Monocyte Fc, Receptor Recognition of Cell-Bound and Aggregated IgG

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Monocyte and macrophage Fc receptors are important components in the recognition of IgG-coated cells and IgG-containing immune complexes. Two proteins have been identified on human peripheral blood monocytes that can function as Fc receptors. FcRI (70 Kd) and FcRII (40 Kd). We studied the role of FcRI and FcRII on human monocytes by examining their binding of IgG-sensitized cells (human IgG anti-D-coated RBCs and rabbit IgG-sensitized sheep RBCs) and their binding of human trimeric IgG. To examine the function of monocyte FcRII, we used an anti-FcRII monoclonal antibody (MoAb) that competes for the FcRII ligand binding site. Preincubation of monocytes with saturating concentrations of anti-FcRII MoAb did not alter the recognition of IgG (anti-D)-sensitized human RBCs by monocytes. Furthermore, ligand-binding studies demonstrated that anti-FcRII antibody altered neither the number nor the affinity of monocyte-binding sites for human IgG trimers. Anti-FcRII inhibited monocyte binding of rabbit IgG-sensitized sheep RBCs, but only at low ionic strength or temperature when increased numbers of monocyte FcRII were expressed. At low ionic strength and 4°C, anti-FcRII also partially inhibited monocyte binding of human trimeric IgG. Thus, monocyte FcRII does not appear to recognize IgG-sensitized RBCs or trimeric IgG at physiologic temperatures and ionic strength. The data suggest that FcRI is the primary Fc receptor on monocytes involved in the binding of IgG (anti-D)-sensitized erythrocytes and low mol wt complexes of IgG.

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as IgG monomer on Sephacryl S-300 chromatography and appeared as IgG by Ouchterlony analysis, immunoelectrophoresis, or polyacrylamide disc gel electrophoretic analysis. The IgG was radiolabeled with \( ^{125}\)I (New England Nuclear Corporation, Boston) with chloramine-T to a specific activity of 0.16 \( \mu Ci/\mu g \). Prior to use, all IgG preparations were centrifuged in a Beckman airfuge (Beckman Instruments, Fullerton, CA), at 100,000 g for 15 minutes to remove IgG aggregates.

IgG trimer was prepared as previously described. Briefly, purified IgG (70 mg/mL in 0.2 mol/L Tris-HCl buffer, pH 8.4) was incubated with a 16-fold excess of dimethyl suberimidate (Sigma Chemical Co., St. Louis) for one to two hours at 30°C. The reaction was then quenched by the addition of a fivefold molar excess glycine (with respect to dimethyl suberimidate) and the mixture immediately applied to a tandem column of Sephadex G-200 (Pharmacia, Piscataway, NJ) and Ultrogel AcA 22 (LKB Instruments, Inc., Gaithersburg, MD) and fractionated into oligomers of defined mol wt. Pools of IgG timer were made and concentrated to 5 to 10 mg/mL prior to their use. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis and refractionation by gel filtration chromatography revealed that the major protein was trimeric IgG (mol wt = 450,000).

Preparation of IgG-coated RBCs. Human RBCs (Rh\(^+\)) from a single donor were sensitized with anti-D antibody as previously described. In brief, 1 x 10\(^8\) RBCs in 1 mL of 0.01 mol/L ethylenediamine-tetracetic acid (EDTA) buffer were incubated with defined amounts of anti-D serum for one hour at 37°C. After washing twice, RBCs were standardized to 1 x 10\(^7\) RBCs in HBSS and 1 mL added to the monocyte monolayers. Similarly, 1 x 10\(^7\) sheep RBCs in 1 mL of 0.01 mol/L EDTA buffer were sensitized by adding 16.4 \( \mu g \) of rabbit IgG antisheep RBC antibody in 1 mL at 37°C for one hour. The IgG-sensitized sheep RBCs were washed twice and resuspended in HBSS to a final concentration of 1 x 10\(^7\) cells/mL and overlayed on the monocyte monolayers.

The number of human IgG/RBC (Rh\(^+\)) was determined as previously reported. RBCs (Rh\(^+\)) sensitized as above were incubated for 30 minutes at 37°C with known amounts of \( ^{125}\)I rabbit antihuman IgG and the number of IgG/RBC determined by reference to previously established standard curves. The number of rabbit IgG per RBC was determined by incubating rabbit IgG radiolabeled with \( ^{125}\)I by the chloramine T method as above, with sheep RBCs and determining the bound radioactivity after washing the sensitized RBCs.

Monocyte recognition of human IgG-coated RBCs (Rh\(^+\)) and rabbit IgG-coated sheep RBCs. The in vitro recognition of IgG-coated RBCs was assessed as previously reported. Briefly, 1 x 10\(^8\) of either IgG-coated human RBCs (Rh\(^+\)) or sheep RBCs were added to monolayers containing 5 x 10\(^7\) monocytes. To assess the role of Fc,RII, monolayers were preincubated with IV.3 monoclonal anti-Fc,RII antibody or an isotype control for 30 minutes. Monocytes and IgG-coated RBCs were then incubated at either 4°C, 23°C, or 37°C for two hours, washed with the appropriate buffer, and stained with Wright’s-Giems. Monocytes (200) were counted under light microscopy to assess the number of IgG-sensitized RBCs bound/monocyte. Monocytes containing at least 1 phagocytized RBC were included with those binding ≥3 RBC/monocyte. Binding of IgG (anti-D)-coated RBCs and rabbit IgG-coated sheep RBCs by human monocytes and its modifications by anti-Fc,RII MoAb were performed in parallel. Positive controls were included in each experiment. The activity of the anti-Fc,RII MoAb in each instance was demonstrated by its ability to inhibit the monocyte binding of rabbit IgG-coated RBCs or the human platelet binding of trimeric IgG. Experiments performed at 23 and 37°C were also performed with shorter incubation times, when phagocytosis of the IgG-coated cells was minimal with this concentration of IgG/RBC. Under these conditions of minimal-to-absent phagocytosis, identical results were observed.

Equilibrium binding studies with \( ^{125}\)I IgG. All assays were performed in HBSS containing 0.1% gelatin, 10 mmol/L EDTA, and 0.1% NaN\(_3\), or with this assay buffer at \( \mu = 0.07 \), as previously described for monococytes and platelets. Before each assay, washed monocytes were incubated for 30 minutes at 37°C in HBSS buffer to permit cell-associated IgG to dissociate from the surface. Further incubation at 37°C did not result in the exposure of additional IgG binding sites. Cells were centrifuged and resuspended to a concentration of 2 x 10\(^7\)/mL (monocytes) or 1 x 10\(^7\)/mL (platelets) in the assay buffer. Increasing concentrations of radiolabeled IgG were added in the presence or absence of a 100-fold excess of unlabeled IgG. The amount of cell-associated and unbound \( ^{125}\)I-IgG were quantitated after rapidly centrifuging the cells through a layer of silicone oil in microfuge tubes. Specific binding was defined as the cell-associated radioactivity inhibited by the presence of a 100-fold excess of unlabeled IgG and represented more than 70% of the total cell-associated counts. Receptor number and affinity constants were determined by Scatchard analysis. The results were also analyzed using nonlinear curve fitting of untransformed data. A series of iterations were performed in which the parameters were systematically adjusted using the Marquardt-Levenberg method until a least squares solution was reached. In this manner the goodness of fit of a one-site model was compared statistically to the goodness of fit of a two-site model. The statistical significance of the improvement of fit was determined by performing an F test on the sum of squares of the residuals. The advantages of this type of analysis have been validated for beta adrenergic receptor subtypes.

To assess dissociation of bound \( ^{125}\)I-trimeric IgG, a 100-fold excess of unlabeled aggregated IgG was added to the cell suspension after equilibrium of binding was achieved (Fig 1). Samples were then assessed over the subsequent three hours for the dissociation of the bound \( ^{125}\)I-IgG trimer. Eighty-one percent of the total \( ^{125}\)I-IgG bound was displaced from the monocyte surface over this period of time. This corresponded to the amount of specifically bound \( ^{125}\)I-IgG, which represented 80% of the total trimeric IgG bound. The half-time for dissociation was 82.5 minutes, which contrasts with the dissociation half-time for monomeric IgG of 24.7 minutes. In the absence of the addition of unlabeled aggregated IgG, the amount of \( ^{125}\)I-IgG trimer bound to the monocyte surface remained constant during the experiment. Thus the data indicate that binding of trimeric IgG is saturable and reversible. Similar methodology was employed to assess the number of Fc,RII sites. Radiolabeled \( ^{125}\)I-IgG anti-Fc,RII MoAb was incubated with monocytes in the presence or absence of a 50-fold excess of unlabeled IgG anti-Fc,RII. The number of Fc,RII sites and the affinity of binding were then determined. In these studies no significant improvement in F value was observed when a two-site model was employed. We used fluorescence flow cytometry to examine whether Fc,RI expression is altered during the association and dissociation of IgG trimer. The anti-Fc,RI antibody (32.2) employed does not compete for the Fc,RII ligand binding site, while the anti-Fc,RII MoAb (IV.3) recognizes an Fc,RII epitope involved in IgG ligand binding. Binding of saturable amounts of IgG trimer to monocytes resulted in a decrease in the expression of Fc,RI and Fc,RII of <10%. Thus during the course of the experiments Fc,RI and Fc,RII expression was assessed with the monocytic line U937 treated with interferon-\( \gamma \). To evaluate whether any of the radiolabeled ligands were internalized by the cells at 37°C, we also exposed monocytes sequentially to proteinase, and acetic acid was used to strip the cells of surface-bound IgG. After equilibrium of binding was achieved, the cells...
were rapidly cooled to 0°C by the addition of ice cold phosphate-buffered saline (PBS) containing 1 mg/mL of bovine serum albumin (BSA; Sigma Chemical Co, St Louis) and 100 U/mL of deoxyribonuclease I (Sigma Chemical Co) in pH 7.2 PBS. After washing the cells three times, the cells were incubated in PBS containing 5 mg/mL of nonspecific protease (Proteinase type XIV, Sigma Chemical Co) at 0°C for one hour. The cells were washed three times and then incubated in 0.025 mol/L acetic acid and 0.3 mol/L NaCl (pH 3.2) for three minutes at 0°C and then rapidly spun through silicone oil. The internalized cell-associated radiolabeled ligand was determined by counting the cell pellet in a gamma counter. In this experiment 86% of the 125I-IgG trimer was specifically bound to the monocyte surface. We observed that 88% of this specifically bound 125I-IgG trimer was removed from the monocyte surface by protease and diluted acetic acid. Thus under the experimental conditions, trimeric IgG was surface bound and displaceable.

Statistics. To determine whether the difference between several means was significant, a Wilcoxon rank sum test for paired data was applied.26

RESULTS

Effect of anti-Fc,RII on monocyte recognition of human IgG (anti-D)-sensitized RBCs and rabbit IgG-sensitized sheep RBCs. We evaluated the role of Fc,RI and Fc,RII in the binding of IgG(anti-D)-coated RBCs using anti-Fc,RII MoAb IV.3. We first determined the amount of MoAb required to occupy all monocyte Fc,RII sites by measuring the amount of anti-Fc,RII antibody necessary for saturation under conditions of equilibrium binding. Using radiolabeled IV.3 anti-Fc,RII MoAb, we observed that monocytes express 7,300 to 38,000 Fc,RII binding sites per cell (37°C, μ = 0.15) at saturation, Kd = 0.15 ± 0.02 nmol/L (Fig 2). Nonlinear curve fitting of the untransformed data was most consistent with a single class of binding sites. We then employed in our inhibition studies a concentration of MoAb (0.3 μg/mL) that is threefold in excess of that necessary to saturate >95% of all monocytes Fc,RII sites.

Monocytes bound IgG(anti-D)-coated RBCs in a dose-response manner that depended upon the concentration of IgG per RBC (Table I). No significant alteration in the recognition of IgG(anti-D)-coated RBCs was observed following preincubation of monocytes with anti-Fc,RII MoAb, and this was observed with a range of MoAb concentrations (0.06 to 3.0 μg/mL). Similar results were observed at several experimental conditions: low (μ = 0.07) and physiologic (μ = 0.15) ionic strength and at both 23°C and 37°C (Tables 1 and 2). No recognition by monocytes of IgG(anti-D)-coated RBCs was observed at 4°C after incubation from one to 18 hours at either low or normal ionic strength. Therefore Fc,RII does not appear to play a role in the recognition of human anti-D–coated RBCs by monocytes.

Monocytes also bound rabbit IgG-sensitized sheep RBCs, and this interaction also depended upon the concentration of IgG per RBC. However, the results with monocyte binding of these erythrocytes sensitized with rabbit IgG antibody were
The binding of anti-D-coated RBCs by blood monocytes was performed at 37°C and ion strength $\mu = 0.15$ and 0.07. Percentage of blood monocytes binding 0, 1, 2, and 3 RBC/monocyte in the presence of anti-Fc.RII was 0.3 $\mu$g/mL. In addition, anti-Fc.RII antibody inhibited monocyte recognition of rabbit IgG-coated sheep RBCs at 23°C ($P < .001$) but only partially and only at low and normal ion strength ($\mu = 0.07$). No significant inhibition by anti-Fc.RII was noted at 37°C, both at low and physiologic ion strength, or at 23°C at physiologic ion strength. Therefore Fc.RII does recognize rabbit IgG-coated RBCs but does so most effectively at low ion strength and at lower temperatures.

Fc.RII appears to recognize aggregated IgG considerably more effectively than it does IgG monomer. In contrast, Fc.RI binds monomeric IgG with high-affinity (kd $\approx$ 2 nmol/L). Therefore we considered the possibility that monocyte Fc.RII might bind human IgG-coated RBCs more effectively in the presence of plasma where monomeric IgG would inhibit Fc.RI. Thus, we examined the binding of human IgG-coated RBCs by monocytes in the presence of increasing concentrations of monomeric IgG. Monocytes were preincubated with anti-Fc.RII MoAb to ascertain the role of Fc.RII. As indicated in Table 4, there was no difference in the IC50 of monomeric IgG when monocytes were preincubated with anti-Fc.RII. Furthermore, concentrations of monomeric IgG that completely inhibited the ability of monocytes to bind IgG-coated RBCs when Fc.RII was unavailable (ie, in the presence of saturating concentrations of anti-Fc.RII) also completely inhibited monocyte binding of IgG-coated RBCs when Fc.RII was available (ie, in the absence of anti-Fc.RII).

Effect of anti-Fc.RII MoAb on IgG ligand binding by monocytes. We also examined the role of Fc.RII in the binding of soluble human IgG ligand. In these studies we employed both trimers and monomers of human IgG, as Fc.RII on other cells preferentially recognizes human oligomeric (eg, IgG trimer) as opposed to monomeric IgG. Monocytes were preincubated with anti-Fc.RII MoAb (0.3 $\mu$g/mL), washed, and the number of Fc receptor-binding sites and affinity constant determined, using either IgG trimer or IgG monomer under conditions of equilibrium binding. As noted, this concentration of IV.3 anti-Fc.RII antibody is threefold greater than that necessary to saturate the MoAb (kd $= 0.15$ nmol/L) was 20-fold greater than that which we observe for IgG trimer and 40 to 100-fold greater than that of IgG monomer. At 37°C and normal ionic strength, anti-Fc.RII did not alter monocyte Fc receptor number or affinity, with either trimeric IgG (Fig 3, Table 5) or monomeric IgG (not shown) in five of five experiments.
of monomeric IgG to monocytes at 4°C, the number of monocyte binding sites for IgG was decreased by anti-FcRII (Fig 4 and Table 5).

On the other hand, under conditions of low ionic strength and at 4°C, the number of monocyte binding sites for IgG trimer was decreased by anti-FcRII (Fig 4 and Table 5). Inhibition by anti-FcRII at 4°C and μ = 0.07 varied among normal monocyte donors from 34% to 63% in four consecutive experiments. We also examined the equilibrium binding of monomeric IgG to monocytes at 4°C, μ = 0.07 following preincubation of monocytes with 0.3 μg/mL anti-FcRII MoAb. Monocytes preincubated with the MoAb expressed 29,300 binding sites for monomeric IgG per cell, kd = 1.3 nmol/L. Control monocytes expressed 32,000 binding sites per cell, kd = 1.4 nmol/L. Thus anti-FcRII inhibited IgG ligand binding at 4°C, μ = 0.07 for trimeric but not for monomeric IgG.

Identical results were observed using a range of MoAb concentrations (0.06 to 3.0 μg/mL).

Table 4. Monocyte Binding of IgG-Coated RBCs in the Presence of Human IgG

<table>
<thead>
<tr>
<th>Monomeric IgG (nmol/L)</th>
<th>% Monocytes Binding</th>
<th>Anti-FcRII</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
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<td>18</td>
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<td></td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

The binding of anti-D–coated RBCs (3,800 IgG/RBC) by monocytes was performed at 37°C, μ = 0.15 in the presence of increasing concentrations of human monomeric IgG. Monocytes were preincubated with either buffer or anti-FcRII (0.3 μg/mL). The mean of two experiments is shown.

Table 5. Monocyte Binding of IgG Trimer: Effect of Anti-FcRII MoAb

<table>
<thead>
<tr>
<th>FcRII Antibody</th>
<th>Monocytes (μ = 0.15, 37°C)</th>
<th>Affinity Constant (kd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer</td>
<td>36.100</td>
<td>4.1 nmol/L</td>
</tr>
<tr>
<td>FcRII Antibody*</td>
<td>36.300</td>
<td>5.2 nmol/L</td>
</tr>
<tr>
<td>Monocytes (μ = 0.07, 4°C)</td>
<td>8.062</td>
<td>154 nmol/L</td>
</tr>
<tr>
<td>FcRII Antibody</td>
<td>628</td>
<td>597 nmol/L</td>
</tr>
<tr>
<td>Monocytes (μ = 0.07, 4°C)</td>
<td>28.400</td>
<td>4.5 nmol/L</td>
</tr>
<tr>
<td>FcRII Antibody</td>
<td>18.800</td>
<td>4.8 nmol/L</td>
</tr>
</tbody>
</table>

*Monocytes and platelets were preincubated with IV.3 anti-FcRII (0.3 μg/mL) antibody. This experiment is representative of five such experiments performed.

To validate the effect of the MoAb on FcRII, we also studied human platelets. Human platelets express FcRII as

![Fig 3: Monocyte binding of human trimeric IgG: Effect of FcRII MoAb.](image)

Equilibrium binding of increasing concentrations of IgG trimer to blood monocytes was performed at 37°C and ionic strength μ = 0.15. Monocytes were preincubated for 30 minutes with either 0.3 μg/mL anti-FcRII antibody (right panel) or an isotype control (left panel). Scatchard plots of the data (lower panels) demonstrate a similar number of FcRI receptor IgG binding sites (B max) and affinity in the presence or absence of the MoAb (also see Table 5).
their only Fc receptor and bind trimeric IgG to FcRII, especially at low ionic strength. In experiments performed in parallel with the monocyte studies, we observed that anti-FcRII inhibited the binding of IgG trimer to human platelets as expected (Table 5).

**DISCUSSION**

Whether the two Fc receptor proteins thus far described on human monocytes have similar or distinct functions is unclear. In our studies we used a high-affinity MoAb that competes for the FcRII ligand binding site. We first determined the amount of this antibody necessary for saturation of normal donor blood monocytes was performed at 4°C and ionic strength μ = 0.07. Monocytes were preincubated for 30 minutes with 0.3 μg/mL anti-FcRII MoAb (right panel) or an isotype control (left panel). Scatchard plots of the data (lower panels) demonstrate that the anti-FcRII MoAb under these conditions substantially inhibited the number of available FcRII binding sites (B max; also see Table 5).

Our experiments suggest that monocyte FcRII does participate in the binding of human trimeric IgG at conditions of low ionic strength and cold temperature. The recognition of rabbit IgG-coated sheep erythrocytes by monocyte FcRII also was increased at these conditions. This propensity for FcRII to interact with IgG ligand at low ionic strength and at 4°C has also been reported with FcRII on human platelets and by others with FcRII on cell lines. We observed that IgG (anti-D)-sensitized RBCs do not bind to monocytes at 4°C. This is in keeping with our understanding of the binding characteristics of FcRI. Binding of soluble human IgG to FcRII on monocytes does not occur as effectively at 4°C as it does at 37°C. At least 18 hours at 4°C is required for the monocyte binding of monomeric IgG by FcRII. On the other hand, we observed that monocyte binding of rabbit IgG-coated cells does occur at 4°C but under conditions that suggest the participation of FcRII. Platelets only express FcRII; thus, their binding of aggregated IgG defines the relationship of IgG to FcRII. While no aggregated IgG binding was observed to these cells at 37°C, our experiments in this time frame under similar conditions (Table 3).

Monocyte FcRII interacts efficiently with murine IgG, particularly at low ionic strength. The capacity of rabbit IgG-sensitized sheep erythrocytes to bind to FcRII on monocytes may also be partly due to this receptor’s ability to interact with certain heterologous species of IgG. Furthermore, an additional factor of potential importance for recognition by monocyte FcRII is the surface density of IgG. The surface area of the sheep erythrocyte is approximately 25% that of human RBCs. Therefore in our experiments, sheep RBCs coated with 1,900 IgG/RBC have a greater density per square micron than our human IgG-coated RBCs (950 to 3,800 IgG/RBC). This increased density of IgG on the cell surface may facilitate interaction with FcRII, particularly since FcRII preferentially interacts with aggregates of IgG of increasing size. Nevertheless, the lack of participation
of FcRII in the binding of rabbit IgG-sensitized cells at 37°C (Table 3) suggests that at 37°C monocyte FcRII is not especially effective.

This absence of FcRII function is not due to decreased availability of FcRII protein at 37°C. Using 125I-IgG anti-FcRII antibody we observed that monocytes express a similar number of FcRII as FcRI sites per cell. Thus FcRII protein is available on the monocyte surface at 37°C. The precise mechanism for the relative unavailability of the FcRII ligand binding site at 37°C and physiologic ionic strength is uncertain. This may reflect an alteration in either FcRII or FcRI. FcRII may undergo an ionic strength or cold-dependent conformational change in the binding site recognized by the Fc ligand; similarly, a change may occur in the cell membrane at low ionic strength and in the cold that increases the availability of the receptor binding site. In support of the latter is our observation that FcRII is increased on the monocyte surface under these conditions. This likely contributes to the increased FcRII function observed. There is precedence for other membrane antigens (eg, the erythrocyte I antigen), increasing their availability at 4°C. The latter change is biologically significant as it causes RBC destruction in cold-hemagglutinin disease. Receptor-ligand interactions also have been observed to occur more efficiently at low ionic strength in other systems, such as that which involves C1q binding to its receptor.

Alternatively, FcRI may become more available for IgG ligand binding at 37°C and physiologic ionic strength. FcRII may undergo a temperature or ionic strength change that increases the availability of its active site at 37°C, μ = 0.15. This might be caused by alterations in receptor mobility, such as that caused by a change in membrane fluidity under these conditions. Changes in experimental conditions might also enhance receptor clustering and thereby influence ligand binding, especially that involving particulate antigens. Our experiments were performed in vitro, and it is worth noting that in vivo plasma factors or cellular derived mediators may also influence the expression or function of these receptors.

There are several known fundamental differences between FcRI and FcRII. FcRII, in contrast to FcRI, only binds oligomeric IgG. FcRI binds monomeric IgG and also oligomeric IgG, presumably through IgG cross-linking. Both FcRI and FcRII ligand binding can be inhibited by monomeric IgG, although effective inhibition of FcRI requires lower concentrations of monomeric IgG (unpublished observations). It has recently been reported that the binding site for human FcRI resides in the C2 domain of IgG. It is uncertain whether this domain or other IgG domains are involved in FcRII ligand binding. Although FcRI and FcRII bind different subclasses of murine IgG, as yet no differential human IgG subclass specificity has distinguished between these receptors.

Our data are consistent with a role for FcRI in the clearance of IgG containing RBCs in autoimmune disease. Autoimmune hemolytic anemia commonly involves the clearance of IgG(anti-Rh*) antibody-coated cells. These experiments suggest that FcRI, as opposed to FcRII, is involved in the clearance of IgG-coated RBCs at physiologic temperatures. Furthermore, we have observed that in vivo modulation of monocyte FcRI correlates with the clinical response due to alteration in the clearance of IgG-coated cells. However, it is important to note that macrophage FcRII (CD16) probably plays an important role in the clearance of IgG-coated cells.

With the recent characterization and isolation of the different human Fc receptor proteins and the early work on the isolation of their genes, the functional role of these Fc receptors has become an increasingly accessible area of investigation. Our studies indicate that monocyte FcRI plays a significant role in the binding and recognition of IgG-containing immune complexes. The function of FcRII on monocytes under physiologic conditions is as yet uncertain. Since FcRII is the only Fc receptor present on human platelets and B lymphocytes, perhaps its major functional role resides on those cells. For example, FcRII may be involved in the binding of immune complexes to platelets in certain patients with immune thrombocytopenic purpura or may participate in Fc receptor-dependent signal transduction on B lymphocytes.

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REFERENCES

27. Carter SD, Leslie RGA, Reeves WG: Human monocyte binding of homologous monomer and complexed IgG. Immunology 46:793, 1982
Monocyte Fc gamma receptor recognition of cell-bound and aggregated IgG

F Gomez, P Chien, M King, P McDermott, AI Levinson, MD Rossman and AD Schreiber