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Porphyromonas gingivalis neutrophil manipulation: risk factor for Periodontitis?

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Abstract

Defining the contribution of individual members of dysbiotic host associated bacterial communities has been difficult. The recent paper by Maekawa et al. in Cell host Microbe describes bacterial manipulation of neutrophil responses by *Porphyromonas gingivalis* as a mechanism that contributes to forming a dysbiotic community.

It has been difficult to define the contribution of individual members of a polymicrobial community when they are associated with chronic inflammatory diseases. One example is periodontitis which is a common disease that results in alveolar bone loss and if left untreated the eventual loss of teeth. A polymicrobial etiology for periodontitis has been well established by studies that show removal of dental plaque, the polymicrobial biofilm found on the tooth surface normally results in disease resolution. Furthermore, extensive microbial composition analyses have identified select oral bacteria, such as *Porphyromonas gingivalis* that are strongly associated with disease sites. However, its relationship to the disease process remains unclear. Examination of *P. gingivalis* revealed that it was capable of inhibiting normal chemokine secretion mechanisms of oral epithelial cells as well as producing a lipid A that was a TLR4 antagonist. These characteristics, which have the potential to alter the entire oral bacterial communities interaction with the host led to the notion that *P. gingivalis* is a keystone species in the oral biofilm [1] and may orchestrate a change in the polymicrobial community leading to dysbiosis and disease [2].

The recent article by Maekawa et al. [3] provides further support and a detailed mechanistic understanding of how *P. gingivalis* can alter the dental plaque polymicrobial community amount and composition. A series of elegant experiments demonstrated that *P. gingivalis* orchestrates a neutrophil host response that results in neutrophil inhibition of bacterial killing while at the same time maintaining a strong cytokine inflammatory response. It accomplishes this manipulative feat by co-activating TLR2 and C5aR in neutrophils. Importantly, the work provides evidence that at least in the mouse chamber model of

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infection; activation of P13K by *P. gingivalis* not only facilitates its own resistance to phagocytosis, it also facilitates the survival of *Fusobacterium nucleatum*, another member of the oral dental plaque community. Furthermore, an in vivo study in the paper provides evidence that activation of TLR2, C5aR, and P13K may actually contribute to an increase in the oral total microbial load consistent with the notion that *P. gingivalis* manipulates these cellular responses to alter the entire microbial community. These data provide convincing support and at least one mechanistic scenario for the notion that *P. gingivalis* interactions with the host can create a dysbiotic oral community.

A key contribution of describing periodontitis as a dysbiotic disease is its emphasis on bacterial community and the ramifications thereof in understanding periodontitis microbial virulence. For example, one ramification of bacterial community thinking is that an increase in the number of community members may lead to disease or that alterations in community structure may select for single species that are sufficient to cause disease. Both of these scenarios have been previously proposed as the non-specific and periopathogenic hypothesis respectively and both have been demonstrated in two different animal models of periodontitis [4, 5]. However, it is not clear if the dysbiotic community described in Maekawa et al. [3] results in alveolar bone loss, the distinguishing characteristic of periodontitis. Nevertheless, manipulation of host innate or immune response systems as described in Maekawa et al. [3] where co-engagement of TLR2 and C5aR leads to significant bacterial community changes is unique. Yet, it may not be appropriate to describe the manipulation of the host response by *P. gingivalis* as a virulence factor since *P. gingivalis* is often found in healthy sites and it is not clear that this manipulation is required for bone loss. Rather, it might at least at this stage be more appropriate to describe the presence of *P. gingivalis* in the oral biofilm as a risk factor for disease rather than a periopathogen as an etiologic agent for disease. This approach allows for the incorporation of other members of the community in the disease process.

P. gingivalis by creating a dysbiotic community has significantly altered the social structure of the dental plaque biofilm. This is similar to the effect that smoking, a risk factor for periodontitis, has in that it has recently been found to create a subgingival microbiome in healthy sites that more closely resembles diseased sites, suggesting that smoking creates “an at-risk-for-harm environment” to create periodontitis [6]. Social structure recognizes that not all bacteria in the community act independently but rather may cooperate or compete for their own or the communities advantage [7, 8]. Cooperation and competition of host associated microbial communities takes place in an environment where innate and immune responses represent environmental factors that contribute to survival. Coevolution of our healthy microbiome communities [9] and their beneficial effects on our own tissue function underscores the communication that exists between our polymicrobial communities and the host [10]. Understanding those interactions that help maintain community stability and contribute to healthy periodontal tissue structure and function as opposed to those like *P. gingivalis* that disrupt community structure and subsequent interactions with the host is an exciting area of study.

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