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Role of alkaline protease in activation of viridans streptococci complement system pathway

Emily V Baker [1], David J Edwards, Rebecca B Schulz, Michael F Hirama [1*]

Abstract

Viridans streptococci are a complex group of normal microorganisms commonly found in the mouth and on mucous membranes. They are beneficial for host health, mainly acting as a barrier against pathogen colonization. However, when viridans streptococci enter the blood, they can act as opportunistic pathogens, resulting in infective endocarditis. This is a life-threatening infection characterized by septic emboli formation and damage to heart valves. Viridans streptococci are also linked to cancer, complicating treatment and resulting in a poor prognosis. These bacteria possess virulence factors, including capsules, adhesins, and secreted products, which contribute to the pathogenesis of infective endocarditis. Despite the importance of viridans streptococci in both health and disease, many questions regarding their interaction with the host remain unanswered. The host immune system can recognize, capture, and kill bacteria. The classical pathway of the complement system is activated when antibodies bound to bacteria interact with complement proteins. Several bacteria possess proteins that interfere with antibody-complement mediation, enhancing their survival. Group A and Group B streptococci, as well as S. mutans, express secreted proteases that inactivate antibodies and proteolytically remove or inactivate complement proteins. Secreted proteases from both the Streptococcus mitis and Streptococcus sanguis groups have anti-complement activity, but their mechanisms are not fully understood. Whether viridans streptococci can trigger the complement system pathway also remains unknown. Alkaline protease is a secreted protease produced by certain viridans streptococcal strains. Although the protease has been suggested to be involved in the pathogenesis of infective endocarditis, little is known about how it affects the host. In this study, the effect of alkaline protease on the complement system pathway was assessed, and its activation of the complement system pathway through MBL and fH was also evaluated.

Keywords: Viridans streptococci; Alkaline protease; Compement system; Classical pathway; Lectin pathway

*Correspondence author e-mail: Hirama_b67@yahoo.com
[1] Nanjing University, 163 Xianlin Avenue, China
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Introduction

A member of the Group B Streptococcus viridans group, Streptococcus sanguinis, is lauded for its dental biofilm formation. Streptococcus gordonii also competes with S. sanguinis for carotenoid biosynthesis. Utilizing specific coaggregation to analyze viridans streptococci features, seven coaggregate pairs involving 16 human viridans group Streptococcus strains were observed. S. gordonii and S. sanguinis were capable of forming mutual coaggregates. Vaccine strategies aimed at preventing the attachment of S. sanguinis or its coaggregation with S. gordonii in dental biofilm might inhibit multiple viridans group streptococci. Viridans streptococci are a well-known group of streptococci, classified as α- or non-hemolytic streptococci based on their pattern of hemolytic activity. They colonize the oral cavity and are normally associated with dental plaque formation, yet they are the most common bacterial species responsible for infective endocarditis. The viridans group includes Streptococcus mitis, Streptococcus sanguis, Streptococcus salivarius, and Streptococcus mutans. Among these, S. sanguinis, S. gordonii, S. mitis, S. norvagiensis, and S. parasanguinis are early colonizers. The pathogenicity of viridans streptococci is not uniform, with S. mutans, S. sanguinis, S. salivarius, and S. mitis showing different strains in terms of virulence. Autoaggregation and coaggregation activities are associated with plaque formation and the pathogenicity of viridans streptococci strains. These activities were previously demonstrated to be mediated by high-molecular weight glycoproteins. Strains S. gordonii CH1 and S. sanguinis SK36 are both highly coaggregative with each other, yet S. sanguinis SK36 possesses a lower capacity for biofilm formation. S. gordonii CH1 strains also recognized different types of sugar-containing polymers. The avirulent type strain S. mitis B6-1 is biofilm defective and negatively influenced by the presence of a pathogenic organism S. mitis B6-n, which interrupted the biofilm formation of other early colonizers involving genetic regulation. So far, no reports have indicated how highly virulent oral streptococci interact with other viridans streptococci and/or contribute to in vivo dental biofilm development in the early colonization stage.

Complement System Pathway

Complement is one of the early lines of defense against infections, bridging innate and specific immunity. Three different pathways can activate the complement system: the lectin, the alternative, and the classical pathways. Activation of the classical pathway occurs downstream of antigen-antibody complex formation, and this results in the: (1) transformation of C1 protein upon binding to the targets; (2) binding of C1 to the Fc portion of antibodies complexed with the antigens or to other molecules. In all cases, an enzymatic subunit is formed, and C1 activates C4 and C2. Activation of the lectin pathway occurs when mannan-binding lectin and H-ficolin, present in the circulation, bind to carbohydrate residues present on the surface of microorganisms and, with the contribution of the MBL-associated serine protease, activate C4 and C2. In the alternative pathway, spontaneously occurring hydrolysis of the thioester bond in

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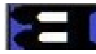
C3 or the activity of C3 convertase, formed in the presence of B, D, or factors H and I, activates C3, which is required for the formation of the membrane attack complex. The classical pathway activity in Streptococcus pneumoniae was reported. Several complement-initiating molecules were identified and suggested to play important roles in disease protection. Despite the overwhelming implication of the association between the activation of the complement system and the potential application related to the control of important pathogens, the characterization and the underlying molecular mechanisms and factors have not yet been completely unraveled. The viridans streptococci are a heterogeneous group of bacteria that inhabit mucosal surfaces and cause several types of disease that differ in severity and dissemination capability. Alkaline proteases are among the most studied enzymes in the field of virulence factors in Gram-positive bacteria. Streptococcus spp. are viridans swimmers that are closely related to Streptococcus pneumoniae, the bacterium responsible for the majority of community-acquired pneumonia.

Alkaline Protease: Structure and Function

In this report, we describe the presence and properties of alkaline protease in fresh viridans streptococci isolates from the human oral cavity and the pathophysiological role of protease in their colonization of the host tissue and general inflammation. Protease production was detected in all strains from the species Streptococcus intermedius, Streptococcus sanguinis, Streptococcus mutans, Streptococcus constellatus, and Enterococcus faecalis, and in 35% of S. sanguis and 47% of S. mitis strains. The pH of the growth medium acted as an induction factor. The genes coding for protease were cloned from genomic DNA, sequenced, and expressed in Escherichia coli. When the protease gene is cloned, no interruption of the gene structure or presence of a sequence in between the bla promoter and the active site codon should exist so that the proper sequence of the gene for the mature peptide appears in the plotted transcript.

Alkaline protease belongs to the proteinase family, a class of more than 1,000 proteases that is characterized by the presence of the catalyzed pentapeptide Asp-Ser-His. Many proteinases such as chymotrypsin, trypsin, and serine proteinase also belong to the family. These proteinases must be designated as serine proteases instead of serine proteinases according to Enzyme Nomenclature. The proteinase structure can be extended to include two distinct subfamilies, known as S1 and S3. These subfamilies have conserved residues in the 194-273 and 86-173 amino acid regions, respectively, that appear to be specific to each subfamily. The proteinases with catalytic triads (Asp, His, and Ser) can be selectively inhibited by inhibitors of proteinase such as alpha-1-antitrypsin, a trypsin inhibitor. However, some proteinases also include other type cuts, such as pepsin.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Enzymatic Activity

Alkaline proteases belong to the group of serine proteases and they are widely distributed in nature. They are known as exopeptidases and can liberate C-terminal amino residues from peptide or protein substrates. The molecule of alkaline protease is mainly globular with more than 50% of the amino acids in α-helix, β-sheet, or β-turn conformation. The neutral (alkaline) nature of alkaline proteases is their main distinction from other subtilisin-like serine proteases. This leads to the fact that alkaline proteases are very stable at high pH and capable of performing enzymatic reactions in alkaline media.

Alkaline proteases have been known for the last 40 years. Many alkaline proteases have been isolated and characterized in great detail regarding their enzymatic and structural properties from different organisms, such as bacteria, fungi, plants, mammals, and overexpressed in different expression systems. Their industrial uses in detergent, food, peptide synthesis, and waste treatment industries are well known. The viridans streptococci bacterium contains an alkaline protease that is unique because of its participation in the activation of the complement system and intriguing structural features, which are the topic of our further discussion.

Substrate Specificity

In order to understand more about enzyme specificity, some experimental studies were performed using purified enzymes, analogs, and molecular models where the naturally occurring substrates are converted into enzyme inhibitors with simple hydrolysable protection groups and stable analogs of the nitrogen located at the substrate binding pocket of a variety of enzymes. It was verified that transition states, like peptide-bound transition analogs such as phosphate or boronic acid, inhibit serine proteases from hydrolyzing substrates through a slowly reversible formation of a covalent enzyme-substrate complex. Thus, the observation that rasfurinase or its mutants are capable of hydrolyzing dipeptides as efficiently as oligopeptides indicates an unusual capability to accommodate the substrate, probably in as much as the carboxyl side of the binding cleft has been reduced to a minimum due to the wider burrow. This also agrees with the observed wide specificity of other cloned Rasfeurinases but not with aspartic protease, a homolog.

In our laboratory, different protease secrets from Bacillus spp. were evaluated upon hydrolyzing the Z-L peptide. The only difference between the five amino acids synthesized in this work is the first amino acid, Cys or His. Additionally, during the analysis of the effect of amino acid composition changes on its activity and specificity, the amino acid Cys in the enzymatic substrate Z-L was replaced with aromatic amino acids Phe, Tyr, or Trp.

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Interaction between Alkaline Protease and Viridans Streptococci

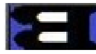
As we have detected that both cell-free protease in S. intermedius-CM and secreted proenzyme within S. intermedius are complement-inhibitory, we hypothesized that the major form of AP should inhibit or activate the alternative complement system present in the commensal S. intermedius inhabiting the host oral cavity environment. Complement-inhibitory AP could provide an evolutionary mechanism for enabling S. intermedius to exist within its specific niche. AP, which was considered to be a virulence factor in pathogenic oral streptococci, exploited the alternative system for bacterial survival and/or potentially inhibits the alternative complement system observed in commensal S. intermedius. The data showed that both complement-inhibitory AP and the major form of AP, which were the same molecules, were secreted and that they were not cell-bound S. intermedius, but were in a cell-associated area.

Our previous data suggest that AP was detected in the outermost layer of the S. intermedius outer membrane. We believed that the proenzyme was directly involved in the commensal S. intermedius, thus allowing the protease to inhibit the alternative complement system. The ability of S. intermedius outer membrane-localized AP was released in S. intermedius-CM. Therefore, AP is considered to be a secreted enzyme. AP was hypothesized to decline complement protein deposition that may occur due to S. intermedius cell division or division of commensal bacteria by surrounding the immediately adjacent host tissue. As a result, complement inhibition was achieved. Based on our data and collected information, we completed the puzzle between S. intermedius and secreted AP.

Role of Alkaline Protease in Complement System Activation

To examine the role of extracellular macromolecules such as surface proteins, we extracted proteins from the cell surface of the viridans group Streptococcus S. sanguinis, S. oralis, S. mitis, and S. intermedius with Achromobacter protease I. Degradation by the enzyme of complement activation products present in heated serum adsorbed to the cells was compared with amounts of the activation products formed. Protease-treated cells—which were complement-resistant as a result—had no CR2 and C3dg compared with untreated cells. Cells in heated serum containing the protease induced significantly lower amounts of CR2 and C3dg compared with cells in serum only. In conclusion, surface proteins of S. intermedius cells are essential for activation of the classical complement system pathway.

In the present study, activation of the three complement system pathways by S. intermedius cells and the roles of extracellular macromolecules are examined. Previous studies have shown that the classical and alternative complement system pathways of Streptococcus dysgalactiae and the alternative complement system pathway of Streptococcus sobrinus are activated. Results are today reported of the classical and alternative complement system pathways—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whose activation is inhibited by mannan—activated by Streptococcus sanguinis, Streptococcus oralis, Streptococcus mitis, and S. intermedius. The present study is the first to demonstrate activation of the lectin complement system pathway by S. intermedius. The extracellular macromolecule is essential for activation of the lectin complement system pathway by S. intermedius, as it is for activation of the two other pathways by the strain.

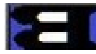
Initiation of the Pathway

The initiation of the viridans streptococci complement system pathway occurs by bacterium-mediated hydrolysis or activation of the zymogen of the alternative pathway C3 convertase. Many streptococci express and secrete a highly active intracellular ATP-dependent serine proteinase, or protease, which has been identified as an alkaline protease. This serine proteinase is expressed in the exchangeable surface protein group of streptococci. It shares the bacteriocinogen signal peptide that is exchanged among the serotype IIc precursor proteins and the ATP-dependent serine proteinases, or the extracellular alkaline proteases of Streptococcus sanguis, gordonii, mitis, and the encapsulated group B, or type III, streptococci. It has been suggested that alkaline protease in streptococci may serve as a microbial protein regulator because its synthesis is processed in two steps with the precursor of higher molecular weight.

We have demonstrated that alkaline protease activity is expressed in S. sanguis V288. Subsequent studies revealed the presence of alkaline protease activity in related streptococci and non-related pathogenic Gram-positive bacteria. The alkaline protease activity in related viridans group streptococci produces an approximately 180-kD protein from S. sanguis chymotryptic cell wall fragments, participates in the activation of the zymogen of the alternative pathway C3 convertase, and hydrolyzes the native C3 activator, fluid-phase C3, and the C3b fragment of complement components in a cell-free system. Finally, the alkaline protease-containing secretion product prepared from S. sanguis chymotryptic cell wall fragments has been subjected to high-pressure liquid chromatography and the alkaline protease activity has been mapped. Focusing on its role in the viridans complement system pathway, we have examined its synthesis and growth of other bacterial species that are responsible for infection at the site of disease onset and that express it.

Amplification and Regulation

Once activation of the alternative complement pathway is initiated by factors Bb and C3b on certain surfaces, the enzymatic activity of C3b-bound factor Bb is greatly enhanced. This already very efficient complex is responsible for driving the amplification process of the alternative complement pathway. It is capable of rapidly forming more and more C3b-bound factor Bb, but this also leads to depletion of factor B from the proximal plasma, although in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humans it is present at a higher concentration of about 2 mg/ml. Complete B-factor depletion following an activation event on a biomaterial surface is a clear marker for biological material-mediated alternative pathway activation. The combination of factor D and properdin stabilizes the factor B-dependent convertase and drives the amplification process; thus, this activity is called the alternative pathway amplification loop.

In addition to this process, an additional amplification loop consistent with the ability of normal human plasma to overcome dense surface complement attack is suggested, that is, the presence of relatively high plasma concentrations of surface regulator proteins and an intracellular calcium gradient, both of which enhance the inactivation rates of each convertase and the terminal complement complex. This newly proposed "inducible positive feedback continuation mechanism" has complementary support from a newly described mechanism common to the activity of the classic, lectin, and alternative complement pathways of activation. The technique of fibroblast cell-mediated formation of alternative complement convertase was used to evaluate CFH activity; albeit slowly, CFH bound to C3b will facilitate the eventual inactivation of these activated surfaces. The casual slow inactivation of other reaction components marked these components already present in the biological membrane. The rapid inactivation of these same components meant that the membrane-bound convertase preceded the precursor inactivation.

Clinical Significance

In this chapter, we demonstrated that neutral proteolytic activity from viridans streptococci cultures is important in the activation of CPM, leading to complement consumption. The neutral protease was shown to be an alkaline protease because it remained active only when the pH of the conditioned media was above 8.5. All VSC strains expressing NadA had neutral protease activity, and the amount of neutral protease in their conditioned media was proportional to the amount of complement components activated. These results further support the role of the Alp2-mediated ComC pathway and the classical ComC pathway in complement component activation when viridans streptococci adhere to salivary pellicle- or saliva-coated surfaces. Overall, our research suggested a novel role of Alp in bacterial complement activation on the salivary pellicle and demonstrated the important association of NadA activation with bacterial survival via complement consumption in a neutrophil-abundant milieu.

The activation of the complement system on a potentially harmful surface is an important event in the surveillance of bacterial infection and the subsequent recruitment of cells of the immune system to the site of infection. In periodontitis, abnormal complement activation leads to complement consumption, and the proteolytic product C5a, a strong proinflammatory mediator, is also found at higher concentrations in the crevicular fluid. These findings indicate a large involvement of complement system activation in the initiation and progression of periodontal

disease and provide a prospect of complement function-oriented design of drugs for the prevention and control of the otherwise serious periodontal disease. The complement system-activating enzymes of periodontitis bacteria have not been accurately characterized, however. In this research, we found that an alkaline protease secreted by clinostaphylococci lysed the functional ComC assembly and thus can be a putative therapeutic target for periodontal disease treatment.

Infections Associated with Viridans Streptococci

The viridans group streptococci (VGS) are indigenous descendants of the major regular human flora, populating almost every human body surface or orifice that contains a mucous membrane. VGS are a frequent cause of bacterial endocarditis, located on the gingiva, and are common organisms in dental caries and periodontal disease. The microorganisms, along with Streptococcus mutans and Streptococcus sanguinis, are major causes of dental caries and stain the teeth with fungi. Fifty-five species, which are heterogeneous in DNA homology and phenotypic characteristics, are included in the VGS group. S. anginosus consists of three different colleagues: S. anginosus. Some members of VGS have been involved in different circumstances in fatal infections, such as defects of the heart and the bacterial course that occurs following systemic hospital treatment. The viridans streptococci were initially evaluated concerning the effect of human polymorphonuclear leukocytes on the activity of the complement system, and the effect of the test on leukopenic polymorphonuclear leukocytes.

The viridans streptococci were initially evaluated concerning the effect of human polymorphonuclear leukocytes on the activity of the complement system, and the effect of the test on leukopenic polymorphonuclear leukocytes. The antimicrobial peptides produced by leukocytes only influence the members of the VGS. Furthermore, the complement-mediated adherence to carbohydrates, such as glucose, appears to be more likely. When an animal is injured, especially when it is in hypoxic tissue, the contemporary anoxemic build-up of the tissue can supply glucose for the most accelerated microbes of the bacteria; hence, glucose could be taken up in the immediate lysate of the leukocytes to protect the patient from the attack of bacteria. The glucose levels appear to have little influence on the direct influence of bacteria on the complement. All the permeates were similarly produced, even if other networks were used, comprised at the same or less level of removals in the VLN-1 sphere and VLN-2 yields. However, the immediate monocytic movement was reinforced in most circumstances by the purification of the two monocyte devices. The access of new area surfaces appears to have no effect.

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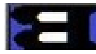
Therapeutic Implications

Activation of the mannose-binding lectin-associated serine protease pathway in most vertebrates is essential for host defense. The complement system is under tight regulation, as uncontrolled activation of its potent effector functions can cause harm and even destroy healthy tissue. Defects in MASP initiation of the complement pathway have been associated with susceptibility to several infections, development of autoimmunity, excessive thrombosis, and non-bacterial inflammation. In humans, this pathway has been described in several bacterial species, but not in the organisms involved in infection or colonization of the oropharynx. Hence, our data on complement activation by viridans streptococci have important implications for therapeutic strategies aimed at both the activation and inhibition of the complement system. Deficiencies in some of the MASPs, in mannose-binding lectin, or polymorphisms that lead to defective components have been related to an increased susceptibility to bacterial infections.

Activation of the complement system by viridans streptococci has important implications for the clinical treatment of patients with these infections, as complement is part of the immune system. Not eliminating the bacteria or creating an inadequate inflammatory process may cause the signs and symptoms of infections to continue. Systemic signs of fever, pain, dyspnea, hypotension, and tachycardia, as well as modulation of adhesion and tissue destruction molecules, are important for the therapeutic strategy against patients with pneumococcal infection. In these cases, an attenuated Th1 response may represent a therapeutic aim. In contrast, pediatricians often express concern about enhancement of this response against viridans streptococci, the tenants of the commensal mitis group, as this enhanced response might promote heart valve destruction, which is in turn supported by the human benefit of using long antibiotic prophylaxes to prevent persistent minimal changes or even more severe forms of rheumatic fever in children with viridans streptococcal pharyngitis.

Conclusion

The present study demonstrates that the alkaline protease ScaC in S. gordonii can regulate human complement activation through proteolytic degradation of complement C3. As several lines of evidence have indicated, the activation of the alternative complement pathway is mediated by the proteins involved in bacterial metabolism, but the cellular protease of the Streptococcus is the first documented protease that can regulate complement activation. For a membrane-bound protease from the secreted protease, the cleaved products of complement C3 have different functions at different infection stages. For the bacteria, they favor survival strategies and immune evasion mechanisms; complement activation enhances the immune resistance capability. For the hosts, they may kill the bacteria more effectively. However, the detailed mechanism of cleavage of C3 by ScaC and the interactions with the span of the downstream signaling cluster are not fully understood. These findings serve as a starting point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for a comprehensive understanding of the key roles played by cell wall–associated matrix proteins in the host immune response to pathogens. Future studies may involve the purification of a practical protease, such as the native ScaC enzyme. The chymotrypsin-like cleavage of C3 activation in serum is further analyzed by immunochemical means in order to substantiate the interactions among ScaC, the cleaved products, and the complement system. Furthermore, the structure–function relationships and biological implications are necessary for actively fine-tuning C3 activation and developing potential immunity-enhancing therapeutic approaches.

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Competing interests

The authors declare no conflict of interest.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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