Porphyromonas gingivalis Sinks Teeth into the Oral Microbiota and Periodontal Disease

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Periodontitis is linked to polymicrobial interactions and the presence of *Porphyromonas gingivalis*. In this issue of *Cell Host & Microbe*, Hajishengallis et al. (2011) demonstrate that *P. gingivalis* colonization in the oral cavity changes the composition of the oral commensal microbiota and accelerates microbiota-mediated bone-destructive periodontitis, indicating that this single, low-abundance species is a keystone in periodontal disease.

Mucosal surfaces are colonized by a complex and dynamic microbial ecosystem termed "microbiota." The microbiota is composed of numerous specialized microbes that are well adapted to grow in their mucosal environment. The mucosal microbiota has a large impact on the host's physiology, metabolism, and immune system. The composition of the microbiota changes readily due to diet, host genotype, antibiotic ingestion, pathogen infection, and other environmental effects. In some instances, changes in the ecological balance of the microbiota can occur, such as an outgrowth of potentially pathogenic bacteria ("pathobionts") and/or a decrease in bacterial diversity, including bacteria beneficial to the host (Round and Mazmanian, 2009). An unfavorable alteration of the microbiota composition is called "dysbiosis" and has been implicated in a variety of diseases (Hill and Artis, 2010). Recent studies have demonstrated that several diseases, including obesity, metabolic disorders, and inflammatory bowel diseases, can be transmitted via the transfer of dysbiotic microbiota (Garrett et al., 2010b).

The oral cavity is home to a complex microbial community that has important implications for human health and disease. Bacteria in the oral cavity often proliferate in an attached multispecies biofilm community called a dental plaque. Dental caries and periodontitis are two major, oral inflammatory conditions that are initiated by the growth of these dental plaques. The role of bacteria in the initiation and maintenance of oral inflammatory disease is complex and likely involves polymicrobial interactions within dental plaques (Darveau, 2010). *Porphyromonas gingivalis* is a gram-negative anaerobic bacterium belonging to the phylum Bacteroidetes and is frequently found in the plaque biofilms on tooth surfaces from individuals with periodontitis. Therefore, it has been strongly implicated in the onset and progression of periodontitis. *P. gingivalis* exhibits aggregative, tissue destructive, and host immune dysregulatory properties mediated by the production of adhesins, fimbriae, proteases, and capsular polysaccharides (Darveau, 2010). However, the fundamental mechanism by which *P. gingivalis* contributes to polymicrobial biofilm disease is still unclear.

Using a murine periodontal model, Hajishengallis et al. demonstrated that, even at low numbers, the colonization of *P. gingivalis* in the oral cavity triggered changes in the amount and composition of the oral commensal microbiota by perturbing the host immune system (Hajishengallis et al., 2011). The authors demonstrated that while the presence of oral commensal microbiota caused gradual bone loss in the periodontal tissue ("naturally occurring bone loss"), the introduction of *P. gingivalis* into the oral microbiota community led to a marked acceleration in periodontal bone loss ("pathological bone loss"). However, because *P. gingivalis* alone failed to induce periodontitis when it colonized germ-free mice and the colonization of *P. gingivalis* in specific pathogen-free mice led to both an increase in the total bacterial load and changes in the composition of the microbiota, *P. gingivalis* is likely to exert its bone-destructive role in cooperation with other, dysbiotic bacteria in the biofilm.

Naturally occurring microbiota in oral biofilm provide constant stimulation of the host innate immune system. This constitutive signaling of innate immune receptors keeps the mucosa in a state of "physiological inflammation" and leads to the continuous production of tissue repair factors and antimicrobial proteins. These factors maintain the mucosal barrier integrity and resist colonization by pathogens. This inflammation is accompanied by the production of cytokines, such as IL-17 and RANKL, that induce periodontal bone loss at a very slow rate. Hajishengallis et al. showed that *P. gingivalis* dramatically accelerated bone loss and that *P. gingivalis*-mediated bone loss was dependent on the complement receptor C5aR (Hajishengallis et al., 2011). It is known that *P. gingivalis* produces gingipain, which enzymatically cleaves the complement component C5 and increases the local concentration of C5a (Figure 1). C5a activates C5aR and typically acts as both a powerful chemoattractant and an activator of phagocytes. However, Hajishengallis et al. have demonstrated that, in the presence of *P. gingivalis*, C5aR signaling acts cooperatively with Toll-like receptor 2 to induce an increase in the cyclic adenosine monophosphate (cAMP) concentration that leads to the inhibition of both the oxidative burst and the killing activity of leukocytes (Hajishengallis et al., 2011; Wang et al., 2010). The authors also

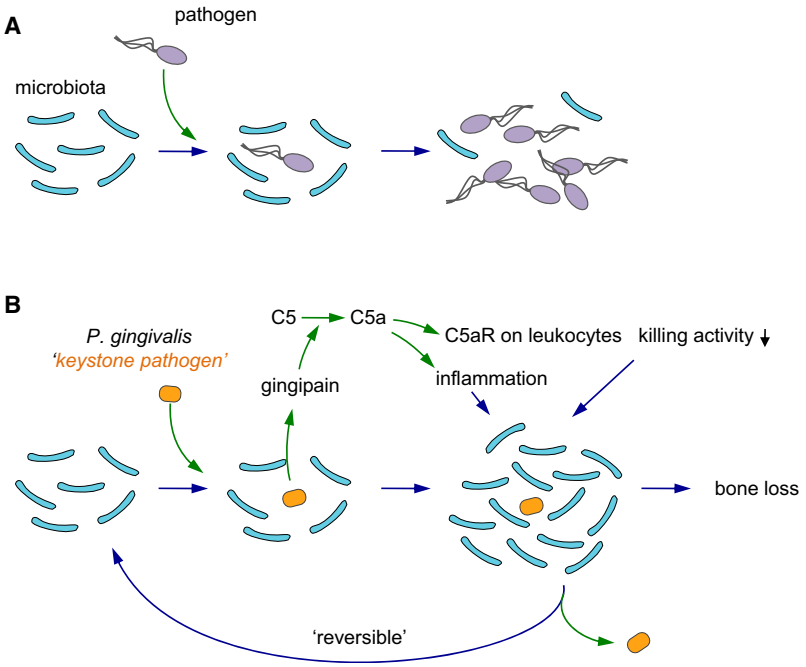

Figure 1. Keystone Species-like Activity of *P. gingivalis* in Periodontitis
(A) Pathogenic bacteria usually induce severe inflammation and outgrow other indigenous bacteria.
(B) In contrast, *P. gingivalis* colonizes at low levels and acts as a "keystone." *P. gingivalis* expresses gingipain, which functions as a C5 convertase-like enzyme and generates high levels of C5a locally for C5aR activation. This C5aR signaling triggers inflammation but inhibits the killing capacity of leukocytes as well. In addition, *P. gingivalis* suppresses the expression of chemokines (not depicted). Therefore, *P. gingivalis* provides the biofilm with a nutrient-rich, gingival inflammatory exudate and promotes its own survival and the growth of other bacteria. As a result, the colonization of *P. gingivalis* dramatically alters the composition of the oral microbiota and induces persistent inflammation for bone resorption.

showed that *P. gingivalis* inhibited the expression of chemokines, such as CXCL1 (a mouse ortholog of human IL-8). These results suggest that *P. gingivalis* induces inflammation either without recruiting leukocytes or through the recruitment of leukocytes with an impaired killing function. This likely provides an inflammatory exudate-rich environment that is beneficial for the persistent infection of *P. gingivalis* and the uncontrolled growth of other bacterial species in the biofilm. This dysbiotic biofilm induces periodontal bone loss much faster than a biofilm with the normal commensal microbiota.

P. gingivalis may fulfill the criteria of a "keystone pathogen" for periodontal disease because the change in the composition of the microbiota and the dramatic acceleration of bone loss is caused by this single, low-abundance species (Figure 1). A keystone species is a species that plays a critical role in maintaining the structure of an ecological community and the impact of which on the community is greater than would be expected, based on its relative abundance. The keystone species concept was first introduced by zoologist Robert T. Paine, who studied a community of seacoast organisms (Paine, 1969). He showed that the starfish *Pisaster ochraceus* played a key role in maintaining the ecological balance of all other community organisms. Without this starfish, two mussel species within the community proliferated unchecked and took over the community, resulting in a severe reduction in community diversity. Keystone species are usually identified when they are removed from an ecosystem, which results in dramatic changes to the rest of the community. Indeed, the selective removal of *P. gingivalis* from the oral cavity using a C5aR antagonist reversed dysbiosis and aberrant inflammation, further supporting *P. gingivalis* as a keystone pathogen (Figure 1).

Several reports have shown that inflammation induced by pathogenic bacteria can lead to changes in the composition and amounts of microbiota (Figure 1). For example, enteric pathogens in the intestine, such as *Citrobacter rodentium* and *Salmonella typhimurium,* actively induce intestinal inflammation and alter the indigenous microbiota composition. A change in the microbiota composition has also been demonstrated in *T-bet*$^{-/-}$*Rag2*$^{-/-}$ mice, in which spontaneous colitis occurs due to the expansion of colitogenic bacteria, such as *Proteus mirabilis* and *Klebsiella pneumoniae* (Garrett et al., 2010a). However, these enteric pathogens colonize the gut at extremely high levels and severely suppress the growth of other indigenous bacteria. *S. typhimurium* accounts for >90% of the total bacterial numbers, and *C. rodentium* replicates to 10^9 CFU/g of intestinal contents (Lupp et al., 2007; Stecher and Hardt, 2008). In contrast, *P. gingivalis* was detected at <0.01% of the total oral microbiota, but dramatically affected the growth of other bacteria to promote inflammation and disease. Therefore, *P. gingivalis* is a unique pathogen because of its relatively low abundance and its mechanism of action, and it can be classified as a keystone pathogen.

Keystone species are clear targets for therapeutic intervention because of their large influence on species diversity and community structure. The authors demonstrated that local administration of a C5aR antagonist efficiently and specifically eliminated *P. gingivalis* from the periodontal tissue and prevented disease progression. Although the reason why a C5aR antagonist specifically depleted *P. gingivalis* is unknown, it is clear that this report suggests a new clinical strategy for the treatment of periodontal diseases and potentially of other diseases associated with dysbiotic microbiota.

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