has been limited. Clinical trials employing P. gingivalis-targeted vaccines, gingipain inhibitors, and fimbriae-blocking antibodies have demonstrated inconsistent efficacy across diverse patient cohorts, suggesting that disease progression is not sufficiently explained by the activity of any single taxon. Concurrently, advances in high-throughput metagenomic sequencing, transcriptomics, and subgingival metabolomics have enabled a resolution of microbial community architecture that was previously unattainable, revealing that species such as Filifactor alocis, Prevotella intermedia, and Treponema denticola exhibit dynamic co-abundance patterns that correlate more robustly with probing depth and clinical attachment loss than P. gingivalis titers alone. Furthermore, host immunogenomic analyses have implicated polymorphisms in interleukin-1β, TNF-α, and Toll-like receptor signaling cascades as modulators that alter community response thresholds independent of specific pathogen load. These converging lines of evidence compel a critical re-examination of the keystone pathogen paradigm and its clinical derivatives. Specifically, they demand inquiry into whether single-pathogen targeting strategies are inherently insufficient and whether a community-ecology model of periodontal dysbiosis better captures disease etiology and informs more effective therapeutic design. The present article is structured as follows: Section 2 details the meta-analytic methodology and inclusion criteria applied to the 47 clinical cohort datasets; Section 3 presents integrated metagenomic and metabolomic findings across cohort strata; Section 4 re-evaluates the keystone pathogen hypothesis in light of these multi-omic data; Section 5 proposes a revised polymicrobial community-dysbiosis framework; and Section 6 discusses clinical and therapeutic implications for next-generation periodontal management protocols.

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