Chapter 4
Complement Involvement in Periodontitis: Molecular Mechanisms and Rational Therapeutic Approaches

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Abstract The complement system is a network of interacting fluid-phase and cell surface-associated molecules that trigger, amplify, and regulate immune and inflammatory signaling pathways. Dysregulation of this finely balanced network can destabilize host-microbe homeostasis and cause inflammatory tissue damage. Evidence from clinical and animal model-based studies suggests that complement is implicated in the pathogenesis of periodontitis, a polymicrobial community-induced chronic inflammatory disease that destroys the tooth-supporting tissues. This review discusses molecular mechanisms of complement involvement in the dysbiotic transformation of the periodontal microbiome and the resulting destructive inflammation, culminating in loss of periodontal bone support. These mechanistic studies have additionally identified potential therapeutic targets. In this regard, interventional studies in preclinical models have provided proof-of-concept for using complement inhibitors for the treatment of human periodontitis.

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4.1   Introduction

Periodontitis is a chronic inflammatory disease that compromises the integrity of the periodontium, i.e., the tooth-supporting structures such as the gingiva, periodontal ligament, and the alveolar bone [1]. The disease is initiated by inflammation caused by dysbiotic bacterial communities forming on subgingival tooth sites [2]. Similarly to other chronic diseases, periodontitis requires a susceptible host. Susceptibility to periodontitis is determined by genetic factors that may predispose to hyperinflammatory responses or by environmental factors (e.g., diet and stress) and risk-related behavior (e.g., smoking) that can modify the host immune response in a destructive direction [3–7]. Regardless of the complexity underlying periodontal disease susceptibility, the control of the host periodontal inflammatory response is considered to be central to the treatment of the disease [1]. Therefore, identifying key inflammatory pathways that mediate periodontal tissue destruction has important translational implications.

Chronic periodontitis affects >47 % of U.S. adults [8] and has been prevalent since antiquity [9]. Severe periodontitis, which affects 8.5 % of adults [8], is not only a common cause of tooth loss, but is also associated with increased risk for atherosclerosis, diabetes, rheumatoid arthritis, and adverse pregnancy outcomes [10–13]. The high prevalence of periodontitis [8], its significant economic burden [14, 15], and the fact that many clinical cases are refractory to standard modes of treatment (combined mechanical and antimicrobial therapy, including scaling and root planning, surgery, and systemically administered antibiotics) [16, 17] underscore the importance of implementing innovative and cost-effective therapeutic interventions. In this review, we summarize published evidence that the destructive host inflammatory response in periodontitis is heavily dependent on the activation of the complement system. Moreover, we discuss recent studies that provided proof-of-concept that complement inhibition is a promising therapeutic strategy for the treatment of this oral disease.

4.2   Complement

Traditionally known as a cascade of antimicrobial proteins in the blood, complement is now recognized as a key system for immune surveillance and homeostasis and a major link between the innate and the adaptive arms of the host immune response [18]. In addition to the classic serum proteins (C1-9), the integrated complement system comprises pattern-recognition molecules, convertases and other proteases, regulators, and receptors for interactions with immune mediators [18]. The complement cascade can be triggered by distinct mechanisms (classical, lectin, or alternative), all of which converge at the third complement component (C3) and lead to the generation of effectors that mediate diverse functions. These include the recruitment and activation of inflammatory cells (via the C3a and C5a anaphylatoxins that activate specific G-protein-coupled receptors, C3aR and C5aR [CD88], respectively),

microbial opsonization and phagocytosis (e.g., through the C3b or C4b opsonins), and direct lysis of susceptible targeted microbes (by means of the C5b-9 membrane attack complex) [18]. It should be noted that the activities of complement are not restricted to a linear cascade of events but rather involve a network of interactions with other systems, which together coordinate the host response to infection or tissue injury. These complement interactions can amplify innate immune and inflammatory responses through synergy with Toll-like receptors (TLRs) [19], provide a barrier against the spread of invading bacteria by potentiating local clotting [20], replenish the immune system through mobilization of hematopoietic stem/progenitor cells from the bone marrow [21] and regulate the activation and differentiation of T-cell subsets [22, 23].

Owing to the operation of a sophisticated system of negative regulators (e.g., the fluid-phase regulators factor H and C4-binding protein and the cell-associated regulators CD46 and CD59), complement is not normally activated on the surface of host cells and tissues [24]. However, disruption of these regulatory mechanisms by specific complement gene mutations or by subversive pathogens can lead to complement over-activation and hence unwarranted inflammation and possibly damage to host tissues. Indeed, genetic defects in complement regulators have been implicated in the development of local or systemic diseases, such as age-related macular degeneration and systemic lupus erythematosus [18, 24, 25]. From a microbial perspective, several pathogens not only hijack soluble negative regulators to protect themselves against complement attack but can also degrade cell-associated regulatory molecules that would otherwise protect host tissues or cells [26–29]. Moreover, it is plausible that complement over-activation can occur for reasons unrelated to compromised regulatory mechanisms, such as when the host fails to clear infections [30, 31]. In such cases, the infection could become chronic providing a persistent stimulus for complement activation.

4.3 Role of Complement in Periodontal Dysbiosis and Inflammation

In order to better understand the role of complement in periodontitis, it is instructive to first discuss the role of bacteria in periodontal disease pathogenesis. Until fairly recently, the prevailing paradigm was that specific organisms were involved in the etiology of periodontitis, the most prominent being a troika of bacteria known as the "red complex," namely, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* [32, 33]. This notion was in part fueled by the bias of culture-based methods to overestimate the abundance of the easily grown species (such as *P. gingivalis*) in the periodontitis-associated biofilms, while neglecting the presence of uncultivable bacteria. However, culture-independent molecular methods used in recent metagenomic studies have revealed a more heterogeneous and diverse periodontitis-associated microbiota than previously known from cultural studies [34–39]. Many of the newly recognized organisms (e.g., certain gram-positive bacteria and other species from the gram-negative genera *Prevotella*, *Megasphaera*,

Selenomonas, *Desulfobulbus*, *Dialister*, *and Synergistes*) show as good or better a correlation with disease than the red complex bacteria [34–39]. Moreover, a recent metatranscriptomic study revealed that the majority of virulence factors that are upregulated in the microbiome of periodontitis patients is primarily derived from the previously underappreciated species that were not traditionally associated with periodontitis [40]. These recent human microbiome analyses and animal model-based mechanistic studies collectively suggest that the pathogenesis of periodontitis involves polymicrobial synergy and dysbiosis [2, 34, 36, 37, 40–49].

The dysbiosis of the periodontal microbiota represents an alteration in the relative abundance or influence of individual components of the bacterial community (relative to their abundance or influence in health) leading to dysregulated host-microbial crosstalk sufficient to induce destructive inflammation and bone loss [1]. Dysbiotic communities exhibit synergistic interactions that can enhance colonization, persistence, or virulence; bacteria known as keystone pathogens are involved in the breakdown of periodontal tissue homeostasis, whereas other, known as pathobionts, can trigger destructive inflammation once homeostasis is disrupted [2]. Certain commensals, though non-pathogenic by themselves in the oral environment, can promote keystone pathogen colonization and, as such, are implicated as accessory pathogens [2]. Briefly stated, according to the polymicrobial synergy and dysbiosis (PSD) model, the host immune response is initially subverted by keystone pathogens with the help of accessory pathogens and is subsequently over-activated by pathobionts, leading to destructive inflammation in susceptible hosts (Fig. 4.1). Therefore, according to the PSD model, periodontitis is not a bacterial infection in the classical sense (i.e., not caused by a single or a select few pathogens) but, rather, represents a polymicrobial community-induced perturbation of host homeostasis that leads to destructive inflammation in susceptible individuals [2].

These recent advances should not be interpreted to suggest that *P. gingivalis* or other red complex bacteria are not important in periodontal disease pathogenesis; simply, their roles need to be re-interpreted in a manner consistent with emerging new evidence. In this regard, it was recently shown that *P. gingivalis* acts as a keystone pathogen at low colonization levels. Specifically, *P. gingivalis* induces the conversion from a symbiotic community structure to a dysbiotic one capable of causing destructive inflammation and periodontal bone loss [44, 50, 51]. In line with this concept, *P. gingivalis* cannot cause disease in germ-free mice despite colonizing this host, that is, it cannot cause inflammatory bone loss in the absence of other bacteria [44]. Contrary to the findings of some of the early culture-based microbiological studies, the recent metagenomic studies using culture-independent molecular methods show that *P. gingivalis* constitutes a quantitatively minor constituent of human periodontitis-associated biofilms [36, 38, 52]. Moreover, in non-human primates where *P. gingivalis* is a natural inhabitant of the subgingival biofilm, a specific vaccine (against a key virulence factor, the gingipain proteases) causes a reduction both in *P. gingivalis* counts and in the total subgingival bacterial load, in addition to inhibiting bone loss [53]. These findings suggest that the presence of *P. gingivalis* benefits the entire biofilm, as predicted by the keystone-pathogen concept [50]. It should be clarified that the mere presence of *P. gingivalis* does not
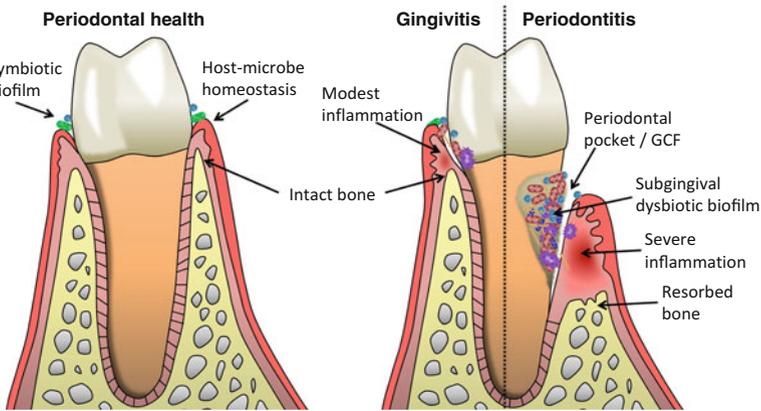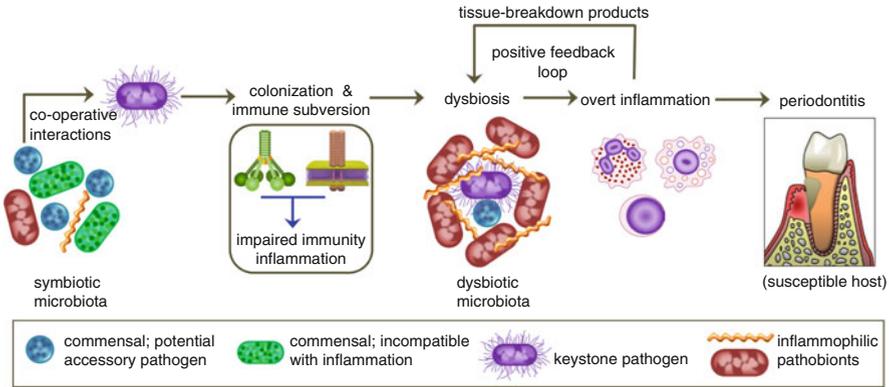
Fig. 4.1 The polymicrobial synergy and dysbiosis (PSD) model of periodontal disease pathogenesis. Periodontitis is induced by a polymicrobial bacterial community, wherein different members have distinct roles that synergize to cause destructive inflammation. Keystone pathogens, the colonization of which is facilitated by accessory pathogens, manipulate the host response leading from a symbiotic to a dysbiotic microbiota, in which pathobionts over-activate the inflammatory response and cause destructive resorption of the supporting bone. Inflammation and dysbiosis reinforce each other by engaging in a positive feedback loop (inflammatory tissue breakdown products are used as nutrients by the dysbiotic microbiota, which further exacerbates inflammation). The *lower panel* shows the progression from periodontal health to gingivitis (gingival inflammation without bone loss) to periodontitis (loss of epithelial attachment, formation of deep periodontal pockets, and inflammatory bone loss). Periodontal pockets serve as a niche that can harbor dysbiotic bacterial communities feeding on the inflammatory spoils (e.g., degraded collagen peptides, haem-containing compounds) transferred with the gingival crevicular fluid (GCF) that bathes the pockets. Redrawn from Ref. [13]. Used by permission

necessarily trigger a transition toward periodontitis. Indeed, *P. gingivalis* can be detected, albeit with reduced frequency, also in periodontally healthy individuals [36, 54]. In this regard, there is considerable strain and virulence diversity within the population structure of *P. gingivalis*. Moreover, key virulence factors (e.g., gingipains and lipid A phosphatases) of this bacterium are regulated by local environmental conditions that likely differ among different individuals [51]. Another potential explanation is that there might be individuals who can resist the capacity of *P. gingivalis* to convert a symbiotic microbiota into a dysbiotic one by virtue of their intrinsic immune status (e.g., alterations in signaling pathways required for immune subversion by *P. gingivalis*). In other words, *P. gingivalis* does not necessarily initiate disease but rather signifies a risk factor for periodontitis [13, 55]

Recent studies in mice and non-human primates indicate that complement is involved in both the dysbiotic transformation of the periodontal microbiota and the inflammatory response that leads to destruction of periodontal bone [44, 47, 56–59]. In this model of periodontal disease pathogenesis, C5aR (CD88) is a target of immune subversion by *P. gingivalis* leading to the dysbiotic transformation of the microbiota, which in turn causes destructive inflammation that is largely dependent on C3 activation (Fig. 4.2). This involvement of C3 may entail synergism with TLRs, as suggested by previous findings on the interactions of complement and the TLR signaling system in the periodontium and other tissues [19, 57, 60].

Intriguingly, whereas *P. gingivalis* can impair the killing capacity of leukocytes such as neutrophils and macrophages, it does not block their ability to induce inflammatory responses [47, 59, 61]. For instance, in human and mouse neutrophils, *P. gingivalis* instigates a C5aR-TLR2 crosstalk which disarms and disassociates a host-protective TLR2–MyD88 pathway from a proinflammatory and immune-evasive TLR2–MyD88 adaptor-like (Mal)–phosphoinositide 3-kinase (PI3K) pathway that prevents phagocytosis of *P. gingivalis* and bystander bacteria [47]. The ability of *P. gingivalis* to exploit C5aR in leukocytes to impair their antimicrobial but not their proinflammatory responses allows uncontrolled growth and altered composition of the microbiota in an inflammatory environment [44, 47, 59]. This documented concept has resolved a long-standing conundrum: on the one hand, periodontal bacteria need to evade immune-mediated killing; on the other hand, they require inflammation as this generates nutrients (e.g., degraded collagen peptides and haem-containing compounds) that periodontitis-associated bacteria need to thrive [62]. In other words, periodontal bacteria cannot afford to evade killing via immunosuppression, even though this represents a common evasion strategy of many other pathogens [63].

It should be noted that *P. gingivalis* can activate C5aR independently of the immunologically activated complement cascade, as this bacterium can release biologically active C5a from C5 through the action of its Arg-specific gingipains [59, 61, 64]. Consistent with this, *P. gingivalis* was shown to retain its capacity to colonize the periodontium of C3-deficient ($C3^{-/-}$) mice, since these mice express normal levels of C5 and C5aR that are required for *P. gingivalis* colonization [56]. Intriguingly, although *P. gingivalis* can colonize $C3^{-/-}$ mice, its dysbiotic effect is transient in this host and the periodontal microbiota cannot be sustained at high levels throughout the experimental period as seen in wild-type [56]. Moreover,
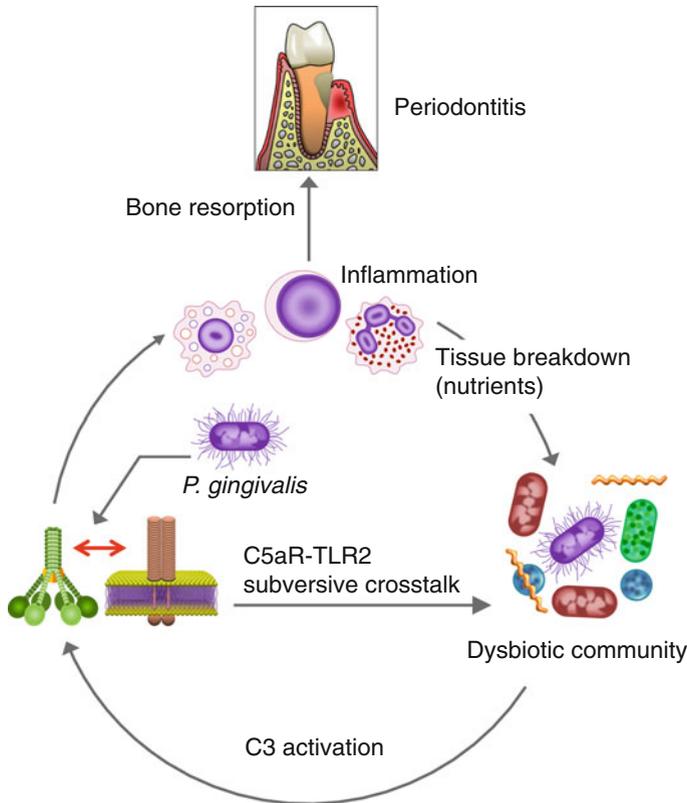
Fig. 4.2 Complement involvement in periodontal dysbiosis and inflammation. Colonization of the periodontium by *P. gingivalis* impairs innate host defense by instigating a subversive C5aR-TLR2 crosstalk, which leads to the dysbiotic transformation of the periodontal microbiota. The dysbiotic microbial community in turn causes C3-dependent inflammatory bone loss, the hallmark of periodontitis. The resulting inflammatory environment selects for inflammophilic bacteria that feed on inflammatory breakdown products, thereby promoting further bacterial growth and dysbiosis. These pathologic interactions generate and perpetuate a vicious cycle of periodontal tissue destruction. Modified from Ref. [50] on the basis of recent studies [47, 56]. Used by permission

P. gingivalis-colonized $C3^{-/-}$ mice exhibit significantly less periodontal inflammation and bone loss than *P. gingivalis*-colonized wild-type mice [56]. Therefore, C3 is crucial for the long-term sustenance of the dysbiotic microbiota and for maximal inflammatory bone loss. The reason why *P. gingivalis*-induced dysbiosis cannot be sustained in $C3^{-/-}$ mice is likely related to the diminished periodontal inflammation, which—as alluded to above—is required for nutrient acquisition. Consistent with the notion that periodontitis-associated bacteria are "inflammo-philic" (from the Greek suffix *philic* indicating fondness), the bacterial biomass of human periodontitis-associated biofilms was shown to increase with increasing periodontal inflammation [36], and anti-inflammatory treatments in animal models suppress the periodontal bacterial load [65–67].

4.4 Clinical Evidence Linking Complement to Periodontitis

The space between the free gingiva and the tooth surfaces is known as the gingival crevice. This anatomical location is bathed with an inflammatory exudate termed gingival crevicular fluid (GCF) [68]. When deepened due to periodontal disease activity, the gingival crevice is referred to as periodontal pocket, which is a niche heavily populated with periodontitis-associated microbial communities [13] (Fig. 4.1, lower panel). The enhanced host inflammatory response in periodontitis is correlated with elevated flow of GCF, in part owing to the increased vascular permeability of the subepithelial blood vessels [69]. Under inflammatory conditions, the GCF contains complement at up to 70–80 % of its concentration in serum, although the serum is not the only source of periodontal complement since it is also produced locally [70–73]. For instance, recruited leukocytes and especially macrophages constitute a source of local production of complement components [74, 75].

The periodontal pockets contain a functional complement system as attested by analyses of collected GCF samples showing robust complement-dependent hemolytic activity [76, 77]. Moreover, GCF collected from periodontitis patients contains activated complement fragments at higher concentrations than in GCF from healthy individuals [72, 78–81]. Consistent with this, complement components and cleavage products are readily detected in chronically inflamed gingiva, whereas complement is undetectable or present at lower levels in healthy gingival biopsy samples [71, 73, 76, 77, 82–84]. An immunohistochemical study revealed weaker expression of CD59 in periodontitis-involved gingiva than in healthy gingival tissue, implying impaired protection of diseased tissues against potential tissue damage by autologous membrane attack complex formation [84].

Using an integrative gene prioritization method and databases from genome-wide association studies and microarray experiments, a recent study has identified C3 among the top 21 most promising candidate genes involved in periodontitis [85]. A genetic basis for periodontal disease is suggested by twin studies and familial aggregation of severe forms of the disease [3, 4, 6]. Although a number of candidate susceptibility genes have been proposed, it remains uncertain whether individual genes play important roles in periodontal disease pathogenesis [3, 4, 6]. In this regard, chronic (or adult-type) periodontitis is a polygenic disease, where multiple genes contribute cumulatively to the overall disease risk (or protection) by influencing the host immune response and the microbiota. Nevertheless, a role for C3 is supported by additional evidence: Induction of experimental gingivitis in human volunteers causes progressive elevation of complement activation (as determined by C3 conversion) correlating with increased clinical inflammatory parameters [81]. Conversely, the resolution of inflammation in periodontitis patients undergoing therapy leads to decreased complement activity, as revealed by reduced C3-to-C3c conversion in the GCF [86]. In a similar context, C3 is among the top 5 % of genes that are most strongly downregulated following periodontal therapy [87]. Importantly, local inhibition of C3 blocks experimental periodontitis in non-human primates [56].

It is of interest to note that despite excessive complement activation in periodontitis, periodontal bacteria have a number of protective mechanisms against complement-mediated killing. For instance, *P. gingivalis* and *Prevotella intermedia* can capture and co-opt physiological soluble inhibitors of the complement cascade, such as the C4b-binding protein [88, 89] (Fig. 4.3). In a similar context, *T. denticola* expresses an 11.4-kDa cell surface lipoprotein which binds complement factor H (hence known as factor H-binding protein) [90]. Moreover, whereas certain bacterial proteases (*P. gingivalis* Arg-specific gingipains and *T. forsythia* karilysin) cleave C5 to release biologically active C5a, the same proteases readily destroy the C5b component, thereby preventing the generation of the membrane attack complex [70, 91] (Fig. 4.3).

In summary, clinical and histological studies in human patients are consistent with the involvement of complement in local tissue destruction in periodontitis.
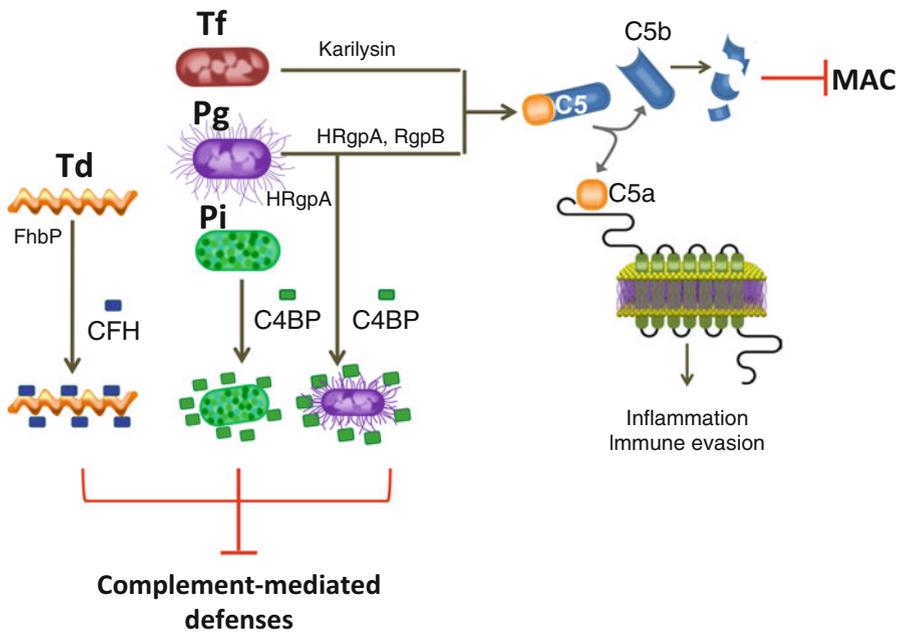

Fig. 4.3 Inhibition of complement-dependent host defenses by periodontal bacteria. *P. gingivalis* (Pg) and *P. intermedia* (Pi) protect themselves against complement by using surface molecules (HRgpA gingipain for *P. gingivalis*, undefined molecule for *P. intermedia*) to capture the circulating C4b-binding protein (C4BP), a physiological negative regulator of the classical and lectin pathways. *Treponema denticola* (Td) hijacks another regulator, the complement factor H (CFH), using a lipoprotein known as factor H-binding protein (FhbP). In this way, the bacteria can prevent complement-dependent opsonophagocytosis and the formation of the membrane attack complex (MAC). Moreover, although *P. gingivalis* and *T. forsythia* proteases can release biologically active C5a from C5 (which leads to immune evasion and inflammation), the generated C5b component is degraded by the same proteases (Arg-specific gingipains HRgpA and RgpB and karilysin), thereby preventing the generation of MAC

This notion is supported by interventional studies in preclinical models, which additionally offer promising targets for treating human periodontitis (below).

4.5   Complement as a Therapeutic Target in Periodontitis

The above-discussed mechanistic studies in mice have implicated both C3 and C5aR in periodontal disease pathogenesis, thereby offering two novel targets for therapeutic intervention in this oral inflammatory disease. In a proof-of-concept study, local intragingival injection of PMX-53, a C5aR antagonist, blocked periodontal inflammation and bone loss in a model of *P. gingivalis*-induced periodontitis, regardless of whether it was administered before or after disease initiation [57]. The same inhibitor inhibited inflammatory periodontal bone loss also in a mouse model of ligature-induced periodontitis where the disease is induced independently of *P. gingivalis* [57]. In this model, a silk ligature is placed around molar teeth, resulting in massive local accumulation of bacteria and development of inflammation and bone loss in conventional (but not germ-free) mice or rats [45, 92]. Work by an independent group using a similar ligature-induced periodontitis model in rats showed that PMX205 (an analog of PMX53) inhibits bone loss when administered in the drinking water, although the efficacy (<20 % protection vs. controls) [93], was reduced relative to the local administration method (50 % protection vs. controls) [57]. These differences in efficacy might be attributed to the different modes of inhibitor administration and/or to the use of different animal species.

More recently, the suitability of C3 as a therapeutic target in periodontitis was evaluated in a non-human primate model [56]. The inhibitor used was Cp40, an improved analog of compstatin, which is a peptidic complement inhibitor acting on C3 [94, 95]. Thus, unlike physiological negative regulators of complement, compstatin and its analogs do not only bind the C3 convertase but also bind and protect C3 from both classical and alternative convertase-mediated cleavage [94, 95]. C3 inhibition is advantageous in that it blocks the generation of downstream effector molecules regardless of the initiation mechanism of complement activation. Moreover, by inhibiting complement at the level of C3, compstatin and its analogs do not interfere with C4b opsonization induced via the classical and lectin pathways. The improved analog Cp40 exhibits plasma half-life values more than 50 h, which exceeds expectations for most peptidic drugs, and is the first compstatin analog with subnanomolar target affinity ($K_D = 0.5$ nM) [96, 114].

The use of a non-human primate preclinical model (specifically cynomolgus monkeys; *Macaca fascicularis*) was necessary for an initial evaluation of the efficacy of Cp40 in periodontitis due to its exclusive specificity for C3 of humans and non-human primates. Importantly, the immune system and periodontal anatomy of the cynomolgus monkey is very similar to that of humans, and periodontitis in this model displays bacteriological, immuno-histological, and clinical features that are highly similar to those observed in human periodontitis [97–101]. The cynomolgus model is thus considerably more predictive of drug efficacy in human periodontitis

compared to widely used models such as those in rodents, rabbits, or dogs. In the Cp40 intervention study, which had a 6-week duration, silk ligatures were placed around posterior teeth on both halves of the lower jaw (mandible) for a split-mouth experimental design. Specifically, one side was treated with active drug (Cp40) and the other with inactive analog (control peptide), therefore, each animal served as its own control. Treatment with Cp40 resulted in decreased clinical indices that measure periodontal inflammation and tissue destruction. The decreased clinical inflammation correlated with lower GCF levels of proinflammatory cytokines (e.g., TNF, IL-1β, IL-17, and RANKL, a key osteoclastogenic factor) and decreased numbers of osteoclasts in bone biopsy specimens [56]. Consistent with the latter, radiographic analysis showed that Cp40 caused a significant inhibition of periodontal bone loss. Interestingly, the GCF levels of osteoprotegerin (OPG), a natural inhibitor of RANKL, were maintained at higher levels in Cp40-treated sites than control sites during the course of the study. Therefore, Cp40 caused a favorable reversal of the RANKL/OPG ratio, which is thought to be a useful biomarker of human periodontitis [102]. This study therefore supports the therapeutic potential of Cp40 in human periodontitis and marks the first time, for any disease, that complement inhibition was shown to inhibit inflammatory processes that lead to bone loss in nonhuman primates. More recently, locally administered Cp40 was shown to inhibit preexisting, naturally occurring chronic periodontitis in non-human primates (Maekawa et al., submitted).

The mechanism(s) by which C3 inhibition blocks periodontal inflammation may not be restricted to mere suppression of the complement cascade. This is because complement pathways (e.g., C3a or C5a receptor signaling) cross-talk with and amplify TLR-mediated inflammatory responses in both systemic and mucosal settings [19, 60] including the periodontium [57]. Complement inhibition may thus also suppress inflammation that is initiated by TLR activation in response to microbial ligands such as lipopolysaccharide, lipoproteins, and bacterial DNA [1, 103]. Moreover, TLR activation can be triggered by endogenous molecules (e.g., biglycan, hyaluronan fragments, and heparan sulfate fragments) that are released upon inflammatory tissue damage and act as danger signals [104, 105]. This suggests that complement may also be involved in the progression of periodontal inflammation; hence complement inhibitors may additionally interfere with this stage of the disease.

4.6 Conclusions and Perspective

There is currently an unmet need for efficacious and safe therapeutics in periodontitis, which is often unresponsive to conventional periodontal treatment [17, 106–108]. At present, there is no satisfactory adjunctive therapy to scaling and root planing for the treatment of chronic periodontitis. The use of antimicrobials and generic antibiotics as adjunctive therapies has met with limited success at best [109]. Therefore, the treatment of periodontal disease should benefit from safe and effective products appropriate for chronic administration. On the basis of evidence

from preclinical models, locally applied complement inhibitors can potentially block periodontal inflammation and thereby provide protection as an adjunctive therapy to standard periodontal treatment. Being a host modulation-based approach, complement inhibition is advantageous to antimicrobial approaches since it is the host response that primarily inflicts damage upon the periodontal tissues. Moreover, as discussed above, the inhibition of periodontal inflammation also exerts indirect antimicrobial effects, since the periodontitis-associated microbiota requires an inflammatory environment to obtain nutrients for its growth and sustenance [56, 65–67].

Compstatin-derived compounds with improved inhibitory potency and pharmacokinetic properties have shown safety and efficacy in several other clinically relevant non-human primate disease models. These involve treatment of age-related macular degeneration, sepsis, hemodialysis-induced inflammation, and paroxysmal nocturnal hemoglobinuria [110–113]. A Cp40-based drug (AMY-101; Amyndas Pharmaceuticals) is currently being evaluated as a novel therapeutic approach to treat complications of ABO-incompatible kidney transplantation and paroxysmal nocturnal hemoglobinuria [114]. The recent interventional periodontal studies in non-human primates suggest that periodontitis may be a promising clinical application for Cp40 and the clinically developed drug candidate AMY-101, a possibility that can be pursued in future clinical trials.

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