Effect of *Porphyromonas gingivalis* infection on gut dysbiosis and arthritis exacerbation in 1 mouse model

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Abstract
Background: *Porphyromonas gingivalis* (Pg) infection causes periodontal disease and is one of the causative bacteria of rheumatoid arthritis (RA) exacerbation. Gut microbiota dysbiosis has shown strong associations with systemic diseases, including RA, diabetes mellitus, and inflammatory bowel disease, and inoculation of periodontopathogenic bacteria (i.e. Pg) can alter gut microbiota composition. Therefore, this study investigated dysbiosis-mediated arthritis exacerbation by Pg oral inoculation in an experimental arthritis model mouse.

Methods: Pg inoculation in the oral cavity twice a week for 6 weeks was performed to induce periodontitis in SKG mice. Concomitantly, a single intraperitoneal (i.p.) injection of laminarin (LA) was administered to induce experimental arthritis (Pg-LA mouse). Citrullinated protein (CP) and IL-6 levels in periodontal, intestinal, and joint tissues, and serum were measured by ELISA. Gut microbiota composition was determined by MiSeq after DNA purification of mouse feces. Fecal microbiota transplantation (FMT) was performed by transferring Pg-RA-derived feces to normal mice. The effect of the Pg peptidylarginine deaminase (PgPAD) in arthritis progression was determined using PgPAD knockout mutant.

Results: Periodontal alveolar bone loss and IL-6 in gingival tissue were induced by Pg oral infection, as well as severe joint destruction, increased arthritis scores (AS), and IL-6 and CP production in serum, joint, and intestinal tissues. Distribution of Deferribacteres and S24-7 was decreased, while CP was significantly increased in gingival, joint, and intestinal tissues of Pg-inoculated experimental arthritis mice compared to experimental arthritis mice without Pg inoculation. Further, FMT from Pg-inoculated experimental arthritis mice showed the reproduction of donor gut microbiota and resulted in severe joint destruction with increased IL-6 and CP production in joint and intestinal tissues. The maximum AS of FMT from Pg-inoculated experimental arthritis was much higher than that of donor mouse. However, inoculation of the PgPAD knockout mutant inhibited the elevation of arthritis scores, ACPA level in serum and reduced CP amount in gingival, joint, and intestinal tissues compared to Pg wild type inoculation.

Conclusion: Pg oral infection exacerbated gut microbiota dysbiosis and joint destruction via increased
CP generation.

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