Streptococcal Protein H Forms Soluble Complement-activating Complexes with IgG, but Inhibits Complement Activation by IgG-coated Targets*

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Andreas Berge‡§, Britt-Marie Kihlberg‡, Anders G. Sjöholm¶, and Lars Bjöck‡

From the Departments of ‡Cell and Molecular Biology and ¶Medical Microbiology, Lund University, S-221 00 Lund, Sweden

Protein H, a surface protein of Streptococcus pyogenes interacting with the constant Fc region of IgG, is known to be released from the streptococcal surface by a cysteine proteinase produced by the bacteria. Poststreptococcal glomerulonephritis and rheumatic fever are conditions in which immune complexes and autoimmune mechanisms have been suggested to play pathogenetic roles. The present study demonstrates that addition of protein H to human serum produces complement activation with dose-dependent cleavage of C3. The activation was IgG-dependent and the result of complexes formed between IgG and protein H. These complexes were size heterogeneous with molecular masses of 400 kDa to 1.4 MDa. Using complement-depleted serum reconstituted with complement proteins, the activation by protein H was found to be dependent of the classical, but independent of the alternative pathway of complement. In contrast to results of experiments based on soluble protein H-IgG complexes, complement activation was inhibited by protein H when IgG was immobilized on a surface. The interaction between C1q and immunoglobulins represents the first step in the activation of the classical pathway, and protein H efficiently inhibited the binding of C1q to IgG immobilized on polyacrylamide beads. Protein H reduced C3 deposition on the IgG-coated beads and inhibited immune hemolysis of IgG-sensitized erythrocytes. Finally, significantly less C3 was deposited on the surface of protein H-expressing wild-type streptococci than on the surface of isogenic mutant bacteria devoid of protein H. The results demonstrate that protein H-IgG complexes released from the streptococcal surface can produce complement breakdown at the sites of infection, whereas complement activation on bacterial surfaces is inhibited. This should have important implications for host-parasite relationships. In addition, soluble protein H-IgG complexes might contribute to immunological complications of streptococcal infections.

Streptococcus pyogenes is an important human pathogen (for a review, see Ref. 1) causing suppurrative infections like pharyngitis, tonsillitis, impetigo, and erysipelas. S. pyogenes is also responsible for a hyperacute and serious shock-like syndrome that is sometimes associated with fasciitis and myositis. Rheumatic fever and glomerulonephritis are delayed sequelae of acute S. pyogenes infections, and several observations suggest that immunological mechanisms contribute to these conditions. Antibodies against S. pyogenes surface components have been reported to cross-react with heart sarcolemma (2) and cardiac myosin (3). Patients with acute post-streptococcal glomerulonephritis (APSGN) show circulating immunoglobulin (Ig) complexes (4), complement activation (4), and deposition of complement proteins in the glomeruli (5).

Complement plays an important role in defense against pathogenic microorganisms (6, 7). Several functionally interesting interactions have been described for S. pyogenes and components of the complement system. M proteins are anti-phagocytic fibrous surface proteins of S. pyogenes (for a review, see Ref. 8). Members of this protein family specifically bind to the complement proteins factor H (9) and C4b-binding protein (C4BP) (10) that regulate complement activation (11–13). S. pyogenes also expresses a surface-associated peptidase, which degrades C5a (14, 15), a chemotactic fragment of C5 (16). Finally, some strains secrete protein SIC, which interacts with terminal complement proteins and inhibits complement-mediated lysis (17).

The starting point for the present investigation was the observation that an extracellular cysteine proteinase of S. pyogenes (SCP) releases a large fragment of protein H from the surface of the bacteria (18). Protein H is a streptococcal surface protein belonging to the M protein family and has high affinity for the constant (Fc) region of IgG (19, 20). The structure of protein H is schematically depicted in Fig. 1. We report that complex formation between protein H and IgG in the fluid phase leads to complement activation. By contrast, the interaction of protein H and IgG on surfaces resulted in inhibition of complement function. Possible implications for virulence and for immunological disease mechanisms are discussed.

EXPERIMENTAL PROCEDURES

Bacteria—The S. pyogenes strain AP1 used in this study is the 40/58 strain from the World Health Organization Collaborating Center for References and Research on Streptococci, Institute of Hygiene and Epidemiology, Prague, Czech Republic. To generate an isogenic mutant bacterium, plasmid-conjugated transduction was used to transfer the wild-type copy of the scpA gene from the cea+ strain 1201 to the cea- strain 31 (21). The transconjugant was selected on卞agar plates containing 5 μg/ml chloramphenicol and +20 μg/ml ampicillin, and the integrated copy of the scpA gene was confirmed by PCR. Two sets of primers were used for the detection of the scpA gene. The first set was specific for the wild-type copy of the scpA gene (primer pair 1: 5′-CTTCAACAGCAGTTCTTAA-3′ and 5′-GGTCGCTTTTGCTCTTCTAT-3′) and the second set was specific for the cloned copy of the scpA gene (primer pair 2: 5′-CGAACACCAATGGTTCACTC-3′ and 5′-TGAGGTAAGCAGTGGTGTT-3′).

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§ To whom correspondence should be addressed: Dept. of Cell and Molecular Biology, Section for Molecular Pathogenesis, Lund University, P. O. Box 94, S-221 00 Lund, Sweden. Tel.: 46-46-2224488; Fax: 46-46-157756; E-mail: andreas.berge@medkem.lu.se.

1 The abbreviations used are: APSGN, acute poststreptococcal glomerulonephritis; Ig, immunoglobulin; C4BP, C4b-binding protein; SCP, streptococcal cysteine proteinase; Fc, constant part of IgG; Fab and F(ab’), monomeric and dimeric variable fragments of IgG; VBS, veronal-buffered saline; C1qBP, C1q, factor D, and properdin; PBS, phosphate-buffered saline; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction.
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A B C1 C2 C3 D

FIG. 1. Schematic representation of protein H. The protein is expressed at the surface of some strains of S. pyogenes, and the IgG-binding activity is in the NH₂-terminal A and B domains (57). The COOH-terminal D domain anchors protein H to the bacterial cell wall. Apart from IgG, protein H also shows affinity for albumin (57), factor H (23), fibrinectype III domains (58), and C4BP (50). These proteins have separate binding sites and interact independently with protein H. The E. coli-produced protein H fragment used in this study is indicated as well as the fragment released from the streptococcal cell surface by the SCP.

FIG. 2. Activation of complement factor C3 in serum by Ig-binding proteins. Bacterial Ig-binding proteins were added to serum. Following incubation for 30 min at 37 °C, the reactions were terminated by cooling and addition of 10 mM EDTA. The samples were analyzed by crossed immunoelectrophoresis utilizing anti-C3 antibodies, and the activation was expressed as the ratio, in percent, between activated C3 and total C3. The proteins analyzed were: proteins A (A), G (A), H (A), L (A1), and M1 (A).
allowed to proceed for 48 h at 4 °C. The gels were immersed in PBS for 24 h and in distilled water for 60 min, dried, and stained with Coomassie Brilliant Blue. Gel filtration experiments were performed on an FPLC Superose-6 column (Pharmacia) equilibrated with PBS containing 0.02% NaN₃. The flow rate was 0.25 ml/min, and 0.5-ml fractions were collected. Before SDS-PAGE fractions were concentrated 10 times by precipitation in 10% trichloroacetic acid (Sigma) and boiled in sample buffer containing 2% SDS and 5% β-mercaptoethanol.

Competitive Binding Assays and C1q Binding to Bacteria—Polyclonal human IgG was coupled to polyacrylamide beads (Immunobeads, Bio-Rad) according to the producer's instructions. ¹²⁵I-Labeled C1q in 0.1 ml of VBS and 0.1% gelatin, 0.1 ml of Immunobeads coupled with IgG, and 0.2 ml of various Ig-binding proteins in the same buffer were mixed and incubated overnight at 37 °C. The reactions were terminated by cooling and addition of 10 mM EDTA. Complement activation was assessed by crossed immunoelectrophoresis with anti-C3 antibodies. The cathodal immunoprecipitate in F was not observed in repeated experiments.

Bacterial surface proteins tested for their capacity to precipitate human IgG in Ouchterlony double immunodiffusion experiments. Ten mg of IgG were added to the central wells. A, 10 μg of each protein were added to the central wells: protein A (PA), protein G (PG), protein L (PL), protein H (PH), M1 protein (M1), and protein PAB (PAB), an albumin-binding protein from Peptostreptococcus magnus. B, dilutions of protein H were added to the peripheral wells and the amounts (micrograms) are indicated.

C3 Deposition Assay—Polyclonal human IgG coupled to polyacrylamide beads was incubated with bacterial proteins in 0.2 ml of PBS containing 0.25% gelatin, 0.25% Tween, and 0.25% bovine serum albu-
min for 20 min, washed twice in VBS 2 containing 0.1% gelatin, and resuspended in 100 ml of the same buffer. 100 ml of 20% serum was added, and the samples were incubated at 37 °C for 20 min. Two ml of cold VBS containing 10 mM EDTA were added. The tubes were centrifuged and the pellets washed. The pellets were resuspended in 200 ml of PBS containing 0.25% Tween and 30,000 cpm of F(ab') 2 anti-C3c antibodies 125I-labeled with the chloramine-T method (41). After 3 h of incubation, 2 ml of the same buffer was added, the tubes were centrifuged, and the radioactivity of the pellets was measured. The same procedure was followed in experiments with albumin-coupled polyacrylamide beads. In other experiments the polyacrylamide beads were exchanged for 100 ml of AP1 or BM27.6 bacteria (2 × 10⁵ cells), omitting the blocking step described for the beads. Data points represent the mean of duplicate determinations of a single experiment. Experiments were performed at least three times.

RESULTS

IgG-dependent Complement Activation in Serum by Protein H—At the streptococcal surface a large IgGFc-binding fragment of protein H is released by SCP (18). To investigate if soluble protein H is capable of activating complement, purified protein H was added to serum. C3 breakdown was then studied by crossed immunoelectrophoresis. M1 protein is expressed at the bacterial surface together with protein H. M1 protein also

FIG. 6. Molecular interactions between IgG, protein H, and C1q analyzed by gel filtration. A, protein H (top), human polyclonal IgG (middle), and a mixture of protein H and IgG (bottom) were run separately on a Superose-6 FPLC column. B, fractions indicated by arrows were concentrated ten times by trichloroacetic acid precipitation and analyzed by SDS-PAGE (10% gel run under reducing conditions). Bands corresponding to monomeric protein H and IgG heavy and light chains are indicated. Their apparent molecular masses are 42, 50, and 25 kDa, respectively. C, gel filtration experiments as in A were performed with the addition of C1q 125I-labeled with lactoperoxidase (33). 125I-C1q was also run separately on the column. Fractions of 0.5 ml from the four runs were collected and the radioactivity of each fraction was measured. C1q shows an unspecific binding to the matrix of the column why a substantial fraction of the radioactivity is retained and subsequently eluted at a volume exceeding 18 ml.
Protein H binds to IgG, but compared with protein H, the affinity is much lower (24). Studies of M1 protein, and of strongly Ig-binding proteins (staphylococcal protein A, streptococcal protein G, and peptostreptococcal protein L) were included in the experiments.

Fig. 2 shows that proteins A, G, H, and L all activate complement in a dose-dependent manner, when added to human serum. M1 protein, however, had no effect also at the highest concentration tested (35 μg). C3 conversion could result either from activation of the classical or the alternative pathway or from a combination of both. To discriminate between these alternatives a C1q-depleted serum was utilized. Reconstitution of the serum with C1q (Fig. 3E) restored complement activation by protein H to the level obtained with intact normal serum (Fig. 3A). Reconstitution with factor D and properdin had no effect (Fig. 3D). The results demonstrated that fluid-phase activation of C3 by protein H is mediated through the classical pathway.

The critical importance of IgG for protein H-induced complement activation in serum was shown with IgGC1qDP-depleted serum (Fig. 4). No C3 cleavage was seen in this serum when protein H and complement proteins were added. The capacity to support protein H-induced complement activation was re-established with polyclonal or monoclonal IgG.

Protein H Forms Soluble C1q-Binding Complexes with IgG—In contrast to proteins A, G, and L, protein H did not form distinct precipitation arcs with human IgG, when tested by double diffusion in agarose (Fig. 5). Diffuse staining was observed between the IgG- and protein H-containing wells, indicating the formation of heterogeneous complexes. Gel filtration experiments were performed to demonstrate and analyze soluble protein H-IgG complexes. Protein H was incubated with IgG at the equimolar concentrations shown to result in complement activation (Fig. 2). Proteins A, G, and L formed insoluble precipitates when incubated with IgG in solution; no visible precipitates were formed between protein H and IgG. Protein H, IgG, and a mixture of the two proteins were each subjected to gel filtration on a Superose-6 column (Fig. 6A). Protein H tends to form multimers (42), which explains the broad peak. The protein H-IgG mixture gave rise to soluble complexes of predicted molecular masses ranging from 400 kDa to 1.4 MDa. Analysis by SDS-PAGE (Fig. 6B) showed that the complexes contained both protein H and IgG. Finally, when radiolabeled C1q was added to the mixture of protein H and IgG, the label appeared together with protein H-IgG complexes (Fig. 6C), reflecting C1q interaction with the complexes.

Inhibition of C1q Binding to Immobilized IgG by Soluble Protein H—Soluble protein H and other Ig-binding bacterial surface proteins were tested for their capacity to interfere with binding of radiolabeled C1q by IgG-coated polyacrylamide beads. Proteins A, G, and H all bind to the Cγ2-Cγ3 interface region of IgG (43–46), whereas the binding site for C1q is in the Cγ2 domain (47). On a molar basis proteins A and H inhibited the binding of radiolabeled C1q with the same efficiency as unlabeled C1q. Protein G unexpectedly increased the uptake of radiolabeled C1q by solid-phase IgG (Fig. 7). The enhanced binding in the presence of protein G was not due to an interaction between protein G and C1q. Thus, C1q did not bind to protein G immobilized on Sepharose (not shown). M1 protein and the Ig light chain-binding protein L had no effect on C1q binding to IgG (Fig. 7). Control experiments with albumin-coated polyacrylamide beads showed that background binding of radiolabeled C1q was low (<5%) in the assay system.

Inhibition of C3 Deposition and Immune Hemolysis by Soluble Protein H—IgG-coated polyacrylamide beads were incubated with human serum and protein H. C3 deposition was measured with radiolabeled anti-C3c F(ab′)2. Protein H completely inhibited C3 deposition (Fig. 8). The same effect was
seen with protein A, whereas protein G enhanced deposition, and proteins L and M1 had no effect (Fig. 8). Besides their IgGFe-binding activity, proteins A and G have weak affinities for Fab fragments of IgG (48, 49). Judging from control experiments performed in the absence of serum this did not influence the results. In other control experiments polyacrylamide beads coated with albumin were incubated with IgGC1qDP-depleted serum reconstituted with Clq. In this case, C3 deposition was at background level, and no effect was seen with any of the Ig-binding proteins (not shown).

Protein H partially inhibited immune hemolysis of IgG-sensitized sheep erythrocytes (Fig. 9). Protein A blocked hemolysis completely, whereas protein G caused a dose-dependent increase of the hemolytic activity (Fig. 9). The effect of protein G is in line with the observation that the protein enhanced binding of Clq to IgG and surface deposition of C3 (see above). None of the proteins affected immune hemolysis of IgM-sensitized sheep erythrocytes (not shown).

C3 Deposition on Intact Streptococci—No binding of radiolabeled Clq was recorded in experiments with protein H-expressing AP1 streptococci preincubated and saturated with human polyclonal IgG, indicating that Fc regions are not exposed in IgG molecules bound to the bacterial surface. Consistent with this finding, incubation of the AP1 streptococci with serum gave little or no C3 deposition (Fig. 10). An isogenic mutant (BM27.6) devoid of protein H was generated by insertional inactivation of the protein H gene in AP1. The C3 deposition on the mutant bacteria was comparatively high (Fig. 10A). Results obtained with C1qDP- or IgGC1qDP-depleted sera reconstituted with Clq or IgG (Fig. 10B) showed that C3 deposition depended on Clq and IgG, i.e. the classical pathway. C4BP, a down-regulator of the classical pathway, is known to interact with members of the M protein family (10), including protein H (50). For this reason, C3 deposition experiments were repeated with a C1qDP-depleted serum devoid of C4BP. With the conditions used, C4BP did not appear to influence C3 deposition on the AP1 or BM27.6 streptococci (Fig. 10C). In conclusion, the results were fully compatible with findings using immune hemolysis and IgG-coated polyacrylamide beads (Figs. 7–9) and strongly suggested that surface bound protein H has an anti-opsonizing effect due to interference with IgGFe-C1q interactions.

**DISCUSSION**

The major conclusion of this investigation is that protein H activates complement when the molecule is part of soluble complexes with IgG, but prevents the activation of complement

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**FIG. 9. The effect of Ig-binding proteins on complement-mediated hemolysis.** Sheep erythrocytes were optimally sensitized with rabbit IgG and preincubated with proteins A (M), G (▲), and H (E) for 20 min and washed twice. An IgGC1qDP-depleted serum (10%) reconstituted with Clq to give 60% of total hemolysis of erythrocytes preincubated with buffer was used as the complement source. The sensitized and preincubated cells were incubated with this reagent. Hemolysis was blocked by EDTA, samples were centrifuged, and the absorbance of the supernatant at 541 nm was measured. Standard deviation was <3% in all experiments.

**FIG. 10. C3 deposition on intact bacteria.** Bacteria (2 × 10⁵ cells) of the AP1 strain expressing protein H, and the AP1 mutant strain BM27.6 devoid of protein H, were incubated for 20 min with serum (2%) in 200 μl. EDTA was added, and the bacteria were washed and incubated with radiolabeled anti-C3c F(ab')² fragments for 180 min at 4 °C. Cells were centrifuged, washed, and the radioactivity of the pellets was measured. In experiments with complement depleted sera the background C3 deposition obtained with unreconstituted serum was consistently 25% or less of the C3 deposition obtained with Clq added. Maximum binding (100%) was defined as the binding obtained with ≈5 × 10⁶ BM27.6 bacteria in the assay system. The complement source and the proteins used to reconstitute the serum are indicated above each panel.
when associated with the bacterial surface. These effects should both provide selective advantages to \textit{S. pyogenes} and help to explain how Ig-binding surface proteins contribute to the virulence (51–53) of this important human pathogen.

It has been demonstrated that an IgG-binding fragment of protein H is released from the streptococcal surface by SCP (18). This fragment covers the entire surface-exposed part of the molecule. The fragment used throughout this study has a similar size excluding only the bacterial cell wall-associated COOH-terminal region (Fig. 1). IgG is one of the most abundant soluble extracellular human proteins, and the high affinity between protein H and IgG, \( 1.6 \times 10^9 \text{M}^{-1} \) (19), suggests that protein H in vivo is always complexed with IgG. When protein H-IgG complexes are released by SCP, the data of this study show that the complexes are soluble and capable of activating the classical complement pathway.

This activation will lead to breakdown of complement in the vicinity of the bacteria, thus preventing assembly and activation of complement at the bacterial surface. On the other hand, complement activation will generate C5a and thereby attract phagocytic cells. From the bacterial point of view, this should be an unwanted effect of the release of protein H-IgG complexes by SCP. However, SCP efficiently and simultaneously releases also a large and biologically active fragment of a C5a peptide (18) associated with the streptococcal surface (14). This enzyme cleaves and destroys C5a as a chemotaxant for polymorphonuclear leukocytes (15).

To initiate complement activation away from the bacterium and to inactivate the C5a that is generated represents sophisticated and rational microbial defense mechanisms. The inhibition of complement activation at the surface of protein H-expressing bacteria should also be beneficial for the microbe. Despite that large amounts of IgG are bound to the bacterial surface (54) through Fe-protein H interactions, the blocking of C1q binding to IgG by protein H was found to be highly effective. As a result, the deposition of opsonic C3 fragments was significantly lower in protein H-expressing \textit{S. pyogenes} than in the isogenic mutant devoid of protein H. The blocking of the C1q-binding region of IgG by surface-associated protein H is in contrast to the soluble IgG-protein H complexes. Here the stoichiometry of complexes apparently results in the exposure of IgG regions capable of interacting with C1q and subsequently activation of the classical pathway of complement.

In contrast to protein H and staphylococcal protein A, protein G of group C and G streptococci unexpectedly enhanced the binding of radiolabeled C1q to IgG. The binding site(s) in IgG for protein H has not yet been defined by x-ray crystallography or NMR. In the case of proteins A and G, it was demonstrated that apart from a shared binding region, the proteins have unique binding sites in IgG. Compared with protein A, the unique protein G-interacting site is located away from the predicted C1q-binding site (43, 47, 55), which explains why protein G does not inhibit the binding of C1q to IgG. Protein G was not found to interact with C1q, and it remains unclear why complexes between protein G and IgG appear to have higher affinity for C1q than IgG itself.

Protein H is expressed by \textit{S. pyogenes} strains of the M1 serotype. This serotype is associated with severe complications of suppurative \textit{S. pyogenes} infections, i.e., the toxic shock-like syndrome, rheumatic fever, and APSGN (for references, see Ref. 56). The data of this study raise the possibility that release of complement-activating IgG-protein H complexes from the bacterial surface could be involved in development of these complications. Like human IgG, rabbit IgG has affinity for protein H (20). When two rabbits were given protein H intra-

\add{2}{A. Berge, I.-M. Frick, A. G. Sjöholm, and L. Björk, unpublished data.}
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