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*J Immunol* 2002; 169:3831-3836; doi: 10.4049/jimmunol.169.7.3831

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The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.
Mac-1 (CD11b/CD18) as Accessory Molecule for FcμRI (CD89)
Binding of IgA

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IgA, the principal ligand for FcμRI, exists in serum as monomeric IgA and at mucosal sites as secretory IgA (SIgA). SIgA consists of dimeric IgA linked by joining chain and secretory component. Human polymorphonuclear leukocytes (PMN) and mouse PMN transgenic for human FcμRI exhibited spreading and elicited respiratory burst activity upon interaction with either serum or SIgA. However, PMN devoid of the β2 integrin Mac-1 (Mac-1+/−) were unable to bind SIgA, despite expression of FcμRI. Consistent with this, serum IgA stimulated Mac-1+/− PMN oxygen radical production, in contrast to SIgA. Binding studies showed the secretory component, by itself, to interact with Mac-1-expressing PMN, but not with Mac-1+/− PMN. These data demonstrate an essential role for Mac-1 in establishing SIgA-FcμRI interactions. The Journal of Immunology, 2002, 169: 3831–3836.

Materials and Methods

Antibodies
dlgA was purified from human serum by HPLC on HR200 Superdex size-exclusion columns (Pharmacia, San Diego, CA). Anti-CD11b mAb M1/70 (rat IgG2b) and 44a (mouse IgG1) were purified from supernatants of American Type Culture Collection hybridomas (Manassas, VA). Anti-CD11b mAb Bear-1 (mIgG1) was obtained from Caltag Laboratories (Burlingame, CA). mAb 14.1 (human IgG1, anti-FcμRI) was produced by immunizing mice transgenic (Tg) for human Ig (23) with recombinant soluble FcμRI (24) in Ribi adjuvant (Sigma-Aldrich, St. Louis, MO). Splenic lymphocyte suspensions were fused to P3 × 63-Ag8.653 mouse myeloma cells (American Type Culture Collection), and hybridomas were selected by ELISA and FACS on FcμRI transfectants (7). mAb 14.1 recognizes FcμRI within extracellular domain 2, outside the IgA-binding site. mAb My43 (IgM anti-FcμRI) blocks the FcμRI ligand-binding domain (25).

Mice

CD11b knockout mice (Mac-1+/−) in the C57BL/6 × 129SV background were kindly provided by Dr. T. N. Mayadas (Harvard Medical School, Boston, MA). mAb 44a was obtained from Caltag Laboratories (Burlingame, CA) and mAb M1/70 from Caltag Laboratories (Burlingame, CA). mAb 14.1 was kindly provided by Dr. T. N. Mayadas (Harvard Medical School, Boston, MA). mAb 14.1 was kindly provided by Dr. T. N. Mayadas (Harvard Medical School, Boston, MA).
Boston, MA) (26–28). To study Mac-1 involvement in human FcαRI function, mice were crossed with human FcαRI (CD89) Tg FVB/N mice (27), yielding four different genotypes: nontransgenic (Ntg) Mac-1−/−, Tg Mac-1−/−, Tg Mac-1+/−, and Tg Mac-1+/+. Mac-1-deficiency does not affect PMN FcR expression levels (27, 28).

PMN isolation

Human PMN were isolated from heparinized venous blood of healthy volunteers by Ficoll-Histopaque (Sigma-Aldrich) density gradient centrifugation. PMN purity determined by cytospin preparations exceeded 95%, and cell viability was >98%.

Before murine PMN isolation, mice were injected s.c. with 15 μg polyethylene glycol (kindly provided by Dr. J. Andresen; Agen, Thousand Oaks, CA) to increase PMN numbers (29, 30). Blood was collected from the retro-orbital plexus 3 days later. Erythrocytes were removed by hypotonic lysis, followed by washing remaining leukocytes with RPMI 1640 medium (Life Technologies, Grand Island, NY) with 10% FCS. FACS analyses, performed on a FACScan (BD Biosciences, San Jose, CA), revealed leukocytes to consist of ~60% PMN, ~35% lymphocytes, ~5% monocytes, and ~1% eosinophils. Cell viability determined by trypan blue exclusion was always >95%.

PMN binding and spreading on IgA

To exclude interference with complement, all Ab preparations were heat-inactivated before use (30 min, 56°C). Glass slides (Menzel, Braunschweig, Germany) were coated with 0.5% (w/v) BSA (Boehringer Mannheim, Mannheim, Germany), 100 μg/ml human serum IgA (ICN Pharmaceuticals, Costa Mesa, CA), dIgA (kindly provided by Dr. C. van Kooten, Leiden University Medical Center, Leiden, The Netherlands), SlgA (Sigma-Aldrich), or IgG (CLB, Amsterdam, The Netherlands) for 3 h at 37°C, and rinsed with PBS. Isolated human or mouse PMN (2 × 10^5 cells) were incubated in RPMI 1640 medium (with 10% FCS) on coated slides for 10 or 30 min at 37°C. Cells were fixed in 3.7% paraformaldehyde, and stained for phallolidin-FITC (1:200, Sigma-Aldrich), or stained for FcαRI and Mac-1 (see Colocalization studies) for 30 min at 20°C. Samples were mounted in Mowiol (with 2.5% 1,4-diazobicyclo-[2.2.2]-octane), and PMN binding and spreading was analyzed by confocal laser scanning microscopy using a Leitz DMRB fluorescence microscope (Leica, Voorburg, The Netherlands) interfaced with a Leica TCS4D confocal laser microscope (Heidelberg, Germany). Cell morphology was imaged just above (0.2 μm) the coated surfaces. PMN diameters were measured orthogonally, and then averaged. At least 30 PMN from three different experiments were analyzed. In Mac-1 blocking experiments, PMN were preincubated with 10 μg/ml anti-CD11b mAb for 30 min at 4°C before SlgA binding. In additional experiments, PMN were preincubated with 0.1 M N-acetyl-d-glucosamine (NADD, Sigma-Aldrich) for 10 min at 20°C, and plated on SlgA-coated slides in the presence of NADD. Cytochalasin D (Sigma-Aldrich) was used at 10 μg/ml to study the role of actin microfilament polymerization in FcαRI-IgA binding.

Respiratory burst measurements

The luminol-ECF method was used for analysis of real-time respiratory burst activity. Polystyrene tubes were coated with PBS, 100 μg/ml of serum IgA, or SlgA for 3 h at 37°C, and blocked with HEPES buffer (containing 20 mM HEPES, pH 7.4, 132 mM NaCl, 6 mM KCl, 1 mM MgSO4, 1.2 mM NaH2PO4, 1 mM CaCl2, 5 mM glucose, and 0.5% (w/v) BSA) for 1 h at 37°C. Isolated mouse PMN (4 × 10^5 cells) in HEPES buffer + F(ab׳)2 of TRITC-labeled donkey anti-rat IgG (Jackson ImmunoResearch Laboratories) were added to each well in a 96-well microtiter plate (Bertihold, Wildbad, Germany). Luminol (150 μM) was injected in all tubes and light emission was recorded continuously for 30 min at 37°C. As a positive control, PMN were stimulated with 100 ng/ml PMA (Sigma-Aldrich), and PMN incubated with luminol only served as negative control. In blocking experiments, PMN were incubated with FcαRI mAb My43 supernatant during the assay (25).

SC binding to cells

Purified recombinant human SC (kindly provided by Dr. B. Corry, State University Hospital, Lausanne, Switzerland) was incubated at 50 μg/ml with isolated human or mouse PMN (2 × 10^5 cells) for 60 min at 4°C. PMN were washed with FACS buffer (0.5% (w/v) BSA, 0.05% azide in PBS), incubated with mouse IgG1 anti-human SC (Sigma-Aldrich) (1:50) for 45 min at 4°C, washed, and incubated with FITC-labeled goat anti-mouse IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) (1:100) for 30 min at 4°C. Controls included PMN incubated with both mouse anti-human SC, and FITC-labeled goat anti-mouse IgG F(ab′)2. FITC fluorescence of PMN was determined by flow cytometry.

Colocalization studies

Human or mouse PMN were incubated on BSA or IgA-coated glass slides for 15 min at 37°C, washed with PBS, and incubated with 20 μg/ml of mAb 14.1 and mAb M1/70 in PBS containing 0.2% (w/v) BSA and 5% rabbit serum (Jackson ImmunoResearch Laboratories) for 30 min at 4°C. PMN were then fixed in 3.7% paraformaldehyde (30 min, 20°C), quenched with 0.1% NaN3, NH4Cl in PBS (5 min, 20°C), washed, and incubated with F(ab′)2 of FITC-labeled rabbit anti-human IgG (DAKO, Glostrup, Denmark) (1:50) and F(ab′)2 of TRITC-labeled donkey anti-rat IgG (Jackson ImmunoResearch Laboratories) (1:125) in PBS with 0.2% BSA for 45 min at 20°C. Slides were washed, mounted, and analyzed by confocal microscopy (see above). As a control, colocalization between FcαRI and the β2 integrin LFA-1 (CD1a/CD18) was analyzed using mAb 17/4 (rat IgG2a anti-mouse CD11a), which was a kind gift from Dr. G. Kral (Vrije Universiteit, Amsterdam, The Netherlands).

Statistical analyses

Data are expressed as means ± SD. Statistical significance was determined by two-tailed unpaired Student’s t tests. Values of p < 0.05 were considered significant.

Results

Role of Mac-1 in FcαRI-IgA binding

To assess Mac-1 involvement in FcαRI-ligand binding, we studied PMN from human FcαRI-Tg mice crossed with CD11b knockout mice (Mac-1−/−). Because FcαRI represents a low affinity IgAR, we analyzed PMN binding to IgA-coated surfaces. Tg Mac-1-expressing PMN efficiently bound and spread onto serum IgA (IgA), dIgA, and SlgA-coated slides within 10 min (Fig. 1, upper panels). PMN spreading capacity on IgA-coated surfaces varied among different IgA forms, and was quantified by measuring PMN diameters (18 ± 4.2 μm on serum IgA, 15 ± 3.3 μm on dIgA, and 14.6 ± 3.7 μm on SlgA). Tg Mac-1−/− PMN bound properly to serum IgA and dIgA, but did not interact with SlgA (Fig. 1, lower panels). Furthermore, Mac-1−/− PMN, exhibited impaired spreading on slides coated with serum IgA (12.1 ± 2.5 μm) or dIgA (11.9 ± 4.2 μm). PMN of Ntg Mac-1−/− littermates, expressing Mac-1, but not FcαRI, served as controls and did not bind human IgA. These data were supported by studies with human PMN. Binding and spreading capacity of human PMN on serum IgA, dIgA, and SlgA was similar to that of Tg Mac-1−/− PMN. However, F(ab′)2 of α-Mac-1 mAb inhibited spreading of human PMN on SlgA, but not on serum IgA slides (data not shown). In addition, all phagocytes bound IgG- or BSA-coated surfaces (Fig. 1), irrespective of FcαRI/Mac-1 expression. Binding of both human and Tg mouse PMN to SlgA was abolished in the presence of cytochalasin D. These results indicate Mac-1 to be required for phagocyte-FcαRI binding of SlgA.

Respiratory burst activity

To study the significance of PMN interaction with immobilized IgA, we investigated respiratory burst activity of mouse (Ntg Mac-1−/−, Tg Mac-1−/−, Tg Mac-1+/−) and human PMN. Both serum IgA and SlgA induced comparable oxygen radical production in Tg Mac-1−/− PMN (Fig. 2, left graph). However, Tg Mac-1−/− PMN were stimulated by serum IgA, but not by SlgA (Fig. 2, middle graph). Importantly, Mac-1-expressing and Mac-1-deficient PMN exhibited similar respiratory burst activity in response to PMA. Ntg Mac-1-expressing PMN did not initiate respiratory activity in response to serum IgA or SlgA (Fig. 2, right graph). Human PMN exhibited comparable oxygen radical production upon interaction with serum IgA or SlgA, albeit that serum IgA-induced respiratory burst activity was significantly faster (data not shown). Blocking studies with My43, an IgM recognizing the
FcαRI ligand-binding domain (25), decreased oxygen radical production close to background levels (data not shown), showing IgA-induced respiratory burst to depend on interaction with FcαRI.

These data demonstrate requirement of both FcαRI and Mac-1 for SIgA-induced respiratory burst activity.

Because our data pointed to an essential role for Mac-1 in FcαRI-IgA interactions, we next studied the distribution of Mac-1 and FcαRI in PMN membranes. Isolated Tg Mac-1<sup>+/−</sup> PMN were

**FIGURE 1.** Mac-1 is crucial for FcαRI-SIgA interaction. Isolated Tg Mac-1<sup>+/−</sup> (upper panels) and Tg Mac-1<sup>−/−</sup> (lower panels) PMN were incubated on BSA (control), serum IgA- (IgA), dIgA-, or SlgA-coated slides for 10 min at 37°C, and stained for actin. Cell morphology was imaged in x/y direction in the FITC (upper panel) and transmission (lower panel) channel by confocal microscopy. Experiments were repeated four times yielding comparable results. Cell diameters (mean micrometers ± SD) of Tg Mac-1<sup>+/−</sup> (upper panels) were 7.6 ± 1.0 (control), 18.0 ± 4.2 (serum IgA), 15 ± 3.3 (dIgA), 14.6 ± 3.7 (SlgA), and of Tg Mac-1<sup>−/−</sup> (lower panels) were 7.7 ± 1.6 (control), 12.1 ± 2.5 (serum IgA), and 11.9 ± 2.1 (dIgA). Bar represents 15 μm.

**Colocalization of Mac-1 and FcαRI**

**FIGURE 2.** IgA-induced respiratory burst activity. Isolated PMN of Tg Mac-1<sup>+/−</sup>, Tg Mac-1<sup>−/−</sup> (left and middle graph) and Ntg Mac-1<sup>−/−</sup> mice (right graph) were incubated in HEPES (control, ▲), serum IgA (IgA, ●), or SlgA (○)-coated tubes. As positive control, PMN were stimulated with PMA (×). Oxygen radical production of PMN was measured in time by chemiluminescence detection. Experiments were performed four times yielding essentially identical results. Statistical analyses of areas below the curve verified Tg Mac-1<sup>+/−</sup> PMN to bind SlgA significantly better (p = 0.001) than Tg Mac-1<sup>−/−</sup> PMN.
incubated on surfaces coated with BSA, serum IgA, or SIgA, whereupon FcαRI and Mac-1 were stained with FITC (green), and TRITC (red), respectively. Tg Mac-1\(^{-/-}\) PMN mediated spreading on both serum IgA (Fig. 3A, upper panel) and SIgA (Fig. 3A, middle panel). FcαRI was expressed on the plasma membrane of PMN, but also in filipodia-like outgrowth of cells. A similar staining was found for Mac-1, and colocalization was indicated in yellow (Fig. 3; merged pictures). Tg Mac-1\(^{-/-}\) PMN did not spread on BSA-coated slides, and exhibited overall membrane staining of FcαRI and Mac-1 (Fig. 3A, lower panel). As a control, FcαRI and \(\beta_2\) integrin LFA-1 membrane staining was examined, which revealed no colocalization (Fig. 3B). Importantly, experiments performed with human PMN revealed FcαRI and Mac-1 expression to colocalize as well (see below).

**Mac-1 binds SC**

Our results demonstrated only Mac-1-expressing PMN capable of binding SIgA-coated surfaces. Next, we evaluated the capacity of Mac-1\(^{-/-}\) and Mac-1\(^{-/-}\) PMN to bind aggregated IgA by flow cytometry. Ntg Mac-1\(^{-/-}\) PMN were ineffective in binding serum IgA-complexes, but interacted well with SIgA complexes. On the contrary, Ntg Mac-1-deficient PMN were unable to bind SIgA complexes (data not shown). These observations pointed to a role for the SC in PMN-SIgA binding. Therefore, we examined the capacity of recombinant SC to interact with isolated human and mouse PMN. As shown in Fig. 4A, Mac-1-expressing PMN readily bound SC, irrespective of the presence of FcαRI. However, binding of SC to Mac-1-deficient Tg and Ntg PMN, was abrogated. SC interacted with human PMN as well (Fig. 4B). These data show SC, either recombinant or present in its normal configuration (i.e., complexed with dIgA), to be capable of interacting with Mac-1.

**Involvement of Mac-1 lectin-binding site in SIgA binding**

We next evaluated the region of Mac-1 involved in SIgA-FcαRI binding. Human PMN were plated on immobilized serum IgA or SIgA in the absence (control) or presence of NADG, which interacts with the Mac-1 lectin-binding domain (31), and were stained with FcαRI and Mac-1 (Fig. 5). Human PMN exhibited spreading on both serum IgA and SIgA, like Tg Mac-1\(^{-/-}\) PMN. Incubation of PMN with NADG resulted in a blockade of PMN binding to SIgA-coated surfaces, whereas binding to serum IgA was barely affected by NADG (Fig. 5, lower panel). The partial colocalization of FcαRI and Mac-1 observed in control PMN bound to serum IgA-coated slides was decreased in the presence of NADG. PMN

**FIGURE 3.** Colocalization of FcαRI and Mac-1 in PMN membranes. A, Tg Mac-1\(^{-/-}\) PMN were incubated on immobilized serum IgA (upper panel), SIgA (middle panel), or BSA (lower panel) for 15 min at 37°C, stained for FcαRI (green) and Mac-1 (red), and analyzed by confocal microscopy. **Right panels** show merges of the two signals (indicating receptor colocalization). B, FcαRI (green) and \(\beta_2\) integrin LFA-1 (red) localization in Tg Mac-1\(^{-/-}\) PMN bound to IgA. Experiments were repeated four times yielding similar results. Bars represent 15 \(\mu\)m.
The present study documents a new role for Mac-1, including cytokine receptors, integrins, and FcR (28, 33). Our data support Mac-1 binding to SC to underlie this phenomenon, implicating the Mac-1 lectin-binding domain to be involved in PMN spreading, although partly inhibiting PMN spreading, did not inhibit binding shown). In contrast, Abs directed against the I-domain of Mac-1, completely incompletely understood (32). Although a number of studies focused on the molecular characterization of FcαRI and IgA, relatively little is known about the biology of FcαRI-IgA interactions. The present study documents a new role for Mac-1, a β2 integrin, in ligand binding of FcαRI. Mac-1 was found to be crucial for interaction of PMN FcαRI with SlgA, and subsequent PMN activation. Our data support Mac-1 binding to SC to underlie this phenomenon, and implicate Mac-1 lectin-binding domain to be involved.

Modulation of receptor-ligand interactions by accessory molecules is well-documented for a number of immune receptors, including cytokine receptors, integrins, and FcR (28, 33–36). IgG binding to FcγRI (CD64) and FcγRIII (CD16a) is dependent on association with the FcγRI γ-chain (36–38). In this study, Mac-1 is identified as a novel accessory protein, crucial for FcαRI-SlgA interaction. In SlgA, SC is covalently ligated to the Cα2 and Cα3 domains within the dIgA Fc region (39), which may interfere with the affinity of FcαRI for SlgA (40–42). The present study demonstrates SC binding to PMN in a Mac-1-dependent manner. When one appreciates the structure of SC, Mac-1 interaction with SC seems rational. SC represents a heavily glycosylated protein belonging to the Ig superfamily (3). Moreover, we observed Mac-1 lectin-binding domain, bearing carbohydrate-binding specificity (31), involved in PMN binding of SlgA.

Physical association between leukocyte membrane proteins (such as FcR-FcR γ-chain, and FcγRIIb-Mac-1) has been documented before (22, 37, 38). Despite clear colocalization of FcαRI and Mac-1, a direct FcαRI-Mac-1 interaction was not apparent from immunoprecipitation experiments (our unpublished data).

Importantly, Mac-1 modulates PMN function upon IgA binding, as indicated by stimulation of a potent respiratory burst. Our data show requirement of both FcαRI and Mac-1 for SlgA-induced respiratory burst activity, because Mac-1-deficient Tg PMN and Ntg PMN were unable to elicit oxygen radical production in response to SlgA. A role for Mac-1 in FcyR functions, including respiratory burst has been shown before (28, 43–45). CD18 interactions with the actin cytoskeleton and associated proteins may enable Mac-1 signaling (46, 47). Furthermore, the present work is consistent with earlier studies documenting a role for β2 integrins in superoxide production of eosinophils mediated by SlgA, and not serum IgA (48). SC by itself was described to activate eosinophil functions, but not PMN functions, which was proposed to relate to an additional (15 kDa) “SC receptor” on eosinophils (49). Indeed, we observed Mac-1-deficient eosinophils capable of interacting with both SC and SlgA (our unpublished data).

In conclusion, this study provides evidence for a crucial role of Mac-1 in phagocyte SlgA binding. Enhanced IgA responses upon incubation of PMN with GM-CSF, TNF-α, or IL-8 have been reported (50–52), although the underlying mechanisms remain to be addressed. We propose Mac-1 involvement in these phenomena to be likely, because of the well-recognized ability of these cytokines and chemokines to activate Mac-1 (53–55). Requirement of two molecules interacting with one ligand may provide immune effector cells with an extra way to regulate their activity. When “first-line” defense
fails, mucosal inflammation leads to PMN recruitment and priming, accompanied by up-regulation of Mac-1, which may trigger more potent FcεRI-mediated responses. We hypothesize Mac-1 to increase affinity of FcεRI-SIgA interaction via binding of SC.

Acknowledgments
We thank Tanya Mayadas for providing CD11b-deficient mice, Jacques Dujs and Cees van Kooten for human dIgA, and Bruce Wines and Jos van Strijp for critically reading the manuscript. Furthermore, we thank Arno Gerritsen and Marc van Dijk for assistance in generating mAb 14.1, and Toon Hesp, Herma Boersma, and Sabine Versteeg for excellent animal care.

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