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Role of Complement in Pathogenesis of Periodontal Disease

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Abstract

Periodontitis is a chronic inflammatory disease that affects the tooth supporting structures. The complement system (complement) was first identified in the late nineteenth century in serum as a collection of heat-labile components which supports the development of antibacterial antibodies following immunization. This review article talk about the role of complement in pathogenesis of periodontal disease.

Keywords: *Complement System, Periodontal Disease, Membrane Attack Complex.*

BACKGROUND

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. [1,2] Similar 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 behaviour (e.g., smoking) that can modify the host immune response in a destructive direction.[3] Regardless of the complexity of the underlying periodontal disease susceptibility, the control of the host periodontal inflammatory response is considered to be central to the treatment of the disease.

The complement system (complement) was first identified in the late nineteenth century in serum as a collection of heat-labile components which supports the development of antibacterial antibodies following immunization. Complement has been established as a factor fostering an immune response and vital to maintaining host-microbial equilibrium in addition to acting as a "first line of defense" (such as C1q and mannose-binding lectin, respectively) to immune complexes (classical pathway) or to carbohydrate moieties exposed on microorganisms or damaged/necrotic host cells (lectin pathway), the classical and lectin pathways are activated.

A tick-over mechanism starts the alternate pathway. All three pathways comply with at C3, the central component of the complement system, and its activation results in a generation of effectors that help antibodies and phagocytes clear microbial pathogens (via C3b opsonization), cause chemotaxis and inflammation (via C3a and C5a anaphylatoxins) and lyse susceptible microbial

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targets via C5b-9, membrane attack complex [MAC]. Complement ought to be seen, nonetheless, as a two- edged weapon that, while protecting the host in normal physiological settings, may also be harmful to other tissues in pathological situations. Hence, persistent complement activation and modification by bacteria in the biofilm in periodontal pockets may result in the localised breakdown of tissue, giving the biofilm vital nutrients and room to proliferate. Complement may even be used by biofilm bacteria to thwart immune responses, maintaining the survival of the biofilm and perhaps facilitating the systemic spread of microorganisms from periodontal pockets. Understanding why certain individuals are unable to heal from periodontitis may be aided by more research on this aspect of complement function.

Research into whether and how complement promotes the systemic spread of periodontal disease-causing bacteria might improve our comprehension of the connection between systemic illnesses and periodontitis. Such information may eventually serve as the foundation for innovative treatment approaches for chronic inflammatory diseases like periodontitis.[4]

Historic Discovery of Complement

An assortment of heat-labile serum components known as the complement system (complement) was first identified in the late nineteenth century to complement the antibacterial antibodies produced after immunization (Tauber AI et al 1989).[5] The word "complement" comes from the fact that IgG and IgM antibodies activate and work with complement proteins. Complement has recently been recognized as a factor supporting adaptive immune response and fundamental to maintaining host-microbial equilibrium in addition to acting as a "first line of defense". [Chaplin H Jr.2005][6] A heat-labile component that could kill pathogens in blood was discovered by Buchner and colleagues in 1891, and they gave it the name alexin (which, in Greek, means "to ward off") [Buchner H 1891]. Jules Bordet demonstrated that immune breakdown required the presence of two factors: a heat-labile lytic factor (similar to alexin) and a heat-stable factor, which he referred to as a sensitizer (which we now know was antibody). This "humoral theory"—immunity conferred due to antitoxic and bacteriocidal substances in body fluids was supported by [Morgan BP 1990][7]

Studies in mice and non-human primates indicated that complement is involved in both the dysbiotic transformation of the periodontal microbiota and the inflammatory response. Pioneering clinical studies by independent groups in the 1970s and 1980s associated periodontitis with an increased abundance of complement activation products in gingival tissue biopsies and gingival cervical fluid obtained from patients relative to healthy control samples. A recent study in human patients with periodontitis and periodontally healthy controls suggested that the complement activation product C3c might be a potential salivary biomarker for periodontitis. [Grande M.A et al] 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. [6] 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.[8]

Complement In Periodontitis

Periodontitis is a prevalent inflammatory disease that leads to the destruction of the tooth-supporting tissues. Recent evidence from clinical microbiome studies and mechanistic studies in animal models have shown that periodontitis is a dysbiotic disease rather than an infection attributed to a select few species. Connective tissue damage and loss of alveolar bone is mediated by a dysregulated and excessive inflammatory response, which includes components of both innate and adaptive immunity but fails to control the dysbiotic microbial challenge that induced it. In fact, the

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destructive periodontal inflammatory response is exploited by the dysbiotic microbial communities to procure nutrients from tissue breakdown products. (Figure:13) 28/ Figure:13 / Complement and TLR involvement in dysbiosis and inflammatory bone loss in periodontitis. (Courtesy Yamada M 2004)[8]

The possible involvement of complement in human periodontitis was first recognized in the 1970s and 1980s by histological and clinical studies analyzing the gingival crevicular fluid (GCF) in periodontal health and disease. GCF samples from periodontitis patients were shown to have complement-dependent hemolytic activity, suggesting that a functional complement system is present in this inflammatory exudate. Activated complement fragments were shown to be highly abundant in the GCF from patients, but were undetectable or present in lower concentrations in GCF from healthy control individuals. Similarly, complement components and cleavage products were also readily detected in chronically inflamed gingiva but were undetected or at lower abundance in healthy tissue samples; the complement components detected in diseased gingiva (and also in GCF) were representative of the entire cascade (e.g., C1q, factor B, Bb, C3, C3a, C3b, C3c, C3d, C4, C5, C5a, C5b, C9).

Importantly, periodontal therapy that resulted in decreased clinical indices of periodontal inflammation and tissue destruction also led to decreased C3 activation in the GCF. Conversely, and consistently, the progression of gingival inflammation during an experimental human gingivitis study was associated with elevated C3 cleavage in the GCF. Specifically, this study examined the cleavage of factor B, C3, and C4 in GCF collected during the experimental period and demonstrated, respectively, their conversion to Bb and C3c but not to C4c, thus implying selective activation of the alternative pathway. (Figure: 14)

An immunohistochemical study showed that the complement regulator CD59 is expressed at lower levels in the gingiva of periodontitis patients as compared to healthy individuals, which might imply compromised protection of periodontitis-involved tissues against MAC-mediated autologous tissue damage. (Figure: 15)

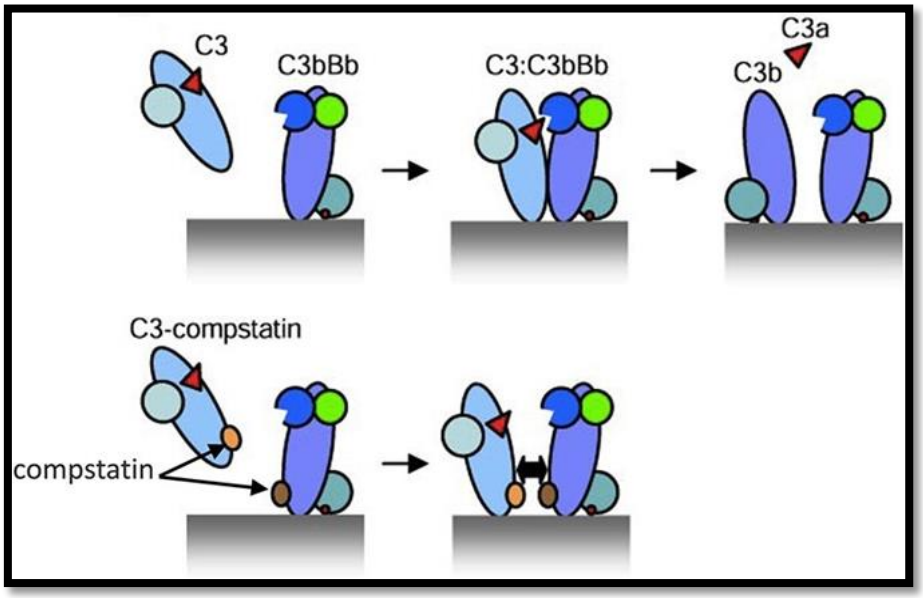

Figure 1: Model of C3 activation and its inhibition by compstatin (Courtesy: Janssen BJ 2007)[9]

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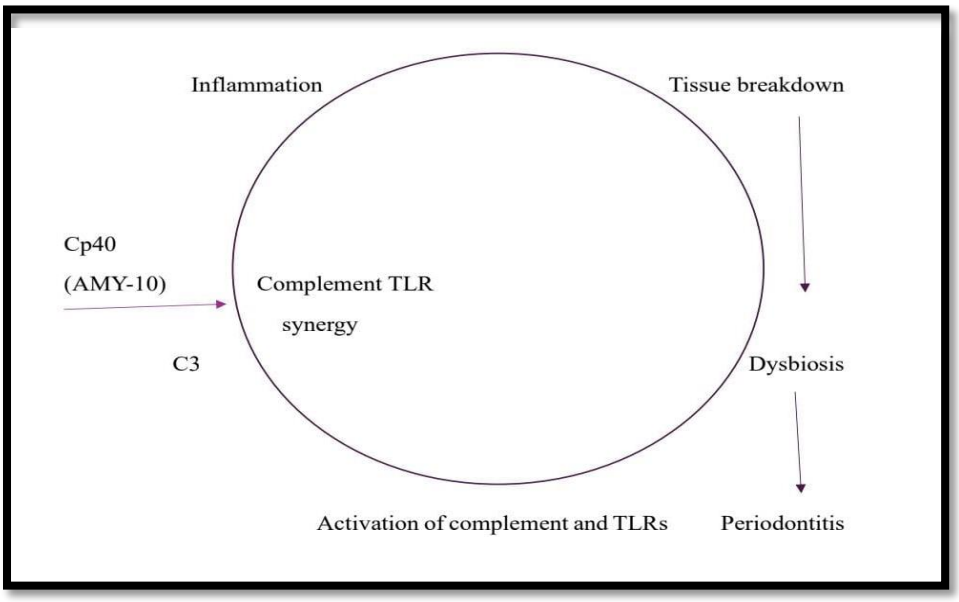

Figure 2: Complement activation and periodontitis

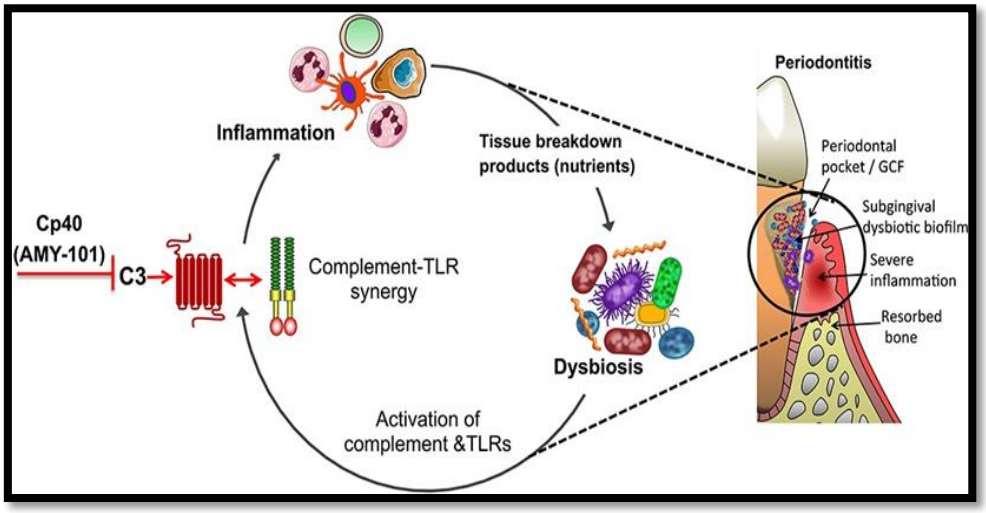

Figure 3: Complement-targeted inhibition blocks a vicious cycle linking destructive inflammation and dysbiosis in periodontitis. (Courtesy Maekawa T 2014)[5]

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. (Figure:3)

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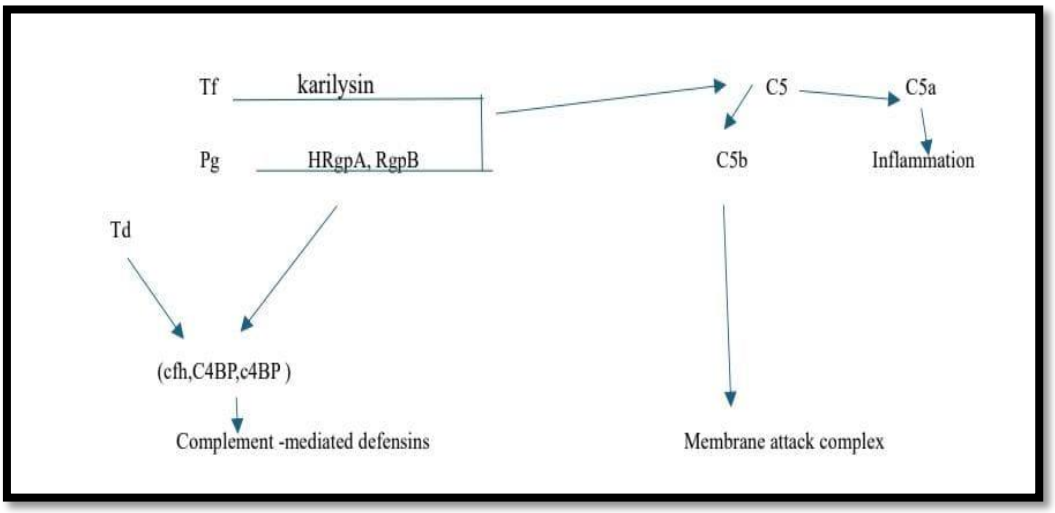

Figure 4: Inhibition of Complement-Dependent Host Defenses by Periodontal Bacteria.

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-3β (GSK3β) 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 IFNγ, leads to impaired immune clearance of P. gingivalis.

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)

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. Clinical and histological observations suggest that complement may be involved in the pathogenesis of human periodontitis.

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. Moreover, experimental induction of gingival inflammation in human volunteers causes progressive elevation of complement cleavage products correlating with increased clinical indices of inflammation.[10]

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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. Importantly, treatment of P. gingivalis -colonized mice with a C5aR antagonist led to the elimination of P. gingivalis from the periodontium and reverses the dysbiotic changes that are required for the development of periodontitis. 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.

CONCLUSION

The multifaceted interactions of complement with other immune cells and physiological systems are reflected in the diversity of inflammatory disorders driven or exacerbated by complement dysregulation or overactivation. Compelling evidence accumulated over the years indicates that complement is causally linked to periodontitis by inducing destructive inflammation and promoting microbial dysbiosis. There is an unmet need for efficacious and safe therapeutics in periodontitis, which is often unresponsive to conventional periodontal treatment. 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. Therefore, the treatment of periodontal disease should benefit from safe and effective products appropriate for chronic administration.

Preclinical animal data suggests that locally administered complement inhibitors may be able to prevent periodontal inflammation and offer resistance in addition to current periodontal treatments. Complement inhibition is a host modulation-based strategy that has an advantage over antibacterial strategies since it is the host response that predominantly damages the periodontal tissues. Furthermore, as was previously mentioned, since the microbiota linked to periodontitis needs an inflammatory environment to acquire resources for development and sustenance, inhibiting periodontal inflammation also has tangential beneficial effects.[11]

Conflict of interest: No conflict of interest present

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