Fibrin(ogen) Is Internalized and Degraded by Activated Human Monocytoid Cells Via Mac-1 (CD11b/CD18): A Nonplasmin Fibrinolytic Pathway

By Daniel I. Simon, Ari M. Ezratty, Stephanie A. Francis, Heimut Rennke, and Joseph Loscalzo

Fibrin(ogen) (FGN) is important for hemostasis and wound healing and is cleared from sites of injury primarily by the plasminogen activator system. However, there is emerging evidence in plasminogen activator-deficient transgenic mice that nonplasmin pathways may be important in fibrin(ogen)olysis, as well. Given the proximity of FGN and monocytes within the occlusive thrombus at sites of vascular injury, we considered the possibility that monocytes may play an ancillary role in the degradation and clearance of fibrin. We found that monocytes possess an alternative fibrinolytic pathway that uses the integrin Mac-1, which directly binds and internalizes FGN, resulting in its lysosomal degradation. At 4°C, FGN binds to U937 monocytoid cells in a specific and saturable manner with a kD of 1.8 μmol/L. Binding requires adenosine diphosphate stimulation and is calcium-dependent. At 37°C, FGN and fibrin monomer (FM) are internalized and degraded at rates of 0.37 ± 0.13 and 0.56 ± 0.03 μg/10⁶ cells/h by U937 cells, 1.38 ± 0.02 and 1.20 ± 0.30 μg/10⁶ cells/h by THP-1 cells, and 2.10 ± 0.20 and 2.52 ± 0.18 μg/10⁶ cells/h by human peripheral blood mononuclear cells, respectively. The serine protease inhibitors, PPACK and aprotinin, and the specific elastase inhibitor, AAPVCK, do not significantly inhibit degradation. However, degradation is inhibited by chloroquine, suggesting that a lysosomal pathway is involved. Factor X, a competitive ligand with FGN for the Mac-1 receptor, also blocks degradation, as does a monoclonal antibody to the α-subunit of Mac-1. Autoradiography of radioiodinated, internalized FGN shows that FGN proteolysis by the pathway produces a unique degradation pattern distinct from that observed with plasmin. In a fibrin clot lysis assay, Mac-1-mediated fibrinolysis contributed significantly to total fibrinolysis. In summary, FGN is internalized and degraded by activated human monocytoid cells via Mac-1 in the absence of plasmin, thereby providing an alternative fibrinolytic pathway. Thus, in addition to the function of cell adhesion, integrins may also act as receptors that mediate the internalization and degradation of bound ligands. © 1993 by The American Society of Hematology.

From the Brockton/West Roxbury V.A. Medical Center; and the Department of Medicine and Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

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Address reprint requests to Joseph Loscalzo, MD, PhD, Department of Medicine, Division of Vascular Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

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MATERIALS AND METHODS

Special reagents. Human plasminogen-free fibrinogen was purchased from Enzyme Research Lab (South Bend, IN). L-glycyl-L-prolyl-L-arginyl-L-proline (GPRP), N-methoxy succinyl-

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L-alanyl-L-lysyl-L-valanyl chloromethylketone (AAPVCK), and 1-(5-isoquinolinesulfonfonyl)-2-methyl-piperazine (H7) were purchased from Sigma Co (St Louis, MO). Tissue-type plasminogen activator (t-PA) was a generous gift of Genentech Corp (South San Francisco, CA). Hirudin was kindly provided by Ciba-Geigy (Basel, Switzerland). D-phenylalanly-L-lysyl-L-arginyl chloromethylketone (PPACK) was purchased from Calbiochem Corp (La Jolla, CA). Sepracell-MN was purchased from Sepratech Corp (Oklahoma City, OK).

**Monocytic antibodies (MoAb).** TS 1/18, an MoAb to the common β2-subunit (CD18) of Mac-1, and LM2/1, an MoAb to the αM-subunit of Mac-1 (CD11b), were generous gifts from Dr Timothy Springer (Boston Children’s Hospital, Boston, MA). 7E3, an MoAb that blocks FGN binding to platelet GPIIb/IIIα, was kindly provided by Dr Barry Coller (SUNY, Stony Brook, NY). LPM19C, an MoAb to the αM-subunit of Mac-1 (CD11b), was purchased from Dako Corp (Carpinteria, CA).

**Cells.** The monoblast cell line U937 and monotypic cell line THP-1 (American Type Culture Collection, Rockville, MD) were maintained in culture in RPMI 1640 containing 20% fetal calf serum, 20 mmol/L hydroxyethylpiperazine ethanesulfonic acid (HEPES), and 2 mmol/L L-glutamine. Human monocytes were prepared from whole blood via continuous density gradient separation using Sepracell-MN. Briefly, equal volumes of whole blood anticoagulated with citrate-phosphate-dextrose (CPD) and Sepracell-MN, and centrifuged at 1,500g for 20 minutes. Monoocyte-enriched mononuclear (>85%) cells are found in the compact opalescent band below the meniscus. Mono- and lymphocytes are mononuclear cells (PBMCs; lymphocytes and monocytes) are found in the compact band below the meniscus. Mono-nuclear cells were washed with 10 mmol/L sodium phosphate, pH 7.4, 0.15 mol/L NaCl (phosphate-buffered saline [PBS]) and 0.7% bovine serum albumin (BSA), mixed in one and one-half volumes of Sepracell-MN, and centrifuged at 1,500g for 20 minutes. Monoocyte-enriched mononuclear cells are found in the compact band below the meniscus, and lymphocyte-enriched mononuclear cells at the bottom of the tube. Cells were counted with a Coulter Counter, Model ZM (Coulter, Hialeah, FL).

**Protein labeling.** Plasminogen-free human FGN and BSA were radiolabeled with [35S] using iodoo-bodies, as previously described. The specific activity of [35S]FGN and [35S]BSA ranged from 3 to 5 × 10⁶ cpm/μg and 1 to 2 × 10⁵ cpm/μg, respectively; total radioactivity was greater than 95% trichloroacetic acid (TCA)-precipitable.

**FGN binding and degradation assays.** The binding of [35S]FGN to monocytes was investigated as described by Altieri et al. Modifications. Briefly, U937 cells at 1.0 × 10⁷/mL were suspended in 10 mmol/L Tris, 0.15 mol/L NaCl, pH 7.4 (TBS), in the presence of 2.5 mmol/L CaCl₂. Varying concentrations of [35S]FGN (0.1 to 4.0 μmol/L) were added to a total volume of 250 μL and the cells were incubated with 10 μmol/L ADP. The incubation was performed at 4°C to limit uptake and internalization of FGN. After 60 minutes, a 100-μL aliquot of the incubation mixture was layered onto 200 μL of silicone oil to separate free from cell-bound FGN. Specific binding was calculated by subtracting nonspecific binding in the presence of inhibitor to the rate of degradation in the presence of ADP-stimulated U937 cells. The fibrin clot was exposed to U937 or THP-1 cells and formed in the presence of inhibitor to the rate of degradation in the absence of inhibitor.

**Clot lysis assay.** The contribution of Mac-1-mediated fibrinolysis to overall clot lysis was investigated as follows. Fibrin clots were formed by the addition of bovine thrombin (1 U/mL) to 0.65 mL of platelet-poor plasma (PPP) to which [125I]-FGN (~280,000 total counts) was added, in the presence and absence of approximately 1 to 2 × 10⁶ ADP-activated THP-1 cells. The fibrin clots were formed in 4-mL test tubes and, after 30 minutes, the tubes were centrifuged at 800g for 10 minutes. The residual supernatant was removed and the tubes were then counted to assess total [125I]-FGN incorporation. To each fibrin clot, 1.0 mL of PPP was added, containing 5 U/mL hirudin to inhibit residual thrombin activity, plus the following: (1) 40 μmol/L PPACK to inhibit endogenous plasminogen activator/plasmin activity; (2) 1.0, 3.2, or 12.5 nmol/L t-PA; (3) 1.0, 3.2, or 12.5 nmol/L t-PA to a fibrin clot containing THP-1 cells; (4) 40 μmol/L PPACK to a fibrin clot containing THP-1 cells; (5) 40 μmol/L PPACK + 400 μmol/L chloroquine to a fibrin clot containing THP-1 cells; and (6) 40 μmol/L PPACK + 0.035 mg/mL
2.5E4
2.0
1.5
1.0
0.5
0.0
0.0
0.5
1.0
1.5
2.0
2.5
Specific Bound (# FGN molecules/cell) vs [FGN] (µM)

FGN binding to monocytoid cells. The specific binding of \[^{125}\text{I}]\text{FGN}\) to U937 cells at 4°C in the presence of 10 µmol/L ADP, 2.5 mmol/L CaCl\(_2\), and 3 mmol/L GPRP was investigated as described in the Materials and Methods. Each point represents the mean ± standard deviation of the number of molecules of FGN bound per cell (n = 4, each performed in duplicate).

RESULTS

Binding and degradation of FGN by monocytoid cells. We initially explored the interaction of FGN with the monocytoid U937 cell line at 4°C to focus on the surface binding of FGN and, in particular, to investigate the internalization and degradation of FGN. As previously shown by Altieri et al. and Wright et al., we confirmed that FGN binds to U937 cells in a specific, saturable manner (Fig 1). Stimulation with ADP was necessary to induce binding, which is calcium-dependent. Analysis of the binding data by the method of Scatchard showed a single class of receptors with a kd of 1.8 µmol/L and a B\(_{max}\) of 1.6 × 10^5 FGN molecules bound/cell.

Because monocytic cells can bind FGN and can actively internalize or phagocytize certain bound ligands, we examined the ability of monocytes to internalize this bound ligand. In addition, we considered the possibility that internalized fibrinogen can be proteolyzed and, therefore, measured the degradation of internalized fibrinogen. At 37°C, FGN is degraded by U937 cells at a rate of 0.37 ± 0.13 µg/10^6 cell/h (n = 11) (Table 1). The capacity of Mac-1 to associate with FGN has been shown to be related to the degree of differentiation of the monocytoid cell and, specifically, to Mac-1 receptor density. Therefore, we explored the rate of FGN degradation in the more differentiated THP-1 monocyte cell line and in human monocyte-enriched PBMCs (Table I). THP-1 cells degraded FGN at a rate of 1.38 ± 0.02 µg/10^6 cell/h (n = 3), and human monocytes at a rate of 2.10 ± 0.20 µg/10^6 cell/h (n = 4).

The degradation of FM by monocytoid cells was also investigated (Table 1). At 37°C, FM was degraded by U937 cells at a rate of 0.55 ± 0.03 µg/10^6 cells/h (n = 3), by THP-1 cells at a rate of 1.20 ± 0.30 µg/10^6 cells/h (n = 6), and by PMBCs at a rate of 2.52 ± 0.18 µg/10^6 cells/h (n = 4).

Mechanism of FGN degradation. To exclude a nonspecific uptake and degradation mechanism, ie, nonreceptor-mediated pinocytosis/phagocytosis, we examined monocytoid cell degradation of FGN compared with that of BSA (Fig 2). Figure 2 shows significantly less degradation of
Table 1. FGN and FM Degradation by Activated Monocytoid Cells

<table>
<thead>
<tr>
<th>Monocytoid Cell</th>
<th>μg FGN Degraded/10⁶ Cells/h</th>
<th>μg FM Degraded/10⁶ Cells/h</th>
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<tbody>
<tr>
<td>U937</td>
<td>0.37 ± 0.13</td>
<td>0.55 ± 0.03</td>
</tr>
<tr>
<td>THP-1</td>
<td>1.38 ± 0.02</td>
<td>1.20 ± 0.30</td>
</tr>
<tr>
<td>PBMC</td>
<td>2.10 ± 0.20</td>
<td>2.52 ± 0.18</td>
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The degradation of FGN and FM by ADP-activated U937 cells, THP-1 cells, and PBMCs at 37°C was investigated as described in the Materials and Methods. Each value represents the mean ± standard deviation of micrograms of FGN or FM degraded per 10⁶ cells per hour (n = 3 to 11).

[¹²⁵I]-BSA compared with that of [¹²⁵I]-FGN by ADP-activated monocytoid cells (0.11 ± 0.06 [mean ± SD] mole BSA degraded/mole FGN degraded). Furthermore, coincubation of [¹²⁵I]-BSA with FGN failed to increase the rate of BSA degradation (0.07 ± 0.09 mole BSA degraded/mole FGN degraded), suggesting that FGN does not stimulate generalized pinocytosis/phagocytosis in this system.

To elucidate the mechanism of FGN degradation by monocytoid cells, incubations were performed in the presence of potential inhibitors (Fig 3). We found that degradation was not significantly inhibited by the serine protease inhibitors, aprotinin and soybean trypsin inhibitor. Similarly, degradation was not inhibited by the tripeptide serine protease inhibitor, PPACK, or specific elastase inhibitor, AAPVCK. This lack of inhibition by both high and low molecular weight serine protease inhibitors and low molecular weight elastase inhibitor argues against a released serine protease or the formation of a "protected pocket" as a degradation mechanism.²⁶,²⁷ All experiments were performed in the absence of plasminogen, and plasminogen-free FGN was used in all cases. However, FGN degradation was inhibited by chloroquine, an inhibitor of lysosomal-dependent proteolytic degradation. Factor X, a competitive ligand with FGN for the Mac-1 receptor,¹⁹ also significantly blocked degradation by 90% ± 15% (mean ± SD).

MoAbs to Mac-1 (CD11b/CD18) inhibit FGN degradation by monocytoid cells. We next turned to a panel of well-characterized MoAbs to define the receptor required for FGN degradation. The MoAb, TS1/18, to the β-subunit (CD18) (shared by Mac-1, LFA-1, and gp150.95) partially inhibited FGN degradation (Fig 4). The α-subunit confers individual receptor identity and ligand specificity. Therefore, the effect of MoAbs, LM2/1 and 2LPM19C, specific for the α-subunit of Mac-1, on FGN degradation was investigated. 2LPM19C blocked degradation by 90% ± 7%, implicating Mac-1 as the receptor responsible for FGN degradation (Fig 3). Interestingly, 2LPM19C is known to block...
FGN binding to Mac-1\(^{23}\), however, only selected epitopes of the \(\alpha\)-subunit of Mac-1 appear to be involved in the degradation of FGN as evidenced by the lack of inhibition by LM 2/1. The MoAb 7E3 did not affect the degradation of FGN by monocytes.

**Proteolytic cleavage of \([^{125}\text{I}]\)-FGN.** The proteolytic cleavage of FGN was investigated by using \([^{125}\text{I}]\)-FGN autoradiography. Figure 5A shows that U937 and THP-1 cells internalize and proteolyze FGN producing well-defined proteolytic fragments (lanes 5 and 6). This cleavage pattern is distinct from that observed with plasmin (lane 2). Importantly, the absence of \([^{125}\text{I}]\)-FGN cleavage in the supernatant of U937/THP-1–exposed cells (lanes 3 and 4) provides additional evidence that this FGN degradation pathway requires internalization. Figure 5B directly compares the degradation patterns of FGN exposed to plasmin with FGN incubated with THP-1 cells under reducing conditions. Again, a unique cleavage pattern is observed for THP-1–degraded FGN, with digestion resulting in three bands of molecular weight (MW) 26, 32, and 37 Kd.

**Mac-1 degrades fibrin and contributes to overall clot lysis.** The contribution of Mac-1–mediated fibrinolysis to overall clot lysis was investigated as described in the Materials and Methods. Figure 6A shows that ADP-activated THP-1 cells (in the presence of 40 \(\mu\)mol/L PPACK to inhibit endogenous plasminogen activators and plasmin) lyse fibrin clots. This component of fibrin clot lysis is secondary to Mac-1, as evidenced by inhibition with the MoAb 2LPM 19C. Figure 6B illustrates the contribution of Mac-1–mediated fibrinolysis to total fibrinolysis over a range of t-PA concentrations. At 1.0 and 3.2 nmol/L t-PA (physiologic concentration), Mac-1–mediated fibrinolysis accounted for 34% and 16%, respectively, of total fibrinolysis (t-PA–mediated + ADP-activated THP-1 cell-mediated).

**FGN accumulates intracellularly at 37°C.** We next turned to immunofluorescence and immunoperoxidase microscopy of fixed, permeabilized cells to localize directly the internalization and degradation of FGN. At 4°C, FGN binding to surface receptors was visualized (Fig 7A); at 37°C, FGN accumulated intracellularly in monocytoid cells (Fig 7B and C), an observation confirmed by immunoelectron microscopy. The requirement for Mac-1 is shown by the reduction in FGN peroxidase product when cells were coincubated with factor X (Fig 7D).

**DISCUSSION**

This study provides evidence for an alternative fibrinolytic pathway that uses the cellular adhesion receptor Mac-1. This pathway involves a two-step mechanism in which Mac-1 on activated monocytoid cells first binds FGN, which is followed by its internalization and lysosomal degradation. In a fibrin clot lysis assay, Mac-1–mediated fibrinolysis contributed significantly to fibrinolysis at endogenous t-PA concentrations. The requirement of this pathway for the internalization of FGN was directly confirmed by \([^{125}\text{I}]\)-FGN autoradiography of cell lysates and immunomicroscopy of fixed, permeabilized monocytoid cells showing the intracellular localization of FGN that was blocked with factor X, a competitive inhibitor of FGN binding to Mac-1.

Precedence for such ligand-receptor binding, internalization, and degradation exists in the low-density lipoprotein pathway involving clathrin-coated pits, as originally described by Brown and Goldstein.\(^{28,29}\) Our observation that...
FGN is internalized and degraded by activated human monocytoid cells via Mac-1 now extends this paradigm to the important integrin class of receptors. We chose to focus on Mac-1 because it is known not only to bind FGN but also to activate factor X, culminating in rapid fibrin formation,16 and, thus, may play a role in modulating fibrin formation/dissolution. Consistent with such a mechanism of ligand-receptor binding and internalization, monocytes contain intracellular pools (intracellular vesicles and peroxidase-negative granules) of Mac-1 that are mobilized to the surface after stimulation with the chemottractant peptide, formyl-methionyl-leucyl-phenylalanine, or other mediators, such as ADP, platelet-derived growth factor, tumor necrosis factor, and 65a.26 Mac-1 receptors are, therefore, well suited for rapid translocation from an intracellular pool to the surface.

Altieri et al18,19 and Wright et al26 have previously reported that activated monocytes and polymorphonuclear leukocytes bind fibrinogen via Mac-1. Our data confirm these observations, but important differences were noted that warrant additional consideration. We found a similar inducible receptor for fibrinogen of relatively low affinity (kd = 1.8 μmol/L) with approximately 1 × 10^5 receptors present per cell. However, in our binding experiments, incubations were performed at 4°C to limit uptake or internalization of bound ligand. Altieri et al performed binding experiments at room temperature and at 37°C, noting that [125I]-FGN binding to monocytes was “considerably reduced at 4°C.”19

Because monocytic cells can bind FGN and actively phagocytize bound ligands, we examined the ability of human monocytes to degrade FGN by performing incubations at 37°C and assaying the supernatant of TCA-treated cell suspensions for acid-soluble radioactive material generated by the cells. U937 cells, THP1 cells, and human PBMCs were found to degrade FGN and FM at rates of 0.37, 1.3, 2.1 μg FGN/10^6 cells/h and 0.55, 1.20, 2.52 μg FM/10^6 cells/h, respectively.

Mac-1 may participate in the degradation of FGN by additional mechanisms. Weitz et al26 and Wright et al26 have described elastase-mediated fibrin(ogen)olysis in a pocket on the membrane surface of neutrophils containing Mac-1–FGN complexes within which secreted elastase is protected from high molecular weight protease inhibitors in the surrounding medium. This mechanism requires the adherence of neutrophils to a ligand-coated surface, which results in a protected zone that excludes molecules with a molecular mass greater than 50,000 daltons.27 Gustafson et al11 have also suggested that neutrophil elastase participates in FGN degradation on neutrophil CD11b/CD18. Our experiments were performed in suspension precluding the formation of a protected pocket. Furthermore, lack of inhibition with the small elastase inhibitor, AAPVCK, and the small serine protease inhibitor, PPACK, as well as the larger serine protease inhibitors, aprotinin and soybean trypsin inhibitor, argues against a released serine protease as the mechanism of FGN degradation that we have observed. The inability of the elastase inhibitor, AAPVCK, to block FGN degradation on monocytes as opposed to its inhibitory effect on neutrophils may relate to differences in these respective cells and their methods of isolation. Indeed, Gustafson et al11 speculate that elastase activity on the neutrophil surface is probably the result of release during the isolation of neutrophils.

The binding of integrin receptors to their ligands is capable of triggering signals stimulating phagocytosis.33–34 Specifically, Gresham et al33 have shown that adhesive proteins containing the Arg-Gly-Asp (RGD) sequence stimulate neutrophil erythrophagocytosis. However, to be distinguished from our findings, the addition of catalase to inactivate products of the myeloperoxidase-hydrogen peroxide-halide system was required to demonstrate stimulated phagocytosis. Whereas previous groups have concentrated on CD11b/CD18-stimulated erythrophagocytosis, we are the first to focus directly on the uptake and degradation of the CD11b/CD18-bound ligand FGN. Three pieces of evidence suggest
Fig 7. Immunolocalization of FGN in monocytoid cells. Immunofluorescence and immunoperoxidase microscopy of fixed, permeabilized monocytoid cells was performed as described in the Materials and Methods to localize intracellular FGN. (A and B) The surface binding of FGN to monocytoid cells was examined at 4°C to limit uptake and degradation (A). A fluorescent-tagged antihuman FGN antibody was used in these experiments. Control incubations in which either FGN or the fluorescent-tagged antibody were omitted showed no background fluorescence. Incubations were performed at 37°C to allow FGN uptake and degradation (B). (C and D) Immunoperoxidase staining of monocytoid cells after incubation at 37°C (C, original magnification × 400). Monocytoid cells were incubated with FGN and 420 nmol/L factor X followed by immunoperoxidase staining (D, original magnification × 400).

that FGN degradation occurs by way of a selective mechanism and not by generalized pinocytosis/phagocytosis: (1) the degradation of [125I]-BSA coincubated with FGN is comparatively negligible (Fig 2); (2) FGN degradation is unaffected by the protein kinase C inhibitor 0.625 μmol/L H7, which inhibits stimulated erythrophagocytosis (data not shown); and (3) FGN degradation does not require the addition of catalase. The recent finding by Handagama et al that the integrin GPIIb/IIIa mediates the endocytosis of FGN into guinea pig megakaryocytes and platelet α-granules lends further support to our data showing FGN internalization and degradation by the different integrin Mac-1 on human monocytes.

The investigation of nonplasmin-mediated fibrinolytic mechanism(s) is particularly relevant in light of the recent report by Carmiliet et al that t-PA gene-inactivated transgenic mice possess an alternative fibrinolytic pathway capable of slowly clearing thrombi with approximately 10%, 16%, and 25% clot lysis at 4, 16, and 24 hours, respectively. The physiologic relevance of Mac-1-mediated fibrinolysis is intriguing in light of similar clot lysis kinetics (Fig 6A). Given the proximity of FGN and monocytes/macrophages
within the occlusive thrombus at sites of vascular injury, we considered the possibility that monocytes may play an ancillary role in the degradation and clearance of fibrin. Intra-vascular thrombosis is the precipitating event in unstable angina and myocardial infarction. Additionally, FGN accumulates in the vessel wall, leading to smooth muscle cell proliferation and endothelial cell toxicity. These data suggest an alternative, plasmin-independent fibrinolytic pathway that uses the integrin Mac-1 on activated monocyte/macrophage, and also suggest a unique mechanism by which monocytes can facilitate dissolution of fibrin thrombi.

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