Mechanism of Complement Activation and Its Role in the Inflammatory Response After Thoracoabdominal Aortic Aneurysm Repair

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Background—Complement activation contributes to ischemia-reperfusion injury. Patients undergoing thoracoabdominal aortic aneurysm (TAAA) repair suffer extensive ischemia-reperfusion and considerable systemic inflammation.

Methods and Results—The degree and mechanism of complement activation and its role in inflammation were investigated in 19 patients undergoing TAAA repair. Patients undergoing open infrarenal aortic surgery (n = 5) or endovascular descending aortic aneurysm repair (n = 6) served as control subjects. Substantial complement activation was seen in TAAA patients but not in controls. C1rs-C1-inhibitor complexes increased moderately, whereas C4bc, C3bBbP, C3bc, and the terminal SC5b-9 complex (TCC) increased markedly after reperfusion, reaching a maximum 8 hours after reperfusion. Interleukin (IL)-1β, tumor necrosis factor α (TNF-α), and IL-8 increased significantly in TAAA patients but not in controls, peaking at 24 hours postoperatively and correlating closely with the degree of complement activation. IL-6 and IL-10 increased to a maximum 8 hours after reperfusion in the TAAA patients, were not correlated with complement activation, and increased moderately in the control subjects. Myeloperoxidase and lactoferrin increased markedly before reperfusion in all groups, whereas sICAM-1, sP-selectin, and sE-selectin were unchanged. No increase was observed in complement activation products, IL-1β, TNF-α, or IL-8 in a mannose-binding lectin (MBL)–deficient TAAA patient, whereas IL-6, IL-10, myeloperoxidase, and lactoferrin increased as in the controls. Two other MBL-deficient TAAA patients receiving plasma attained significant MBL levels and showed complement and cytokine patterns identical to the MBL-sufficient TAAA patients.

Conclusions—The data suggest that complement activation during TAAA repair is MBL mediated, amplified through the alternative pathway, and responsible in part for the inflammatory response. (Circulation. 2003;108:849-856.)

Key Words: ischemia • reperfusion • aneurysm • cytokines • inflammation

The complement system is an integrated part of innate immunity. It is able to discriminate between self and nonself and between normal self and altered self, eg, in disruption of the endothelium that normally protects the tissue against homologous complement attack. The initial and crucial event in ischemia-reperfusion injury is endothelial cell activation. The pathophysiology of ischemia-reperfusion injury is complex, with activation of neutrophils and release of reactive oxygen species and other inflammatory mediators. Since it was demonstrated that specific complement inhibition with soluble complement receptor 1 (sCR1) markedly attenuated the tissue damage in experimental myocardial infarction, a large body of evidence has accumulated demonstrating an essential role for complement in ischemia-reperfusion injury. This is supported by studies showing a therapeutic benefit of complement blockade in various ischemia-reperfusion injury models, as reviewed elsewhere. Complement activation occurs early in the setting of ischemia-reperfusion injury and leads to the release of biologically active substances, such as the anaphylatoxins C3a and C5a, and formation of the inflammatory and cytolytic terminal complement complex C5b-9 (TCC). Activation of complement may induce numerous secondary inflammatory reactions, such as expression of adhesion molecules, accumulation and activation of leukocytes, release of reactive oxygen species and arachidonic acid metabolites, and production of cytokines and chemokines.
The systemic inflammatory response associated with ischemia-reperfusion injury contributes to morbidity and mortality after thoracoabdominal aortic aneurysm (TAAA) repair. Despite substantial evidence of the importance of complement in experimental ischemia-reperfusion injury, there are no published data on the occurrence and possible consequences of complement activation after TAAA. The aim of the present study was to elucidate the degree and mechanism of complement activation during and after TAAA repair and to relate this activation to other aspects of the inflammatory response.

Methods

Study Design and Patients

The study was prospective and observational and was approved by the regional ethics committee. Nineteen TAAA patients older than 18 years of age with a confirmed diagnosis of TAAA extending from the sixth intercostal space to below the renal arteries or from the diaphragm to below the renal arteries (Crawford extent III and IV, respectively) who were undergoing surgical repair without cardio-pulmonary bypass were included. Patients with abdominal aortic aneurysm undergoing conventional laparotomy (n=5) or endovascular stent graft implantation in the descending aorta (n=6) were studied for comparison. In the former group, temporary visceral ischemia was limited to regions supplied by the inferior mesenteric artery or internal iliac arteries, whereas there was no visceral ischemia in the latter group. All patients gave written informed consent before inclusion. Preoperative patient demographics are detailed in the Table.

Surgical Procedures

Both conventional and endovascular procedures were performed in general anesthesia. Each patient received 5000 to 10 000 IU of heparin sodium intravenously before aortic clamping or insertion of the endograft. The renal arteries were perfused with cold (4°C) crystalloid Ringers acetate with verapamil, whereas visceral arteries were temporarily occluded with balloon catheters. Segmental intercostal and lumbar arteries were reattached to the graft if technically feasible. Shed blood was collected with a Hemonetics Cellsaver Device (Hemonetics Corp) and reinfused. Conventional repair of abdominal aortic aneurysm was undertaken by a standard transperitoneal approach with aortic cross-clamping below the renal arteries. Endovascular repair was performed with an endograft inserted through the common femoral artery, which was occluded to give temporary distal ischemia of 1 lower extremity.

Blood and Plasma Transfusions

Red cell concentrates were given to all TAAA patients: 16 patients received 2 to 9 (median 4) U, whereas 3 patients received 17, 30, and 65 U, respectively. Four of 6 patients undergoing endovascular stent grafting and 1 of 5 patients undergoing open infrarenal aortic surgery received 1 to 2 U of red cells. Plasma (Octaplas; Octapharma) was given to all TAAA patients except for 1 (patient A); 17 patients received 4 to 14 (median 7) U, whereas 1 patient received 62 U. None of the patients in the control group received Octaplas.

Blood Sampling

Blood samples were obtained at the following time points: T1, immediately before surgery; T2, before aortic clamping; T3, before aortic declamping; T4, immediately after aortic declamping; T5, 2 hours after aortic declamping; T6, 8 hours after aortic declamping; T7, 24 hours after surgery; and T8, 72 hours after surgery. Venous blood was collected in tubes containing EDTA and placed on crushed ice. After immediate centrifugation at 4°C, plasma was collected and stored at −70°C until analysis. Serum was obtained from tubes without anticoagulants after the blood was left to clot for 2 hours at room temperature and was stored at −70°C.

Complement Analyses

Mannose-Binding Lectin Antigen and Function

The concentration of mannose-binding lectin (MBL) was quantified by a double-antibody ELISA. Briefly, a monoclonal anti-human MBL antibody (HYB-131–01, Antibodyshop) was used as capture antibody. Standard was from the MBL ELISA (Antibodyshop, Copenhagen, Denmark), which gave a lower detection limit of 15 ng/mL. A mouse biotinylated monoclonal anti-human MBL (HYB-131–01, Antibodyshop) was used as detection antibody, and development was by streptavidin-peroxidase and substrate...
the function of MBL was measured according to a previously described method.\(^1\)\(^7\)

**Complement Activation Products**

The following assays were performed principally as described previously: C1rs-C1-inhibitor complexes (C1rs-C1inh), from the classic pathway\(^1\)\(^8\); C4bc, reflecting the classic and the MBL pathway\(^1\)\(^9\); the alternative pathway C3 convertase C3bBbP\(^2\)\(^0\); C3bc, indicating activation of any initial pathway\(^2\)\(^1\); and the soluble terminal complement complex (TCC), indicating complete activation of the terminal pathway.\(^2\)\(^2\)

Results for all assays are given in arbitrary units (AU) per milliliter based on fully activated serum (heat-aggregated IgG for C1rs-C1inh and C4bc, and zymosan for the remaining), defined to contain 1000 AU/mL. The antibodies to C1 inhibitor and C4bc were a kind gift from Professor C.E. Hack, Amsterdam, the Netherlands.

**Cytokines and Chemokines**

ELISA kits for interleukin (IL)-1\(\beta\), tumor necrosis factor (TNF)-\(\alpha\), and the chemokine IL-8 were from R&D Systems. IL-6 and IL-10 kits were from Bender MedSystems, MedSystems Diagnostics GmbH.

**Neutrophil Activation**

Myeloperoxidase (MPO) and lactoferrin (LF) were quantified in ELISA as described previously.\(^2\)\(^3\),\(^2\)\(^4\)

**Soluble Adhesion Molecules**

The soluble adhesion molecules sP-selectin (sCD52P), sE-selectin (sCD62E), and sICAM-1 (sCD54) were quantified with ELISA kits from Bender MedSystems.

**Statistics**

Data are medians with 95% nonparametric CIs. Probability values below 0.05 were considered significant. Comparisons among groups were performed with the \(x^2\) or Kruskal-Wallis tests. Variables measured repeatedly were analyzed by 2-way repeated-measures ANOVA with logarithmic or rank transformation if necessary (SPSS PC program package). Subsequent intergroup comparisons were performed with the Kruskal-Wallis test, and time-related changes within groups were compared with Friedman’s test. As a summary measure, the area under the time curve for the activation parameters was calculated for each patient. Correlations were analyzed with Spearman rank correlation coefficient. To investigate the relationship between complement activation and postoperative complications in the TAAA patients, the area under the TCC curve was compared between patients experiencing any postoperative complication and patients with an uneventful recovery by Mann-Whitney \(U\) test.

**Results**

**Complement**

**MBL Concentration and Function**

MBL concentration and function did not change by time in either group. MBL deficiency (antigen level below 100 ng/mL and undetectable function) was found in 3 of the 19 TAAA patients and in 2 of the control subjects. Two of the 3 TAAA patients (patients B and C) received MBL-containing plasma (Octaplas) transfusion perioperatively, whereas 1 (patient A) did not (Figure 1). Patient B received 5 U of Octaplas between T4 (aortic declamping) and T6 (8 hours after aortic declamping). Patient C received 6 U of Octaplas between T4 (aortic declamping) and T7 (24 hours after aortic declamping). Both patient B and patient C attained plasma MBL concentrations above the lower range of the MBL-sufficient TAAA patients, whereas no change in MBL concentration was seen in patient A, who did not receive plasma. Complement activation and inflammatory responses in patient A were strikingly different from those of the other TAAA patients but identical to those of the control patients (no complement activation or increase in IL-1\(\beta\), TNF-\(\alpha\), or IL-8 but an increase in IL-6 and IL-10), whereas the 2 MBL-deficient patients receiving plasma (patients B and C) displayed inflammatory responses similar to those of the MBL-sufficient TAAA patients. Patient A was further investigated to exclude other complement deficiencies. Classic complement total hemolytic activity (CH50) was normal, and incubation of the serum by heat-aggregated IgG and zymosan in vitro yielded C1rs-C1inh complexes, C4bc, C3bBbP, C3bc, and TCC identical to those obtained by activation of normal serum.

**Complement Activation**

C1rs-C1inh increased moderately in the TAAA group from 17 (15 to 21) AU/mL at baseline to 27 (23 to 33) AU/mL 8 hours after aortic declamping (T6; \(P<0.01\)), whereas no increase was observed in the controls (Figure 2, left panel). Because of significant differences at baseline (T1) among the 3 groups, the percentage changes from baseline were compared, and the percentage of C1rs-C1inh increase in the TAAA group was significantly higher (\(P<0.01\) at T6) than in the controls. C4bc increased markedly in the TAAA group from 6 (5 to 8) AU/mL at baseline to 89 (74 to 104) AU/mL at T6 (\(P<0.01\)). No increase was observed in the controls, and the difference between TAAA and controls was signifi-
cant \( (P < 0.001 \text{ at T6; Figure 2, middle panel}) \). The relative increase in C4bc (reflecting classic and MBL pathways) was substantially more pronounced than the increase in C1rs-C1inh (classic pathway only). C3bBbP (alternative pathway) increased in the TAAA group from 11 (7 to 17) AU/mL at baseline to 47 (36 to 65) AU/mL at T6 \( (P < 0.01) \). No increase was observed in the controls, and the difference between TAAA and controls was significant \( (P < 0.001 \text{ at T6; Figure 2, right panel}) \). C3bc (all pathways) increased in the TAAA group from 12 (8 to 15) AU/mL at baseline to 69 (48 to 96) AU/mL at T6 \( (P < 0.01) \). No increase was observed in the controls, and the difference between TAAA and controls was significant \( (P < 0.01 \text{ at T6; Figure 3, right panel}) \). All complement activation products reached a maximum 8 hours after aortic declamping and declined thereafter. In the MBL-deficient TAAA patient (patient A) who did not receive plasma, there were no increases in any of the activation products (Figures 2 and 3).

**Cytokines and Chemokines**

Two distinct activation patterns were revealed: IL-1\( \beta \), TNF-\( \alpha \), and IL-8 increased in the TAAA group only, reached a peak 24 hours postoperatively (T7), and were closely correlated with the degree of complement activation. IL-6 and IL-10, on the other hand, reached a maximum 8 hours after aortic declamping (T6) in the TAAA group, were not correlated with the degree of complement activation, and also increased in the control groups.

**Figure 2.** Initial complement activation. C1rs-C1inh complexes (left), reflecting classic pathway activation, were slightly increased in TAAA patients (open circles). In contrast, substantial increases in C4bc (middle), reflecting classic and/or lectin pathway activation, and in C3bBbP (right), reflecting alternative pathway activation, were seen in TAAA group. No complement activation was found in controls (closed circles indicate open infrarenal aortic surgery group) or in MBL-deficient TAAA patient who did not receive plasma (patient A, dotted line). Data (medians and nonparametric 95% CIs) are presented as percent increases from baseline (T1 = sample before surgery).

**Figure 3.** Activation of C3 and C5-C9. C3bc (left) reflects activation of all initial pathways, whereas TCC (right) indicates complete activation of terminal pathway. Substantial complement activation was seen in TAAA group (open circles), whereas no activation was detected in controls (closed circles indicate open infrarenal aortic surgery group) or in MBL-deficient TAAA patient who did not receive plasma (patient A, dotted line). Data are medians and nonparametric 95% CIs.
IL-1β increased in the TAAA group from <8 pg/mL (<8 to 9 pg/mL; 8 = lower detection limit) at baseline to 69 (48 to 90) pg/mL 24 hours postoperatively (T7; \( P < 0.0001 \)), whereas no increase was observed in the controls (Figure 4, left panel). TNF-α increased in the TAAA group from <78 pg/mL (lower detection limit) at baseline to 868 (603 to 1210) pg/mL at T7 (\( P < 0.0001 \)), whereas no increase was observed in the controls (Figure 4, middle panel). IL-8 increased in the TAAA patients from <63 pg/mL (lower detection limit) at baseline to 70 (<63 to 207) pg/mL at T7 (\( P < 0.0001 \)), with detectable levels in 10 of the 19 patients. No increase was seen in the controls (Figure 4, right panel). The degree of complement activation, as measured by the area under the TCC curve, was significantly correlated with the areas under the IL-1β (\( r = 0.66; P = 0.007 \)), TNF-α (\( r = 0.68; P = 0.006 \)), and IL-8 (\( r = 0.81; P < 0.0005 \)) curves. The MBL-deficient TAAA patient who did not receive plasma transfusion (patient A) had undetectable levels of TNF-α, IL-1β, and IL-8 (Figure 4).

IL-6 increased in the TAAA group from 6 (3 to 19) pg/mL at baseline to a maximum of 186 (114 to 271) pg/mL 8 hours after aortic declamping (T6; \( P < 0.0001 \); Figure 5, left panel). IL-6 also increased significantly in the control groups, although less extensively, and showed later time points for maximal concentrations: from 13 (3 to 150) pg/mL at baseline to 108 (27 to 122) pg/mL 24 hours postoperatively (T7) in the laparotomy group (\( P < 0.05 \); Figure 5, left panel) and from 8 (3 to 86) pg/mL at baseline to 81 (33 to 131) pg/mL 72 hours postoperatively (T8) in the endovascular group (\( P = 0.001 \)). IL-10 increased in the TAAA group from 8 (7 to 9) pg/mL at baseline to a maximum of 281 (156 to 581) pg/mL 8 hours after aortic declamping (T6; \( P = 0.01 \); Figure 5, right panel). IL-10 increased only slightly in the control groups, from 6 (6 to 7) pg/mL at baseline to 35 (7 to 50) pg/mL.

Figure 4. IL-1β, TNF-α, and IL-8. IL-1β (left), TNF-α (middle), and IL-8 (right) peaked at T7 (24 hours postoperatively) and correlated closely with degree of complement activation in TAAA patients (open circles). These cytokines did not increase in controls (closed circles indicate open infrarenal aortic surgery group) or in MBL-deficient TAAA patient who did not receive plasma (patient A, dotted line). Broken line indicates lower detection limit of assays. Data are medians and nonparametric 95% CIs.

Figure 5. IL-6 and IL-10. IL-6 (left) and IL-10 (right) peaked at T6 (8 hours after aortic declamping) and did not correlate with degree of complement activation in TAAA patients. Smaller increases were observed in controls (closed circles indicate open infrarenal aortic surgery group) and in MBL-deficient TAAA patient who did not receive plasma (patient A, dotted line). Data are medians and non-parametric 95% CIs.
83) pg/mL at 8 hours after aortic declamping (T5; P = 0.01) in the laparotomy group (Figure 5, right panel) and from 8 (6 to 17) pg/mL at baseline to 15 (8 to 27) pg/mL 72 hours postoperatively (T8) in the endovascular group (P = 0.01). Notably, IL-6 and IL-10 peaked at the same time as the complement activation products in the TAAA group (8 hours after aortic declamping), but there was no correlation between complement activation (area under the curve) and areas under the IL-6 (r = 0.32; P = 0.18) or IL-10 (r = 0.20; P = 0.42) curves. Both IL-6 and IL-10 increased in the MBL-deficient TAAA patient who did not receive plasma (patient A), comparable to the controls (Figure 5).

**MPO and LF**

MPO increased significantly (P < 0.01) both in the TAAA group and in the controls, without significant differences among the groups (Figure 6, left panel). LF increased significantly (P < 0.01) by time in all groups, slightly more in the TAAA group than in the controls at T7 and T8 (Figure 6, right panel). Although the increases in MPO and LF occurred before complement activation, there was a significant correlation between complement activation (area under the curve for TCC) and areas under the MPO (r = 0.70; P = 0.001) and LF (r = 0.63; P = 0.004) curves, which indicates a complex pattern of neutrophil activation during TAAA repair.

**Adhesion Molecules**

The soluble adhesion molecules sCD62P, sCD62E, and sCD54 were detected at physiological concentrations and did not increase in any group.

**Plasma Transfusions**

To exclude plasma transfusions as a source of inflammatory markers, Octaplas was tested for cytokines and found to contain undetectable levels. Furthermore, no correlation was found between the number of plasma transfusions and changes in complement activation products, cytokines, or neutrophil degranulation products (P = 0.13 to 0.63).

**Discussion**

This is the first report to demonstrate activation of complement in open TAAA surgical repair. Activation occurred after reperfusion (aortic declamping) and peaked 8 hours after declamping for all activation products. No increase in activation products was seen in the control groups, which indicates that the extended ischemia-reperfusion injury, including that of the visceral area, during TAAA repair was responsible for the activation. A systemic increase in complement activation products reflects a substantial activation, and the lack of activation products in the control subjects does not exclude local complement activation or low-grade systemic activation not detected because of rapid turnover or dilution of the activation products. Detection of increased activation in a systemic blood sample reflects the top of the iceberg only. Hitherto, such an extent of activation as seen in the TAAA patients has mainly been observed during extracorporeal circulation and in serious clinical conditions such as septicemia. This underscores the potency of the activation that occurs during TAAA repair.

Complement has been implicated in the pathogenesis of ischemia-reperfusion injury in experimental models, and both classic, alternative, and lectin pathway mechanisms of activation have been postulated. There are 2 lines of evidence for the role of classic pathway activation in ischemia-reperfusion injury: the presence of naturally occurring complement-fixing antibodies binding to damaged endothelium and the beneficial effect on tissue damage by specific blocking of the classic pathway. The alternative pathway may be activated directly or as an amplification of classic or lectin pathway activation. In early studies performed before the lectin pathway was discovered, lectin pathway activation may have been misinterpreted as alternative pathway, because the efficacy of
the lectin pathway may depend in part on amplification by the alternative pathway. In fact, recent studies have highlighted the role of the lectin pathway in ischemia-reperfusion injury. Hypoxia and reoxygenation of human endothelial cells induced MBL-dependent complement activation, and inhibition of MBL markedly reduced rat myocardial ischemia-reperfusion injury. The present study revealed a slight but significant increase in C1rs-C1inh in the TAAA patients but not in the controls. This indicates classic pathway activation and is most likely due to the ischemia-reperfusion injury, because no increase was found in the controls. C4bc reflects both classic and lectin pathway activation. The increase in C4bc in the TAAA group was substantial (15 times baseline values) compared with the increase in C1rs-C1inh (1.5 times baseline values), which suggests that the lectin pathway might be responsible for most of the activation. This is further supported by the fact that 1 patient with MBL deficiency (patient A) who did not receive plasma showed no increase in complement activation products, in contrast to the 2 MBL-deficient patients (patients B and C) who did receive plasma and attained MBL concentrations in the lower range of the MBL-sufficient patients. Notably, we excluded other complement deficiencies in patient A and showed that serum from this patient in vitro generated normal amounts of the complement activation products tested in the present study, which suggests that the MBL deficiency was responsible for the lack of response in this patient. The substantial alternative pathway activation observed in the TAAA patients may be caused either by a primary triggering of the alternative pathway or more likely by amplification due to lectin or classic pathway activation, as discussed above. Of particular interest in this regard is a recently published report showing that experimental intestinal ischemia-reperfusion injury is abolished in complement factor D knockout mice and restored by addition of factor D.

Theoretically, the plasma transfusions could be responsible for the increases in inflammatory markers. Plasma was given to the TAAA patients only and not to the controls, and plasma is known to contain complement activation products. However, several lines of evidence suggest that plasma transfusion could not explain the findings. First, there was no correlation between the number of plasma units transfused and the increase in complement activation products, which would have been expected if the increase was due to transfused plasma. Second, we have previously shown in patients undergoing coronary bypass surgery that there were no differences in the complement activation products C3bc and TCC between the group receiving Octaplas and the group not receiving plasma. Thus, the transfused activation products are most likely diluted immediately after transfusion and rapidly cleared from the circulation. Finally, we quantified the cytokines in Octaplas and found them to be below the lower detection limit in the assays, and therefore, transfused cytokines could not explain the increases in the TAAA group.

A striking dichotomy was observed for the release of cytokines in the TAAA group. IL-1β, TNF-α, and IL-8 correlated very closely with the degree of complement activation. Furthermore, they were not increased in the controls, in whom no complement activation was observed. The time delay between the peak of complement activation products (8 hours after aortic declamping) and these cytokines (24 hours postoperatively) supports the hypothesis that synthesis of IL-1β, TNF-α, and IL-8 may be complement dependent, although a causal relationship cannot be proved in this clinical setting. In contrast, IL-6 and IL-10 did not correlate with the degree of complement activation and peaked at the same time as the complement activation products in the TAAA patients. They also increased in the controls, which indicates that IL-6 and IL-10 were synthesized in a complement-independent manner. This dichotomy is further underscored by the fact that the MBL-deficient TAAA patient (patient A) who showed no complement activation displayed a cytokine pattern identical to that of the control patients. The present data are in accordance with previous studies on cytokines in TAAA repair, although a possible relation to complement has not been described previously, and sufficient attention has not been paid to a time difference in their release. In one study, IL-10 was found to increase rapidly after aortic declamping, peaking at 30 minutes. IL-1 and TNF were increased by the first postoperative day in another study. In a third study, IL-6 and IL-10 peaked 4 hours postoperatively, together with TNF-α and IL-8, apparently in contrast to the present findings. However, the time patterns for the cytokines were also somewhat diverging in this study. IL-6 and IL-10 decreased rapidly by 8 hours after declamping, in contrast to TNF-α and IL-8, which remained at relatively higher concentrations during the postoperative course. The pathophysiological role of cytokines in the systemic inflammatory response after clinical TAAA repair is controversial. One study showed a relationship between complications and increased TNF-α and IL-6, whereas another investigation found no correlation between complications and increases in IL-1 and TNF. However, in an experimental study with 30 minutes of supraceliac aortic clamping, lung performance was significantly improved by neutralization of TNF or IL-1, which suggests that both of these mediators contributed to the disturbed homeostasis after TAAA repair. The present data highlight complement as a possible inducer of the proinflammatory response after TAAA repair and complement inhibition as a possible therapeutic approach in this condition.

In summary, the present data suggest that complement activation is a consistent phenomenon in complement-sufficient patients undergoing TAAA repair. This activation appears to be mediated mainly via the lectin pathway and amplified through the alternative pathway and may contribute to the release of proinflammatory cytokines.

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