Elucidation of the enteric metabolic exacerbation of periodontal disease in diabetes and the mechanism of enhanced gluconeogenesis

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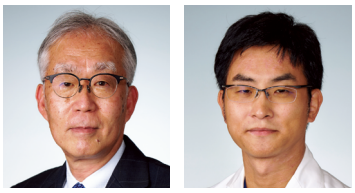

Abstract

Several hypotheses have been proposed to explain the molecular mechanisms that connect oral health deterioration, exemplified by conditions such as dental caries and periodontal disease, with overall health status. However, the precise nature of this causal relationship is not fully understood. Under the working hypothesis that "dysbiosis of the oral microbiota induces dysbiosis of the gut microbiota and exacerbates the overall health," our research group established an experimental mouse model of periodontitis by oral administration of *Porphyromonas gingivalis* (*Pg*), a periodontal pathogen, to diabetic mice (db/db) for one month. Metaproteomic and metabolomic analyses were conducted on liver and fecal samples collected from the experimental mice. The results revealed that alterations in the gut microbiota and metabolites due to the deterioration of the oral environment resulted in increased hepatic gluconeogenesis via the portal vein, which worsened the pathophysiology of diabetes.

Background & Results

Numerous reports have suggested a relationship between deterioration of oral health, represented by periodontal disease, and various systemic diseases. However, the precise molecular mechanisms linking oral environmental deterioration to overall health remain unclear. Several hypotheses have been proposed, including bacteremia resulting from bacterial infections originating in the periodontal tissues or the chronic production of inflammatory cytokines, such as TNF-α, in inflamed periodontal tissues, leading to systemic circulation. Multiple studies have indicated that deterioration of the gut microbiota influences systemic diseases. Therefore, a working hypothesis has been proposed that oral bacteria, when ingested with food and saliva, can cause dysbiosis in the gut microbiota, leading to systemic disturbances, such as colorectal cancer, NAFLD, and liver cancer.

Our research group has investigated the association between periodontitis and diabetes and has conducted studies to elucidate the underlying molecular mechanisms. Our study revealed that prolonged oral administration of *Pg*, a representative periodontal pathogen, in diabetic mice (db/db) resulted in destruction of the alveolar bone, which supports the teeth and exacerbates hyperglycemia over time. Furthermore, a metaproteome analysis of fecal samples from these mice revealed that the gut microbiota underwent alterations due to the oral administration of *Pg* (Figure 1).

Proteome and metabolome analyses of mouse liver revealed reduced glycogen content, elevated intermediate metabolites of glucose metabolism, decreased citric acid cycle-related enzymes, and increased expression of the glucose metabolism-related enzyme PCK1. Additionally, biochemical and histological analyses demonstrated enhanced expression of PCK1, a molecule related to gluconeogenesis, and its transcription factor FOXO1 in the livers of these mice (Figure 2).

These findings suggest an increase in glycogen breakdown and a decrease in energy metabolism within the mitochondria, suggesting that the ingestion of *Pg* from the oral cavity leads to enhanced gluconeogenesis in the liver via the enterohepatic pathway.

Significance of the research and Future perspective

In this study, we elucidated a part of the mechanism by which the deterioration of the oral environment, influenced by the onset and progression of periodontitis, comprehensively affects gut bacteria. This finding sheds light on the adverse effects of periodontitis on the overall health. As our understanding of these mechanisms deepens, we can expect advancements in our knowledge of the causes and processes of periodontitis, which is the most prevalent infectious disease worldwide. Additionally, this improved understanding may contribute to the development of new diagnostic methods and treatment approaches for lifestyle diseases that are exacerbated by deterioration of oral health.

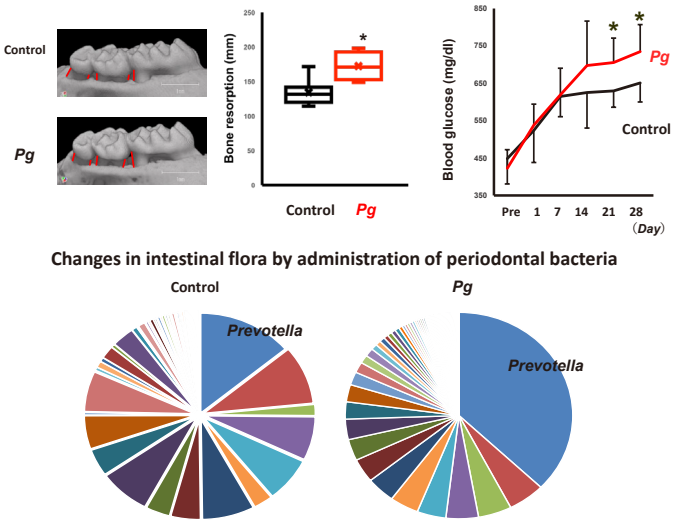

Fig.1 Each color of the pie chart indicates the composition of bacteria at the genus level.
Prevotella was increased by the *Pg* administration.

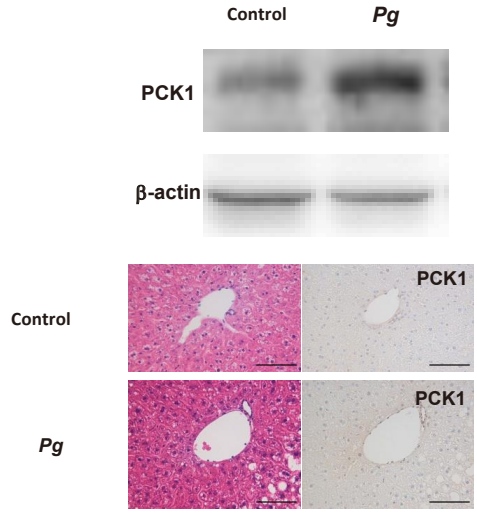

Fig.2 Oral administration of *Pg* increased the expression of gluconeogenesis-related molecule (PKC1) in the liver of diabetic mice.

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Treatise Kashiwagi, Yoichiro; Murakami, Shinya et al. Porphyromonas gingivalis induces entero-hepatic metabolic derangements with alteration of gut microbiota in a type 2 diabetes mouse model. Sci Rep. 2021;11(1):20016. doi: 10.1038/s41598-021-97868-2

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Keyword periodontal disease, gut microbiota, diabetes, glucose metabolism disorder, oral-gut axis