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Binding sites for C-reactive protein on human monocytes are distinct from IgG Fc receptors

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SUMMARY

Previous investigations have provided evidence to suggest that C-reactive protein (CRP), an acute-phase reactant, binds to human monocytes at a membrane site that is either identical to or physically associated with IgG Fc receptors. To characterize further the relationship between monocyte CRP binding sites and IgG Fc receptors, monocytes were allowed to attach to surfaces coated with IgG or CRP and binding-site redistribution was assessed. Binding was measured by using protein-coated sheep erythrocytes (E). When attached to control (gelatin or albumin) surfaces, greater than 60% and 43% of monocytes formed rosettes with E-IgG and E-CRP, respectively. Following adherence to surface immobilized CRP, the proportion of cells binding E-IgG was unchanged; however, fewer than 20% of monocytes bound E-CRP. When attached to IgG-coated surfaces, fewer than 20% of monocytes formed rosettes with either E-IgG or E-CRP. In order to determine whether the unidirectional modulation of CRP and IgG binding sites was the result of CRP binding directly to a subclass of IgG Fc receptors, fluid-phase IgG-blocking studies were performed. When monocyte monolayers were preincubated with either monomeric or heat-aggregated IgG, a dose-dependent reduction in E-IgG binding was observed. In contrast, all concentrations of fluid-phase IgG failed to inhibit monocyte binding of E-CRP. These data indicate that CRP binds to human monocytes at a site physically associated with but distinct from IgG Fc receptors.

INTRODUCTION

C-reactive protein (CRP) is found in trace amounts in normal human serum (Gewurz, 1982). Following the onset of infection, inflammation or tissue injury, levels of this acute-phase protein increase as much as 1000-fold (Gewurz, 1982). CRP is a 120,000 MW cyclic pentamer comprised five apparently identical subunits (Gotschlich & Edelman, 1965). While CRP is structurally distinct from immunoglobulin, these proteins share a number of functional similarities including the capacity to bind C1q (Claus *et al.*, 1977) and activate the complement cascade (Kaplan & Volanakis, 1974) and initiate inflammatory reactions (Abernethy & Francis, 1937).

CRP, like IgG, additionally has the capacity to interact with human mononuclear phagocytes (Zeller *et al.*, 1986a, b). The presence of CRP on a particle surface has been reported to facilitate particle ingestion by human monocytes, a process blocked by heat-aggregated IgG (Mortensen *et al.*, 1976). Recently our laboratory observed that aggregated CRP markedly enhances the monocyte respiratory burst response to aggregated IgG (Zeller *et al.*, 1986b). This effect is selective for IgG Fc-receptor-mediated stimulation, as no enhancement of cell reactivity occurred when other activators were employed (Zeller *et al.*, 1986b). Taken together, these data support a relationship between CRP binding sites and IgG Fc receptors on human monocytes.

Attachment of mononuclear phagocytes to surface-immobilized ligands has been used to study movements of cell membrane proteins and the potential associations between receptors (Michl *et al.*, 1979). The present study examines the relationship between CRP binding sites and IgG Fc receptors on human monocytes by establishing whether these molecules can be reciprocally removed from the apical cell surface following monocyte attachment to IgG- or CRP-coated surfaces. CRP binding sites were also characterized and compared to IgG Fc receptors following monocyte exposure to fluid-phase IgG.

Abbreviations: AHS, autologous human serum; BSA, bovine serum albumin; CRP, C-reactive protein; E, erythrocytes; GEL, gelatin; HSA, human serum albumin; M199, Medium 199; M199-BSA, M199 containing 1% BSA; PLL, poly-L-lysine; SAP, serum amyloid P component.

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MATERIALS AND METHODS

Materials

Human CRP was purified from inflammatory fluids and characterized as previously described (Potempa *et al.*, 1983). Serum amyloid P component (SAP) was isolated from human

plasma (Potempa, Kubak & Gewurz, 1985). Human IgG (Gamastan) was purchased from Miles Laboratories (Elkart, IN). Globulin-free human serum albumin (HSA), fraction V bovine serum albumin (BSA) and poly-L-lysine (PLL) (MW >70,000) were obtained from Sigma Chemical Company (St Louis, MO). Medium 199 (M199) was purchased from Gibco Laboratories (Grant Island, NY). All other chemicals of reagent grade quality were purchased from local vendors.

Human mononuclear leucocytes

Mononuclear leucocytes were purified from peripheral venous blood samples obtained from healthy human volunteers using a previously described protocol (Zeller *et al.*, 1986b). The proportion of monocytes was determined by latex ingestion. Cell viability, established by trypan blue dye exclusion, was routinely greater than 95%.

Protein-coated sheep erythrocytes

Sheep erythrocytes were exposed to 25 μg/ml of tannic acid and coated with test ligands [i.e. HSA, gelatin (GEL), CRP, SAP or IgG] utilizing a previously established procedure (Bevilacqua *et al.*, 1981). Protein-coated erythrocytes, prepared in this way, were stored for up to 1 week at 4°. Before use, erythrocytes were washed four times with phosphate-buffered saline and suspended in M199 containing 1% BSA (M199-BSA).

Protein-coated coverslips

Round glass coverslips were acid washed, rinsed in distilled water, air-dried, placed into 16-mm diameter tissue culture wells and treated sequentially with 0·1 mg/ml PLL, 2·5% glutaraldehyde and 1 mg/ml of test ligands using a previously described protocol (Michl *et al.*, 1979). Unreacted aldehyde groups were quenched by an overnight incubation with 0·2 M glycine. Before use, culture wells were washed twice with M199.

Attachment of monocytes to protein-coated surfaces

Routinely, monocytes ($0{\cdot}25 \times 10^6$ cells), suspended in M199 containing 10% autologous human serum (AHS), were added to culture wells containing protein-coated glass coverslips and allowed to adhere for 60 min at 37° in a 5% CO_2 in air atmosphere. Non-adherent cells were removed by washing twice with M199-BSA.

In certain experiments, monocyte attachment to protein-coated glass coverslips was performed in M199 containing 10% heat-inactivated AHS. Results were identical to those obtained with fresh AHS (data not shown).

Particle binding to adherent monocytes

Protein-coated sheep erythrocytes were incubated with monocyte monolayers (>95% monocytes) for 60 min at 37° in a 5% CO_2 in air atmosphere. Following three washes with M199-BSA, coverslips were stained with Wright–Giemsa, removed from culture wells, mounted onto glass slides and examined by light microscopy. Data were expressed as the proportion of monocytes binding at least three erythrocytes (percentage positive monocytes). In addition, the total numbers of sheep erythrocytes bound to 100 monocytes (attachment index) was determined. In certain experiments, monocytes were incubated with either monomeric or heat-aggregated IgG (Zeller *et al.*, 1986b) for 30 min prior to the addition of sheep erythrocytes.

Table 1. Modification of monocyte binding activity following attachment to ligand-coated surfaces

	Test particle†		
Surface*	E-HSA	E-CRP	E-IgG
HSA	17±6	47±15	90±2
CRP	12±5	18±6	89±3
IgG	1±0·3	6±2	16±6

* The indicated proteins (1 mg/ml) were coupled to poly-L-lysine-coated glass coverslips with glutaraldehyde. Monocytes were allowed to adhere to the protein-coated surfaces for 60 min.

† Monocyte monolayers were incubated with sheep E bearing the indicated test proteins. Values represent the proportions of monocytes (mean±SEM) that bound at least three sheep E ($n=4$).

Statistical analysis

Data were expressed as mean±SEM. Statistical analyses were performed using the Student's *t*-test. *P* values of ≤0·05 were considered to be significant.

RESULTS

Detection of IgG and CRP binding sites on human monocytes

Human monocytes were incubated with differing numbers of sheep erythrocytes ($0{\cdot}25$–$0{\cdot}5 \times 10^7$) coated with varying concentrations of test proteins (0·5–2 mg/ml) to establish optimal binding conditions. Following adherence to glass coverslips and exposure to $0{\cdot}5 \times 10^7$ erythrocytes coated with 1 mg/ml concentrations of protein, 73±5% and 43±9% of monocytes formed rosettes with E-IgG and E-CRP, respectively. Under these conditions, fewer than 20% of monocytes bound erythrocytes treated with tannic acid alone or tannic acid followed by the control proteins, HSA or SAP.

Binding of CRP and IgG to human monocytes following attachment to ligand-coated surfaces

When monocytes were allowed to spread onto HSA-coated surfaces, greater than 40% of cells expressed binding sites for CRP (Table 1). To determine whether CRP binding occurred at a site that is modulated following engagement with ligand, monocytes were adhered to CRP-coated surfaces. Following attachment to surface immobilized CRP, the proportion of monocytes binding CRP-coated erythrocytes was reduced by 62%. A comparable (82%) reduction in monocyte binding of IgG-coated erythrocytes occurred following monocyte attachment to surface-immobilized IgG.

To determine whether CRP and IgG binding sites could be reciprocally modulated, IgG binding was measured following monocyte attachment to the surface immobilized CRP. Although the CRP-coated surface reduced CRP binding to monocytes, no significant reduction in IgG binding occurred. In

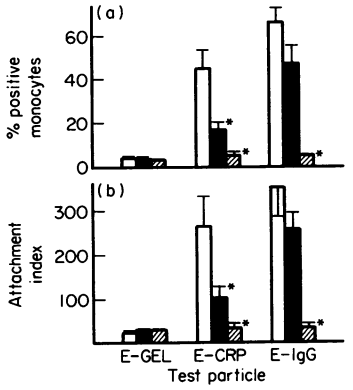

Figure 1. Modification of monocyte binding following attachment to CRP- and IgG-coated surfaces. Monocytes were allowed to adhere to glass coverslips that were coated with gelatin (□), CRP (■), or IgG (▨), washed and further incubated with the indicated test particles. Binding is expressed in (a) as the proportion of monocytes with at least three attached sheep E (% positive monocytes). Data in (b) indicate the total numbers of sheep E bound to 100 monocytes (attachment index). Values represent the mean ± SEM of four experiments. * Significantly different from monocyte particle binding when attached to control (GEL) surface, $P < 0.05$.

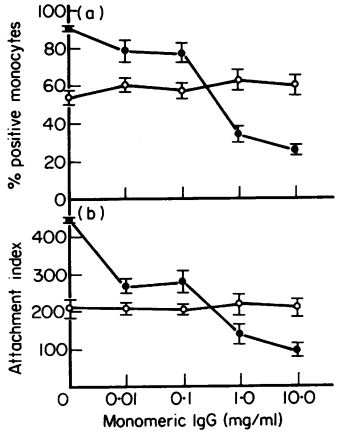

Figure 2. Selective modification of IgG binding to monocytes by fluid-phase monomeric IgG. Monocytes, attached to gelatin-coated surfaces, were preincubated with the indicated concentrations of monomeric IgG for 30 min at 37°. Monolayers were overlaid with sheep erythrocytes (E) coated with either IgG (●) or CRP (○) and incubation was continued for 60 min. Binding is expressed in (a) as the proportion of monocytes with at least three attached sheep E (% positive monocytes). Data in (b) indicate the total numbers of sheep E bound to 100 monocytes (attachment index). Values represent the mean ± SEM of three experiments. Less than 2% of monocytes bound gelatin-coated E under all conditions (data not shown).

contrast, monocyte attachment to the IgG-coated surface significantly reduced the proportion of CRP-binding monocytes.

In order to establish whether the choice of control protein played a role in particle binding or receptor modulation, experiments in Table 1 were repeated using GEL-coated erythrocytes and coverslips. Figure 1 illustrates that fewer than 2% of monocytes bound GEL-coated erythrocytes under all coverslip treatment conditions, with a mean attachment index of 18. As reported in Table 1, the CRP-coated coverslips significantly reduced monocyte binding of CRP-coated erythrocytes; however, monocyte attachment to CRP-coated surfaces did not reduce IgG binding. Surface immobilized IgG significantly diminished the proportion of monocytes binding either IgG or CRP. Comparable results were obtained when binding data were expressed as an attachment index. These data indicate that IgG immobilized on a culture surface can modify the binding of CRP to human monocytes; however, CRP does not induce loss of monocyte IgG Fc receptors.

Effect of fluid-phase IgG on monocyte binding of CRP and IgG

To evaluate whether blocking of IgG Fc receptors on the apical cell surface would influence CRP binding to monocytes, cells were preincubated with fluid-phase monomeric IgG. Figure 2 illustrates that low doses (0·01 and 0·1 mg/ml) of monomeric IgG, previously reported to selectively block binding to the high affinity IgG Fc receptors (Looney, Abraham & Anderson, 1986a), produced only a 15% reduction in the proportion of monocytes binding E-IgG (Fig. 2a). When higher concentrations of monomeric IgG were employed to block both high and low affinity receptors, a 72% reduction in proportion of IgG binding monocytes was observed (a). When data were evaluated as an attachment index (b), a similar biphasic reduction in IgG binding occurred, with a maximal reduction in attachment index (79%) occurring at 10 mg/ml of monomeric IgG. In contrast, monomeric IgG failed to reduce monocyte rosetting of CRP-coated erythrocytes at all concentrations evaluated. Similar results were obtained by preincubating monocytes with heat-aggregated IgG, which binds to both high and low affinity IgG Fc receptors. For example, by using 0·5 mg/ml of heat-aggregated IgG, the proportion of monocytes binding E-IgG decreased from 75 ± 5% to 33 ± 8%. In contrast, E-CRP bound to 48 ± 3% and 48 ± 5% of monocytes in the absence and presence of heat-aggregated IgG, respectively. These results indicate that CRP and IgG do not interact with human monocytes at identical membrane determinants.

DISCUSSION

Previous investigations employing CRP complexes or aggregates have identified CRP binding sites on human monocytes (James, Hansen & Gewurz, 1981b; Zeller *et al.*, 1986a, b), neutrophils (Zeller *et al.*, 1986c; Shephard *et al.*, 1986; Muller & Fehr, 1986) and lymphocytes (James *et al.*, 1986b; James, Hansen & Gewurz, 1981a). CRP interaction with leucocytes has been reported to enhance cell-mediated cytotoxicity by lymphocytes (Vetter *et al.*, 1983), facilitate particle uptake by phagocytes (Hokama, Coleman & Riley, 1962; Kindmark, 1971; Mortensen *et al.*, 1976; Mortensen & Duskiewicz, 1977; Kilpatrick & Volanakis, 1985) and enhance monocyte and neutrophil respiratory burst responses to IgG Fc receptor engagement (Zeller *et al.*, 1986b, c). The present study, utilizing CRP-coated sheep erythrocytes in a rosetting assay, confirms that human monocytes express binding sites for CRP. In addition, these data represent the first report that monocyte binding sites for CRP can be modulated within the plasma membrane following engagement with ligand.

Those studies examining CRP interactions with human leucocytes have pointed to a relationship between CRP binding sites and IgG Fc receptors. In the case of the monocyte, it has

been demonstrated that heat-aggregated IgG reduces uptake of CRP-C-polysaccharide-coated particles (Mortensen *et al.*, 1976). Our observation that aggregated CRP enhances IgG-induced chemiluminescence but not respiratory burst activity elicited by phorbol myristate acetate or serum-opsonized zymosan also speaks of a relationship between these binding specificities (Zeller *et al.*, 1986b). Neutrophil interaction with CRP can be likewise reduced with fluid-phase IgG complexes (Muller & Fehr, 1986; Buchta, Pontet & Fridkin, 1987) or following cell attachment to IgG-coated surfaces (Kilpatrick & Volanakis, 1985).

The present study further examined the relationship between CRP binding sites and IgG Fc receptors by allowing monocytes to spread onto ligand-coated surfaces. This approach, allowing receptors to redistribute within the plasma membrane following engagement with ligand, has been previously employed to discriminate C3 and IgG Fc receptors on phagocytic cells (Michl *et al.*, 1979). Our data confirmed earlier reports (Wright & Silverstein, 1982) that monocyte attachment to IgG-coated surfaces reduces IgG-coated erythrocyte binding to the apical membrane. In contrast, when monocytes were attached to CRP-coated surfaces no reduction in IgG binding occurred, suggesting that these binding sites are unrelated. The distinctiveness remained unclear, however, due to the further observation that IgG-coated surfaces reduced binding of CRP-coated erythrocytes to human monocytes. This non-reciprocal redistribution of binding sites following monocyte attachment to CRP- and IgG-coated surfaces was comparable to that reported for phorbol ester-treated neutrophils (Kilpatrick & Volanakis, 1985).

Our observations that CRP binding to human monocytes is reduced following attachment to IgG-coated surfaces, whereas IgG binding to cells is not diminished following attachment to CRP-coated surfaces, could be explained by one of two mechanisms. On the one hand, it is plausible that CRP binding sites are identical to a subclass of IgG Fc receptors. If CRP binding occurs selectively at either the 72,000 MW high affinity (FcγRI) (Anderson, 1982) or 40,000 MW low affinity (FcγRII) (Looney *et al.*, 1986a) IgG Fc receptor, surface-immobilized CRP would induce the redistribution of a single subclass of Fc receptor; the second receptor subclass would then be maintained on the apical cell surface for binding of IgG-coated erythrocytes. Alternatively it is possible that CRP does not bind directly to a subclass of IgG Fc receptors, but rather to a distinct membrane site that is physically associated with and co-caps with a subclass of IgG Fc receptors. Co-modulation of distinct receptors following macrophage attachment to surface-immobilized ligands has been reported previously (Sung, Nelson & Silverstein, 1985; Sung, 1985).

To discriminate between these possibilities, monocyte monolayers were exposed to fluid-phase IgG. When heat-aggregated IgG was employed, a dose-dependent reduction in IgG–erythrocyte binding was observed. In contrast, fluid-phase heat-aggregated IgG failed to block CRP binding to monocyte monolayers. High and low doses of monomeric IgG were also utilized in fluid-phase blocking experiments, in a attempt to discriminate binding to high and low affinity IgG Fc receptors. Those experiments revealed that concentrations of monomeric IgG greater than 0·1 mg/ml were required to optimally block binding of IgG-coated erythrocytes to human monocytes. At all doses of monomeric IgG tested, no reduction of CRP binding was observed. These data indicated that although CRP interacts with human monocytes at membrane sites that co-cap with IgG Fc receptors, CRP and IgG do not bind at identical sites.

These fluid-phase blocking studies would appear to contradict the results of Mortensen and co-workers, demonstrating that aggregated IgG blocked monocyte uptake of CRP-C-polysaccharide complement-coated erythrocytes (Mortensen *et al.*, 1976). It is plausible that while aggregated IgG fails to block CRP binding to monocytes, unoccupied IgG Fc receptors may be required for CRP-dependent particle uptake. The further observation that aggregated IgG was more effective at blocking uptake of IgG-opsonized particles than uptake of CRP-coated particles suggests that these two binding sites may not be identical (Mortensen *et al.*, 1976).

Our results indicating that CRP binds to human monocytes at sites physically associated with but distinct from IgG Fc receptors are similar to those reported for human neutrophils. In those studies (Kilpatrick & Volanakis, 1985), whereas surface-immobilized IgG-containing immune complexes reduced CRP association with the apical surface of neutrophil monolayers, CRP-erythrocyte uptake was not reduced by fluid-phase exposure to monoclonal antibody 3G8, which recognizes the low affinity 50,000–70,000 MW (FcγRIII) IgG Fc receptor (Fleit, Wright & Unkeless, 1982), or monomeric IgG, which selectively blocks the inducible 72,000 MW high affinity (FcγRI) IgG Fc receptor on neutrophils (Perussia *et al.*, 1983). Neither fluid-phase immune complexes nor IgG aggregates were used in an attempt to block binding to all IgG Fc receptors in those studies. Therefore, in the case of the neutrophil, the possibility still remains that CRP is binding to the 40,000 MW low affinity (FcγRII) IgG Fc receptor recognized by the IV3 monoclonal antibody (Looney *et al.*, 1986b). FcγRII is the only known IgG Fc receptor common to human monocytes, neutrophils and platelets (Looney *et al.*, 1986a, b; Rosenfeld *et al.*, 1985). Since these three cell types undergo metabolic and functional alterations in response to aggregated forms of CRP (Potempa *et al.*, 1988), it is tempting to speculate that CRP is interacting with a membrane determinant associated with the 40,000 MW low affinity IgG Fc receptor.

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