Enhancement of Migration Inhibitory Factor Activity by Plasma Esterase Inhibitors*

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The plasma esterase inhibitors α₁-macroglobulin, α₁-antitrypsin, Cl-inhibitor, antithrombin-heparin cofactor, and, as previously described, soybean trypsin inhibitor (Kunitz) and diisopropylphosphorofluoridate (9) enhance the response of guinea pig macrophages to migration inhibitory factor. To obtain this effect, macrophages are incubated with inhibitors prior to assay. The data suggest that (a) the enhancement of migration inhibitory factor response is due to the inhibition of esterases associated with the macrophage through a distinct active site on the inhibitors, and (b) that the active sites of antithrombin-heparin cofactor and soybean trypsin inhibitor, which interact with the macrophage enzymes, are different from the active sites of these inhibitors which interact with thrombin and trypsin, respectively. Chemical modification of the active site of antithrombin-heparin cofactor for thrombin and of soybean trypsin inhibitor for trypsin does not affect their capacity to enhance the migration inhibitory factor response. From studies with thrombin, it was known that antithrombin-heparin cofactor has a heparin binding site. Addition of heparin was found to prevent the migration inhibitory factor-enhancing effect of antithrombin-heparin cofactor. The present results suggest that plasma esterase inhibitors may play a regulatory role in the response of macrophages to mediators of cellular immunity.

The cellular immune response plays an important role in the body's defense against certain infections and in tumor and transplantation immunity (2). These reactions involve, in part, the activation of macrophages by lymphocytes. Lymphocytes obtained from sensitized animals or humans can be stimulated in vitro by the specific antigen, or by mitogens, to produce a number of soluble mediators which act on the macrophage. One of these factors, which has been most extensively studied, is called migration inhibitory factor (3, 4). This factor, a glycoprotein with a molecular weight of 35,000 to 55,000 (5), inhibits the migration of macrophages out of capillary tubes (6). Migration inhibitory factor, or a closely related mediator, is also capable of activating macrophages in terms of enhancing cell adherence to vessel surfaces, ruffled membrane activity, phagocytosis, glucose oxidation, bacteriostasis, and tumor cytotoxicity (7, 8).

In previous studies, it was shown that the response of macrophages to migration inhibitory factor is enhanced when the cells are pretreated with iPr₂P-F⁺ or soybean trypsin inhibitor (Kunitz). These studies suggested the presence of serine esterases on the macrophage which counteract the action of migration inhibitory factor (9). In this report it is shown that the plasma esterase inhibitors, α₁-macroglobulin, α₁-antitrypsin. Cl-inhibitor, and antithrombin-heparin cofactor, are also capable of affecting the factor-macrophage interaction. This further documents the presence of an esterase on the macrophage. The concentration of inhibitors necessary to enhance the migration inhibitory factor response of macrophages was determined and found to be in the physiological range. In addition, detailed studies of the mechanism of action on the macrophage of one plasma esterase inhibitor, antithrombin-heparin cofactor, are described. These investigations indicate that all plasma esterase inhibitors studied enhance migration inhibitory factor action on the macrophage, and that small amounts of these inhibitors are sufficient to produce a striking effect. Other plasma proteins do not enhance the response of macrophages to migration inhibitory factor. These findings are supported by considerable evidence that the esterase inhibitors block a wide variety of plasma esterases.

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‡The abbreviations used are: iPr₂P-F⁺, diisopropylphosphorofluoridate; Hank’s BSS, Hank’s balanced salt solution.

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expressed as the percentage of the inhibition of the migration of these preincubated with the various esterase inhibitors or with Hank's BSS, exudate cells (more than 80% macrophages), which had been either land) medium, with 100 units/ml of penicillin and 100 fig/ml of 

Materials and Methods

Chemicals—Antithrombin-heparin cofactor was purified from human plasma, as described (13). It showed one band on disc electrophoresis, pH 8.4, and was homogeneous on immunoelectrophoresis. ωα-Macroglobulin (100 μg/ml) was a gift of Dr. Edward J. Goetzl, Robert B. Brigham Hospital, Harvard Medical School, Boston, and contained no detectable C1-inhibitor, α,α-antitrypsin, and inter-α-trypsin inhibitor activities, as assessed by counterimmunoelectrophoresis, and with detectable plasmin or plasminogen activator activities. It showed one major and three minor bands on disc electrophoresis. C1-inhibitor (24,000 units/ml (14) was obtained from Mrs. Diane Pratt, Robert B. Brigham Hospital, Harvard Medical School, Boston, and showed on disc electrophoresis, pH 8.4, one major band, the inhibitor, and a minor band, a contaminant lacking antiesterase activity. C1-α-antitrypsin (200 μg/ml) was a gift from Dr. David Bing, Center for Blood Research, Harvard Medical School, Boston, and gave one band on disc electrophoresis, pH 8.4. The following materials were used without further purification: ribonuclease (WRAF 91 B, 3100 units/mg, Worthington Enzymes, Inc., Freehold, N.J.), one band on disc electrophoresis, pH 8.4); bovine transferrin (82-034, Miles Laboratories, Kankakee, Ill.); myoglobin (M-0630, type I, Sigma Chemical Corp., St. Louis, Mo.); and human IgM γ-globulin (obtained from Dr. Peter Schur, Robert B. Brigham Hospital, Harvard Medical School, Boston). The latter was homogenous by counterimmunoelectrophoresis. Further studies were carried out to be sure that the enhance-

Production of Migration Inhibitory Factor—Migration inhibitory factor-rich and control lymphocyte supernatants were obtained as previously described (15). Briefly, 2.4 x 10⁷/ml of guinea pig lymph node lymphocytes were incubated with and without concanavalin-A (10 μg/ml) for 24 hours in 2 ml batches. Concanavalin-A was added to the control supernatants after incubation. The resulting supernatants were filtered over a Sephadex G-100 column in phosphate-buffered saline. The migration inhibitory factor-containing activity and control Sephadex G-100 fractions were pooled and concentrated to 1/100 the original volume of the supernatant and stored at -70°C.

Assay for Migration Inhibitory Factor—Two milliliters of medium containing 0.7 to 3.0 10⁶ of the concentrated factor solution in Eagles minimum essential (Microbiological Associates, Inc., Bethesda, Maryland) medium, with 100 units/ml of penicillin and 100 μg/ml of streptomycin, were made to contain 15% normal guinea pig serum. Using a capillary tube migration assay (16), the media were assayed for migration inhibitory factor activity on normal guinea pig peritoneal exudate cells (more than 80% macrophages), which had been either preincubated with the various esterase inhibitors or with Hank's BSS, as a control (see below). Migration inhibitory factor activity was expressed as the percentage of the inhibition of the migration of these cells (%).

\[ \text{average migration in migration} \times 100 \] 
\[ \text{inhibitory factor-containing fractions} \]
\[ \text{average migration in control fractions} \]

At least 20% inhibition must be obtained for significant activity. Small amounts of migration inhibitory factor and control fractions were chosen, so that migration inhibitory factor, by itself, produced little or no inhibition of migration of peritoneal exudate cells. This made evaluation of enhancing effects possible.

Treatment of Macrophages with Various Esterase Inhibitors—1.5 x 10⁷ guinea pig peritoneal exudate cells, induced by intraperitoneal mineral oil injection (10), were suspended in 2 ml of Hank's BSS containing 5 to 200 μg/ml of ωα-macroglobulin, α,α-antitrypsin, anti-thrombin-heparin cofactor, soybean trypsin inhibitor, or with 250 to 1000 units/ml of C1-inhibitor. Control cells were suspended in Hank's BSS alone. The cells were incubated at 37°C for 1 hour, during which they were preincubated with the inhibitor. The cells were washed three times by centrifugation in Hank's BSS, resuspended in Eagle's minimum essential medium with serum, and assayed for migration inhibitory factor activity.

Assay for Antithrombin and Antithrombin-Heparin Cofactor Activity—The assay for antithrombin activity was performed as described in Ref. 13. Briefly, 0.1 ml of the sample and 0.1 ml of human thrombin, both in 0.1 m Tris-HCl/0.1 m NaCl at pH 8.3, were combined, and the mixture was incubated at 37°C for 3 minutes. Following incubation, 0.1 ml was added to 0.3 ml of a 5 mg/ml fibrinogen solution in Tris-HCl buffer, and the clotting time was recorded.

The assay for heparin cofactor activity was performed as outlined in Ref. 13. To a 0.1-ml aliquot of sample in Tris-HCl buffer, 0.1 ml of 25 units/ml of heparin and 0.2 ml of fibrinogen solution were added. The mixture was incubated for 1 min at 37°C, and 0.1 ml of human thrombin (approximately 0.002 absorbance units/ml) was added, and the clotting time was recorded.

Assay for Soybean Trypsin Inhibitor Activity—the assay for antitrypsin activity of soybean trypsin inhibitor was performed by measuring the inhibition of benzoylarginine ethyl ester cleavage by a trypsin standard solution (17) after the addition of unaltered and modified soybean trypsin inhibitor (SBI) to the standard solution (18) at pH 8.0, 15 mM CaCl₂, and 0.001 M benzoylarginine ethyl ester, containing 0.033 mg/ml of benzoylarginine ethyl ester, and the activity of the trypsin determined by measuring the rate of hydrolysis of the ester in a Zeiss PMQ II spectrophotometer, at 254 nm, against a benzoylarginine ethyl ester control.

Modification of Antithrombin-Heparin Cofactor and Soybean Trypsin Inhibitor by 2,3-Butanedione (18)—Antithrombin-heparin cofactor (500 μg) was dialyzed at room temperature against either 0.19 M 2,3-butandione and 0.39 M NaCl in 0.01 M EDTA (pH 9.5) or 0.39 M NaCl in 0.01 M EDTA without 2,3-butandione. Thereafter, treated and untreated antithrombin-heparin cofactor was dialyzed extensively against the latter buffer. Twenty milligrams of soybean trypsin inhibitor (SBI) was dissolved in 2 ml of 0.2 M potassium phosphate buffer, pH 6.0, and 2,3-butandione was added to a concentration of 0.12 M. The solution was incubated at room temperature for 12 hours and then dialyzed extensively against potassium phosphate buffer. The activity of the modified antithrombin-heparin cofactor was determined as described (13). Treatment with 2,3-butandione ablated both the antithrombin activity of antithrombin-heparin cofactor and the anti-trypsin activity of soybean trypsin inhibitor.

Effect of Plasma Esterase Inhibitors on Response of Macrophage to Migration Inhibitory Factor—Migration inhibitory factor action was markedly enhanced when the macrophages were preincubated with the plasma esterase inhibitors antithrombin-heparin cofactor and α,α-antitrypsin (Table I) and ωα-macroglobulin and C1-inhibitor (Table II). The esterase inhibitors themselves did not alter the migration of macrophages at the concentrations used. Studies on the dose response of the inhibitors indicate that 10 μg/ml of ωα-macroglobulin and antithrombin-heparin cofactor, 500 units/ml of C1-inhibitor (approximately 0.25 μg/ml of inhibitor), and 100 μg/ml of α,α-antitrypsin produce a significant enhancing effect (Fig. 1). Further studies were carried out to be sure that the enhancement of migration inhibitory factor activity by the esterase inhibitors was not simply due to a nonspecific effect caused by
inhibitors used. Therefore, that enhancement of migration inhibitory factor (MIF) activity was not the result of denatured Cl-inhibitor. We conclude, therefore, that enhancement of MIF activity in macrophages is caused by the interaction with the macrophage. This might partly explain why heparin suppresses the migration inhibitory factor-enhancing effect of macrophages, since heparin binds to the macrophage. By interacting with the macrophage, heparin could disrupt the interaction of MIF with the macrophage. The antithrombin-heparin cofactor activity of human plasma was found to contain 1.7 times the antithrombin-heparin cofactor activity of human plasma, using a limiting concentration of MIF. Each horizontal line indicates a single experiment.

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**Table II**

Enhancement of migration inhibitory factor response by preincubation of macrophages with αr-macroglobulin and C1-inhibitor

Cells were divided into two parts. The control cells and the cells preincubated with αr-macroglobulin or C1-inhibitor were assayed for migration inhibitory factor (MIF) activity, using a limiting concentration of MIF. Each horizontal line indicates a single experiment.

<table>
<thead>
<tr>
<th>αr-Macroglobulin</th>
<th>C1-inhibitor</th>
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<tbody>
<tr>
<td>Inhibitor</td>
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preincubation of macrophages with proteins. Tranferrin, RNase, myoglobin, and human IgM (the latter is a possible contaminant of αr-macroglobulin), 50 μg/ml, as well as αr-macroglobulin, as the esterase inhibitor control, were incubated with macrophages under the same conditions. Whereas the αr-macroglobulin, as expected, gave strong enhancement of migration inhibitory factor activity (from 0 to 77% and 16 to 50%), the other proteins caused no enhancement. In addition, a-denatured C1-inhibitor did not have any effect. We conclude, therefore, that enhancement of migration inhibitory factor activity is a specific effect particular to the plasma esterase inhibitors used.

Since all of the plasma esterase inhibitors tested were derived from human plasma, we determined the concentration of one of these inhibitors, antithrombin-heparin cofactor, in guinea pig plasma, using the antithrombin-heparin cofactor test. Guinea pig plasma was found to contain 1.7 ± 0.2 times the antithrombin-heparin cofactor activity of human plasma (90 determinations).

Effect of Heparin on Action of Antithrombin-Heparin Cofactor—Studies using heparin were carried out for several reasons. As shown in studies involving thrombin inactivation, antithrombin-heparin cofactor has a binding site for heparin (13). We therefore considered the possibility that the heparin binding site on antithrombin-heparin cofactor is necessary for the interaction with the macrophage. This might partly explain why heparin suppresses the in vivo cellular immune response in the guinea pig (24).

Macrophages were incubated with antithrombin-heparin cofactor and antithrombin-heparin cofactor was abolished by 2,3-butanedione treatment, but the migration inhibitory factor-enhancing effect was still present. Both experiments indicate that the modification of arginyl residues in the active sites of soybean trypsin inhibitor and antithrombin-heparin cofactor does not alter their migration inhibitory factor-enhancing activities. Fig. 2 shows experiments in which macrophages were preincubated with 2,3-butanedione-modified antithrombin-heparin cofactor and soybean trypsin inhibitor and then were assayed for migration inhibitory factor enhancement. Although 99% of the antithrombin activity of soybean trypsin inhibitor can be prevented by pretreatment of the inhibitor with cyclohexadiene or 2,3-butanedione. These substances modify arginyl residues of the inhibitor (20-22). Likewise, the antithrombin activity of antithrombin-heparin cofactor is destroyed by pretreatment of the inhibitor with 2,3-butanedione (13). In contrast, 2,3-butanedione treatment of soybean trypsin inhibitor and antithrombin-heparin cofactor does not alter their migration inhibitory factor-enhancing activities. Fig. 2 shows experiments in which macrophages were preincubated with 2,3-butanedione-modified antithrombin-heparin cofactor and soybean trypsin inhibitor and then were assayed for migration inhibitory factor enhancement. Although 99% of the antithrombin activity of soybean trypsin inhibitor was abolished by 2,3-butanedione treatment, but the migration inhibitory factor-enhancing effect was still present. Both experiments indicate that the modification of arginyl residues in the active sites of soybean trypsin inhibitor and antithrombin-heparin cofactor has no effect on the interaction of the inhibitors with the macrophage, and suggests a different active site, a finding consistent with the multivalency of other esterase inhibitors (23).
factor activity from 15 to 30% with and from 15 to 37% without rather than to a nonspecific interaction of heparin with the due to its interaction with antithrombin-heparin cofactor, because this reagent is known to destroy the heparin binding site of antithrombin-heparin cofactor (13). Guanidinated antithrombin-heparin cofactor with 0-methyl-isourea, in a manner analogous to heparin. To test this hypothesis, we treated antithrombin-heparin cofactor with O-methyl-isourea, because this reagent is known to destroy the heparin binding site of antithrombin-heparin cofactor (13). Guanidinated antithrombin-heparin cofactor was found to enhance the migration inhibitory factor response of macrophages as well as unaltered antithrombin-heparin cofactor. The data from three experiments are shown in Table IV. Thus, binding of antithrombin-heparin cofactor to the macrophage through a heparin binding site seems not to be obligatory for its enhancing action. However, a short-term effect of heparin on antithrombin-heparin cofactor similar to that on thrombin (13) cannot be ruled out because of the long time required for the migration inhibitory factor assay.

**DISCUSSION**

The experiments presented here demonstrate that the plasma esterase inhibitors, α₂-macroglobulin, α₂-antitrypsin, C1-inhibitor, and antithrombin-heparin cofactor enhance the response of the macrophage to migration inhibitory factor, and that the effect of antithrombin-heparin cofactor can be prevented by the presence of heparin. Treatment of antithrombin-heparin cofactor and soybean trypsin inhibitor with 2,3-butanedioine, in order to modify arginyl residues, abolishes their antithrombin and antitrypsin activities, respectively, but has no influence on their migration inhibitory factor-enhancing capacities.

These findings, along with previous results using iPr₂P-F (9), indicate that an esterase on the macrophage is involved in the modulation of the cell's response to migration inhibitory factor. Furthermore, the small effective concentrations of the plasma esterase inhibitors studied suggest that they may interact in vivo with the macrophage and may play a role in enhancing the cell's response to lymphocyte mediators. Thus, it is likely that these inhibitors play a regulatory function in these cellular processes. A control function of esterases is now established in a variety of other systems. Cell-bound esterases play a role in serotonin release from platelets and in neutrophil exocytosis (26), neutrophil chemotaxis (27), and release of histamine from mast cells (28).

Studies dealing with plasma esterase inhibitors have shown that each of them inhibits a variety of plasma proteinases: α₂-antitrypsin (10, 29, 30) inhibits plasmin, thrombin, and activated prothrombin; α₂-macroglobulin (11) inhibits plasmin, thrombin, and kallikrein; and C1-inhibitor (10, 31) blocks kallikrein, plasmin, and activated prothrombin. Recently, it has been shown that C1-inhibitor enhances the chemotactic responsiveness of leukocytes (32). Antithrombin-heparin cofactor is shown to inhibit virtually all of the serine proteinases of
that anticoagulants inhibit delayed hypersensitivity reactions in vivo in the guinea pig supports these results (24). Administra-
tion of heparin or warfarin to sensitized guinea pigs leads to 
a diminution or abolition of cellular immunity. Chondroitin 
sulfate, an acidic mucopolysaccharide without anticoagulatory 
activity, has no effect. Furthermore, heparin does not inhibit 
nonimmunologic types of inflammation. Also, it was found

the coagulation and fibrinolytic systems. These include throm-
bolin, plasmin, Factors IXa, Xa, and XIa, and kallikrein (12).

It is further of note that the action of a single inhibitor on 
different esterases is accomplished by means of different active 
sites (33-35). For example, studies indicate that antithrom-
bolin-heparin cofactor, which is known to have both anti-
thrombin and antiplasmin activity (13, 36), has two different 
binding sites for these two enzymes. The modification of arg-
inyl residues of this inhibitor with cyclohexadione, 2,3-butan-
dione or phenylglyoxal virtually abolishes antithrombin activ-
ity without a comparable effect on its antiplasmin activity (37).
Furthermore, modification of arginyl residues on α1-antitrypsin 
with phenylglyoxal blocks the action of this inhibitor on 
trypsin, but not on chymotrypsin (30), suggesting two distinct 
binding sites on the inhibitor for these enzymes. Thus, the 
finding that antithrombin-heparin cofactor and soybean 
trypsin inhibitor, altered by 2,3-butanedione, are active on 
macrophages is still consistent with their acting as esterase 
inhibitors.

It is also possible, although less likely, that the macrophage 
esterase binds to the same arginine-containing active site on antithrombin-heparin cofactor and soybean trypsin inhibitor, 
as do thrombin and trypsin (13, 38), but that the alteration of 
the arginyl residues in the active site does not affect the 
interaction of the macrophage esterase with the inhibitor. 
Indeed, substitution of Arg-63 with Phe in soybean trypsin 
inhibitor was shown not to diminish soybean trypsin inhibitor 
activity, indicating that Arg-63 is not obligatory for the 
esterase action (39). However, in all cases known, chemical 
modification of arginyl residues in enzyme inhibitors (20, 22), 
or in enzymes (40-43), destroys their activities when arginine is 
in the active site of these substances.

Of interest is the finding that heparin prevents the enhance-
ment of migration inhibitory factor activity by antithrombin-
heparin cofactor. Experiments with O-methyl-isourea indicate that 
heparin does not act by competing for a macrophage 
mucopolyaccharide binding site on antithrombin-heparin cofactor. 
These experiments show that antithrombin-heparin cofactor is 
still active on the macrophage when its heparin binding site is 
destroyed. More likely, the highly negatively charged 
antithrombin-heparin cofactor-heparin complex is repelled 
from the negatively charged macrophage surface, preventing 
antithrombin-heparin cofactor from acting on the cell. The fact 
that anticoagulants inhibit delayed hypersensitivity reactions in vivo in the guinea pig supports these results (24). Administra-
tion of heparin or warfarin to sensitized guinea pigs leads to 
a diminution or abolition of cellular immunity. Chondroitin 
sulfate, an acidic mucopolysaccharide without anticoagulatory 
activity, has no effect. Furthermore, heparin does not inhibit 
nonimmunologic types of inflammation. Also, it was found

that fibrin accumulation can be consistently detected in 
delayed hypersensitivity skin reactions and can be inhibited by 
warfarin (44).

The significance of macrophage esterases in vivo, as well as 
their possible natural substrates, is unknown. A variety of 
plasma proteinases are activators in the pathways of the acute 
inflammatory responses. The kinins and anaphylatoxins are 
immediately destroyed by enzymes, upon generation, and 
recently an activator of the chemotactic fragments of C9, C3b, 
and C5b all was described (45). In light of these facts, the 
macrophase esterase might well be an inactivator of migration 
inhibitory factor itself, or might participate in a series of 
enzymatic interactions resulting, finally, in an activation of the 
macrophage. It seems reasonable to assume that the effect of 
plasma esterase inhibitors on macrophages has a regulatory 
function in vivo. At the inflammatory site, the inhibitors might 
escape into the tissue from the blood vessels and increase the 
macrophage response to lymphocyte mediators and possibly 
increase the activation of defense mechanisms.

The findings presented in this report extend the importance 
of plasma esterase inhibitors, from their role in humoral 
systems to the field of cellular immunity. Further studies will 
be required to characterize the esterases on the macrophage 
and their substrates, to demonstrate their role in vivo, and to 
determine whether they also act on macrophage activation.

Acknowledgments—We wish to thank Dr. John David and 
Roberta David for their help and suggestions. We wish, further, 
to acknowledge the excellent technical assistance of Ms. Alma 
Mednic and Ms. Judith Shaw.

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TABLE IV
Untreated antithrombin-heparin cofactor and 
O-methyl-isourea-treated antithrombin-heparin cofactor exhibit 
similar enhancement of migration inhibitory factor response

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H G Remold and R D Rosenberg


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