Metabolic traits of *Fusobacterium nucleatum* enhancing nutritional synergy in oral biofilms and their impact on periodontal disease

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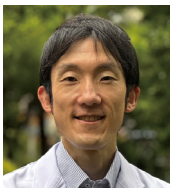

Abstract

Biofilms are diverse microbial communities with high affinity for the oral cavity and are direct causal entity of periodontal disease. Recently, the concept of community pathogenicity, where multidimensional interconnectivity enables a collective function, has gained attention as a pathogenic mechanism. *Fusobacterium nucleatum* is known for its ability to bind with various oral bacteria through abundant adhesion factors. This study demonstrates that *F. nucleatum* can influence the onset and progression of periodontal disease through nutritional interactions between different bacterial species via metabolite exchange.

Background & Results

Our previous research demonstrated that the early colonizer *Streptococcus gordonii* uses an arginine-ornithine antiporter (ArcD) to export ornithine, which supports the biofilm growth of *F. nucleatum* through a cross-feeding mechanism. In this study, metabolomic analysis and gene expression profiling of *F. nucleatum* during co-culture with *S. gordonii* revealed that *F. nucleatum* upregulates the expression of ornithine decarboxylase (FN0501) and metabolizes ornithine provided by *S. gordonii* into putrescine. The significant reduction in putrescine production was observed when co-cultured with an *S. gordonii arcD* mutant, indicating that putrescine production by *F. nucleatum* depends on release of ornithine from *S. gordonii*.

Polyamines, including putrescine, are known to trigger various physiological responses in many bacteria. Evaluating the effects of polyamines on *Porphyromonas gingivalis*, a major periodontal pathogen, revealed that putrescine not only promotes biofilm development but also enhances subsequent dispersal, accelerating the biofilm life cycle. In mixed biofilm experiments with the three species, cocultures with an Δ*arcD* mutant significantly suppressed both biofilm formation and dispersal of *P. gingivalis* (Fig.1). Additionally, analysis of 102 dental plaque samples showed a high co-occurrence of putrescine production gene modules from *S. gordonii* and *F. nucleatum* with *P. gingivalis* genes in subjects with severe periodontitis (Fig. 2). These findings suggest that a nutrient network centered on *F. nucleatum* can play a role in the development of periodontal disease (Fig. 3).

Significance of the research and Future perspective

The systemic impact of periodontal disease is increasingly being discussed with a focus on the oral-gut connection. Among the key players, *F nucleatum* has drawn attention for its association with colorectal cancer, highlighting its multifaceted nature. It is highly plausible that the metabolic characteristics of *F. nucleatum* play a significant role in this multifaceted behavior, warranting further investigation. Given that periodontal disease, once exacerbated, is difficult to control and cannot be fully restored to its previous state, emphasis should be placed on prevention over treatment. A deeper understanding of how the nutritional interactions within oral biofilms contribute to pathogenicity is needed for the persuit of biofilm control strategies as preventive measures.

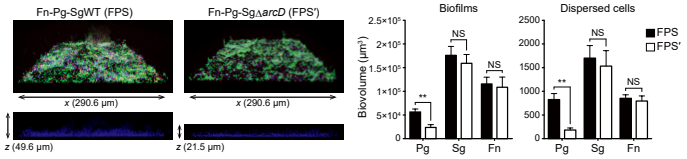

Figure 1

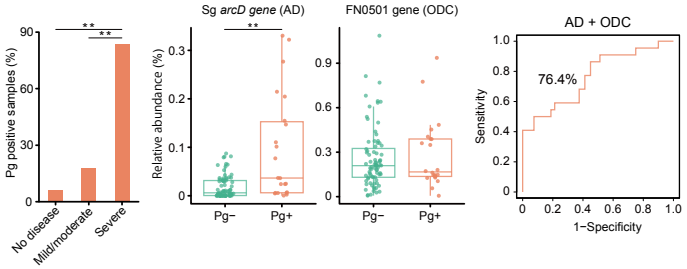

Figure 2

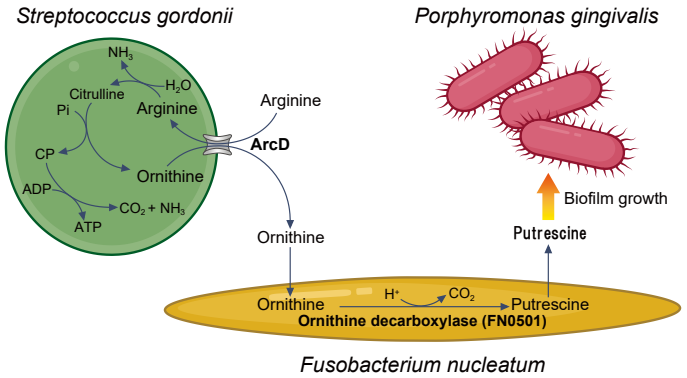

Figure 3

Patent

Treatise Sakanaka, Akito; Kuboniwa, Masae et al. *Fusobacterium nucleatum* metabolically integrates commensals and pathogens in oral biofilms. mSystems. 2022, 7(4). doi: 10.1128/msystems.00170-22

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