



Review

Complement and dysbiosis in periodontal disease

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ABSTRACT

Signaling crosstalk between complement and Toll-like receptors (TLRs) normally serves to coordinate host immunity. However, the periodontal bacterium *Porphyromonas gingivalis* expresses C5 convertase-like enzymatic activity and adeptly exploits complement–TLR crosstalk to subvert host defenses and escape elimination. Intriguingly, this defective immune surveillance leads to the remodeling of the periodontal microbiota to a dysbiotic state that causes inflammatory periodontitis. Understanding the mechanisms by which *P. gingivalis* modulates complement function to cause dysbiosis offers new targets for complement therapeutics.

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Introduction

Microbial pathogens which successfully disarm, suppress, or delay host defenses target preferentially innate immunity (Finlay and McFadden 2006) and particularly key systems such as complement and the Toll-like receptor (TLR) family of pattern-recognition receptors (Hajishengallis and Lambris 2011). Collectively, complement and TLRs sense pathogens through “pattern recognition” and “missing-self recognition” strategies and trigger the activation of antimicrobial and inflammatory responses, as well as the initiation of the adaptive immune response (Kawai and Akira 2010; Ricklin et al. 2010). Until relatively recently, both systems were primarily investigated as separate entities. However, a substantial body of literature has demonstrated extensive crosstalk between complement and TLR signaling pathways (Hajishengallis and Lambris 2010; Hawlisch et al. 2005; la Sala et al. 2005; Zhang et al. 2007). Both synergistic and antagonistic interactions between complement and TLRs have been described which apparently serve to invigorate the host response or regulate it to prevent unwarranted inflammatory responses (Ricklin et al. 2010). Therefore, pathogens targeting complement and/or TLRs have the opportunity to infiltrate an extensive network of signaling pathways in ways that could impair innate host defense and, moreover, deregulate the induction of adaptive immunity or divert it in ways that favor their survival.

In this review we focus on *Porphyromonas gingivalis*, a gram-negative oral anaerobic bacterium recently shown to manipulate complement–TLR crosstalk to enhance its survival and virulence (Hajishengallis et al. 2007; Hajishengallis et al. 2011; Liang et al. 2011; Wang et al. 2007; Wang et al. 2010) (Fig. 1). Importantly, these subversion mechanisms are highly relevant in the context of the collective virulence of the microbial community in which *P. gingivalis* resides. Specifically, *P. gingivalis* can act as a “keystone pathogen” which remodels the commensal microbiota into a dysbiotic partner that disrupts the homeostatic balance with the host tissue leading to destructive inflammation in periodontitis (Hajishengallis et al. 2011) (Fig. 2).

Periodontitis is a biofilm-driven chronic inflammatory disease that affects the tooth-supporting tissues (periodontium) leading, in some cases, to tooth loss (Pihlstrom et al. 2005). This oral disease affects the majority of adults, whereas an estimated 10–15% develops severe periodontitis, which increases the patients' risk for atherosclerosis, aspiration pneumonia, diabetes, adverse pregnancy outcomes, and perhaps rheumatoid arthritis (Genco and Van Dyke 2010; Lalla and Papapanou 2011; Lundberg et al. 2010; Pihlstrom et al. 2005; Tonetti et al. 2007; Xiong et al. 2006).

Periodontitis is characterized by dramatic changes in the numbers and composition of the periodontal bacterial community relative to health (Moore et al. 1982; Socransky 1977; Socransky and Haffajee 2005). It has recently been proposed that periodontitis fundamentally represents disruption of host–microbial homeostasis caused by dysbiosis of the periodontal microbiota (Darveau 2010; Hajishengallis et al. 2011). According to this notion, changes in the relative abundance of individual components of the microbiota compared to their abundancies in health can lead

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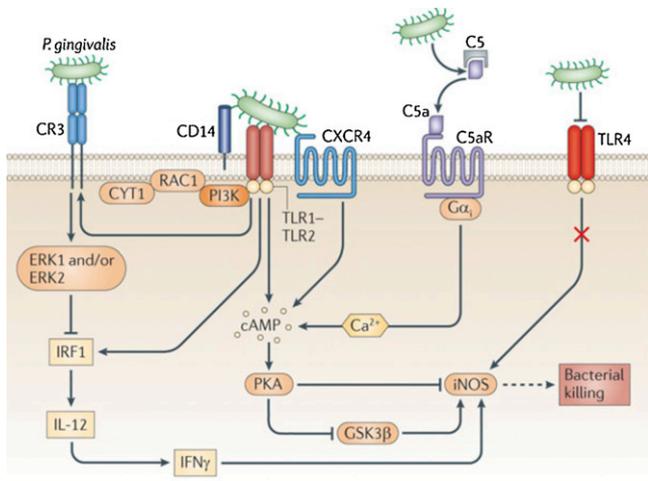


Fig. 1. Exploitation of signaling crosstalk by *P. gingivalis*. *P. gingivalis* interacts with Toll-like receptor (TLR)-2 (as part of a CD14–TLR2–TLR1 signaling complex) and with TLR4. The activation of TLR4 is suppressed by the bacterium's atypical lipopolysaccharide which acts as an antagonist. The TLR2 response is manipulated through crosstalk with other innate receptors. By means of Arg-specific cysteine proteinases that release biologically active C5a from C5, *P. gingivalis* activates the C5a receptor (C5aR) and induces intracellular Ca^{2+} signaling which synergistically enhances the otherwise weak cAMP responses induced by TLR2 activation alone. Maximal cAMP induction requires the participation of CXC-chemokine receptor 4 (CXCR4), which is activated directly by the bacterium's fimbriae. The resulting activation of the cAMP-dependent protein kinase A (PKA) inactivates glycogen synthase kinase-3 β (GSK3 β) and inhibits the inducible nitric oxide synthase (iNOS)-dependent killing of the pathogen in macrophages. An additional pathway induced downstream of TLR2 is an inside-out signaling pathway, mediated by RAC1, phosphatidylinositol-3 kinase (PI3K) and cytohesin 1 (CYT1), which transactivates complement receptor-3 (CR3). Activated CR3 binds *P. gingivalis* and induces extracellular signal-regulated kinase-1/ERK2 signaling, which in turn selectively downregulates IL-12 p35 and p40 mRNA expression through suppression of interferon regulatory factor 1 (IRF1). Inhibition of bioactive IL-12, and secondarily IFN γ , leads to impaired immune clearance of *P. gingivalis*.

From Hajishengallis and Lambris (2011).

to alterations in the host–microbial crosstalk sufficient to initiate inflammatory disease.

Although *P. gingivalis* is a quantitatively minor component of periodontal pathogenic biofilms, its presence has been associated

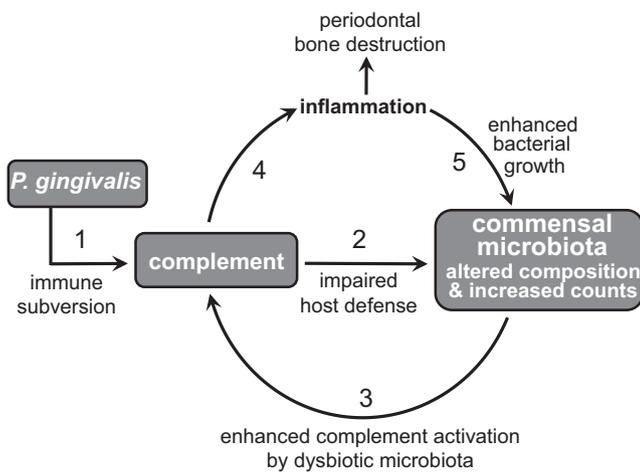


Fig. 2. *P. gingivalis* exploits complement and causes dysbiotic inflammation. *P. gingivalis* subverts complement and impairs host defense leading to altered composition and increased numbers of periodontal commensal bacteria which, in turn, cause complement-dependent periodontal inflammation and bone loss. The inflammatory environment is favorable to further bacterial growth as it provides the dysbiotic microbiota with a nutrient-rich gingival inflammatory exudate. Numbers indicate a possible sequence of events, although the overall process represents a self-feeding cycle that drives and sustains persistent inflammation.

with progressive bone loss in periodontitis patients (Chaves et al. 2000; Doungudomdacha et al. 2000; Kumar et al. 2006; Moore et al. 1982; Moore et al. 1991; Socransky et al. 1998). However, the fundamental mechanism by which *P. gingivalis* may contribute to a polymicrobial disease such as periodontitis has remained elusive until recently. As alluded to above, useful insights have been provided by a study in the mouse model of periodontitis which demonstrated that *P. gingivalis* can act as a keystone pathogen which reshapes an otherwise harmless periodontal microbiota into a disease-provoking microbiota (Hajishengallis et al. 2011).

The capacity of *P. gingivalis* to act as a keystone member of the periodontal microbiota is dependent, in great part, upon its ability to exploit complement and TLRs (Hajishengallis et al. 2011) (Table 1). Subversion of complement and TLRs might also account for the ability of *P. gingivalis* to relocate to systemic tissues and contribute to disease. In this regard, *P. gingivalis* is a common isolate from aspiration pneumonia and lung abscesses (Finegold 1991; Okuda et al. 2005) and has been detected in a viable state in atherosclerotic plaques (Kozarov et al. 2005). Below we summarize and discuss recently established mechanisms whereby *P. gingivalis* can manipulate complement to sabotage its functions and its productive interactions with TLRs. In this way, the host response is diverted to favor the pathogen and its microbial community leading to dysbiosis and destructive inflammation in the periodontal tissue.

Complement inhibition by *P. gingivalis*

The interactions of *P. gingivalis* with complement are complex and include both inhibitory and stimulatory effects (Krauss et al. 2010) (Table 1). This is not surprising given that complement mediates diverse functions (Ricklin et al. 2010), some of which could involve effective antimicrobial action (targets of inactivation), while certain complement-dependent inflammatory pathways could benefit the periodontal bacteria (targets of activation). *P. gingivalis* can suppress complement activation, regardless of the initiation pathway involved (classical, lectin, or alternative) through gingipain-dependent degradation of C3 (Popadiak et al. 2007). All three gingipain enzymes can cause complement inactivation, although the Arg-specific enzymes (HRgpA and RgpB) are more potent than the Lys-specific gingipain (Kgp) (Popadiak et al. 2007). As a consequence of complement inhibition, the deposition of opsonins or the membrane attack complex on the surface of *P. gingivalis* is suppressed, whereas ablation of its gingipain activity by chemical or genetic means reverses these effects (Potempa and Pike 2009). For increased safety against complement, this bacterium seems to hijack physiological inhibitors of the complement cascade. Indeed, *P. gingivalis* uses its HRgpA to capture the circulating C4b-binding protein on the bacterial cell surface, and in this way to negatively regulate the classical pathway C3 convertase (Potempa et al. 2008).

It should be noted that other periodontal bacteria associated with periodontitis, such as *Prevotella intermedia*, *Tannerella forsythia*, and *Treponema denticola*, also possess mechanisms for escaping complement. Interpain A (InpA), a streptopain-like cysteine protease secreted by some *P. intermedia* strains, degrades C3 and contributes to resistance against the antibacterial activity of complement (Potempa et al. 2009). Karilysin, a metalloprotease expressed by *T. forsythia* confers resistance to killing by human complement by acting at different stages of complement activation. Specifically, karilysin inhibits the classical and lectin pathways by degrading MBL, ficolin-2, ficolin-3, and C4, whereas it blocks the terminal pathway by degrading C5 (Jusko et al. 2012). Importantly, both InpA and karilysin synergize with gingipains in these functions suggesting that *P. gingivalis*, *P. intermedia*, and *T.*

Table 1
Subversion of complement and TLRs by *P. gingivalis*.

Mechanism	Effector molecules	Refs.
1 Inhibition of complement activation by degrading the central complement component (C3)	Gingipains, especially HRgpA & RgpB	Popadiak et al. (2007), Potempa et al. (2009)
2 Hijacking negative regulators of complement (C4b-binding protein)	HRgpA	Potempa et al. (2008)
3 Proactive generation of C5a for instigating subversive C5aR–TLR2 crosstalk	HRgpA & RgpB	Liang et al. (2011), Wang et al. (2010)
4 Transactivation of CR3 and exploitation of CR3-mediated phagocytosis	Fimbriae	Liang et al. (2011), Wang et al. (2007)
5 Suppression of TLR2-induced IL-12 via CR3 binding or C5aR activation	Fimbriae or HRgpA & RgpB	Hajishengallis et al. (2007), Liang et al. (2011)
6 TLR4 evasion by expressing dephosphorylated tetra-acylated lipid A	Lipid A 1- and 4-phosphatases & deacylase	Coats et al. (2009)
7 TLR4 antagonism by expressing monophosphorylated tetra-acylated lipid A	Lipid A 4-phosphatase & deacylase (lipid A 1-phosphatase suppressed by hemin)	Coats et al. (2005), Coats et al. (2009)

forsythia together can better promote the survival in the dental biofilm of bystander bacterial species, which could otherwise be readily eliminated by the bactericidal activity of complement. *T. denticola* expresses a 11.4-kDa cell surface lipoprotein which can bind factor H (McDowell et al. 2009). This function suggests that *T. denticola* may escape complement-dependent killing by means of surface-bound, biologically active factor H. Interestingly, however, after full-length factor H becomes associated with *T. denticola*, the bacterium uses its serine protease dentilisin to cleave factor H and generate a 50-kDa factor H fragment that remains attached to the bacterial surface (McDowell et al. 2009). An interesting question is whether the attached fragment retains useful complement inhibitory activity to protect *T. denticola* against complement. Alternatively, through this mechanism, dentilisin may in fact inactivate factor H and deregulate complement, thereby promoting local inflammation which could also be beneficial for periodontal bacteria (see next section).

Intriguingly, the HRgpA and RgpB gingipains of *P. gingivalis* display C5 convertase-like activity and generate biologically active C5a, whereas C5b is destroyed (Wingrove et al. 1992). In heat-inactivated human serum, *P. gingivalis* can rapidly generate >30 nM of C5a (Wang et al. 2010). This activity seems counterproductive for the adaptive fitness of this pathogen, since C5a is probably the most potent effector of the complement cascade and generally promotes host defense, e.g., through chemotactic recruitment and activation of leukocytes (Guo and Ward 2005; Hopken et al. 1996). Strikingly, however, *P. gingivalis* exploits C5a to manipulate TLR signaling (below).

Hijacking of C5aR–TLR2 crosstalk

The TLR system senses *P. gingivalis* primarily through TLR2, as shown by *in vitro* and *in vivo* observations, which additionally have excluded a significant role for TLR4 (Burns et al. 2006; Hajishengallis et al. 2006b). The lack of significant TLR4 involvement in the host response to *P. gingivalis* is counterintuitive given that this is a gram-negative bacterium that expresses a lipopolysaccharide. However, *P. gingivalis* utilizes specific lipid A 1- and 4-phosphatases and a deacylase which in concert generate a tetra-acylated and dephosphorylated lipid A structure that is biologically inert (Coats et al. 2009). Moreover, high concentrations of hemin (as can be found in inflamed periodontal sites) suppress the lipid A 1-phosphatase activity and lead to the generation of a monophosphorylated lipid A, which acts as a TLR4 antagonist (Coats et al. 2005; Coats et al. 2009) (Table 1). These unique LPS features allow *P. gingivalis* to evade or antagonize TLR4 activation at the receptor level. Moreover, this pathogen has evolved sophisticated complement-dependent strategies to selectively intercept only a subset of TLR2 signaling events (Kagan 2010; Wang et al. 2010). In

this way, *P. gingivalis* can filter out pathways that could result in its elimination, whereas it can selectively maintain or enhance host responses that favor its survival.

Specifically, *P. gingivalis* instigates a C5aR–TLR2 subversive crosstalk that undermines the killing function of macrophages. Indeed, *P. gingivalis*-generated C5a locally activates C5aR and stimulates G α i-dependent intracellular Ca²⁺ signaling which synergistically enhances an otherwise weak cAMP response by *P. gingivalis*-induced TLR2 activation alone. In this crosstalk pathway, which additionally involves the participation of the CXC chemokine receptor-4, elevated and sustained production of cAMP leads to the activation of the cAMP-dependent protein kinase A which inactivates the glycogen synthase kinase-3 β and impairs nitric oxide-dependent killing of *P. gingivalis* (Hajishengallis et al. 2008; Wang et al. 2010).

The *P. gingivalis*-induced C5aR–TLR2 crosstalk also regulates cytokine production in favor of the pathogen (Liang et al. 2011). Specifically, *P. gingivalis* proactively and selectively inhibits TLR2-induced IL-12p70, whereas the same C5aR–TLR2 crosstalk upregulates inflammatory and bone-resorptive cytokines (IL-1 β , IL-6, and TNF). *In vivo*, the ability of *P. gingivalis* to manipulate TLR2 activation via the C5a–C5aR axis allows it to escape IL-12p70-dependent immune clearance and to cause inflammatory bone loss in a murine model of experimental periodontitis (Liang et al. 2011). Therefore, by targeting C5aR, *P. gingivalis* not only can promote its survival but also cause destructive inflammation.

Because the C5aR–TLR2 crosstalk inhibits only a subset of TLR2 signaling events, C5aR was characterized as a “TLR modulatory receptor” as opposed to “TLR inhibitory receptors”, such as IL-10 receptor or TGF- β receptor, which block most, if not all, inflammatory responses (Kagan 2010). In fact, it would not be in the “best interest” of *P. gingivalis* to induce a generalized immunosuppression, since such action would spare the bacterium from leukocytes but, on the other hand, would probably starve it to elimination. In this regard, *P. gingivalis* is a proteolytic and asaccharolytic organism the survival and growth of which depend crucially on inflammatory tissue break down products (degraded proteins) and gingival inflammatory fluid-derived hemin, a source of essential iron (Krauss et al. 2010). Therefore, inflammation is exploited by *P. gingivalis* as a means for survival, although in a chronic setting this causes collateral damage to the periodontium.

Exploitation of the TLR2–CR3 inside–out signaling pathway

P. gingivalis appears to use a number of distinct but reinforcing mechanisms to escape leukocyte killing. Thus, in addition to exploiting the C5aR–TLR2 crosstalk, it can also take advantage of the TLR2 inside–out signaling pathway for complement receptor 3 (CR3) transactivation. CR3 is a β_2 integrin (CD11b–CD18)

the binding activity of which is tightly regulated: In resting cells, CR3 displays a low-affinity conformation, whereas a rapid and transient shift to a high-affinity state can be triggered through inside–out signaling by chemokine or anaphylatoxin receptors (Abram and Lowell 2009). More recently, TLRs were also shown to mediate inside–out signaling for CR3 activation (Han et al. 2010; Harokopakis and Hajishengallis 2005; Sendide et al. 2005). Tight regulation of the CR3 binding activity is important since this is a functionally versatile molecule involved in the phagocytosis of apoptotic cells, leukocyte trafficking, and regulation of cytokine production (Ricklin et al. 2010).

However, CR3 activation may come under the control of *P. gingivalis*: The pathogen induces TLR2-mediated transactivation of CR3 through an inside–out pathway that involves Rac1, PI3K and cytohesin-1 (Harokopakis and Hajishengallis 2005; Harokopakis et al. 2006). This mechanism allows *P. gingivalis* to bind activated CR3 for a relatively safe “outside–in” entry into macrophages. Indeed, CR3-deficient macrophages are superior to wild-type macrophages in the intracellular killing of this oral pathogen (Hajishengallis et al. 2006a; Wang et al. 2007). Moreover, pharmacological inhibition of CR3 greatly facilitates the intracellular killing of *P. gingivalis* (Hajishengallis et al. 2007). Antagonistic blockade of CR3 also suppresses *P. gingivalis*-induced periodontal bone loss in the mouse periodontitis model (Hajishengallis et al. 2007).

Although CR3 is a phagocytic receptor, it is not linked to strong microbicidal mechanisms such as those activated by Fc γ R-mediated phagocytosis (Caron and Hall 1998; Lowell 2006). This is possibly because CR3 is heavily committed with the phagocytosis of iC3b-coated apoptotic cells, which are not normally recognized as danger (Kim et al. 2004; Mevorach et al. 1998). Furthermore, at least under certain conditions, CR3-derived phagosomes do not fuse with lysosomes (Gatfield and Pieters 2000). These observations may explain why CR3 is a target of exploitation by *P. gingivalis*. Moreover, CR3 binding by the fimbriae of *P. gingivalis* inhibits IL-12p70 production by macrophages (Hajishengallis et al. 2007) (Fig. 1). Not surprisingly, therefore, the TLR2–CR3 crosstalk pathway is exploited by several pathogens in addition to *P. gingivalis* (Harokopakis and Hajishengallis 2005; Oliva et al. 2009; Sendide et al. 2005).

In the context of the periodontitis–atherosclerosis connection (Seymour et al. 2007) and the observation of viable *P. gingivalis* in atherosclerotic plaques (Kozarov et al. 2005), it is intriguing to hypothesize that the intracellular persistence of *P. gingivalis* in macrophages (Huang et al. 2009; Wang et al. 2007) might allow this organism to exploit these cells as “Trojan horses” to relocate to systemic tissues and subsequently infect permissive cells (e.g., endothelial cells). Although this hypothesis remains to be tested, the capacity of *P. gingivalis* for cell exit and infection of new host cells has already been demonstrated (Li et al. 2008; Yilmaz 2008).

***P. gingivalis* as an orchestrator of complement-dependent dysbiotic inflammation**

As pointed out above, there are stark differences in the composition of the periodontal microbiota in health and disease (Darveau 2010; Moore et al. 1982; Socransky 1977). The assumption that these differences signified bacterial specificity in the etiology of periodontitis led to significant progress, including the identification of a number of bacterial species as putative periodontal pathogens. In addition to *P. gingivalis*, *T. denticola* and *T. forsythia* were also shown to be strongly associated with periodontitis. These three species together comprise the so-called “red complex” and are frequently isolated together from diseased sites (Holt and Ebersole 2005; Socransky et al. 1998). Over the years much of periodontal research focused on identifying virulence factors of

these three bacteria in the context of a conventional infectious disease (Holt and Ebersole 2005).

However, the dramatic differences in the composition of the microbiota in periodontal disease versus health could alternatively be interpreted by a non-classical view of microbial etiology of disease. According to this viewpoint, periodontal pathogens may not directly cause periodontitis but rather reshape the normally symbiotic microbiota into a dysbiotic one that disrupts the normal homeostatic relationship with the host tissue. In this context, *P. gingivalis* was suspected to be an orchestrator of periodontal disease by virtue of its sophisticated strategies to subvert host immunity. Specifically, the capacity of *P. gingivalis* to impair innate immunity could alter the growth and development of the entire periodontal biofilm. The overgrowth of a dysbiotic biofilm, stabilized by the presence of *P. gingivalis*, could in turn break down the host–microbial homeostasis in the periodontium and trigger destructive inflammation. This hypothesis led to the studies showing that *P. gingivalis* can act as a keystone member of the disease-provoking periodontal microbial community (Hajishengallis et al. 2011). The “keystone species” concept was originally proposed by the ecologist R.T. Paine in 1969 (Paine 1969). In the ecological literature, keystones are species whose effects on their communities are inordinately large relative to their abundance. Such species are thought to constitute the “keystone” of the community’s structure in a way reminiscent of a keystone in an arch (reviewed by Hajishengallis et al. in press; Hajishengallis et al. 2012).

Consistent with the above discussed hypothesis, the colonization of the murine periodontium by *P. gingivalis* was shown to be accompanied by significant alterations in the numbers and community organization of the commensal bacteria, followed by inflammation and destruction of the tooth-supporting bone (Hajishengallis et al. 2011). Intriguingly, *P. gingivalis* caused these dysbiotic alterations while present only at very low numbers, specifically <0.01% of the total bacterial counts. Moreover, *P. gingivalis* failed to cause periodontitis by itself in germ-free mice despite its ability to colonize their periodontium (Hajishengallis et al. 2011). Therefore, the dysbiotic microbiota that develops in the presence of *P. gingivalis* is most likely the eventual cause of the disease.

A major question addressed in the same study was whether complement was involved in *P. gingivalis*-instigated dysbiosis. Since C5aR was shown earlier to be critical for the ability of *P. gingivalis* to subvert leukocytes (Liang et al. 2011; Wang et al. 2010) (Fig. 1), it was hypothesized that C5aR-deficient mice would be resistant to *P. gingivalis*-induced dysbiosis. Indeed, this bacterium failed to alter the commensal microbiota in the absence of C5aR. Moreover, an isogenic mutant of *P. gingivalis* lacking gingipain activity failed to alter the commensal microbiota in normal mice (Hajishengallis et al. 2011). In both cases, the failure to transform the normal commensal microbiota into a dysbiotic state prevented the development of periodontal inflammation and bone loss. Therefore, mice are protected from *P. gingivalis*-induced dysbiosis when the pathogen does not have access to C5aR or lacks the enzyme to exploit this receptor. In contrast, under conditions that allow C5aR exploitation by *P. gingivalis* (i.e., wild-type mice orally inoculated with the wild-type organism), there is uncontrolled growth of commensal bacteria which leads to complement-dependent inflammation that destroys the periodontal bone (Hajishengallis et al. 2011). Periodontal inflammation may also generate tissue breakdown products (e.g., degraded proteins and hemin), which serve bacterial nutritional needs and can stabilize the transition to a disease-provoking microbiota (Fig. 2). In this regard, the inflammatory changes in the periodontium can be better exploited by proteolytic and asaccharolytic bacteria, that is, species associated with periodontal disease rather than health (Darveau 2010). Those

bacteria that cannot utilize these nutrients, or for which host inflammation is detrimental, are likely to be outcompeted or eliminated. As outlined above, complement is centrally involved in this self-feeding vicious cycle of periodontal dysbiosis and destructive inflammation (Fig. 2).

Therapeutic implications in human periodontitis

Complement components can be found in active form in the gingival crevicular fluid at up to 70% of their concentration in serum, although certain components can be found at much higher levels reflecting local production in the periodontium (Potempa et al. 2009). Clinical and histological observations suggest that complement may be involved in the pathogenesis of human periodontitis (Hajishengallis 2010). Indeed, inflamed gingiva or samples of crevicular fluid from periodontitis patients have increased levels of activated complement fragments relative to control samples from healthy individuals (Beikler et al. 2008; Courts et al. 1977; Niekrash and Patters 1986; Nikolopoulou-Papaconstantinou et al. 1987; Patters et al. 1989; Rautemaa and Meri 1996; Schenkein and Genco 1977). Moreover, experimental induction of gingival inflammation in human volunteers causes progressive elevation of complement cleavage products correlating with increased clinical indices of inflammation (Patters et al. 1989).

Although the data from the human studies are correlative, the findings that C5aR-deficient mice are resistant to experimental periodontitis establish an intimate link between complement and periodontal pathogenesis (Hajishengallis et al. 2011; Liang et al. 2011). Importantly, treatment of *P. gingivalis*-colonized mice with a C5aR antagonist leads to the elimination of *P. gingivalis* from the periodontium and reverses the dysbiotic changes that are required for the development of periodontitis (Hajishengallis et al. 2011). This observation provides a causal link between complement and periodontitis and offers proof-of-concept that dysbiotic diseases could be treated by specific targeting of keystone pathogens. From a periodontal point of view, the same observation suggests that complement therapeutics may find application in the treatment of human periodontitis.

Conclusions

The subversive action of *P. gingivalis* on complement may explain, at least in part, its ability to persist in the periodontium and establish dysbiotic inflammation. *P. gingivalis* is perhaps the first documented case of a keystone pathogen in microbial ecology as it fulfills the criteria of low abundance and major influence on the microbial community, which is remodeled in a way that promotes periodontal pathogenesis (Hajishengallis et al. 2011). Moreover, available evidence suggests that keystone pathogens may underlie the etiology of also other polymicrobial inflammatory diseases (Hajishengallis et al. in press). Although established in the mouse model, the keystone pathogen concept is consistent with observations in non-human primates and in humans (reviewed by Darveau et al. 2012). Briefly, immunization of *Macaca fascicularis* with a gingipain-based vaccine resulted in suppression of the counts of indigenous *P. gingivalis* accompanied by a reduction in the total subgingival bacterial load and protection against bone loss (Page et al. 2007). Moreover, *P. gingivalis* is a quantitatively minor component of human periodontitis-associated biofilms (Doungudomdacha et al. 2000; Kumar et al. 2006; Moore et al. 1982), despite its association with progressive bone loss in periodontitis patients (Chaves et al. 2000; Moore et al. 1991). Nevertheless, even at this low abundance, *P. gingivalis* exploits complement and triggers dysbiotic changes that set the stage for inflammatory periodontitis. The ongoing elucidation of the

mechanisms underlying these interactions may facilitate the development of novel therapeutic interventions in human periodontitis.

Recuse note

Dr. John D. Lambris is the section editor for the journal and Dr. George Hajishengallis is the a guest editor of this issue. This manuscript was handled by Dr. Wilhelm Schwable, Editor-in-Chief, and Dr. Lambris was not involved in any way with the editorial process or decision.

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