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MUCOSAL IMMUNOLOGY

Two routes to success

Organisms that promote dysbiosis (a compositional shift in the microbiota), such as the bacterium *Porphyromonas gingivalis*, are faced with a conundrum: on the one hand, they need to evade immune-mediated killing but on the other hand, they require inflammation, as this produces the nutrients that they need to survive through tissue breakdown. In a new study, Hajishengallis and colleagues reveal how *P. gingivalis* manipulates host neutrophils to solve this problem.

P. gingivalis is a pathogen of the oral cavity, a location in which neutrophils are known to act as the main phagocytes. Because the bacterium requires intact signalling through complement C5a receptor (C5AR; also known as C5AR1) to drive dysbiosis, and because it is recognized by Toll-like receptor 2 (TLR2), the authors postulated that *P. gingivalis* exploits these pathways in neutrophils to avoid killing yet promote periodontal inflammation.

> “host neutrophils are ‘manipulated’ by *P. gingivalis* … [to] ensure bacterial survival and the perpetuation of inflammation”

Using an *in vivo* model that allows the quantitative assessment of bacterium–neutrophil interactions, they found that *C5ar*$^{-/-}$ or *Tlr2*$^{-/-}$ mice had reduced numbers of viable *P. gingivalis*. The inhibition or loss of either C5AR or TLR2 had the same effect on *P. gingivalis* survival, suggesting that these receptors probably engage in cooperative crosstalk to prevent bacterial killing. Similar findings were obtained using human neutrophils *in vitro*.

But how does this crosstalk promote bacterial survival? The TLR2 adaptor myeloid differentiation primary response protein 88 (MYD88) is known to contribute to the clearance of *P. gingivalis* and, consistent with this, the bacterium showed enhanced survival in *Myd88*$^{-/-}$ mice compared with wild-type mice. Further analysis revealed that *P. gingivalis* triggers the proteasomal degradation of MYD88, through ubiquitylation by the E3 ligase SMURF1, thus avoiding immune-mediated killing. Notably, this required crosstalk between C5AR and TLR2, as inhibiting either of these two receptors reversed the ability of the bacterium to trigger MYD88 degradation.

Interestingly, blocking C5AR or TLR2 in *Myd88*$^{-/-}$ mice reduced bacterial survival, suggesting that *P. gingivalis* must use an additional, MYD88-independent mechanism to mediate signalling downstream of these two receptors. Indeed, the authors found that the bacterium takes advantage of another pathway downstream of C5AR–TLR2 that prevents killing through phagocytosis. Specifically, the TLR2 adaptor MYD88 adaptor-like protein (MAL) activates phosphoinositide 3-kinase (PI3K), which, in turn, suppresses actin polymerization through the RHO GTPase RHOA, thereby inhibiting phagocytosis.

The TLR2–MAL–PI3K pathway was also found to sustain the inflammation that *P. gingivalis* and the periodontal microbiota require, as inhibiting MAL or PI3K reversed the production of pro-inflammatory cytokines. This almost eliminated *P. gingivalis* from the periodontal tissue and reversed the *P. gingivalis*-mediated increase in microbial load.

So, host neutrophils are ‘manipulated’ by *P. gingivalis* through two distinct mechanisms that together ensure bacterial survival and the perpetuation of inflammation. The authors propose that targeting the different components of this pathway could be a useful strategy for the treatment of dysbiotic, inflammatory diseases.

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ORIGINAL RESEARCH PAPER Maekawa, T. *et al.* *Porphyromonas gingivalis* manipulates complement and TLR signaling to uncouple bacterial clearance from inflammation and promote dysbiosis. *Cell Host Microbe* **15**, 768–778 (2014)