Protection from *Streptococcus pneumoniae* Infection by C-Reactive Protein and Natural Antibody Requires Complement But Not Fcγ Receptors

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Protection from *Streptococcus pneumoniae* Infection by C-Reactive Protein and Natural Antibody Requires Complement But Not Fcγ Receptors¹

Carolyn Mold,* Bojana Rodic-Polic,* and Terry W. Du Clos²††

*Streptococcus pneumoniae* is an important human pathogen and the most common cause of community-acquired pneumonia. Both adaptive and innate immune mechanisms provide protection from infection. Innate immunity to *S. pneumoniae* in mice is mediated by naturally occurring anti-phosphocholine (PC) Abs and complement. The human acute-phase reactant C-reactive protein (CRP) also protects mice from lethal *S. pneumoniae* infection. CRP and anti-PC Ab share the ability to bind to PC on the cell wall C-polysaccharide of *S. pneumoniae* and to activate complement. CRP and IgG anti-PC also bind to FcγR. In this study, FcγR- and complement-deficient mice were used to compare the mechanisms of protection conferred by CRP and anti-PC Ab. Injection of CRP protected wild-type, FcγR-chain-, FcγRIII-b, and FcγRIII-deficient mice from infection. Complement was required for the protective effect of CRP as cobra venom factor treatment eliminated the effect of CRP in both γ-chain-deficient and wild-type mice, and CRP failed to protect C3- or C4-deficient mice from infection. Unexpectedly, γ-chain-deficient mice were extremely sensitive to pneumococcal infection. This sensitivity was associated with low levels of natural anti-PC Ab. γ-chain-deficient mice immunized with nonencapsulated *S. pneumoniae* produced both IgM- and IgG PC-specific Abs, were protected from infection, and were able to clear the bacteria from the bloodstream. The protection provided by immunization was eliminated by complement depletion. The results show that in this model of systemic infection with highly virulent *S. pneumoniae*, protection from lethality by CRP and anti-PC Abs requires complement, but not FcγR. *The Journal of Immunology*, 2002, 168: 6375–6381.

The development of mice deficient in individual Fcγ receptors has provided a critical tool for understanding the roles of these receptors in inflammation, autoimmunity, and host defense (1). Mice deficient in the Fcγ γ-chain lack FcγRI and FcγRIII as well as FcεRI (2). γ-chain-deficient mice and mice deficient in FcγRIII have reduced immune complex clearance, decreased inflammatory responses to immune complexes, and are protected from Ab-mediated autoimmune diseases (1, 3). In contrast, FcγRIIb-deficient mice generally have enhanced Ab responses and increased susceptibility to autoimmune disease (1, 4–6). The role of FcγR in protection against infection has been studied to a more limited extent with different results depending on the pathogen. Passive protection of mice by IgG1 Ab against *Cryptococcus neoformans* is decreased in *S. pneumoniae* (7), whereas passive protection against malaria is apparently FcγR-independent (8). Conversely, FcγR are required to establish infection in a mouse model of cutaneous leishmaniasis, in which FcγR provide a means for invasion of macrophages by the parasite (9).

*Streptococcus pneumoniae* is an important pathogen in humans and is the number one cause of community-acquired pneumonia (10, 11). The clinical importance of this disease has increased with the evolution of antibiotic resistant strains (12). Very young and very old individuals are most susceptible to systemic infection and although protective anti-capsular Ab can be produced following immunization, the innate immune response is clearly important in controlling this infection in the nonimmune host. Innate resistance to systemic infection with *S. pneumoniae* has been studied extensively in mice. Naturally occurring Abs of the T15 idiotype, which bind the phosphocholine (PC)³ moiety of the pneumococcal cell wall C-polysaccharide (PnC), are protective (13). These natural Abs are produced in response to normal gut flora and are derived from a single germline V₉ gene (V₉μ₁) (14). Mice lacking these protective anti-PC Abs as a result of the *sid* mutation (13), neonatal suppression by anti-T15 treatment (13, 15), or targeted genetic deletion of the V₉μ₁ gene (16) all have increased susceptibility to *S. pneumoniae* infection. T15-idiotype-positive mAb of the IgM, IgG2a, IgG2b, and IgG3 isotypes can passively protect mice against infection (17, 18). All of the protective Abs activate complement (18, 19). However, IgG Abs are 10-fold more protective than IgM Abs suggesting a role for FcγR as well (20).

C-reactive protein (CRP) is an acute-phase reactant named for its ability to undergo calcium-dependent interaction with PnC. The demonstration that passively administered CRP protected mice from *S. pneumoniae* infection established a role for CRP in host defense (15, 21). More recently, mice transgenic for human CRP were found to be protected from pneumococcal infection as well as *Salmonella enterica* infection (22, 23). CRP activates the classical complement pathway (24) and the importance of complement in CRP-mediated host defense has been studied (19, 25, 26). The results of these studies indicated that CRP protection in pneumococcal infection involves both complement-dependent and complement-independent mechanisms. The proposed mechanism of

³ Abbreviations used in this paper: PC, phosphocholine; PnC, *S. pneumoniae* cell wall C-polysaccharide; CRP, C-reactive protein; Pn3, *S. pneumoniae* serotype 3; CVF, cobra venom factor.
CRP protection against *S. pneumoniae* infection is opsonization of bacteria by CRP and complement for phagocytosis and killing. The identification of FcγR as the receptors for CRP on leukocytes makes it possible to examine the relative roles of direct interaction of CRP with FcγR and CRP activation of complement in protection against pneumococcal infection (27, 28). The purpose of the present study was to examine the role of FcγR and complement in protection against systemic *S. pneumoniae* infection by CRP and anti-PC Ab.

**Materials and Methods**

**Reagents**

Human CRP was purified from pleural fluid by affinity, gel filtration, and ion exchange chromatography as previously described (29). The purity of the CRP preparations was determined by 12.5% SDS-PAGE on overloaded and normal samples. The gels were stained with a sensitive silver stain. No bands other than the major 25 kDa CRP band were seen. Specifically, no contamination by IgG was seen. PC-BSA was produced according to the method of Chesebro and Metzger (30). The molar coupling ratio of PC to BSA was 15:1.

**Mice**

FcγRIIb-deficient (4) and FcγRIIb-γ-chain-deficient mice (2) were bred at the Department of Veterans Affairs Animal Facility (Albuquerque, NM) from breeder pairs purchased from The Jackson Laboratory (Bar Harbor, ME). The γ-chain-deficient mice do not express FcγRI, FcγRII, or FcγRII. The FcγRIIb- and FcγRIIb-γ-chain-deficient (3) mice lack individual receptor expression only. FcγRII-deficient mice and control mice (B6 × 129F2 and C57BL/6) that were age and sex-matched to the deficient mice were purchased from The Jackson Laboratory. B6 × 129F2 mice served as controls for γ-chain- and FcγRIIb-deficient mice. C57BL/6 mice served as controls for FcγRII-deficient mice. C3- (31) and C4-deficient (32) mice were bred from heterozygous breeder pairs purchased from The Jackson Laboratory. Mice were genotyped by PCR using the primer sequences provided by The Jackson Laboratory and homozygous-deficient and homozygous wild-type mice from the same colony were used. Mice were used between 7 and 12 wk of age. Both male and female mice were used. The number of male and female control and deficient mice was matched in each individual experiment, and the males and females were distributed equally among treatment groups in each experiment. There was no apparent effect of sex on the results in any of the experiments. All experimental procedures involving animals were approved by the Institutional Review Board of the Veterans Affairs Medical Center (Albuquerque, NM).

**Bacteria and infection**

*S. pneumoniae* serotype 3 (Pn3) and R36A (a nonencapsulated variant of type 2 *S. pneumoniae*) were purchased from the American Type Culture Collection (Manassas, VA). Pn3 were passaged through mice to maintain virulence and stored at −80°C. One or two colonies from an overnight blood agar plate were inoculated into Todd-Hewitt broth containing 0.5% yeast extract and grown to log phase. The concentration of Pn3 was estimated by absorbance at 600 nm. Pn3 were diluted in saline and injected i.v. into the retro-orbital plexus into mice in 0.1 ml. Plate counts of the inoculum were used to determine the CFU injected. Where indicated, CRP was injected i.v. via the contralateral retro-orbital plexus 15 min before Pn3. Mortality was measured for 7 days with no deaths occurring later than 4 days after infection.

Mice were immunized by i.p. injection of 5 × 10⁷ heat-killed R36A as described (33) and challenged 7 days later. Mice were depleted of complement by treatment with cobra venom factor (CVF) (*Naja naja kaouthia*; Quidel, San Diego, CA) as previously described (34). Complement depletion was induced by three i.p. injections of 4 U CVF at 12-h intervals beginning 36 h before study.

**Clearance**

Mice were injected in the left retro-orbital plexus with −5 × 10⁷ CFU Pn3 0.2 ml of saline. Blood samples (50 μl) were collected from all mice at 1 min, 1 h, and 4 h, diluted in PBS and plated on blood agar plates. CFU recovered per mouse were calculated from the blood counts and body weight.

**Ab levels**

Anti-PC and anti-DNP Ab levels in serum from control and deficient mice were determined by ELISA. Immulon II microtiter plates (Dynatech Laboratories, Alexandria, VA) were coated with 5 μg/ml PC-BSA (conjugated in our laboratory) or DNP-BSA (Sigma-Aldrich, St. Louis, MO), washed, blocked, and incubated with a 1/50 dilution of the serum to be tested. Plates were developed with biotinylated isotype-specific Abs to mouse IgG, IgA, and IgM (Caltag Laboratories, Burlingame, CA), HRP-conjugated streptavidin, and substrate (3,3′,5,5′-tetramethylbenzidine; BD Biosciences, San Diego, CA). Absorbance was read at 450 nm.

**Data analysis**

Graphical and statistical analyses were performed using GraphPad Prism software (San Diego, CA). Survival curves were plotted by the method of Kaplan and Meier and compared by the log-rank test (Mantel-Haenszel software (San Diego, CA)). Survival curves were plotted by the method of Chesebro and Metzger (30). The molar coupling ratio of PC to BSA was determined by 12.5% SDS-PAGE on overloaded and normal samples. The gels were stained with a sensitive silver stain. No bands other than the major 25 kDa CRP band were seen. Specifically, no contamination by IgG was seen. PC-BSA was produced according to the method of Chesebro and Metzger (30). The molar coupling ratio of PC to BSA was 15:1.

**Results**

**CRP protection against pneumococcal infection requires complement, but not FcγR, chain**

CRP binds to FcγRI and FcγRIIb on mouse leukocytes (27). The opsonic activity of CRP requires FcγRI, and is absent in phagocytes from γ-chain-deficient mice (35). Therefore, γ-chain-deficient mice were used to determine the role of CRP interaction with phagocytic FcγR in protection from *S. pneumoniae* infection. B6 × 129 control mice and γ-chain-deficient mice were injected with 0, 100, or 200 μg of CRP and Pn3 and survival was measured for 7 days (Fig. 1). CRP provided protection against lethality in wild-type mice, increasing survival from 20% in the absence of...
CRP to >85% in mice injected with 200 μg of CRP. CRP provided partial protection in γ-chain-deficient mice as well, increasing survival from 0% in the absence of CRP to 50% in mice injected with 200 μg of CRP.

To determine whether CRP-mediated protection required complement, wild-type and γ-chain-deficient mice were treated with CVF 2 days before challenge (Fig. 1) and then with 200 μg of CRP and Pn3. All of the complement-depleted mice died from the infection despite injection of CRP. These results indicate that in this model, CRP-mediated protection requires complement and can be provided by complement alone in the absence of FcγR.

CRP-mediated protection against pneumococcal infection requires the classical complement pathway

S. pneumoniae activate the alternative complement pathway in the absence of CRP, but primarily activate the classical pathway in the presence of CRP (36, 37). CVF-treated mice lack the major complement opsonins (C3b and iC3b) generated by all pathways of activation. The failure of CRP to protect against Pn3 in CVF-treated mice could be due either to a requirement for CRP activation of the classical pathway or to a combination of alternative pathway activation by the bacteria and direct opsonization by CRP. C3- and C4-deficient mice were used to distinguish between these possibilities. C3-deficient mice are similar to CVF-treated in mice lacking C3b and iC3b. C4-deficient mice lack only the classical pathway. Both strains of mice were highly susceptible to Pn3 infection and neither was protected by 100 μg CRP (Fig. 2). These results indicate that CRP-mediated protection against Pn3 requires the classical pathway. Innate immunity to Pn3 was also decreased in both C3- and C4-deficient mice as shown by the greater mortality of deficient mice than wild-type mice in the absence of CRP. No additional role for the alternative pathway was apparent as there was no difference between survival curves in C3- and C4-deficient mice either in the presence or absence of CRP.

CRP protection in pneumococcal infection does not require FcγRIII or FcγRIIb

The γ-chain is required for expression and signaling through FcγRI and FcγRIII, both of which mediate phagocytosis (2). Binding and functional studies indicate that CRP binds to FcγRI and to FcγRIIb. FcγRIIb is a nonphagocytic receptor found on lymphocytes as well as phagocytic cells. Mice deficient in FcγRIII or FcγRIIb were used to determine the roles of these receptors in CRP-mediated protection. For FcγRIII- and FcγRIIb-deficient mice, CRP provided nearly complete protection from infection (Fig. 3A). Survival curves were not significantly different between FcγRIII- and FcγRIIb-deficient mice and control mice injected with CRP. In addition, neither FcγRIII- nor FcγRIIb-deficient mice showed the increased susceptibility to Pn3 infection that was seen in the γ-chain-deficient mice (Fig. 3B). A different wild-type strain (C57BL6) was used as the control strain for FcγRIII-deficient mice. Survival of C57BL/6 mice did not differ from B6 × 129 mice in the absence of CRP (Fig. 3B). Survival of C57BL/6 mice following CRP treatment and Pn3 infection was not significantly different from survival of B6 × 129 mice treated in the same way (not shown).
Susceptibility to pneumococcal infection is increased in γ-chain-deficient mice

In the experiments described above, it was apparent that γ-chain- and complement-deficient mice were more susceptible to infection than wild-type mice. This was evident both in the survival time and in percent survival (Figs. 1 and 2). The survival curves for FcγRIII-deficient, FcγRIib-deficient, B6 × 129 and C57BL/6 mice injected with 700 CFU were not significantly different (Fig. 5B). Complement-deficient mice have been reported to be more susceptible to infection (31), but to our knowledge γ-chain-deficient mice have not (1). To further compare the susceptibility to infection between wild-type and γ-chain-deficient mice, decreasing doses of Pn3 were injected. Nearly 40% of wild-type mice survived challenge with 70 CFU and 50% survived challenge with 7 CFU of Pn3 (Fig. 4). None of the γ-chain-deficient mice survived even the lowest dose of Pn3, although the survival time was prolonged (20.5-h median survival with 7 CFU and 17.5-h median survival for mice infected with 70 CFU). The median survival time for wild-type mice was 72.5 h for mice infected with 70 CFU. At each dose of bacteria, the difference in survival curves between wild-type mice and γ-chain-deficient mice was significant at the p < 0.0001 level.

FIGURE 4. γ-chain-deficient mice have increased susceptibility to infection with Pn3. B6 × 129 mice (WT) or γ-chain-deficient mice (γKO) were injected i.v. with 70 or 7 CFU Pn3. The mice were monitored for mortality over 7 days of observation (no mortality was seen after 96 h). Survival of γ-chain-deficient mice was significantly lower than survival of B6 × 129 mice at both doses of Pn3 (p < 0.0001).

γ-chain-deficient mice have lower levels of IgM anti-PC Abs than wild-type mice

The increased susceptibility of γ-chain-deficient mice to pneumococcal infection suggested a role for IgG in innate immunity. Natural Abs to PC have been shown to provide protection against S. pneumoniae (13). Therefore, the levels of anti-PC Abs in control and γ-chain-deficient mice were measured. Surprisingly, γ-chain-deficient mice had significantly lower levels of IgM anti-PC Abs than wild-type mice (Fig. 5A; p = 0.032). This was not a general defect in natural Abs, as levels of IgM and IgG Ab to DNP were normal in γ-chain-deficient mice (Fig. 5B). Very low levels of IgG anti-PC Abs were found in both wild-type and γ-chain-deficient mice, and IgA anti-PC was undetectable in serum from either strain. IgM anti-PC Ab levels in C57BL/6 mice and FcγRIib-deficient mice were similar to IgM anti-PC Ab levels of B6 × 129 mice and higher than those of γ-chain-deficient mice (not shown). All of the strains of mice were housed in the same room and the FcγRIib-deficient mice were bred in the same facility as the γ-chain-deficient mice.

FIGURE 5. γ-chain-deficient mice have lower levels of IgM anti-PC Abs than B6 × 129 mice. Levels of IgM anti-PC (A) and IgM anti-DNP Abs (B) in untreated γ-chain-deficient and B6 × 129 mice (WT) were determined by ELISA using PC-BSA and DNP-BSA. Results are mean ± SEM absorbance readings at a 1/50 dilution of serum for 10 mice in each group. γ-chain-deficient mice had lower levels of anti-PC Abs than wild-type mice (p = 0.032). Anti-DNP Ab levels did not differ between strains.

γ-chain-deficient mice produce anti-PC following immunization and are protected from pneumococcal infection

To determine whether γ-chain-deficient mice lacked the ability to respond to PC, mice were immunized with a single injection of heat-killed nonencapsulated S. pneumoniae, R36A. Immunization with R36A results in anti-PC Abs with peak levels appearing after 7 days (33). The γ-chain-deficient mice produced high levels of IgM and lower levels of IgG anti-PC Abs following immunization (Fig. 6). These Ab levels were equivalent to those of immunized B6 × 129 mice. Furthermore, immunized γ-chain-deficient mice were protected from infection with 70 CFU S. pneumoniae (Fig. 7A). Immunity was mediated by Ab and complement, because depletion of complement with CVF before infection abrogated the protection (Fig. 7A).

Protection against systemic S. pneumoniae infection is associated with clearance of the bacteria from the bloodstream by the liver and spleen (18, 26). To determine the role of Ab and complement in clearance of bacteria, γ-chain-deficient mice were injected with Pn3 and viable bacteria in the bloodstream were measured over the next 4 h (Fig. 7B). Nonimmune γ-chain-deficient mice did not clear Pn3. Immunized γ-chain-deficient mice cleared the bacteria beginning at 1 h, and this clearance was eliminated in mice treated with CVF to deplete complement. These results indicate that γ-chain-deficient mice can be protected from Pn3 infection by anti-PC Ab as well as by CRP and that for either opsonin, complement is also required. The increased susceptibility of γ-chain-deficient mice to S. pneumoniae arises from a lack of natural Abs to PC, and not from a failure of FcγR-mediated clearance functions during infection.
ceptibility apparently results from a failure of the host to prevent death from S. pneumoniae infection. We have shown that IgG anti-PC Abs after immunization with R36A play a role as well. The leukocyte receptors for CRP have recently been described (15, 21, 23). In previous studies, complement depletion decreased the protective effect of CRP (19, 25), suggesting that direct opsonization by CRP might not require complement to be effective. However, in the present study using highly virulent Pn3, the role of CRP in protection is clearly demonstrated. First, the innate opsonization of pneumococcal bacteria by CRP contributes to natural protection from infection. Second, neither CRP nor anti-PC Ab require FcR to protect mice from infection. This increased susceptibility apparently results from a failure of γ-chain-deficient mice to produce protective PC-specific Abs in response to natural immunogens in the gut.

The protective effect of CRP in pneumococcal bacteremia has been described (15, 21, 23). In previous studies, complement depletion decreased, but did not eliminate the protective effect of CRP (19, 25), suggesting that direct opsonization by CRP might play a role as well. The leukocyte receptors for CRP have recently been identified by our laboratory as FcγR (27, 28, 38, 39). CRP binds to FcγRI and FcγRII on both human and mouse leukocytes. In the mouse, where FcγRII is a nonphagocytic receptor, direct opsonic activity of CRP requires the γ-chain-associated receptor FcγRII (35). Thus, γ-chain-deficient mice lack phagocytic receptors for CRP and can be used to test the role of direct opsonization by CRP in protection from infection. CRP was protective in γ-chain-deficient mice, indicating that CRP binding to FcγRII is not required for protection. Complement was required. Previous studies (19, 25) have observed a protective effect of CRP in complement-depleted mice. However, this effect was not observed in the present study using highly virulent Pn3. Therefore a role for FcγR in the protective effect of CRP on pneumococcal infection in the absence of complement could not be evaluated. While this paper was in review, it was reported that CRP expression from a transgene decreased bacteremia in FcR γ-chain-deficient mice following pneumococcal infection (40). These findings are consistent with the data presented in this study. However, those studies did not assess survival.

It is of some interest that mouse CRP is expressed at low levels in mice and increases slightly during the acute phase response to levels of ~2–3 μg/ml. It is unclear whether these low levels of CRP contribute to natural protection from S. pneumoniae infection. However, these mice are much less resistant to infection than mice given human CRP suggesting that mouse CRP is of minor importance. The major acute phase reactant in the mouse, serum amyloid P component, fails to protect mice from S. pneumoniae infection (21).

The relative requirements for the alternative and classical pathways of complement activation in CRP-mediated protection were examined. Complement-deficient mice were highly susceptible to infection and were not protected by CRP. By comparing C3-deficient mice, lacking opsonization through all pathways, and C4-deficient mice, lacking only the classical pathway, these studies demonstrate that classical pathway activation by CRP is required for protection. CRP activates complement only through the classical pathway and increases the amount of C3b and iC3b bound to S. pneumoniae (37, 41). The requirement for C4 in CRP-mediated protection indicates that it is complement activation by CRP that is essential rather than cooperation between CRP and complement activation mechanisms.
IgM anti-PC Abs in administered IgG anti-PC Abs are protective at lower doses than S. pneumoniae was unexpected. Despite the importance of FcγRI in inflammatory responses, deficiencies in these receptors, unlike complement deficiencies, have not generally been associated with increased susceptibility to infection in the nonimmune host (1). One previously reported host defense defect in these mice was an inability of passive Abs to protect mice from Cryptococcus neoformans infection (7). Another study demonstrated no defect in the natural sensitivity to influenza virus infection but found that immunized γ-chain-deficient mice were not protected from infection despite normal Ab responses (42).

There are several possible mechanisms for the increased susceptibility to infection in the γ-chain-deficient mice. It seemed likely that the mice could be deficient in clearance of bacteria due to the lack of FcγRI or FcγRIII. FcγRIII-deficient mice did not display increased susceptibility to infection. This suggested the hypothesis that resistance to infection was normally mediated by natural IgG Abs, directed against bacterial Ags interacting with FcγRI. This is also consistent with previous findings that passively administered IgG anti-PC Abs are protective at lower doses than IgM anti-PC Abs in xid mice (18).

Surprisingly, the defect in γ-chain-deficient mice was related to reduced levels of PC-specific IgM. Levels of IgG and IgA anti-PC Abs were very low in both control and γ-chain-deficient mice. There were no differences in the levels of anti-DNP Abs between the strains suggesting that the decrease was not a general deficiency in natural Abs. Decreased IgM anti-PC was also not related to breeding conditions, because FcγRIIB-deficient mice from the same facility had normal Ab levels. The decreased Ab to PC was not due to an inability to respond to PnC, as γ-chain-deficient mice produced substantial levels of IgM and IgG anti-PC Abs in response to immunization with R36A. Immunized γ-chain-deficient mice were protected from S. pneumoniae infection with nine of ten mice surviving challenge with 70 CFU of Pn3. Thus, γ-chain-deficient mice are able to produce PC-specific protective Abs, and FcγR are not required for such Abs to be effective. Protection of immunized γ-chain-deficient mice was complement-dependent as it was eliminated by CVF treatment before challenge.

A novel and as yet incompletely understood finding is the decrease in the levels of “natural” Abs to PC in γ-chain-deficient mice. It is known that the development of these Abs is dependent on the presentation of Ags on bacteria of the gut flora as they are not present in germfree mice (14). The lack of natural Abs in γ-chain-deficient mice suggests a defect in the presentation of these Ags to the immune system. The only γ-chain-associated receptor that has been implicated in Ag presentation is FcγRI. Targeting Ag to this receptor enhances presentation to Ag-specific T cells by 100- to 1000-fold (43). Studies in deficient mice showed that FcγRI, but not FcγRIII or FcεRI, was required for enhanced responses to immune complexes (44). Although polysaccharide Ags have not been thought to require presentation to T lymphocytes, it has recently been shown that dendritic cells pulsed with R36A induce T cell-dependent anti-PC responses (45). Therefore, one possible explanation for the decreased natural Ab levels is the reduced ability to present Ags. These mice are clearly able to mount an immune response to PC as demonstrated by the response induced by R36A immunization shown in this study. However, at suboptimal amounts of Ag, the role of FcγRI may be important. The direct importance of FcγRI, as opposed to other γ-chain-associated receptors, will be addressed in future studies using mice specifically deficient in FcγRI.

In summary, these findings support the central role of complement in the protection of mice from pneumococcal bacteremia. The role of complement is to clear the bacteria through opsonophagocytosis (46). Although both Ab and CRP can interact with Fcγ receptors, their role in protection from this pathogen is probably minor.

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