Rabbit alveolar macrophages exhibit high affinity binding sites for \( \alpha \)-macroglobulin-protease complexes. The binding of \( \alpha \)-macroglobulin-\( ^{125} \)I-trypsin complexes (\( \alpha M^{125} \)I-T) to cells obtained by bronchial lavage was specific for macrophages and was dependent on cell number. The association of \( \alpha M^{125} \)I-T complexes to cells was time-dependent and saturation was reached at 45 to 60 min. The initial rate of binding, as defined by the time it takes to reach half-maximal saturation, appeared temperature-independent and the maximum amount of cell-associated \( \alpha M^{125} \)I-T increased with increased temperature. Exposure of cells to paraformaldehyde interfered with metabolic activity and prevented the temperature-dependent accumulation of \( \alpha M^{125} \)I-T by macrophages. Under these conditions, a temperature dependence in binding rate could be discerned. Studies of the concentration dependency of association of \( \alpha M^{125} \)I-T to cells revealed that at 20°C saturation of cells with ligand was asymptotically approached. Following treatment of cells with paraformaldehyde or incubation of cells at 0°C, a concentration-dependent saturation of binding activity could be demonstrated. These and other observations suggest that the temperature dependence association of \( \alpha M^{125} \)I-T with cells resulted from both binding to cell surface receptors and events subsequent to binding. In the companion paper, we demonstrate that at physiological temperatures receptor-bound \( \alpha M^{125} \)I-T is rapidly internalized (Kaplan, J. and Nielsen, M. L. (1979) J. Biol. Chem. 254, 7329–7335).

Radiolabeled complexes bound to cells did not exhibit any measurable rate of dissociation at 0°C. Rabbit \( \alpha M^{125} \)I-T and \( \alpha \)-human \( \alpha \)-macroglobulin \( \alpha \)-trypsin complexes were bound to macrophages at identical rates and apparently to the same receptor. Human \( \alpha \)-macroglobulin complexes could compete with rabbit \( \alpha M^{125} \)I-T complexes for binding sites, although at a 10-fold higher concentration of the human protein.

Binding of labeled complexes to cells required divalent ions, and complexes bound to cells in the presence of divalent ions could be removed by treatment with Ca\(^{2+}\) and Mg\(^{2+}\) free solutions containing EDTA.

Proteases can produce tissue damage as a result of direct proteolytic attack or by activating plasma “cascade” reactions. Among the cascade reactions which result from endoprotease activity are fibrin formation, complement activation, and kinin generation (cf. Ref. 1). The activation of these plasma components is in part prevented by high levels of plasma protease inhibitors.

\( \alpha \)-Macroglobulins constitute a major part of plasma anti-protease activity and have unique characteristics. Proteases bound to \( \alpha \)-macroglobulins retain enzyme activity and, depending on substrate size and configuration, exhibit a spectrum of esterase and protease activities (2). For example, trypsin bound to \( \alpha M \) has undiminished esterase activity toward low molecular weight substrates such as \( \alpha \)-N-benzoyl-DL-arginine-p-nitroanilide/HCl (3–5). Although some protein substrates such as albumin are not cleaved, \( \alpha M \) is capable of proteolysis. It has been shown that \( \alpha M \) can convert chymotrypsinogen into chymotrypsin (6) and can generate biologically active kinin (7).

The proteolytic activity of \( \alpha M \)-protease complexes in vitro is usually not expressed due to the rapid clearance of such complexes by cells of the monocyte-phagocyte family (8–10). DeBanne et al. (11) demonstrated that rabbit macrophages in vitro readily took up complexes of \( \alpha M \) and subtilisin. In this communication we present a quantitative analysis of the interaction between \( \alpha M \) and specific receptors on the surfaces of rabbit alveolar macrophages. In a companion paper we demonstrate that binding of \( \alpha M \)-protease complexes results in the rapid internalization and subsequent intracellular degradation of the bound complex (12).

**EXPERIMENTAL PROCEDURES**

**Methods**

**Cells**—Rabbit alveolar macrophages were obtained by bronchial lavage as previously described (13). The cells were incubated at a concentration of 1 to 2 \( \times \) \( 10^7 \) cells/ml in minimal essential media.

**Isolation of \( \alpha \)-Macroglobulins**—Rabbit blood was withdrawn via cardiac puncture into heparinized syringes. All operations were carried out at 4°C. The blood was placed in 50-ml plastic tubes which contained EDTA and soybean trypsin inhibitor at a final concentration of 2 mM and 10 \( \mu \)g/ml, respectively. The tubes were centrifuged at 1800 \( \times \) \( g \) for 15 min and the plasma decanted. It was then delipidated by centrifugation at 100,000 \( \times \) \( g \) for 12 h. Delipidated plasma was applied to an agarose column (Bio-Gel A-5, bed volume 900 ml), and the column was eluted with 0.1 M NaCl buffered with 0.02 M Tris-HCl, pH 7.65 (measured at 20°C), at a flow rate of 10 ml/h. Fractions containing \( \alpha M \) were pooled and concentrated by positive pressure through a PM10 Amicon filter. This preparation was used or was further separated into \( \alpha \)-human \( \alpha \)-macroglobulins and \( \alpha \)-rabbit \( \alpha \)-macroglobulins. This was accomplished by eluting the preparation with 0.07 M Tris-HCl, pH 7.65 (measured at 20°C), at a flow rate of 10 ml/h. Fractions containing \( \alpha M \) were pooled and concentrated by positive pressure through a PM10 Amicon filter. This preparation was used or was further separated into \( \alpha \)-human \( \alpha \)-macroglobulin and \( \alpha \)-rabbit \( \alpha \)-macroglobulin. The fractions were then diluted with a diethylaminoethyl cellulose column (Whatman DE52, column bed volume 900 ml) equilibrated with the same buffer. The column was eluted (flow rate, 20 ml/h) with a linear gradient of 0.05 M (350 ml) to 0.5 M.
m (350 ml) NaCl in 0.02 M Tris-HCl, pH 7.65. Fractions were assayed for absorbance (A280), conductivity, and, following addition of trypsin, SBTI-resistant protein esterase activity.

**Assay for Protease Esterase Activity**—Protease esterase activity was determined using α-N-benzoyl-DL-arginine-p-nitroanilide/HCl (5) or the active site titrant nitrophenyl p-guanidino benzozate/HCl (14).

**SBTI-resistant Protein Esterase Activity**—The distinctive characteristic of αM as a protease inhibitor is that bound trypsin retains its esterase activity (G-5). The esterase activity of bound trypsin is protected from inactivation by SBTI, whereas trypsin not bound to αM is inactivated (4). Thus, trypsin esterase activity in the presence of SBTI was used to identify the presence of αM.

**Preparation of αM-αM**—Purified αM or the separated αM and αM was reacted with an excess of trypsin for 30 min at 20°C. The mixture was then applied to a Sephadex G-200 column (bed volume 300 ml) equilibrated with 0.1 M NaCl buffered with 0.02 M Tris-HCl, pH 7.65, and eluted (flow rate 10 ml min⁻¹) with the same buffer. αM-αM which eluted with the void volume was determined by positive pressure filtration using PM10 Amicon filters.

**Iodination of Trypsin**—To 20 ml of a solution of trypsin (1 mg ml⁻¹) in 0.02 M sodium borate, pH 7.6, containing 1 mM CaCl₂ and 0.1 M NaCl was added 1 mg of Na⁺¹²⁵I (1 to 2 μl, New England Nuclear, specific activity 17 Ci mg⁻¹) followed by 10 μl of chloramine-T (10 mg ml⁻¹). The reaction mixture was applied to a Sephadex G-10 column (bed volume 5 ml) and equilibrated and eluted with 0.02 M sodium borate, pH 7.6, containing 0.1 M NaCl and 1 mM CaCl₂. Samples in the void volume containing αM-αM were pooled and the specific activity was determined. Specific activities were found to be in the order of 10 Ci mg⁻¹ mol⁻¹.

**Preparation of αM-αM**—Equimolar amounts of αM and αM-αM were exposed in a desiccator chamber at 6°C for 8 weeks. Processing and storage was according to the procedure of Lowry et al. (18) and employing bovine serum albumin as a standard. Pinocytic activity was measured using a-N-benzoyl-nL-arginine-p-nitroanihde/HCl (350 ml) NaCl in 0.02 M Tris-HCl, pH 7.65. Fractions were assayed for alcohol (A₂₈₀), conductivity, and, following addition of trypsin, SBTI-resistant protein esterase activity.

**Materials**

Trypsin, SBTI, α-N-benzoyl-DL-arginine-p-nitroanilide/HCl, bovine serum albumin (Fraction V), α-diamidine, and hors eradish peroxidase were purchased from Sigma Chemical Co. Nitrophenyl p-guanidino benzozate/HCl was purchased from Nutritional Biochemicals.

**RESULTS**

**Isolation of αM**—Fractions containing αM, obtained by agarose chromatography, contained two major proteins when examined by polyacrylamide gel electrophoresis (Fig. 1, panel C). Following reaction with trypsin and isolation by chromatography on Sephadex G-200, polyacrylamide gel electrophoresis again revealed only two proteins (Fig. 1, panel D). When not complexed to trypsin these two proteins can be isolated by ion exchange chromatography, αM eluted as a sharp symmetrical peak, while the αM was retained and subsequently eluted as a broad peak with a prominent trailing edge (Fig. 2). When analyzed by polyacrylamide gel electrophoresis, each component exhibited one major band (Fig. 1, panels A and B). In contrast, human plasma had only one αM as seen by gel electrophoresis (data not shown). These observations show that the isolation procedure results in a highly purified preparation of protease binding αM.

Studies of human αM (3) or rat αM (15) have demonstrated that αM binds proteases in an equimolar ratio. Examination of the trypsin binding capacity of rabbit αM, employing SBTI to inhibit unbound trypsin, revealed trypsin to αM ratios much less than 1 (0.2 to 0.4 mol of trypsin/mol of αM).

** Autoradiography**—Slides for autoradiography were coated with Kodak NTB-2 emulsion diluted 1:2 with distilled water and were exposed in a desiccator chamber at 6°C for 8 weeks. Processing and development were performed according to standard procedures (17). After development, slides were stained for microscopic examination with 1% Giemsa in 0.1 M phosphate buffer, pH 7.5.

**Additional Procedures**—Protein determinations were done according to the procedure of Lowry et al. (18) and employing bovine serum albumin as a standard. Pinocytic activity was determined by measuring the uptake of horseradish peroxidase as described elsewhere (19).

![Fig. 1. Polyacrylamide gel electrophoresis of αM and αM-αM. αM isolated from rabbit plasma by agarose chromatography showed two major bands (A), αM-αM formed in the presence of SBTI was eluted from the gel as a single band (B). The mixture of αM and αM-αM was applied to a Sephadex G-200 column and the void volume contained both αM and αM-αM (C). Following reaction with trypsin and isolation by chromatography on Sephadex G-200, polyacrylamide gel electrophoresis again revealed only two proteins (Fig. 1, panel D).](http://www.jbc.org/content/139/2/1732/fig/1)
aM). However, following isolation of aM·125I-T by Sephadex G-200 chromatography the molar ratio of trypsin to aM approached unity (0.8 to 0.9); protein recovery was only 30%. Even though aM isolated by agarose chromatography is antigenically pure (data not shown) and chromatographically pure, 30 to 70% of such preparations are not capable of binding trypsin and are apparently degraded by trypsin.

Similar results have been obtained with isolated aM and aM·125I-T. As seen in Fig. 2, aM·125I-T had a higher SBTI-resistant protease esterase activity (2- to 3-fold) than aM·T. Following reaction with 125I-T and isolation of aM·125I-T, aM·125I-T exhibited a higher trypsin binding capacity than aM·T. Following pretreatment of cells with paraformaldehyde markedly reduced the temperature-dependent accumulation of aM·125I-T seen in cells incubated at 20°C (Fig. 3), whereas paraformaldehyde pretreatment of cells has no effect on either the initial rate or extent of aM·125I-T accumulation of cells maintained at 0°C.

Treatment of cells with paraformaldehyde inhibits both metabolic activity and membrane-associated events (20). The data in Table II demonstrate that pretreatment of macrophages with 1% paraformaldehyde led to an inhibition of endocytic activity as measured by the uptake of horseradish...
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Horseradish peroxidase is internalized by both fluid and receptor-mediated pinocytosis in rabbit alveolar macrophages (21). Similar results are obtained when cells are pretreated with either 0.1 mM N-ethylmaleimide or 1 mM phenylglyoxal monohydrate, agents which inhibit endocytic activity in other cell types (11, 12, 23). These observations suggest that rigorous kinetic analysis of the binding of αM-125I-T to cells at physiological temperatures is complicated by metabolic events subsequent to ligand-receptor binding. In a companion paper we demonstrate that receptor-bound αM-125I-T exhibits a temperature-dependent internalization (12).

Paraformaldehyde pretreatment of cells allows an analysis of receptor-ligand interactions. For example, a temperature dependence in the rate of binding between cells incubated at 0°C and paraformaldehyde-treated cells can easily be discerned in Fig. 3, with the kinetics of binding conforming to pseudo-first order kinetics.

Dissociation of Bound αM-125I-T—The rate of dissociation of bound αM-125I-T from macrophages was examined by incubating cells with labeled probe and then washing and incubating cells in media without probe. No discernible loss of cell-associated radioactivity occurred following incubations of up to 2 h at either 0°C or 20°C. One explanation for this observation is that binding of complexes to surface receptors induces the internalization of the complex. At 20°C this explanation may pertain (12). However, at 0°C endocytic activity was severely inhibited (Table II), and another explanation must be sought.

Incubation of cells, prelabeled at 0°C with αM-125I-T, with a high concentration of unlabeled αM-T (10^-7 M) for up to 4 h at 0°C also did not result in dissociation of labeled complexes from cells. These results suggest that αM-125I-T complexes are avidly bound to macrophage surfaces.

Concentration Dependence of Binding of αM-125I-T to Cells—Fig. 4 demonstrates the relationship between the concentration and association of αM-125I-T to cells at 20°C. A complex curve is obtained in which saturation of cells by ligand is asymptotically approached. The amount of cell-associated αM-125I-T continues to increase in the presence of high concentrations of αM-125I-T. However, treatments which prevent endocytic activity significantly alter the concentration dependency of binding. For example, treatment of cells with paraformaldehyde reduces the total amount of αM-125I-T associated with cells at 20°C and saturation of binding sites is clearly demonstrated. Similar results were obtained when the concentration dependency of αM-125I-T binding to unixed cells at 0°C was studied. Saturation of binding sites was again observed and the concentration of αM-125I-T leading to half-maximal saturation, 2.0 × 10^-9 M, was similar to that observed at 20°C with paraformaldehyde-exposed cells. Under these conditions alveolar macrophages are capable of binding 9 to 11 × 10^4 molecules of αM-125I-T-cell^-1.

Specificity of Receptors—Rabbit plasma contains two separable αM capable of binding proteases. To determine whether these species bind to the same or different receptors

![Fig. 4. Association of αM-125I-T to macrophages as a function of αM-T concentration. Macrophages were incubated with different concentrations of αM-125I-T for 90 min either in the presence or absence of αM-T. The binding of αM-125I-T to cells prefixed with paraformaldehyde was also determined. ▲—▲, association with control cells at 20°C; △—△, association with paraformaldehyde-treated cells at 20°C; ○—○, association with control cells at 0°C.](http://www.jbc.org/)

![Fig. 5. Effect of incubation with cells on distribution of 125I radioactivity. Preparations of αM-125I-T were incubated with macrophages at 20°C. At specified times the cells were pelleted by centrifugation and samples of the supernatant applied to gel electrophoresis. The gels were then fractionated and the distribution of 125I radioactivity determined. A, Coomassie blue staining pattern of unlabeled αM-T; B, distribution of 125I radioactivity in αM-125I-T prior to incubation with cells; C, distribution of 125I radioactivity in supernatant following a 2-h incubation with cells.](http://www.jbc.org/)
38.0% of $^{125}$I radioactivity was associated with $\alpha M$,$\beta$-$T$ and the remainder with $\alpha M$,$\gamma$-$T$ (Fig. 5B).

Examination of supernatants obtained following incubation of $\alpha M$,$\beta$-$T$ with cells did not reveal any change in the distribution of $^{125}$I radioactivity. Thus, after incubations ranging from 2 min to 2 h (at which point 40% of the input radioactivity had become cell associated), the distribution of $^{125}$I between $\alpha M$,$\beta$-$T$ and $\alpha M$,$\gamma$-$T$ was identical with that observed prior to the experiment (Fig. 5C). These results suggest that both $\alpha M$,$\beta$-$T$ and $\alpha M$,$\gamma$-$T$ bind to cells at apparently identical rates. Additionally, all radioactivity applied to the gel migrated as either $\alpha M$-$T$ or $\alpha M$-$T$. It should be noted that $\alpha M$-$T$ constitutes a greater percentage of mass than $\alpha M$-$T$ (Fig. 5A), thus suggesting a higher specific activity for $\alpha M$-$T$.

To determine whether $\alpha M$-$T$ and $\alpha M$-$T$ bind to the same class of receptors, we examined the ability of $\alpha M$-$T$ or $\alpha M$-$T$ to compete with $\alpha M$,$\beta$-$T$ for binding sites. Fig. 6 demonstrates that $\alpha M$-$T$ was as efficient as $\alpha M$-$T$ in preventing the binding of $\alpha M$,$\beta$-$T$. Additionally, human $\alpha M$-$T$ could prevent the binding of rabbit $\alpha M$,$\beta$-$T$ to macrophages although at a 10-fold higher concentration than rabbit $\alpha M$-$T$. These results suggest that both $\alpha M$-$T$ and $\alpha M$-$T$ occupy the same site.

Uncomplexed $\alpha M$ could, at high concentrations, partially inhibit binding of $\alpha M$,$\beta$-$T$ to cells. The small amount of displacement was probably the result of protease complex formation which occurred during the isolation procedure. Albumin at concentrations up to 2 mg·ml$^{-1}$ (2.9 x 10$^{-5}$M) had no effect on binding of $\alpha M$,$\beta$-$T$ to macrophages.

**Requirement of Divalent Ions for Binding Activity**—While formation of $\alpha M$-$T$ does not require divalent ions, there does appear to be an absolute divalent ion requirement for binding of $\alpha M$-$T$ to cells. Table III demonstrates that in the absence of divalent ions binding of $\alpha M$,$\beta$-$T$ to cells was abolished. Addition of 0.1 mM CaCl$_2$ restored 100% binding activity, whereas addition of 1 mM MgCl$_2$ resulted in a 50% recovery of binding activity. Bound $\alpha M$,$\beta$-$T$ could be quantitatively removed from cells by incubation with Ca$^{2+}$- and Mg$^{2+}$-free HBSS containing 5 mM EDTA. Incubation of cells with $\alpha M$,$\beta$-$T$ for up to 2 h at 0°C followed by treatment with Ca$^{2+}$- and Mg$^{2+}$-free HBSS containing 5 mM EDTA removed 90 to 97% of cell-associated radioactivity. These data suggest procedures for distinguishing internalized $\alpha M$,$\beta$-$I$-T from cell surface-associated $\alpha M$,$\beta$-$I$-T (12, 21).

**Table III**

<table>
<thead>
<tr>
<th>Incubation</th>
<th>fmol·10$^6$ cells$^{-1}$</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM Ca$^{2+}$, 1 mM Mg$^{2+}$ (HBSS)</td>
<td>185.2</td>
<td>100.0</td>
</tr>
<tr>
<td>-Ca$^{2+}$, -Mg$^{2+}$</td>
<td>9.2</td>
<td>5.0</td>
</tr>
<tr>
<td>1 mM Ca$^{2+}$</td>
<td>200.4</td>
<td>108.0</td>
</tr>
<tr>
<td>0.1 mM Ca$^{2+}$</td>
<td>214.9</td>
<td>119.0</td>
</tr>
<tr>
<td>0.01 mM Ca$^{2+}$</td>
<td>107.1</td>
<td>57.4</td>
</tr>
<tr>
<td>1 mM Mg$^{2+}$</td>
<td>94.9</td>
<td>51.3</td>
</tr>
<tr>
<td>0.1 mM Mg$^{2+}$</td>
<td>73.7</td>
<td>39.8</td>
</tr>
<tr>
<td>0.01 mM Mg$^{2+}$</td>
<td>36.9</td>
<td>19.9</td>
</tr>
<tr>
<td>+1 mM Ca$^{2+}$ + 1 mM Mg$^{2+}$, wash with Ca$^{2+}$-Mg$^{2+}$-free HBSS + 5 mM EDTA</td>
<td>8.6</td>
<td>4.6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

$\alpha M$-protease complexes are avidly bound to macrophage surface receptors. At 0°C half-maximal saturation of surface receptors with $\alpha M$,$\beta$-$I$-T occurs at a concentration of 2.0 x 10$^{-10}$M and in the absence of endocytosis receptor-bound complexes do not exhibit measurable rates of dissociation. These observations are consistent with the macrophage function of regulating protease activity and partially confirm a previous study of DeBanne et al. (11). We have extended this work by examining the initial interaction between $\alpha M$-protease complexes and surface receptors. At temperatures of 20°C (as used in the study of DeBanne et al. (11)) or greater, analysis of the binding of $\alpha M$,$\beta$-$I$-T to receptors is complicated by events that occur subsequent to binding, such as internalization of occupied receptors (12) followed by the reappearance of binding activity.5 Treatments which inhibit metabolic and/or endocytic activity alter the time and concentration dependence of binding (cf. Fig. 4). Saturation of binding at 20°C cannot really be measured in control cells but is clearly demonstrated in paraformaldehyde-treated cells. These observations demonstrate the necessity of distinguishing between the binding of ligands to receptors and events subsequent to binding.

While humans contain only one species of protease-binding $\alpha M$ (3, 24), rabbits and other animals contain two species of protease-binding $\alpha M$. These species are separable by gel electrophoresis (Fig. 1) or ion exchange chromatography (Fig. 2). Studies have suggested that rabbit $\alpha M$ and $\alpha M$ are immunologically and metabolically distinct (24). Antibodies directed against rabbit $\alpha M$ exhibit cross-reactivity with human $\alpha M$ but not rabbit $\alpha M$ (24). Our data, however, demonstrate that both rabbit $\alpha M$-$I$ and $\alpha M$-$T$ bind to the same macrophage receptor. Human $\alpha M$ exhibits immunological cross-

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**Fig. 6.** Competition between $\alpha M$,$\beta$-$I$-T and different preparations of $\alpha M$ for binding to surface receptors. Macrophages were incubated with a constant amount of $\alpha M$,$\beta$-$I$-T (10$^{-7}$M) and different amounts of either $\alpha M$-$T$, $\alpha M$-$T$, or human $\alpha M$-$T$ for 60 min at 0°C. Specifically bound cell-associated radioactivity was determined as described. 100% binding was determined by measuring the binding of $\alpha M$,$\beta$-$I$-T to surface receptors in the absence of any competitor. Nonspecific binding was determined by measuring radioactive bound in the presence of rabbit $\alpha M$-$T$ (10$^{-7}$M). Binding of $\alpha M$,$\beta$-$I$-T in the presence of rabbit $\alpha M$-$T$ (O—O), rabbit $\alpha M$ (A—A), and human $\alpha M$-$T$ (O—O).
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reactivity with rabbit αM but not α2M; however, human αM-T can compete with both rabbit αM-T and α2M-T for macrophage surface receptors. We have also observed that rabbit αM-125I-T can bind to mouse macrophage tumor cells (PU-5, J774). DeBanne et al. (11) demonstrated that the binding activity of αM-protease complexes was independent of the bound protease. These results suggest that conversion of αM to αM-protease complexes reveals the cells surface binding site which appears undetected by immunological approaches.

If extreme care is taken αM can be prepared essentially free of protease complexes as defined by the inability of such preparations to compete with αM-125I-T for cell surface binding sites (cf. Fig. 6). However, when proteases are activated during the isolation procedure they appear to preferentially bind to αM. This is suggested by the fact that αM exhibits a greater trypsin binding capacity than α2M. Yet, based on electrophoretic mobility and cell binding activity, the latter are converted to protease complexes. These results suggest that extreme care should be taken in adjusting for different specific activities when binding of αM-protease complexes to surface receptors is studied.

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