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Complement and Its Role in Periodontal Pathogenesis

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Abstract

Complement system is one of the major effector mechanisms of humoral immunity and is also an important effector mechanism of innate immunity. The activity of blood serum that complicates the action of antibody is termed as complement. The complement system belongs to a group of biological effector mechanism called triggered enzyme cascade which also includes the fibrinolytic and kinin system. The role of thecompliment system includes clearing immune complexes as seen in patients with auto immune disease (SLE).

Inherited and spontaneous deficiencies in many of the complement proteins have been described in humans. Complement may play a significant role in periodontal infection which includes neutralizing pathogens and their toxin, recruitment of the acute and chronic inflammatory cells, opsonization and local hormone like regulation of connective tissue changes. In health, complement levels in GCF are about 1/35 of serum, but in periodontal inflammation it increases, there is concomitant increase in complement levels to 25% of serum. This review article discusses the evidences linking the complement system with periodontal inflammation along with the pathogen.

Keywords: Complement, receptor, periodontitis.

Introduction

Periodontitis is usually interpreted as a destructive chronic inflammatory condition caused by the accumulation of bacterial plaque. It is an oral infection driven chronic inflammatory disease. Although, complement system is centrally involved the in host defense, its over activation / deregulation may excessively amplify inflammation and contribute to immunopathogenecity due to inherent host genetic factors.[1]

The principle that promotes or complements the ability of the antibodies and phagocytic cell to clear pathogens is termed as complement, which goes back to the history of late 19th century when Hans Ernst found that blood serum contains a 'factor' capable of killing bacteria[2]. In 1896,

Jules Bordet demonstrated that this principle has got two components one heat stable for specific antimicrobial activity and the other heat labile for non-specific antimicrobial activity. Traditionally, the complement has been considered as the antimicrobial enzyme system found in serum and GCF . The host defense and inflammation is dependent on the complement system

The later one initially named 'alexene' was later called as 'COMPLEMENT' by Paul Ehrlich in late 1980s to describe the heat sensitive activity in serum that is complementary to that of antibody in causing lysis of bacteria. Although complement system is centrally involved in host defense, its overactivation or deregulation may amplify inflammation & contribute to immune pathology. Since periodontitis is oral infection causing chronic inflammatory disease that exerts systemic impact on health, this paper reviews the evidence linking complement system & periodontal inflammation along with the pathogenesis. Furthermore, it discusses interventional strategies that could complement current periodontal treatment which is often not sufficientto reverse the destructive inflammation.

Role

Basic functions include

- Inflammatory process
- Opsonization
- Lysis
- Solubilisation and clearance of immune complex.
- Cross talk and regulation with other systems like TLR.
- Bridges innate to adaptive immune responses.

Other functions

- Skeletal (ClqRp and C3)and vascular development (ClqRp and C3a)
- Tissue regeneration (C3a and C5a)
- Functional links between the innate immune system/ complement and other cellular networks that influence normal developmental pathways.
- Normal reproduction (C3, complement regulatory proteins and CRs)
- Hematopoiesis (C3a) , neuronal and CNS development (C5a and CRs)
- Cell proliferation and apoptosis (C3a, C5a and sublytic MAP)

Components

The integrated complement systemincludes theserum protein, membrane – bound regulators, receptors – for interaction with various immune mediators.

Immunochemistry of complement system

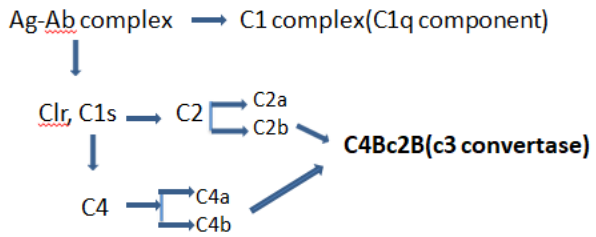
Compounds of complement system are pro-enzymes that are cleaved to form enzymes. The principal participants include 11 proteins named from C1-C9, B&D. In addition to the antibacterial function, the complement system participates in development of inflammatory reaction, opsonization, phagocytosis lysis and regulation of the toll like receptors (TLR 1&2). This system gets, activated by immune complexes and immunologic molecules like endotoxins and the activation occurs by three mechanisms as

1. Classical pathway
2. Lectin pathway
3. Alternate pathway

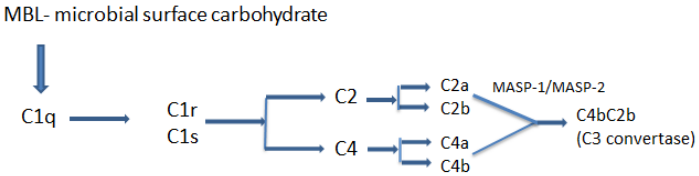
Classical pathway:-(Initiated by the antigen antibody complexes IgM/IgG)

The binding of antibody to antigen triggers the system that orchestrates a series of critical events. Only IgM&G can activate complement system resulting in binding of C1q subcomponent of the trimolecular complex C1(C1q + cir + cis). This activation of C1 with internal proteolysis of cir&cisintiates the complement cascade. C4 + C2 serve as asubstrates that are cleared to form C4a, C4b, C2a, C2b

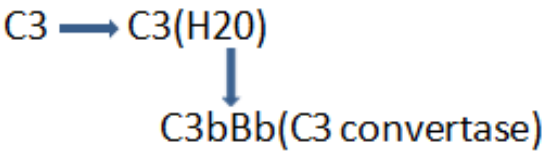
respectively C4b C2b complex called C3 convertase cleaves C3 to C3a & C2b. C3a released into the surrounding tissue fluids and bind to receptors on basophils and mast cells to release histamine, Because of its role in anaphylaxis C3a is called as 'anaphylatoxine'. Similarly macrophages and neutrophils have receptors for C3b and can bind to C3b coated cell orparticle preparatory to phagocytosis. This effect qualifies C3b as an 'opsonin'.[3]



Lectin pathway: This pathway is triggered through interaction of the secreted pattern-recognition receptor, the Mannose binding Lectin (MBL) with specific carbohydrate groups on the surface of a variety of microorganisms[4]. Both the classical &Lectin pathway then proceed through C4 and C2 cleavage products for the generation of classical or lectinconvertase.



Alternative Pathway: This is induced by Lipo polysaccharides &Lipo-oligosacharides. This pathway is also called as properdin pathway as it strictly required participation of the plasma protein properdin attached to the microbial surfaces. Alternative pathway also serves as amplification loop for the complement activation throughthe classical or lectin pathways, thereby an initially week stimulus can get markedly amplified and thus alternate pathway may potentially contribute to more than 80% of the complement activation even when the initial trigger is provided by other two ways[5].



So all these three pathways converge at the third components of the complement(c3) which upon activation by pathway specific that leads to the generation of a number of effector molecules. These include C3a & C5a anaphylatoxins that activate a protein coupled receptors (C3aR and C5aR respectively) and mediate mobilization and activation of leukocytes. The C3b and iC3b opsonins that promote phagocytosis; the C5b-9 membrane attack complex (MAC) which lysis targeted pathogens.

Complement receptors:[6]

1. C1q receptors:

C1q

Role : 1) Initiation of classical /lectin pathway

2)Opsonin

3)Removes apoptotic cells, immune complexes and pathogens

4) Triggerschemotaxis

Associated receptors

1- C1qRp- mediates phagocytosis

2- CR1- accelerates dissociation of C3 convertases , cofactor for factor 1, helps processing immune complexes, phagocytosis of c3 and c1q opsonized particles, a CD35, mainly a receptor for C3b and C4b

Functions: as a regulatory protein – serves as a cofactor for factor I mediated cleavage of the C3b/C4b also deaccelerating effect on c3convertases ,as a receptor – promotes binding and phagocytosis of C3b and C4b coated particles

3- CR2 – a CD21, binds to iC3b, C3 dg and C3d fragments of C3 , regulates Bcell functions , involved in antibody - response to Tcell dependent and independent antigen
4- CR3- a CD18, adhesion molecule belonging to leukocyte integrin family, binds to iC3b and mediates phagocytosis of microorganisms [7].
5- CR4- a CD 18, adhesion molecule similar to CR3
6- C3aR- functions include-
7- C5aR – chemotaxis, chemokinesis, cell aggregation and adhesion
8- C5L2- binds to C5a, C5 adhesion antigen, also C3a,C4a

Periodontal inflammation: Periodontitis is an inflammatory disease that causes destruction of the tooth supported tissues. Although bacteria populating the tooth associated biofilm are essential for initiation of periodontitis, it is actually the host inflammatory response , rather than direct bacterial action , that causes periodontal tissue damage. The reason why host response often fails to control periodontal infection is not known. The disruption of host homeostasis by periodontal pathogens may be a major contributing factor. Eg. Pathogen manipulation P.gingivalis – key organism) of pattern recognition and response mechanisms may disturb the homeostasis host – bacterial interactions, thus leading to non- protective and non- resolving chronic inflammation [8].

Complement and its role in periodontal pathogenesis:

Periodontitis is an oral infection causing chronic inflammatory disease.

Although, complement system is centrally involved in host defense, its over activation / deregulation (due to inherent host genetic defects / due to pathogen subversion) may excessively amplify inflammation and contribute to immunopathology.

Overall available evidence suggests, that complement activation / subversion contribute to periodontal pathogeneses.

Complement related clinical associations in periodontitis.

1. Activated/functional complement components are observed at significantly higher levels in GCF of patients than in healthy controlseg. Factor B, Bb, C3, C3b, C3c, C4, C5aand C9.
2. Activated / functional complement components are observed abundantly in a chronically inflamed gingiva (eg. C1q, factor B, Bb, C3, C3a, C3b, C3c, C3d, C5, C56, C9) Induction of experimental human gingivitis causes progressive elevation of complement cleavage fragments (Bb, C3) correlating with increased clinical indices.
3. C3 conversion to C3c in GCF increases with the increasing periodontal pocket depth and decreases dramatically after periodontal therapy [9].
4. C3 falls among top 5% genes that most strongly down regulate after periodontal therapy
5. A case of aggressive periodontitis (with Severe gingival angioedema) has been linked to deregulated complement functions(esp. C1INH deficiency)
6. Partial C4 gene deficiencies are seen more frequently in periodontal patients.
7. Single nucleotide polymorphism of C5 is seen more prevalently in periodontitis patients.
8. An immunohistochemical study showed weak expression of CD59 in gingiva of periodontitis patients compared to healthy controls; suggesting reduced protection of diseased tissues against autologous MAC mediated tissue damage. Studies show, even sub lytic amounts of C5b- g MAC could cause periodontal tissue destruction. The non -lethal concentrations of C5b-g induce activation of phospholipase A2, release arachidonic acid and

synthesize PGE2 potentially causing periodontal bone loss.

The above observations collectively suggest a role for complement activation in periodontal inflammation and pathogens.

Protective Role of complement in periodontitis :

C4- protective nature, its deficiency is seen more commonly in the periodontitis patients.

C3b- promotes opsonization and phagocytosis ofthe periodontal bacteria there by controlling infection.

Periodontopathic Bacteria & Complements

P. gingivalis: P.gingivalis is the keystone species in periodontitis .it is believed to promote the survival and virulence of biofilm community. By interacting with complements it attenuates the activation of complement cascade. Central complement component C3 is inactivated by P.gingivalis and also the proteolytic action is mediated by cysteine proteases, the gingipain .More potent complement inactivation is caused by HRgPA and RgP [10].

HRgpA also hijacks the complement regulatory proteins – C4BP, factorH, on the bacterial cell wall, thus acquires the ability to negatively regulate classical / lectin pathway C3 convertase.

P.gingivalisleads to host tissue damage by causing the proteolytic shedding of CD46 from the surface of oral epithelial cells , thus rendering them potentially susceptible to unintended complement attack.

Pathogens promote own survival by sophisticated manipulation of complement system

P.gingivalis and P.intermedia stimulate local inflammatory responses that result in nutrient acquisition. Thus induced inflammation in nonproducing from the host point of view and become non resolving and chronic.

Direct binding and activation of CR3 ,CR3 -a beta 2 integrin

Roles

- Ic3b mediated phagocytosis
- Leukocyte migration
- Cytokine release
- Interacts with host molecules (iC3b, ICAM-1) and microbial molecules(P.gingivalis fimbriae)

P.gingivalis activates CR3, through CD14, TLR-2 and P13-K mediated inside out signaling and also directly with the bacterial fimbriae

P.gingivalis induced CR3 dependent responses induce: cytokine release (TNF-alpha, IL-1 beta, IL-6) and cause periodontal bone resorption.

Inflammatory response (recruitment of neutrophils)

P.gingivalis enzymatically attacks C5 and releases the C5a which then enhances cAMP production.[11]

The activation of the cAMP dependent PKA pathway impairs iNOS – dependent killing of pathogen.

Exploitation of crosstalk interactions between the TLRs and complement.

- P.gingivalis- TLR-2- Cascade 1- induction of proinflammatory and anti-microbial responses, manipulated byP.gingivalis. Cascade 2 – proadhesivepathway, involves cross talk between TLR-2 and complements.
- Fimbriae of P.gingivalisbinds to CR-3 and stimulates its phagocytosis, but does not promote the killing of P.gingivalis.
- P.gingivalis–CR3 interaction releases an extracellular signal regulated kinase ½(ERK), which inhibits IL-12(key cytokine for IF-gamma production and microbicide 60% activity.)
- P.gingivalismay indirectly generate a functional C5a by exploiting the physiological crossalk between the coagulation and the complement systems which activates the extrinsic pathway.

- Excessive C5a may incapacitate its anti-microbial action by rendering neutrophils immunologically paralyzed, without affecting macrophage activity. C5a also down regulation IL- 1alpha activity.
- Also C5a supports the intracellular survival of P.gingivalisin macrophage , thus supporting its C5a hijack theory.
- P.gingivalis and P.intermediasynergise in complement attenuation
- P.intermedia(like p.g) stimulate the local inflammatory responses that result in nutrient acquisition

causes microbial enzyme- dependent generation of specific complement fragments (anaphylotoxins , I C3b)

T. denticola

- Hijacks employment regulatory protein ,factor H and protects itself against alternative pathway.
- Dentilism causes a microbial enzyme dependent generation of specific complement fragments
- Not an initial pathogen , but it is chronically persisting nature in periodontal tissues.
- T. denticola definitely cannot prevent the initiation of the complement cascade , but it may be protected from killing by- hijacking and employing specific down regulating factors , also its co-existence with P.gingivalis may provide protective mechanisms.
- T.denticolaexpress a factor H binding protein which binds to the full length factor H and escapes complement killing.
- However, the organism uses its serine protease dentilism to generate an H fragment , thus negating the action of factor H binding protein . but the action of dentilism is slow thus providing time to T. denticola to escape complement killing.
- T.denticola causes hydrolysis of C3 – iC3b. This, Ic3b is taken up by phagocytes via CR-3 .however iC3b mediated phagocytosis is associated with only weak killing mechanism / immune suppressive signaling.

T. forsythia

- Its interaction with complement system is unknown.
- Preliminary data suggests T. forsythia proteases may play an essential role in neutralizing complement.

P.gingivalis and P.intermedia:

Both the above organisms show biphasic virulence effects:

- At low concentration of the proteases (gingipain and interpain) and at long distance from dental plaque-

(1)Activate classical pathway

(2)Activate C1 complex and deposit C1q on bacterial surfaces of P.gingivalis and P.intermediawhich are resistant to complement lysis

(3)Eliminates complement sensitive commensal bacteria, could otherwise compete with pathogens for space and nutrients.

(4) Inflammatory serum exudates provides nutrients.

- At high concentrations of the proteases(in a developed film)
- Proteases synergistically inhibit bactericidal---
- Degradation of C3 causes inactivation of complement dependent bacterial opsonization and lysis.
- Degradation of C5 leads to prevention of MAC formation.
- Both mechanisms protect, complement sensitive bacteria in proximity and promote biofilm development
- Also C3a and C5a produced above to retain their biological activity, fuelinflammation and result in tissue damage of nutrient generation.

Thus as we know the complement system (along with TLRs) functions as a major defense against microbial infection.

However in course of evolution, successful pathogens have learned to breach these systems and to exploit their communication hubs. The various mechanisms by various microorganisms explain at least in the part, their ability to persist and establish chronic infections in otherwise hostile environment of their host.

Complement system involvement in periodontitis: A number of clinical & histologic studies suggest the complement involvement in periodontal infection. These studies show that activated complement fragments are abundantly found in gingival circular fluid (GCF) of periodontitis patients where as they are absent or present at low concentrations in normal individuals. Complement components & cleavage products covering full complement Cascade (C1q, B, Bb, C3, C3a, C3c, C3d, C4, C5a, C5b and C9) are present in chronically inflamed gingiva. Similarly CGF from periodontitis patients displays complement – depended hemolytic activity. Suggesting the presence of functional complement system similarly there is progressive elevation of cleavage products correlating with increased indices of periodontitis.

Moreover the central component C3 is the most strongly downregulated and also C3 conversion into C3c in GCF deceases dramatically after periodontal therapy. Neutrophils, the key-players in the host-mediated inflammatory tissue injury in periodontitis are found in great numbers in the gingival crevice called 'trafficking neutrophils'. Similarly small non-lethal concentrations of the C5b-9 MAC are also seen in the gingiva which induces activation of phospholipase A2, release of arachidonic acid and synthesis of prostaglandins. The mechanism can potentially cause periodontal bone destruction. So collectively all these observations suggest the definite role of complement activation in periodontal inflammation and its pathogenesis.

Complement system in GCFs serum and its role in periodontitis: As the plaque accumulation & gingival inflammation measurably increases the concentration of cleavage products of C3 also shows a hike in GCF. In the variety of periodontal diagnosis including health gingivitis adult periodontitis, rapidly progressive periodontitis and localized juvenile periodontitis .Various percentage of C3 clearage products were noted and also it differed from periodontitis and gingivitis. The percentage of C3 clearage products correlated with measurements of plaque, gingivitis pocked depth & bleeding on probing.

In localized juvenile periodontitis C4 cleavage products are elevated instead of C3 as in Localized juvenile periodontitis, the complement system is activated by the classical pathway unlike the others as they are activated by alternate pathway. In LJP classical pathway is activated because of the extraordinarily high levels of antibodies to antibodies to Aggregatibacteractinomycetemcomitans.

These assessments are based on the fact that several of the complement proteins behave as acute phase reactants, that is certain inflammatory conditions induce increased synthesis of these proteins in lines, resulting in elevate serum concentrations.

Complement in gingival tissues: Activation of complement in immunopathologic states frequently involves the formation of complement fixing immune complexes within diseased tissues similarly, immunoglobulins and antibodies to plaque microorganisms can be detected in gingival tissues [12]. Inflamed tissues also show reactivity of complement activation fragment with receptor molecules. Double label immunofluorescence technique, shows staining of antigen-antibody-complement complexes in diseased gingival tissue. Products of complement activation in particular C5a & C3a along with complement activating substances

are seen in gingiva and is capable of activating exogenous sources of complement.

Complement in periodontal pathogenesis: Periodontitis is a well prevalent chronic inflammatory disease that causes destruction of tooth supporting structures which in its severest form causes tooth exfoliation and or a significant impact on system health. Although bacteria associated biofilm is the cause for initiation of inflammation, it is actually host related inflammatory response to the challenge rather than the bacterial action itself that primarily cause tissue damage. The bacteria associated with the periodontitis comprises a group of gram-ve anaerobic organisms which are termed as 'red complex' pathogens. These include porphyromonasgingivalis, Treponema denticola and Tanerella forsythia. The endotoxins produced by these gm-ve bacteria and antigen-antibody complexes activated complements to produce the inflammatory mediators, including both anaphylatoxic and chemotactic activities.

Complement activation by plaque bacteria: Individual gram-veand+ve bacteria and the dental plaque have the ability to activate complement system [13]. Gram+ve bacteria like A Viscosus, Streptococcus mutansandS.sanguis activate both classical and alternate complement pathways while the LPS of fusobacteriumnucleatum activates only alternate pathway. P.gingivalis also activated by its LPS. Through this activation a number of biologically active complement proteins are generated.

Complement Interaction with bacterial enzymes: Bacterial proteases directly act on complement proteins to release biologically active fragments that lead to immunopathologicresponses.In particular P.gingivalis have a capacity to inactivate plasma proteins including immunoglobulin ,plasma proteinase inhibitors, alpha 1 antitrypsin, alpha 2 macroglobulin and components of kinin , clotting and fibrionlytic systems [14]. Thus these organisms with proteolytic potential evade host defense mechanisms by destroying opsoninssuch as complement and immunoglobulin, which may be an important virulence factor.

Though disruption of host homeostasis by the periodontal pathogenic microorganisms may be a major contributory factor, the actual reasons as to why the host response fails to control or reverse the disease profession are still under study. But pathogen manipulations of the pattern recognition and response mechanism are the factors that modify the homeostatic host – bacterial interactions that lead to non-protective and non-resolving chronic inflammation. Thus the periodontal disease can be prevented by controlling inflammation and counter acting microbial suppression of host response.

Regulation of complement system: As the complement system has potentially destructive nature for host tissues, its activation should be tightly controlled by the membrane bound and soluble regulatory proteins which are present in high concentrations in blood plasma. Deficiencies of control proteins lead to over activation with significant morbidity and mortality. The complement regulatory proteins restrict complement activation at several stages of complement cascade as of activation or initiation, amplification (convertase formation) and membrane attack. At the activation stage, C1 inhibitors (C1INH) plays an important role in both classical and lectin pathways. Also association of C4b and C2a is blocked by binding C4b binding protein or membrane cofactor protein (MCP). Similarly inhibitor bound C3b and C4b are cleaved by factor V which are required for classical / lectin C3convertase formation.

In the amplification stage, C3 convertases are dissociated by C4b BP, CRI, factor H and delay accelerating factors. CD59 referred as protectininhibitits,the terminal step of

MAC formation .Similarly ,fH related protein 1 (FHR-1) ,directly binds with C5 to block C5 convertase activity and downstream the formation of MAC.

Complement therapy in inflammatory diseases: As C3 is a central component for all these pathways , therapeutic inhibition of C3 must be effective in complement related diseases [15]. But the fact is certain pathway when activated contributes to inflammation and tissue damage while the other pathways prone to be protective against infectious pathogens. Thus, there is a strong rationale for the selective inhibition of specific complement pathways, so that the other pathways are kept intact to mediate protective functions. Hence complete inhibition of C3 level to prevent the inflammatory tissue damage will compromise host defense and increase the risk of infections. But in case of topical interventions, the risks are relatively minimal.

Complement receptor 3 in periodontal pathogenesis:

Complement receptor CR3 is a beta 2 integrin, a member of related group of leukocyte cell surface glycoproteins which in concert with other molecules contribute to immunity and inflammation, including the iC3b mediated phagocytosis, promotion of leukocyte migration to sites of extravascular inflammation and induction of cytokine responses. It also co-associates with pattern recognition receptors in activated macrophages. P.gingivalis an important etiological agent in periodontitis is strong in activating CR3 leading to activation of ligand binding capacity of CR3 which in turn leads to induction of cytokines like TNFalpha, IL- 1beta, IL-6 contributing to innate host defense.

So, heritable deficiencies of these molecules contribute to recurrent infections along with impaired pus formation, delayed wound healing and granulocytosis. In particular the periodontal manifestations may include severe periodontitis in both primary and permanent dentitions, rapidly progressive alveolar bone loss, recession, gingival clefting , tooth migration excessive amounts of C5a become paralyzed from its antimicrobial function. Similarly the ability of neutrophils to form the front line 'defense wall' against advancing microbes largely fails despite being viable and capable of eliciting responses including the release of reactive oxygen species. Since reactive oxygen species donot discriminate between microbial and host cells, they are likely to cause collateral damage to periodontal tissues.

In particular P. gingivalis employs specific gingipains to generate functional C5a in high concentrations which suppresses all these mechanisms of complement activation and thus contributes to periodontal pathogenesis. C5aR combines with TLR2 to produce maximum inflammatory response in periodontium. Thus, specific complement targeted therapeutic approach becomes necessary for selective inhibition of defined components with compromising host defense. The C5 receptors antagonists (C5aRA) were hence introduced to counteract the synergistic effect of C5Ar and TLR2. Also they confer combined antimicrobial and anti- inflammatory effects in periodontitis and periodontal bone loss is largely reduced.

So it is suggested that C5aR inhibitors may have an important therapeutic implication in periodontitis as it inhibits allthe pro inflammatory pathways and bone resorptive cytokines. Local administration is more safe as systemic inhibition of complement may predispose to increased susceptibility to microbial infection and severe gingival inflammation as CR3 is a major receptor on phagocytosis for complement coated bacterial. But the CR3 mediated cytokine induction is an immune – pathological 'double edged sword' which also has the pathophysiological consequences in periodontal disease if their production is prolonged and excessive.

In this regard, the CR3 induced cytokines (TNFalpha, IL-1 beta, IL-6) cause periodontal bone resorption , whereas CR3 mediated inflammatory cell migration amplifies the periodontal inflammation. N3eutrophils which are major effector of inflammation induced periodontal tissue destruction, shows high levels of CR3 that facilitates the 'neutrophiltrafficking'. Thus, neutrophils and other inflammatory phagocytes are recruited in the tissue due to activation of CR3 which exacerbates periodontal inflammation.

Importance of targeted C5a-C5aR axis in periodontitis: the complement activated fragment C5a mediates the chemotactic recruitment and activation of neutrophils and other inflammatory cells. Although C5a protects the host against pathogens, P.gingivalis exploits C5a contributing to the colonization on periodontal tissue which is required to produce microbial dysbiota(increased colony counts and altered composition)

Complement related clinical association in periodontitis: Activated and functional complement components are observed at significantly higher levels in GCF of the pattern than in healthy controls eg. Factor B,Bb, C3,C3b,C3c, C4,C5a,C9. In chronically inflamed gingiva complement components are observed abundant. In experimental human gingivitis causes progressive elevation of complement cleavage fragments B6,C3 correlating with increased clinical indices ,C3 conversion to C3c in GCF increases with increasing periodontal pocket depth and decrease dramatically after periodontal therapy.

C3 falls among top 5% genes that most strongly down regulates after periodontal therapy. More frequently in the periodontal patients partial C4 gene deficiencies are seen. Nucleotide polymorphism of C5 is seen more prevalent in periodontitis patients. An immunohisto chemical study should expression of CD59 is given in periodontitis patients compound complement in healthy controls, suggested a reduced protection of diseased tissue agent autologous MAC- mediated tissue damage.

Studies show, even sublytic amounts of C5b-9MAC could cause periodontal tissue destruction. The non-lethal concentration of C5b-9 induces activation of phospholipase A2 release arachidonic acid and synthesizes PGE2 – potentially causing periodontal bone loss. The above observations collecting suggesting a role for the complement activation in Pdl inflammation and pathogenesis.

Protective role of complement in periodontitis:

C3b- promotes opsonization and phagocytosing periodontal bacteria, thereby controlling inflammation. C4 is generally protective in nature, its deficiency is seen more common in periodontitis in patients.

Deficiencies of thecomplement components

1. Deficiencies in theclassical pathway

(a) C1q , C1r, C1s, C2 (most common) and C4 deficiencies produce classical pathway deficiency .eg. SLE – auto immune disease, defect in clearing immune complexes, seen in classical pathway deficiencies.

(b) Deficiency of MBL has been associated with increased susceptibility to various infectioneg. Cystic fibrosis, rheumatoid arthritis.

2. Deficiencies of C3:

Associated with higher susceptibility of infection eg.Glomerulonephritis.

3. Deficiencies in alternative pathway-

Less common, deficiency of properdin and factor D result in abnormal activation of alternative pathway.

4. Deficiencies of late complements- this leads to inability to form MAC which results in factor to lyse foreign pathogen eg. Meningococcal and gonococcal infection.

5. Deficiencies of complement regulatory proteins and complement receptors-

Since C3 is the central complement component its therapeutic inhibition can be an effective approach to treat the complements related diseases. However there is a strong rationale for selective inhibition of specific complement pathways implicated in pathology to keep intact the pathways that mediate protective functions.eg: recombinant C1- INH – for the treatment of hereditary angioedema, 1st complement targeted drug

Anti C5 antibody- for PNH

Under trials :

C3 inhibitor campstalin(POT-4)- macular degeneration

C5aR antagonist PMX – RA and psoriasis

Therapeutic intervention in periodontal pathogenesis: CR3 deficient mice elicit high levels of IL-12 that enhances clearance of P.gingivalis .Hence , CR3 inhibition may be use for therapeutic control of P.gingivalis infections.

Conclusion

Complement can be considered to be the fire of the immune system. When this fire ignites, it radiates the local area with molecules (C2a, C3a and C5a) that enhances the inflammatory response and enables the endothelium and leukocyte to examine and diagnose the problems. In addition it facilitates phagocytosis destruction of foreign substances or direct destruction of cells via membrane attack complex.

The high prevalence of periodontitis with the fact that many periodontitis cases are refractory to conventional treatment procedures underscore the importance of implementing innovative & cost-effective therapeuticinterventions. In periodontitis apart from the causative microorganisms, complement system is a target of immune subversion that leads to the dysbiota transformation of the micro biota causing complement dependent destructive inflammation seen with non-resolving nature.

Thus, functional mapping of complement system in periodontitis greatly facilitates complement targeted therapeutic intervention & such information help us to identify those specific pathways that are to be blocked to reverse inflammatory pathology or conversely enhanced to promote host defense. So, in future, the complementary therapeutic interventions to target specific complement molecules in parallel with a regular periodontal treatment could revolutionize the way periodontal patients are managed.

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