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Mast Cell Chymase Modifies Cell-Matrix Interactions and Inhibits Mitogen-Induced Proliferation of Human Airway Smooth Muscle Cells

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Asthma is characterized clinically by airway narrowing and bronchospasm and is accompanied by prominent inflammation and smooth muscle (ASM) hypertrophy and hyperplasia. A wide variety of mast cell-, eosinophil-, and T cell-derived inflammatory mediators have been implicated in this response, and the role of stromal cells, such as ASM and epithelial cells, in perpetuating airway inflammation is now recognized. While acute inflammation typically resolves with restoration of normal function, the chronic inflammatory stimuli in asthma can lead to structural alterations within the airway, referred to as airway remodeling.

The composition and integrity of extracellular matrix (ECM) proteins play a critical role in maintaining the structure and function of the airway and in regulating cell growth. For example, vascular smooth muscle cells proliferate on monomer, but not fibrillar, collagen (1), while changes in the architecture of a fibronectin matrix can inhibit cell cycle progression (2). In fibroblasts, integrin-mediated adhesion to ECM is necessary for mitogen-induced sustained ERK activation and expression of cyclin D1 (3, 4). Recently, it has been shown that adhesion to fibronectin and other ECM proteins is antiapoptotic for human ASM cells (5), again emphasizing the importance of cell-matrix interactions in maintaining cell viability and growth.

One of the factors that contribute to the injury and repair processes within the airway is activation of proteases and turnover of ECM components. The composition of the ECM is tightly controlled and involves a dynamic process of matrix deposition and degradation. In asthma, not only is there an increase in matrix deposition, but there is also an imbalance between matrix-degrading enzymes and inhibitors of these proteases (6). Mast cells, which are present in increased numbers in the asthmatic airway, are a rich source of the neutral protease chymase, which can degrade several basement membrane components. Recent data suggest that proteases also play a critical role in regulating the expression of CD44, the primary receptor for the matrix glycosaminoglycan hyaluronan. In this study we investigated the effects of chymase treatment on human ASM cell function. We found that chymase degraded the smooth muscle cell pericellular matrix. This was accompanied by an increased release of fibronectin and soluble CD44, but not soluble ICAM-1 or soluble hyaluronan, into the conditioned medium. In addition, chymase inhibited T cell adhesion to ASM and dramatically reduced epidermal growth factor-induced smooth muscle cell proliferation. These data suggest that the local release of mast cell chymase may have profound effects on ASM cell function and airway remodeling.

The hallmarks of chronic, severe asthma include prominent airway inflammation and airway smooth muscle (ASM) hypertrophy and hyperplasia. One of the factors that contribute to the injury and repair processes within the airway is activation of proteases and turnover of extracellular matrix components. Mast cells, which are present in increased numbers in the asthmatic airway, are a rich source of the neutral protease chymase, which can degrade several basement membrane components. Recent data suggest that proteases also play a critical role in regulating the expression of CD44, the primary receptor for the matrix glycosaminoglycan hyaluronan. In this study we investigated the effects of chymase treatment on human ASM cell function. We found that chymase degraded the smooth muscle cell pericellular matrix. This was accompanied by an increased release of fibronectin and soluble CD44, but not soluble ICAM-1 or soluble hyaluronan, into the conditioned medium. In addition, chymase inhibited T cell adhesion to ASM and dramatically reduced epidermal growth factor-induced smooth muscle cell proliferation. These data suggest that the local release of mast cell chymase may have profound effects on ASM cell function and airway remodeling.

The composition and integrity of extracellular matrix (ECM) proteins play a critical role in maintaining the structure and function of the airway and in regulating cell growth. For example, vascular smooth muscle cells proliferate on monomer, but not fibrillar, collagen (1), while changes in the architecture of a fibronectin matrix can inhibit cell cycle progression (2). In fibroblasts, integrin-mediated adhesion to ECM is necessary for mitogen-induced sustained ERK activation and expression of cyclin D1 (3, 4). Recently, it has been shown that adhesion to fibronectin and other ECM proteins is antiapoptotic for human ASM cells (5), again emphasizing the importance of cell-matrix interactions in maintaining cell viability and growth.

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The role of proteinases in airway remodeling remains an area of active investigation, although the effects of metalloproteinases and serine proteinases on ASM cells are not well defined in cellular systems. While it is known that mast cell tryptase can induce ASM cell proliferation, in part through activation of p42/44 mitogen-activated protein kinase (MAPK) (18, 19), the direct effects of chymase on ASM cells have not been extensively studied. This is important, because mast cells residing in the airway connective tissue and submucosa secrete both chymase and tryptase.

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In this study we investigated the effects of chymase treatment on human ASM cells. We found that chymase degraded the smooth muscle cell pericellular matrix, resulting in increased release of fibronectin and soluble CD44 (sCD44) into the conditioned medium. In addition, chymase dramatically reduced epithelial growth factor (EGF)-induced smooth muscle cell proliferation without affecting ERK activation or expression of cyclin D1. Finally, chymase treatment inhibited T cell adhesion to cytokine-activated ASM cells. These data suggest that the local release of mast cell chymase may have profound effects on ASM cell function and may contribute to airway remodeling.

Materials and Methods

Abs and reagents

Mouse anti-human LFA-1 (TS1/22) was purchased from American Type Culture Collection (Manassas, VA) and purified from hybridoma supernatants. Mouse anti-β1, integrin (PS1D2) was obtained from Developmental Studies Hybridoma Bank (University of Iowa, Iowa City, IA). Mouse anti-human CD44 (Hermes III and 5F12) were gifts from E. Butcher (Stanford NC), respectively. Mouse anti-human ICAM-1 (RR6.5) was a gift from R. Rothlein (Boehringer Ingelheim Pharmaceutical, Ridgefield, CT). Rabbit anti-human EGF receptor and anti-cyclin D1 were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Rabbit anti-phospho-MAPK was purchased from Cell Signaling Technology (Indianapolis, IN).

Human airway smooth muscle cell culture

Human airway smooth muscle cells isolated from the trachealis muscle of human tracheal tissue of transplant donors were maintained in Ham’s F-12 medium (Life Technologies, Grand Island, NY) supplemented with 10% FBS (HyClone Laboratories, Logan, UT), 2 mM glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin (all from Sigma-Aldrich, St. Louis, MO). These cells retain smooth muscle-specific actin staining and responsiveness to contractile agonists, as previously described (20). Third and fourth passage cells were used in all experiments.

Synthesis of recombinant chymase, enzymatically inactive mutant, and inhibitor

Recombinant human chymase (rHC) was expressed as a pseudo-zymogen using a baculovirus insect cell system and was purified as previously described (21). The primary structure of rHC differed from that of native chymase by two residues in positions that do not affect biochemical or structural properties. The rHC-H57A variant is a catalytically inactive form of chymase in which the His residue of the catalytic triad was mutated to Ala. The mutation of His57 to Ala was achieved using the overlap-extension PCR method and was produced and purified in the same manner as rHC. The production of the variant recombinant α1-antichymotrypsin rACT-P3P3 has been previously described (22). The P3P3 stock was shown to be endotoxin free.

The concentration of rHC was determined based on specific activity under standardized conditions as previously established. The value for rHC is 2.7 μmol (min/mg) -1 in 0.4 M Tris-HCl (pH 8), 1.8 M NaCl, 9% DMSO, and 1 mM succinyl-Ala-Ala-Pro-β-nitroanilide. The extinction coefficient for pNA is 8800. The concentration of rHC-H57A was determined by A280 nm, assuming an extinction coefficient empirically determined as 25,000 M -1 cm -1. The variant was demonstrated to bind to soybean Bowman Birk inhibitor with similar affinity as rHC, indicating that rHC-H57A was well folded. The concentration of stock solutions of the serpin rACT-P3P3 was estimated by A280 nm, assuming an extinction coefficient empirically determined as 45,200 M -1 cm -1. The inhibitory activity was determined by titration of chymotrypsin of known concentrations (23). Recombinant HC is irreversibly inhibited by rACT-P3P3, forming the characteristic 1/1 covalent serpin-protease complex. Complexes were formed by incubation of chymase at an [His57] concentration of -2. Reaction buffer was 10 mM 3-[N-morpholino] propane sulfonic acid (pH 6.8) and 2.0 M NaCl. Residual enzyme activity, assessed after a 15-min incubation, was <1%.

ELISA

The release of sCD44 was quantified using a sandwich ELISA. Briefly, plates were coated with Hermes III anti-CD44 mAb, and test samples were added at room temperature for 2 h. Affinity-purified CD44-Fc fusion protein containing the complete extracellular domain of CD44-H was used as a standard (24, 25). Bound sCD44 was detected using an FITC-conjugated anti-CD44, followed by incubation with alkaline phosphatase-conjugated anti-FITC mAb and developed with p-nitro-phenyl phosphate substrate. Fibronectin was also detected using an ELISA, as previously described (26). Soluble ICAM-1 was quantified using a commercial ELISA (R&D Systems) according to the manufacturer’s instructions.

Smooth muscle cell proliferation

Proliferation assays were performed as previously described (27). Briefly, ASM cells were growth-arrested for 48 h in Ham’s F-12 containing 0.1% BSA. Subsequently, cells were treated, where indicated, with increasing doses of chymase for 24 h, then stimulated with EGF (10 ng/ml). Incorporation of [3H]thymidine was used to determine DNA synthesis, and manual cell counts were performed in parallel. Each condition was determined in triplicate and reported as the mean ± SEM.

T cell adhesion

A quantitative adhesion assay was performed as previously described (28). Briefly, ASM cells were treated with chymase (5 nM) in the absence or the presence of TNF (1000 U/ml) overnight. Peripheral blood T cells were isolated using RosetteSep (StemCell Technologies, Vancouver, Canada). [3H]Thymidine-labeled T cells, activated with ionomycin (250 nM; Sigma-Aldrich) and phorbol 12,13-dibutyrate (5 ng/ml; Sigma-Aldrich) were added and incubated for 1 h at 37°C. After gentle washing to remove unattached cells, adherent cells were lysed with 1% Triton X-100. Radioactivity was measured using a scintillation counter, and percent adhesion was expressed as (adherent counts/input counts) x 100.

Immunoblotting

Cells were stimulated as indicated in the figures, and cell lysates were prepared as previously described (29). Fifteen micrograms of protein was separated by SDS-PAGE on an 8% gel, transferrred to a polyvinylidene difluoride membrane, and immunoblotted as previously described (29).

Results

Chymase disrupts cell-associated matrix and releases sCD44

To determine the effect of chymase on ASM, cells were treated with chymase overnight. Visual inspection of the cells suggested degradation of the ECM and revealed a dramatic change from a flattened monolayer to a more stellate appearance (Fig. 1A). Degradation of matrix was quantitatively evidenced by an increase in fibronectin detected in the medium from cells treated with chymase (Fig. 1B). The time course and magnitude of the increase in soluble fibronectin were consistent with the release of existing proteoglycan rather than de novo synthesis. Indeed, chymase induced only a moderate increase in fibronectin gene expression after 6 and 24 h (data not shown).

CD44, which promotes cell adhesion and migration, is abundant on the surface of many cell types. However, CD44 also exists in a soluble form (sCD44), the level of which is increased in inflammatory states. Studies suggest that in some systems sCD44 is released from cells through the action of a chymotrypsin-like protease (30, 31). Given the dramatic effects of chymase on smooth muscle-associated matrix, we investigated whether chymase promoted the release of sCD44. Using an ELISA, we measured the concentration of sCD44 in the conditioned medium of chymase-treated ASM cells. ASM cells released a low basal level of sCD44 (Fig. 2). After 3 h of chymase treatment, however, there was a significant increase in sCD44 in the medium (Fig. 2). In contrast, there was no accompanying increase in sICAM-1 levels (data not shown), suggesting that the effects of chymase were selective and did not result in cleavage of all surface receptors. No increase in
sCD44 was observed when cells were treated with an enzymatically inactive mutant of chymase, establishing the need for proteolytic cleavage to solubilize the receptor. Similarly, pretreatment of chymase with a selective chymase inhibitor, P3P3/H11032, prevented the release of sCD44 (Fig. 2). However, addition of the metalloproteinase inhibitor 1,10-phenanthroline had no effect on chymase-induced release of sCD44 (Fig. 2), suggesting that the effect of chymase was not due to activation of an endogenous metalloproteinase. Given that surface expression of CD44 was unchanged following chymase treatment (Fig. 3), these data suggest that rather than being cleaved directly from the cell surface, sCD44 may be an integral part of the pericellular matrix, which is released upon treatment with proteases. Interestingly, no increase in soluble hyaluronan was detected (data not shown).

Chymase inhibits T cell adhesion to ASM cells

We previously showed that integrins and CD44 mediate adhesion of T cells to human ASM cells (28). We therefore examined whether treatment with chymase would modulate cytokine-induced expression of cell adhesion molecules. ASM cells were treated with TNF overnight in the presence or the absence of chymase, and then analyzed by flow cytometry for expression of CD44 and ICAM-1. The constitutively high expression of CD44 was not significantly decreased following treatment with chymase (Fig. 3). TNF-induced up-regulation of ICAM-1 expression also was not inhibited by chymase (Fig. 3).
We next determined the effect of chymase treatment on T cell adhesion to ASM. ASM cells were treated with chymase overnight. In some instances cells were also stimulated with TNF to increase the expression of ICAM-1 (28) and then were incubated with activated human peripheral blood T cells. As previously reported, activated T cells adhered to unstimulated and cytokine-treated ASM cells (Fig. 4). Adhesion to chymase-treated unstimulated ASM was significantly decreased (Fig. 4A). Blocking $\beta_1$ and $\beta_2$ integrins inhibited adhesion to a similar degree as chymase treatment, while isotype-matched Abs had no effect on adhesion (data not shown). These data suggest that integrin-mediated adhesion of T cells to smooth muscle-associated matrix components such as fibronectin predominates in ASM cells with low expression of ICAM-1 and that this interaction is disrupted in chymase-treated cells.

In contrast, there was no significant difference in T cell adhesion to TNF-treated ASM cells in the absence or the presence of chymase (Fig. 4B). Blocking anti-integrin Abs had similar effects on T cell adhesion to TNF-stimulated cells regardless of chymase treatment. These data suggest that binding of activated T cells via integrins to ICAM-1 and VCAM-1 predominates in cytokine-treated ASM cells and is not disrupted following chymase exposure despite the loss of matrix components.

Chymase inhibits EGF-induced ASM cell proliferation

Previous studies reported a pro-mitogenic effect of tryptase on ASM cells (18, 32, 33); however, the effects of chymase on human ASM cell growth remain unknown. We therefore investigated the effects of chymase, both alone and in combination with EGF, on smooth muscle cell proliferation. Growth-arrested ASM cells were treated with increasing concentrations of chymase and then stimulated with EGF. Chymase alone had no effect on smooth muscle cell DNA synthesis, as measured by incorporation of $[^3H]$thymidine. Chymase treatment, however, inhibited EGF-induced DNA synthesis in a dose-dependent manner (Fig. 5), which was confirmed by cell counts and 3-[4,4-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assays for viability (data not shown). Cells incubated with an enzymatically inactive chymase showed no inhibition of EGF-induced proliferation. Growth inhibition was not due to cleavage of the EGF receptor from the surface of ASM cells, since the expression of the receptor was unchanged, as assessed by flow cytometry (Fig. 6). In other experiments we also determined that chymase abrogated thrombin-induced growth (data not shown), suggesting that chymase has effects on both receptor tyrosine kinase- and G protein-coupled receptor-mediated signaling pathways.

A potential mechanism by which chymase could inhibit EGF-induced growth is by degrading EGF. To test this hypothesis we pretreated EGF with chymase, then inactivated the chymase with a specific inhibitor, P3P3. Chymase-treated EGF was then used in a proliferation assay. As shown in Fig. 7, chymase-treated EGF stimulated a similar degree of thymidine incorporation as did untreated EGF, suggesting that the effects of chymase were not simply due to ligand degradation.

Chymase inhibits EGF-induced ASM cell proliferation

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Chymase does not inhibit EGF-induced signal transduction in ASM cells

Previous data suggested that cyclin D1 expression is necessary for entry into S phase by ASM cells (34). Cells were treated with chymase, then stimulated with EGF. EGF induced a gradual increase in cyclin D1 expression over 24 h, which was unaffected by the presence of chymase (Fig. 8). We next studied the effects of chymase on activation of the upstream signaling pathway involving ERK, which has also been shown to be necessary for mitogen-induced ASM cell proliferation (35, 36). Similar to the effects on cyclin D1 expression, chymase treatment had little effect on the phosphorylation of ERK (Fig. 8). In other experiments we found that chymase did not activate caspases, suggesting that chymase did not inhibit cell growth by inducing apoptosis (data not shown), as has been reported in vascular smooth muscle cells (37).

Discussion

We have shown that chymase significantly inhibits EGF-induced smooth muscle cell proliferation. This effect was not due to cleavage of either EGF or the EGF receptor nor to chymase-induced ASM cell apoptosis (A.L. Lazaar and R.K. Hoffman, unpublished observations). Rather than having a direct effect on EGF-induced proliferation, we propose that the ability of chymase to inhibit mitogen-induced proliferation is probably due to disruption of the ECM by the protease, with subsequent effects on downstream growth-signaling pathways. Several investigators have demonstrated that attachment to matrix is essential for sustained MAPK activation and growth factor-induced cell cycle progression (reviewed in Ref. 3). Interestingly, EGF-induced MAPK activation and expression of cyclin D1 were unaffected, which is probably due to the presence of residual matrix components that allow for integrin-mediated attachment and MAPK activation (4). Further studies are necessary to determine the effects of chymase on other downstream signaling pathways, such as phosphatidylinositol 3-kinase, which are necessary for smooth muscle cell proliferation (38).

The hyaluronan receptor CD44 is ubiquitously expressed on hematopoietic and stromal cells, where it functions as an adhesion molecule and plays an important role in lymphocyte recirculation and tumor metastasis (39). CD44 exists in several forms: as a transmembrane protein, as a cell-associated protein that is incorporated as a component of the pericellular matrix, and as a soluble form released into the fluid compartment. Soluble CD44 can be detected in plasma, and studies suggest that shedding of sCD44 may be mediated by a metalloproteinase or chymotrypsin-like protease (30, 31, 40). Soluble CD44 retains the ability to bind its ligand hyaluronan (41) and therefore is likely to have biological relevance consistent with the increased levels found in numerous disease states, such as cancer, rheumatoid arthritis, and asthma. While it may be a marker of tissue injury, sCD44 may also be important in the deposition of pericellular matrix through interactions with other CD44-associated matrix components (41). Soluble CD44 may act as a sink for low m.w. hyaluronan, which has proinflammatory effects and is increased in areas of inflammation (42–44). Finally, sCD44 may alter the migratory potential of resident pulmonary cells, such as myofibroblasts.

We have demonstrated that incubation of ASM cells with chymase results in a significant release of sCD44 into the culture medium. Cleavage of the transmembrane form of CD44 does not appear to be the major source of this sCD44, as surface expression of CD44 measured by flow cytometry did not change detectably upon chymase treatment, although our data do not rule out the possibility that chymase induces increased turnover of CD44.

Rather, we propose that the source of CD44 may be a reservoir of sCD44 associated with the ECM, and the rapid appearance of sCD44 in the conditioned medium probably reflects the release of existing protein rather than de novo synthesis and cleavage of the integral membrane form of CD44. We have demonstrated that bronchial epithelial cells spontaneously release sCD44 that is subsequently incorporated into high m.w. complexes containing hyaluronan, fibronectin, collagen, and chondroitin sulfate (J. Cichy and E. Puré, manuscript in preparation). A similar low level of spontaneous release of sCD44 was shown for untreated ASM cells, suggesting that the matrix underlying these cells may also sequester CD44. The disruption of the ECM by chymase digestion of fibronectin and possibly other components may dislodge CD44 from this reservoir. Further studies will be necessary to determine whether sCD44 coassociates with matrix components produced by human ASM cells.

Just as proteases are important in models of tumor migration, similar mechanisms may be applicable for understanding the pathogenesis of airway remodeling in asthma. Early studies focused on the direct effects of mast cell proteases such as chymase on the regulation of bronchoconstriction, mucus secretion, and neuropeptide activity within the airway (45, 46). More recently, chymase has been shown to convert angiotensin I to angiotensin II, an agent that induces ASM cell hypertrophy (47). In addition, chymase cleaves big endothelin to endothelin-1, an ASM cell mitogen that also promotes airway hyper-reactivity, hyaluronan-induced smooth muscle cell proliferation, and secretion of collagen and other matrix proteins (13, 48–50).

A direct role for chymase in modulating smooth muscle cell proliferation, however, is controversial. Our data and those reported by others (51) suggest that chymase inhibits the growth of human airway and vascular smooth muscle cells in vitro due to effects on matrix structure and to activation of TGF-β. In contrast, in vivo data suggest that transgenic overexpression of a rat chymase in vascular smooth muscle promotes cell proliferation, possibly through production of angiotensin II (52). Our studies provide no source of angiotensin II. Thus, there are many factors that may determine the marked differences in the results in the various model systems. In vivo, the effect of chymase on surrounding tissues may be dependent on local physiology.

Studies have shown that the matrix metalloproteinase (MMP) progelatinase B (MMP-9) can be converted to an enzymatically active form by chymase (53). MMP-9 is present in the bronchoaveolar lavage of asthmatics (54, 55) and is secreted by ASM in response to inflammatory cytokines (56). In some systems CD44 has been shown to act as a docking site for proteolytically active MMP-9 (57); immobilized active MMP-9 then cleaves latent TGF-β1 to its active form (58). Interestingly, while mast cell-derived chymase has been shown to release latent TGF-β from epithelial cell cultures (59), it has a variable ability to activate latent TGF-β directly (51, 59, 60). One could speculate that local release of chymase by mast cells, and potentially by ASM cells (61), activates MMP-9 and induces the release of latent TGF-β, which, in turn, is activated by either MMP-9 or chymase. Thus, active TGF-β could promote fibrosis in areas of injury. Similarly, accumulation of low m.w. matrix constituents following degradation by chymase could result in further proinflammatory or profibrotic stimuli. Paradoxically, chymase indirectly may serve to limit some of the pathological changes seen in chronic severe asthma. For example, chymase has been shown to inhibit the expression of collagen, inhibit vascular smooth muscle proliferation, and induce apoptosis (37, 51). In addition, increased levels of active TGF-β may actually prevent smooth muscle cell hyperplasia by inhibiting the response to growth factors (62, 63).
In summary, we have demonstrated that chymase has significant effects on ASM cell function. Chymase degrades the pericellular matrix of ASM, with subsequent release of sCD44 and fibronectin, and profoundly inhibits mitogen-induced ASM cell growth. The interactions between ASM cells and the mast cell proteases tryptase and chymase are complex and may be cell type and species specific. While tryptase appears to be a smooth muscle cell mitogen, chymase may, in fact, have either pro- or anti-mitogenic effects. In addition, whereas chymase clearly degrades matrix proteins, its indirect effects, such as activation of endothelin-1 and TGF-β, may promote matrix deposition. The balance between these varying effects probably plays an important role in determining the severity of airway remodeling seen in chronic inflammatory diseases such as asthma.

References


