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C1qRP, the C1q Receptor That Enhances Phagocytosis, Is Detected Specifically in Human Cells of Myeloid Lineage, Endothelial Cells, and Platelets

Ronald R. Nepomuceno and Andrea J. Tenner

The complement component C1q can interact with a variety of different cells, resulting in multiple functional consequences depending on the cell type. mAbs R3 and R139, which recognize a 126,000 \( M_r \) (reduced) cell surface protein, are able to abrogate the C1q-mediated enhancement of monocyte phagocytosis. The cDNA encoding this C1q receptor that modulates phagocytosis, C1qRP, has recently been cloned. Using a DNA probe based on the coding region of the receptor, Northern blot and RT-PCR analysis of RNA isolated from different cell types showed C1qRP expression in cells of myeloid origin and in endothelial cells, but not in cells of lymphoid origin nor in the Hela epithelial-like cell line or iliac artery smooth muscle cells. FACS analysis of cell surface expression of C1qRP, as detected by mAb R139 and R3, corresponded in all cases to the mRNA levels detected. Using the anti-C1qRP mAb, the 126,000 \( M_r \) receptor was also detected in lysates of human platelets. Interestingly, C1qRP is not expressed by the promyelocytic leukemia cell line HL-60, and differentiation of these cells with various chemical compounds did not induce C1qRP expression. It has been reported that C1q can induce specific receptor-mediated responses in fibroblasts. However, RNA and cell surface expression analysis for C1qRP indicate that this particular C1q receptor is not expressed by either human gingival or human skin fibroblasts. These data demonstrate selective expression of C1qRP in specific cell types and support the hypothesis that there is more than one C1q receptor mediating the diverse responses triggered by C1q.

and R3, the mAbs that recognize C1qRP, have been used to demonstrate surface expression of the receptor on cells of myeloid origin, such as U937 cells, monocytes, and neutrophils (26), and on human endothelial cells (27), but the receptor is not found on cells of lymphoid origin, including lymphocytes, the Raji B cell, and CEM T cell lines (26). Interestingly, the mAbs R139 and R3 inhibit the C1q-mediated enhancement of monocyte phagocytosis, but are not able to affect the superoxide production triggered by C1q in neutrophils, suggesting that the receptors that mediate these two responses differ in some way. However, since C1qRP is present on the surface of neutrophils, the possibility of this receptor playing a role in the C1q triggering of superoxide anion release cannot be completely excluded.

Two other proteins with a macromolecular structure strikingly similar to C1q are also able to mediate enhanced phagocytosis by human monocytes through C1qRP, mannos-binding lectin (MBL) and pulmonary surfactant protein A (SPA) (28, 29). However, unlike C1q, neither MBL nor SPA is able to trigger the neutrophil superoxide production (30). These data combined with the lack of inhibition of C1q-mediated superoxide production by the anti-C1qR, mAbs, have led us to propose that there are at least two distinct receptors on myeloid cells: C1qRP, which modulates phagocytosis, and C1qRP2, which triggers superoxide anion generation. The presence of more than one C1q receptor on the different cell types, as well as different C1q receptors on the same cell type, would be similar to that seen for IgG and C3 receptors (31, 32). To further characterize the cell type-specific expression of C1qRP and to verify that receptor expression correlates with superoxide production, we determined the expression of C1qRP in various human cell types at both the protein and mRNA level. These studies provide a critical, initial step in determining whether C1qRP, in addition to enhancing monocyte phagocytosis, participates in some of the other functions triggered by C1q.

Materials and Methods

Media, reagents, and Abs

RPMI 1640 medium, DMEM, SuperScript preamplification system for first-strand cDNA synthesis kit, TRIZOL reagent, RadPrime DNA labeling system, Taq DNA polymerase, and salmon sperm DNA were purchased from Life Technologies (Grand Island, NY). Human serum albumin, mannos-binding lectin, was purchased by Baxter Healthcare Corporation (Glendale, CA), which modulates phagocytosis, and C1qRP2, which triggers superoxide anion generation. The presence of more than one C1q receptor on the different cell types, as well as different C1q receptors on the same cell type, would be similar to that seen for IgG and C3 receptors (31, 32). To further characterize the cell type-specific expression of C1qRP and to verify that receptor expression correlates with surface mAb reactivity, molecular probes based on the recently cloned C1qRP, cDNA, as well as the R139 and R3 Abs, were used to determine the expression of C1qRP, in various human cell types at both the protein and mRNA level. These studies provide a critical, initial step in determining whether C1qRP, in addition to enhancing monocyte phagocytosis, participates in some of the other functions triggered by C1q.

Cells and cell culture

The U937, THP-1, and HL-60 human cell lines were obtained from the American Type Culture Collection (Rockville, MD). CEM cells were a kind gift from Dr. E. Remold-O’Donnell (Center for Blood Research, Boston, MA). U937, K562, and Raji cells were cultured in RPMI 1640 medium containing 10% heat-inactivated bovine calf serum (HyClone Laboratories, Logan, UT). Human monocytes and gingival fibroblasts were biopsied from normal volunteers and, like the HeLa cell line, were cultured in DMEM supplemented with 10% FCS, 1 mM sodium pyruvate (BioWhittaker, Walkersville, MD), and 0.1 mM nonessential amino acids solution (Life Technologies). HL-60 and CEM cells were cultured in RPMI 1640 containing 20 or 10%, respectively, FCS (HyClone). THP-1 cells were grown in RPMI 1640, 10% FCS, and 5 × 10−5 M 2-mercaptoethanol. Human peripheral blood monocytes and lymphocytes were isolated by counter-flowsed centrifugation using a modification of the technique of Lionetti et al. (34) as described (4). Blood units were collected into CPDA1 blood-pack units (Baxter Healthcare Corp., Deerfield, IL) at the UCI Medical Plaza, Irvine, CA. Cells in each preparation were checked for homogeneity according to size analysis on a Coulter Channelizer (Miami, FL). Neutrophils were isolated from blood drawn from normal volunteers into EDTA-containing system, and lymphocytes were separated using the Immunopur kit (Irvine Teknika Corp., Durham, NC) and dextran sedimentation as described (15), the residual RBC were removed by hypotonic lysis.

FACS analysis

Cells were washed in HBSS containing 1 mM Ca2+, 1 mM Mg2+, 0.2% sodium azide, and 0.2% human serum albumin (FACS buffer), and subsequently incubated for 30 min on ice with mAbs R139, biotinylated R3, or isotype-matched control Abs. Cells were washed three times in FACS buffer, then incubated with either FITC-conjugated F(ab)2 anti-mouse IgG (Tago, Burlingame, CA), or PE-conjugated streptavidin (Becton Dickinson, San Jose, CA) for 30 min on ice. In some experiments, cells were then incubated with FITC-anti-CD3, PE-anti-CD19, or PE-anti-CD33 (Becton Dickinson). After washing three times in FACS buffer, the cell-associated fluorescence was measured using a FACScan or FACS Calibur (Becton Dickinson).

Northern blot analysis

HUVEC total RNA designated BC was a kind gift from Dr. Bruce Cronstein (New York University Medical Center, New York, NY). HUVEC total RNA designated JW and human iliac artery smooth muscle cell total RNA were kind gifts from Dr. Jeff Winkles (American Red Cross Holland Laboratory, Rockville, MD). Total RNA from monocytes and neutrophils was isolated using the RNA isolation kit purchased from Stratagene (La Jolla, CA). For other cell types, mRNA was isolated using the MicroFast-Track mRNA isolation kit (Invitrogen, San Diego, CA) and total RNA was isolated using TRIZOL reagent (Life Technologies) according to manufacturer’s instructions. RNA was heat denatured for 15 min at 65°C and then separated by electrophoresis through 1% agarose gels containing formaldehyde. The RNA was transferred overnight in 10× SSPE to maximum strength nitran (Schleicher & Schuell, Keene, NH) and UV cross-linked to the membrane. A C1qRP-specific probe, based on a 1458 bp cDNA insert corresponding to 74.5% of the coding region of C1qRP, was generated by the random priming method using the RadPrime DNA labeling system (Life Technologies) and [32P]-labeled dCTP (DuPont-NEN Research Products, Boston, MA). A similarly-generated probe for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (a kind gift from Dr. Hung Fan, University of California, Irvine, CA) was used as a control for monitoring the level of RNA loaded. Hybridization of the probes were conducted for 16 to 20 h at 42°C in 50% formamide, 5× SSPE, 5× Denhardt’s reagent, 0.1% SDS, and 0.1 mg/ml salmon sperm DNA. After washing twice in 6× SSPE, 0.1% SDS for 15 min each at room temperature, twice in 1× SSPE, 0.1% SDS for 15 min at 37°C, and once in 1× SSPE, 0.1% SDS for 30 min at 60°C, bound probes were detected by autoradiography.

RT-PCR analysis for C1qRP expression

Total RNA isolated as described above was treated with RQ1 RNase-free DNase (Promega, Madison, WI) according to the manufacturer’s instructions. First-strand cDNA synthesis from 2 μg of total RNA was conducted using the SuperScript preamplification system (Life Technologies) with random hexamers as primers. As a control for the presence of residual genomic DNA in the RNA preparations, parallel cDNA synthesis reactions were conducted in the absence of the reverse transcriptase. Two micrograms of the 20-μl cDNA synthesis reaction were used in 50-μl PCR reactions containing 20 mM Tris-HCl (pH 8.4), 50 mM KCl, 1.5 mM MgCl2, 0.2 mM dNTPs, 0.1 μM of each primer, and 2 U of Taq DNA polymerase (Life Technologies). The C1qRP primers that amplify a 538-bp cDNA are 5′-AGCTGAGCGCTGCCGAGGCCCA-3′ for the sense primer and 5′-TTGGCCGCAGAGGCAAAGGGCA-3′ for the antisense primer. RT-PCR control amplimer sets for human β-actin and transferrin receptor were purchased from Clontech (Palo Alto, CA). After an initial 2-min denaturing at 94°C, PCR amplification was performed for 30 cycles of denaturing for 30 s at 94°C, annealing for 30 s at 60°C, and extension for 1 min at 72°C in a Perkin-Elmer DNA thermal cycler (Norwalk, CT). PCR

5 R. R. Nepomuceno, S. Rutz, M. Park, and A. J. Tenner. C1qRP is a heavily

products were resolved on 1% agarose gels run in TAE according to standard protocols (35) and stained with ethidium bromide.

**Platelet C1qRP Immunoprecipitation**

Normal human platelet lysate (in 20 mM Tris-HCl, pH 8, 0.1 M NaCl, 1% Triton X-100, 10 mM N-ethylmaleimide, 0.01% leupeptin) was kindly provided by Dr. Diane Nugent of Children’s Hospital of Orange County, Orange, CA. The total protein concentration of the lysate was 8.25 mg/ml. The immunoprecipitation was performed as described (26) using 333 μl of the platelet lysate or 8.3 × 10^6 cell equivalents of freshly elutriated (4) human monocytes (in the above lysis buffer) per sample. Precipitated material was separated by SDS-PAGE, transferred to nitrocellulose (Schleicher & Schuell) as described (25), and probed with the biotinylated R3 mAb. Bound Ab was detected chemiluminescently with streptavidin-horse-radish peroxidase and the HRPL Western kit (National Diagnostics, Atlanta, GA).

**Results**

**FACS analysis of C1qRP cell surface expression**

The mAbs R139 (IgG2b) and R3 (IgM) recognize the extracellular domain of C1qRP, which was previously shown to be expressed on human monocytes, neutrophils, the U937 monocyte-like cell line, and endothelial cells (26, 27), but not on lymphocytes or the Raji and CEM lymphoblastoid cell lines (26). To further examine the cell surface expression of C1qRP on other cell types, the two mAbs were used in FACS analysis of various primary and established cell lines. Of the cells examined in this study, the acute monocytic leukemia cell line THP-1 and the chronic myelogenous leukemia cell line K562 were found to express C1qRP, at substantially lower levels, however, compared with U937 cells (Fig. 1). The epithelial-like HeLa cell line was not reactive with either of the anti-C1qRP mAbs. Human fibroblasts have been reported to bind and respond functionally to C1q (21, 22, 36, 37); however, neither human skin or gingival fibroblasts express C1qRP as determined by R139 and R3 reactivity (Fig. 1).

Interestingly, the promyelocytic leukemia cell line HL-60, which consists primarily of neutrophilic promyelocytes, does not express C1qRP, despite the fact that human neutrophils express the receptor at relatively high levels (26). This lack of receptor expression may be due to the difference in differentiation state of the cell line compared with circulating neutrophils (38). To test this hypothesis, HL-60 cells were induced to both a monocytic differentiation (with 1α,25-dihydroxy-vitamin D₃ and PMA) and granulocytic differentiation (with DMSO and retinoic acid) over a 6-day period. FACS analysis of the differentiated cells showed no increase in R139 and R3 reactivity over untreated HL-60 cells (data not shown). Differentiation was verified by the changes in morphology and adherence of the cells, by the expected increases in CD14 expression for monocytic differentiation (39), and in CR3 expression for granulocytic and monocytic differentiation (40), as determined by FACS analysis and by an increase in phorbol 12,13-dibutyrate-induced superoxide production by DMSO and retinoic acid differentiated cells.

**Northern blot analysis**

Because the mAbs are specific for distinct epitopes on the receptor protein, it is possible that C1qRP may be present on different cell lines but that the mAb-binding epitopes may be missing, altered, or in a different conformation, such that they are no longer accessible to the Abs. Therefore, RNA isolated from the different cell types was subjected to Northern blot analysis using a 1458-bp cDNA fragment corresponding to approximately 75% of the receptor’s coding region to test for the presence of C1qRP RNA. C1qRP mRNA from U937 cells migrates as a single species of 6.7 kb in denaturing agarose gels (25) and is easily detected (Fig. 2). The single 6.7-kb RNA transcript was found in all cell types in which receptor expression was detected by the mAbs, including U937 cells, monocytes, endothelial cells, THP-1 cells, and neutrophils (Fig. 2, A and B). Receptor RNA was detected, albeit at very low levels, in mRNA isolated from K562 cells (Fig. 2A), consistent with the level of protein expression detected by the anti-C1qRP Abs. Conversely, C1qRP expression was not detected in mRNA isolated from skin or gingival fibroblasts, HeLa, Raji, or CEM cells (Fig. 2A), consistent with the lack of detectable surface immunoreactivity with R139 and R3 (Fig. 1 and Ref. 26). In total RNA isolated from elutriated lymphocytes, HL-60 cells, and iliac artery smooth muscle cells, C1q receptor expression was also not detected (Fig. 2B).

**RT-PCR analysis**

To verify the results of the Northern blot analysis, RT-PCR, a more sensitive method for the detection of C1qRP RNA transcripts in the various cells, was employed. Total RNA was isolated from the cells and used to generate cDNA using random hexamers as primers. The resulting cDNA was then used as the template in PCR reactions to amplify a 538-bp fragment of C1qRP that corresponds to 27.5% of the protein coding region. As shown in Figure 3, U937 cells, monocytes, neutrophils, THP-1, and endothelial cells express the receptor. Again, K562 cells express a lower level of the receptor RNA. Consistent with the pattern of receptor expression...
determined by the other methods, HL-60, HeLa, Raji, CEM, and both skin and gingival fibroblast RNA do not contain a detectable amount of C1qRP transcripts. While C1qRP mRNA was not detected in these cell lines, either the \(\beta\)-actin gene or the transferrin receptor gene, each of which is expressed at low levels in these cells, was detected, verifying the presence of RNA from the different cell types in the RT-PCR reactions. In all cases, control reactions in the absence of reverse transcriptase to check for genomic DNA contamination were negative (data not shown).

Surprisingly, cells from the elutriated lymphocyte population consistently contained a low level of C1qRP message detectable by RT-PCR. Although these cells appear to be negative by Northern blot (Fig. 2B), and FACS analysis of the lymphocyte population stained with the R139 mAb are distinctly negative, cells stained with the R3 mAb occasionally demonstrate a very slight increase in their mean fluorescence intensity vs control cells (26). While the population did not contain any monocytes as determined by size analysis on a Coulter Channelizer (data not shown), it is possible that the isolated population does contain a small number of myeloid progenitor cells, such as peripheral blood dendritic cells (41), that express C1qRP, even in an undifferentiated state, similar to

U937 and K562 cells. Cells of myeloid lineage have the cell surface marker CD33, which distinguishes these cells from other blood leukocytes. However, FACS analysis of elutriated lymphocytes stained with an anti-CD33 Ab did not detect a positive population of myeloid cells (data not shown). Additional FACS analyses demonstrate that the elutriated lymphocyte population contained neither CD3\(^+\) T cells nor CD19\(^+\) B cells, which also stained positive with the anti-C1qRP Abs (data not shown), and thus the source of the RT-PCR signal remains unknown.

**FIGURE 2.** Northern blot for detection of C1qRP RNA. mRNA (2 \(\mu\)g per lane) isolated using oligo(dT) cellulose (A) or total RNA (8.75 \(\mu\)g HUVEC, 10 \(\mu\)g all others) (B) was subjected to agarose gel electrophoresis under denaturing conditions. The RNA was transferred to nylon membranes, then hybridized with a \(^{32}\)P-labeled C1qRP-specific probe generated by the random priming method. After washing and exposing to autoradiographic film, the same membrane was stripped, hybridized to a \(^{32}\)P-labeled GAPDH probe, washed, and exposed to film. HUVEC were obtained from Drs. Bruce Cronstein (BC) and Jeff Winkles (JW).

**FIGURE 3.** RT-PCR for detecting C1qRP RNA. Two micrograms of DNase-treated total RNA from each cell type was used to generate cDNA using random primers and SuperScript II reverse transcriptase at 42°C. After separate PCR reactions with primers specific for C1qRP cDNA or the human \(\beta\)-actin or human transferrin receptor gene products, equal volumes of reaction products were subjected to agarose gel electrophoresis, stained with ethidium bromide, and photographed under UV light. Control reactions for genomic DNA contamination were conducted in the absence of the reverse transcriptase and were consistently negative (data not shown).

**Human platelets express C1qRP.**

The reported C1q-mediated effects on human platelets include inhibition of the collagen-induced platelet aggregation (10, 42, 43) and induction of \(\alpha_{IIb}\beta_3\) integrins, expression of P-selectin, and procoagulant activity (44). These functional observations, along with the demonstration that free C1q binds specifically to human platelets (10), suggest that surface C1q receptors exist on these cells. To determine whether C1qRP could have a role in platelet function in response to C1q, detergent extracts of isolated human platelets were subjected to immunoprecipitation and detection with the anti-C1qRP mAbs. As shown in Figure 4, a 100,000 \(M_r\) (non-reduced) band similar in size to C1qRP precipitated from U937 detergent extracts is detected in the platelet lysate. Additionally, this platelet molecule reacts with both the R139 and R3 mAbs, indicating that platelets do in fact express C1qRP.
were immunoprecipitated with 5 μg of isotype-matched control IgG2b mAb (lanes 1 and 3) or the R139 mAb (lanes 2 and 4). After separation by SDS-PAGE under nonreducing conditions, the precipitated proteins were transferred to nitrocellulose and probed with biotinylated R3 mAb.

FIGURE 4. Immunoprecipitation of C1qRp from human platelet lysate. U937 cell lysate (lanes 1 and 2) and human platelet lysate (lanes 3 and 4) were immunoprecipitated with 5 μg of isotype-matched control IgG2b mAb (lanes 1 and 3) or the R139 mAb (lanes 2 and 4). After separation by SDS-PAGE under nonreducing conditions, the precipitated proteins were transferred to nitrocellulose and probed with biotinylated R3 mAb. Positions of the m.w. standards are indicated on the right.

Discussion

Expression of C1qRp, the receptor that modulates phagocytosis in vitro upon ligation with C1q, was found to be limited to cell types that actively phagocytose (with the exception of platelets), supporting the hypothesis that this particular C1q receptor plays a specific role in modulating this important host defense mechanism. C1qRp is detected on human cells of myeloid lineage, including monocytes, neutrophils, and the U937, THP-1, and K562 cell lines, and HUVECs as determined by FACS, Northern blot, and RT-PCR analyses. Interestingly, C1qRp is also expressed on human platelets, although the function of this receptor on platelets has yet to be analyzed. For the most part, the receptor was not detected in cells of lymphoid lineage, including PBL and the Raji and CEM lymphoblastoid cell lines, the exception being a low level of C1qRp message detected by RT-PCR in RNA isolated from elutriated lymphocyte populations. However, because of the sensitivity of the RT-PCR technique, it may be possible that the detected C1qRp message is the result of amplification of RNA from myeloid progenitor cells, which are similar in size to the lymphocyte population and thus copurify with these cells. The fact that cells gated on CD3′ or CD19′ fluorescence were not stained with the anti-C1qRp Abs supports the hypothesis that peripheral lymphocytes do not express this C1q receptor. However, future studies with either more highly purified subpopulations of cells or immunohistochemical staining of tissues should identify the cell population responsible for this C1qRp mRNA expression. C1qRp is also not expressed by fibroblasts or the HeLa epithelial-like cell line. Thus, importantly, these data demonstrate that this particular C1q receptor does not participate in the binding and responses of fibroblasts to C1q and that the binding activity of C1q to cells such as Raji is not mediated by C1qRp. Iliac artery smooth muscle cells also do not express C1qRp (Figs. 2B and 3). However, C1q can still bind (11) and trigger superoxide release from these cells (45), consistent with the hypothesis that the receptors modulating C1q-mediated superoxide generation and enhanced phagocytosis are distinct.

The promyelocytic cell line HL-60, in which C1qRp was not detected at either the protein or RNA level, is one exception in the pattern of C1qRp expression in cells of myeloid lineage. These cells consist primarily of neutrophilic promyelocytes. Thus, since blood neutrophils that express C1qRp are terminally differentiated, the HL-60 cells may not be at a differentiation state in which the receptor is expressed. Thus far, our studies using various chemical agents to induce differentiation of these cells have not resulted in C1qRp expression. We conclude that additional factors or differentiation parameters must be present to induce C1qRp expression in the HL-60 cell line.

The pattern of expression of C1qRp reported here sharply distinguishes this receptor from two other reported C1q-binding proteins, which have been termed cC1qR and gC1qR. Ghebrehiwet and colleagues, and later others, isolated a 60,000 M, protein termed cC1qR, since it was originally characterized as binding to the collagen-like region of C1q. More recent reports suggest that it may be identical to calreticulin (46), a Ca2+-binding protein found in several cellular compartments, with many postulated functions (47, 48). In contrast to the restricted expression of C1qRp, the 60,000 M, protein is present on human B cells, Raji cells, and human T cells (49–52) as well as on most other cell types tested (11, 53–56). There is some in vitro evidence that C1qRP is involved in C1q-induced platelet aggregation (reviewed in Ref. 57). However, a C1q response mediated by this 60,000 M, protein has yet to be demonstrated on myeloid or endothelial cells.

gC1qR is another protein identified as binding the globular heads of C1q (58). While originally reported to be a 33-kDa glycoprotein expressed on the surfaces of vascular and blood cells (58–60), the apparent lack of a transmembrane domain or a consensus sequence for glycosylphosphatidylinositol anchoring does not make it obvious how gC1qR attaches to the membrane for the reported surface detection of this protein. Recent studies by van den Berg and coworkers and Muller-Esterl and colleagues demonstrate that gC1qR is not detected significantly on the surfaces of most of these cells by FACS analysis (61, 62). Rather, they propose that this 33-kDa protein is a soluble, intracellular or vesicular protein that can be secreted, but not as cell surface receptor. Additionally, Herwald and coworkers and Lim et al. have demonstrated kininogen-binding (63) and vitronectin-binding (64) activities for this 33-kDa protein independent of C1q. A cellular response to C1q mediated by gC1qR has not yet been demonstrated.

The relatively high levels of expression of C1qRp on endothelial cells is quite interesting in that C1q has been shown to bind to endothelial cells in a receptor-mediated fashion (7, 8) and has been shown to mediate binding of immune complexes and aggregates to endothelial cells in vitro (9). In addition, C1q bound to immune complexes induces an increase in the adhesive properties of endothelial cells for leukocytes (27) and, alone, mediates the binding of the S. minnesota Re mutant to pulmonary endothelial cells and elevates the level of superoxide anion release from these cells in response to the bacteria (20). While both the 60,000 M, cC1qR and 33,000 M, gC1qR-binding proteins have been shown to be expressed by endothelial cells (27, 55, 62), thus far, the only function demonstrated by either cC1qR or gC1qR derived from endothelial cells is the inhibition of complement-mediated lysis of C1q-sensitized erythrocytes by cC1qR (65, 66). Whether or not C1qRp, cC1qR, or gC1qR is involved in the C1q-mediated increase in endothelial cell adhesiveness for leukocytes, or the binding and destruction of bacteria by endothelial cells triggered by C1q, remains to be investigated.

The ability to selectively enhance a defense mechanism such as phagocytosis with limited, if any, additional effects on other systemic functions in immunocompromised patients, including those with AIDS, individuals with genetic immunodeficiencies, or patients undergoing surgery with high risk of infection, may provide a highly effective means of promoting positive clinical outcomes for these patients. In addition to C1q, MBL, and SPA, other agents such as cytokines (67, 68) and specific extracellular matrix proteins (69) have also been shown to enhance phagocyte function.
However, some of these cytokines, such as TNF-α and granulocyte-macrophage CSF, also trigger massive superoxide anion release from neutrophils directly, which would have devastating effects on host tissues (70). Additionally, TNF-α has been shown to activate integrated HIV-1 and cause enhanced virus production on host tissues (70). Additionally, TNF-α has been shown to activate integrated HIV-1 and cause enhanced virus production on host tissues (70). Additionally, TNF-α has been shown to activate integrated HIV-1 and cause enhanced virus production on host tissues (70). Additionally, TNF-α has been shown to activate integrated HIV-1 and cause enhanced virus production on host tissues (70).

In summary, the data provided here help delineate the specific receptor interactions possibly involved in mediating particular C1q-induced functions. Subsequent identification of critical ligand-receptor interaction sites should facilitate the design of selective modulators of desired responses (enhanced phagocytic capacity via C1qRα) without the induction of proinflammatory cytokines or generation of toxic superoxide anions.

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