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Review

Role of complement in host–microbe homeostasis of the periodontium

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ABSTRACT

Complement plays a key role in immunity and inflammation through direct effects on immune cells or via crosstalk and regulation of other host signaling pathways. Deregulation of these finely balanced complement activities can link infection to inflammatory tissue damage. Periodontitis is a polymicrobial community-induced chronic inflammatory disease that can destroy the tooth-supporting tissues. In this review, we summarize and discuss evidence that complement is involved in the dysbiotic transformation of the periodontal microbiota and in the inflammatory process that leads to the destruction of periodontal bone. Recent insights into the mechanisms of complement involvement in periodontitis have additionally provided likely targets for therapeutic intervention against this oral disease.

1. Introduction

Complement can be produced locally or systemically [1] and plays important roles in immunity and inflammation through direct effects on innate and adaptive immune cells or through crosstalk and regulation of other signaling pathways [2,3]. Complement activities are therefore not restricted to a linear cascade of events but involve a network of interactions with other systems to better coordinate the host response to infection or other insults. These connections of complement can enhance innate immune defense through synergy with toll-like receptors (TLRs) [3], provide a barrier against the spread of invading bacteria by potentiating local clotting [4], and replenish the immune system through mobilization of hematopoietic stem/progenitor cells from the bone marrow [5,6]. Complement also influences the activation and differentiation of T-cell subsets [7,8].

Besides the classical group of serum proteins (C1–9), the integrated complement system includes pattern-recognition molecules, convertases and other proteases, regulators, and receptors for interactions with immune mediators [2]. The complement cascade can be triggered via distinct pathways (classical, lectin, or alternative), which converge at the third complement component (C3). The activation of the classical pathway is initiated by antigen–antibody complexes recognized by the C1q subunit of C1, whereas the lectin pathway can be triggered through interaction of a secreted pattern-recognition molecule (the mannose-binding lectin; MBL) with specific carbohydrate groups on microbial surfaces. Both the classical and lectin pathways proceed through C4 and C2 cleavage to generate the classical/lectin C3 convertase. The alternative pathway is initiated by low-level, spontaneous hydrolysis of C3 to C3[H_2O], which forms the initial alternative pathway C3 convertase in the presence of factors B (fB) and D (fD). As long as there is no sufficient negative regulation (as is normally the case of microbes or other non-self surfaces), this initiation is followed by rapid propagation of the alternative pathway through an amplification loop [2,7]. The alternative pathway can also be triggered by bacterial lipopolysaccharide and lipooligosacharide via the plasma protein properdin attached to bacterial surfaces [9,10] and can potentially contribute to ≥80% of the total complement activation [11]. C3 activation by pathway-specific C3 convertases leads to the generation of effector molecules involved in (a) the recruitment and activation of inflammatory cells (e.g., the C3a and C5a anaphylatoxins that activate specific G-protein-coupled receptors, C3aR and C5aR [CD88], respectively); (b) microbial opsonization and phagocytosis (e.g., through the C3b opsonin); and (c) direct lysis of targeted pathogens (by means of the C5b-9 membrane attack complex [MAC]) [2].

As alluded to above, complement is not normally activated on the surface of host cells and tissues. However, disruption of the regulatory mechanisms involved can lead to excessive complement activation, inflammation, and damage to host tissues. For instance, deficiencies, hypo-functional polymorphisms, or mutations in complement regulators have been implicated in the development of local or systemic diseases, such as age-related macular degeneration and systemic lupus erythematosus [2,12,13].

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Microbial pathogens may also contribute to complement deregulation or dysfunction. In this regard, pathogens can hijack negative regulators of complement to protect themselves against host defense mechanisms, or they can degrade regulatory molecules that protect host tissues or cells [14–16]. Moreover, pathogens can exploit complement receptors to proactively promote their survival and persistence in the host [17]. These mechanisms can contribute to defective bacterial clearance and enhanced inflammation, thereby promoting infection-driven inflammatory diseases.

Periodontitis is an inflammatory disease in which complement appears to form a major link between infection and inflammation [18]. Chronic periodontal inflammation is initiated and perpetuated by a dysbiotic microbiota and may lead to tooth loss as a result of the destruction of the supporting alveolar bone [19,20]. This is a highly prevalent disease, affecting nearly half of U.S. adults [21]. In its most severe form, which affects 8.5% of U.S. adults [21], periodontitis can influence systemic health and increase the risk for atherosclerosis, diabetes, and possibly rheumatoid arthritis [22–25].

In this review, we summarize and discuss the published evidence supporting a crucial role for complement in the initiation and progression of periodontitis (Table 1). Specifically, excessive activation of complement or subversion of its normal functions contributes to the breakdown of host–microbe homeostasis in the periodontal tissue (periodontium), thereby precipitating inflammatory disease. This evidence comes from both clinical observations and experimental animal studies.

2. Role of the microbiota in periodontitis

In order to better understand the interplay between bacteria and complement in periodontitis, it is instructive to first consider the role of bacteria in the pathogenesis of this chronic oral inflammatory disease. Until fairly recently, the identities of the organisms associated with periodontal disease or health were restricted to those that could be cultured in the laboratory. Cultural characterization of the periodontal microbiota in the late 1970s and early 1980s revealed dramatic compositional changes in disease as compared to health [26–31]. One way to interpret these findings was that the disease-associated microbiota contained novel pathogenic species that were either absent or barely detectable in health. On the basis of cluster analysis and association with different disease severities, oral bacteria were historically divided into six groups of different potential pathogenicity, commonly referred to by their color-coded designations [32]. Foremost among these groups was the so-called “red complex”, a group of three Gram-negative anaerobic species, including *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, the detection of which was strongly associated with each other and with diseased sites [32]. Also associated with periodontal lesions, the “orange” complex comprised species members of the genus *Prevotella*, *Fusobacterium*, and *Campylobacter*, as well as *Streptococcus constellatus* and *Eubacterium nodatum*. The other four complexes (“blue”, “yellow”, “green”, and “purple”) primarily consisted of early colonizers of the tooth surfaces [32].

With the advent of culture-independent, molecular-based methods of bacterial identification and enumeration, such as 16S rDNA amplification and high-throughput sequencing, our understanding of the bacterial composition of the periodontal region has changed [33–35]. The in-depth study of thousands of plaque samples derived from a variety of clinical periodontal conditions has demonstrated a more heterogeneous and diverse periodontal microbiota than previously thought [33–35]. In addition to the consensus periodontal pathogens, *P. gingivalis*, *T. forsythia*, and *T. denticola*, newly recognized non- or poorly cultivable organisms that increase in number in diseased sites include the Gram-positive *Filifactor alocis* and species in the genera *Prevotella*, *Megasphaera*, *Selenomonas*, and *Desulfobulbus* [33,34,36–39]. Many of these newly recognized organisms show as good a correlation (or better) with disease as does the classical red complex [37,39,40]. It is now increasingly recognized that chronic periodontitis is not a bacterial infection in the classical sense, i.e., caused by a single or a limited number of pathogens. Rather, periodontal disease is the result of a polymicrobial community-induced perturbation of host homeostasis in susceptible individuals [20,41]. Bacterial constituents of these communities often exhibit synergistic interactions that can enhance colonization, persistence, or virulence, and some bacteria may be involved in the breakdown of periodontal homeostasis, whereas other may trigger destructive inflammation once homeostasis is disrupted [20].

3. Mechanisms used by periodontal bacteria for protection against complement

The space between the free gingiva and the tooth surfaces, known as the gingival crevice, constitutes a niche for periodontitis-associated microbial communities [41]. The gingival crevice is bathed with an inflammatory exudate, termed gingival crevicular fluid (GCF) [42]. In a clinically healthy periodontium, in which the tooth-associated biofilm is usually confined to the gingival margin, the GCF represents a slow-flowing transudate of plasma proteins. However, if the biofilm is left undisturbed for 2–4 days, the biofilm enters the crevice by proliferation and spreading or by relocation of dislodged bacteria. The host response is therefore escalated and manifested by increased flow of GCF (in part due to increased vascular permeability of the subepithelial blood vessels) and chemotactic recruitment of inflammatory cells, mostly neutrophils [43]. Under inflammatory conditions, the GCF contains complement at up to 70–80% of its concentration in serum, although certain components can be found at higher levels in GCF reflecting local production of complement [44–47]. Therefore, the periodontal bacteria constantly encounter complement and, in cases of chronic periodontitis, it is reasonable to think that the bacteria have evolved mechanisms to resist its antimicrobial actions.

Studies with several periodontal bacteria, such as *P. gingivalis*, *Prevotella intermidia*, *T. forsythia*, and *T. denticola*, indicate that they interact with complement in complex ways that include both inhibitory and stimulatory effects [15,16,48,49]. This seemingly contradictory microbial behavior is probably due to the dynamics of survival tactics of periodontal bacteria: on the one hand trying to evade immune clearance, and on the other to stimulate inflammation and the flow of GCF as a source of nutrients [16] (Fig. 1).

P. gingivalis expresses Arg- and Lys-specific cysteine proteinases known as gingipains, which can degrade C3, thereby potentially inhibiting complement activation regardless of the initiation pathway involved [44]. All three gingipains can degrade C3, although the Arg-specific enzymes (HRgpA and RgpB) are more potent in this regard than the Lys-specific gingipain (Kgp) [44]. As a consequence, the deposition of opsonins or the C5b-9 MAC on the pathogen surface is suppressed, unless the activity of the gingipains is inhibited by chemical or genetic means [50,51]. Consistent with these findings, *P. gingivalis* displays exquisite resistance to the lytic action of complement in vitro [44,50]. Unexpectedly, however, Arg- and Lys-gingipain – deletion mutants maintained resistance to killing in 20% normal human serum (a similar viability to that seen in heat-inactivated serum) despite increased deposition of complement fragments or complexes (C3d and C5b-9 MAC) [50]. This finding suggested that the mechanism of serum resistance is largely independent of the Arg- and Lys-gingipains and has, in fact been attributed to the presence of a surface anionic polysaccharide