Interleukin-1β Secreted from Monocytic Cells Induces the Expression of Matrilysin in the Prostatic Cell Line LNCaP*

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Matrilysin is a matrix metalloprotease that is overexpressed in cancer cells of epithelial origin and in normal tissues during events involving matrix remodeling such as the cycling endometrium. We previously observed that inflamed ductule and acinar epithelia in the prostate also overexpress matrilysin. The presence of infiltrating macrophages in these areas prompted us to determine if factors secreted from monocytes could induce matrilysin expression in a human prostatic cell line. Conditioned media collected from the monocyte cell line THP-1 following lipopolysaccharide treatment substantially induced matrilysin protein and mRNA expression in LNCaP prostate carcinoma cells. Matrilysin expression in LNCaP cells was also induced by recombinant interleukin (IL)-1 (50 pM), but not by equimolar concentrations of recombinant tumor necrosis factor-α or IL-6. The matrilysin-inducing activity of THP-1 conditioned medium was completely abrogated by preincubation with a neutralizing antibody to IL-1β. Transient transfection analyses with a chimeric human matrilysin promoter-chloramphenicol acetyltransferase reporter construct demonstrated that IL-1β activates transcription through the matrilysin promoter in LNCaP cells. This is the first report of matrilysin induction by an inflammatory cytokine in a cell line of epithelial origin, and the results suggest a potential mechanism for the overexpression of matrilysin in inflamed ducts and glands of the prostate.

The matrix metalloproteases are a family of enzymes that degrade extracellular matrix proteins. Matrilysin (PUMP-1, MMP-7) is a relatively recently described matrix metalloprotease belonging to the stromelysin enzyme subclass (reviewed in Ref. 1). Matrilysin is capable of degrading a diverse set of extracellular matrix proteins including proteoglycans, fibronectin, entactin, laminin, gelatin, and elastin. The expression of matrilysin has been demonstrated in the cycling endometrium (2); the involuting rat prostate (3) and uterus (4); developing mononuclear phagocytes (5); and cancers of the breast (6), lung and upper respiratory tract (7), skin (8), stomach and colon (9, 10), and prostate (11). A unique feature of matrilysin expression is that it appears to predominate in epithelial cells of glandular tissue, while other matrix metalloproteases, such as stromelysin and the gelatinases, are more commonly expressed by cells in the stromal compartment (1). The expression of matrilysin during normal and pathological events that involve matrix remodeling and the cell type specificity of this expression imply an important role for matrilysin in these events.

In the normal prostate, we have observed that inflamed ductule and acinar epithelia frequently express high levels of matrilysin (11, 12). It has been clearly demonstrated by in situ hybridization that the overexpression of matrilysin mRNA is confined to the epithelial cells of these structures and is not present in the surrounding stroma or infiltrating leukocytes (12). Immunohistochemical analysis confirmed that the expression of matrilysin mRNA in the prostate epithelium correlates with the expression of matrilysin protein.

We have speculated that the high levels of matrilysin expression in inflamed prostate epithelial cells might be due to the presence of infiltrating macrophages within these structures. During the inflammatory process, these cells secrete factors such as tumor necrosis factor-α (TNF-α)1 and interleukin-1 (IL-1), which are known to induce the expression of matrix metalloproteases in a variety of cell types such as connective tissue cells, endothelial cells, monocytes/macrophages, neutrophils, and tumor cells (reviewed in Ref. 13). The induction of stromelysin-1 (MMP-3) and interstitial collagenase (MMP-1) expression by IL-1 in chondrocytes and synovial fibroblasts has been particularly well studied (14–24). While the induction of matrilysin and other matrix metalloproteases by inflammatory cytokines has been observed in cultured glomerular mesangial cells (25) and some glial cell lines (26), there have been no reports on the effect of inflammatory cytokines on matrilysin expression in cells of glandular epithelial origin.

The purpose of the work reported here was to determine if factors secreted from monocytic cells could induce matrilysin expression in a prostatic cell line and, if so, by what mechanism. We report that IL-1β secreted from monocytic cells induces matrilysin expression in LNCaP cells and that the mechanism of this induction involves an increase in matrilysin gene transcription.

**EXPERIMENTAL PROCEDURES**

**Cell Culture—**LNCaP and THP-1 cells were obtained from American Type Culture Collection (Rockville, MD) and were maintained in RPMI 1640 medium supplemented with 10% fetal calf serum and penicillin (100 units/ml)/streptomycin (100 μg/ml). All cells were maintained in a humidified incubator at 37 °C and 5% CO₂. For all experiments, LNCaP cells were seeded in full medium and allowed to attach for 20–24 h prior to treatment. To generate THP-1 conditioned medium (THP-1 CM),

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1 The abbreviations used are: TNF-α, tumor necrosis factor-α; IL, interleukin; THP-1 CM, THP-1 conditioned medium; LPS, lipopolysaccharide; ELISA, enzyme-linked immunosorbent assay; MOPS, 3-(N-morpholino)propanesulfonic acid; HMP, human matrilysin promoter; CAT, chloramphenicol acetyltransferase.
THP-1 cells at a density of $1 \times 10^6$ cells/ml were incubated for 4 h in serum-free RPMI 1640 medium containing 5 μg/ml lipopolysaccharide (LPS) (Sigma) and then clarified by centrifugation and passed through a 0.2-μm filter. Recombinant human IL-1α, IL-1β, and IL-6 and neutralizing antibodies against the IL-1 proteins were purchased from Genzyme Diagnostics (Cambridge, MA); recombinant TNF-α was from Boehringer Mannheim; and antibody against mouse IL-2 was from Collaborative Biomedical Products (Bedford, MA).

**ELISA**—An antibody sandwich assay was developed for detection and quantification of matrilysin. The capture antibody (10D2, a mouse monoclonal antibody produced in the laboratory of Dr. Raymond Nagle using defined promatrilysin from Dr. Mark Navre, Syntex, Palo Alto, CA) was coated onto 96-well ELISA plates (Costar, Cambridge, MA). This antibody is specific for human promatrilysin, and therefore, the ELISA does not detect active matrilysin. The detection antibodies included antibody Rb2, a rabbit polyclonal antibody to human matrilysin (12), followed by a horseradish peroxidase-conjugated goat anti-rabbit antibody (Pierce) used to detect bound Rb2. Horseradish peroxidase activity was quantitated using a hydrogen peroxide-phenyldiamine (Sigma) colorimetric system. Purified promatrilysin was used to generate a standard curve for each assay. No cross-reactivity was observed with either purified gelatinase A or gelatinase B (a gift from Dr. Eric Howard, University of Oklahoma). The assay was linear in the range of 0.2–12.5 ng/ml. Samples were diluted prior to analysis until the readings fell within the linear range of the assay, and the results were multiplied by the dilution factor.

**Northern Analysis**—Total RNA was isolated from cells by the acid guanidinium thiocyanate/phenol/chloroform method (27). Equal amounts of RNA (20 μg) were electrophoresed on a MOPS/formaldehyde-agarose (1%) gel. The RNA was transblotted onto a nylon membrane (GeneScreen™, DuPont NEN) and cross-linked with ultraviolet light (GS Genelinker™, Bio-Rad). The membranes were then hybridized with a $^{32}$P-labeled random-primed probe generated from a full-length matrilysin cDNA (28) using the RTS RadPrime DNA labeling system (Life Technologies, Inc.) and washed according to the manufacturer's instructions. The membranes were then exposed to a storage phosphor screen (Molecular Dynamics, Inc., Sunnyvale, CA). A Molecular Dynamics PhosphorImager equipped with the ImageQuant software package was used for obtaining and analyzing digital images from the screens. As a control for loading and transfer of RNA, all membranes were stripped and reprobed for glyceraldehyde-3-phosphate dehydrogenase as described above with a probe generated from an 800-base pair $XbaI-PstI$ fragment from pHcGAP (American Type Culture Collection).

**Western Analysis**—Detection of matrilysin protein in media by Western analysis was done as described previously (29). Rb2 was used as the primary antibody, and horseradish peroxidase-conjugated goat anti-rabbit antibody was used as the secondary antibody. Bands were visualized by treating the membranes with Western blotting ECL detection reagent (Amersham International, Buckinghamshire, United Kingdom) and exposing them to Kodak autoradiographic film.

**Monoclonal Constructs**—To generate the heterologous human matrilysin promoter (HMP) construct used in these studies, 1170 base pairs of the HMP located directly upstream of the TATA box were amplified by polymerase chain reaction and subcloned into pBLCAT2 (30). Polymerase chain reaction amplification of the HMP (kindly provided by Dr. R. Nagle) was done using the following heterologous primers, which contained either HindIII (upstream primer) or $XbaI$ (downstream primer) restriction site sequences linked to matrilysin promoter-specific sequences (matrilysin-specific regions of each primer are underlined): upstream sense primer, 5'-GCGGCGAGCTCTAGAGCTTCTCAGCCTCG-3' and downstream antisense primer, 5' TAGCTCCAGCATATTGCTTCTGCTTGCCGCTG-3'. The resultant 1217-pair $XbaI$-PstI amplification product was digested with HindIII/$XbaI$, gel-purified, and directionally cloned into HindIII/XbaI-digested pBLCAT2 immediately upstream of the thymidine kinase minimal promoter. The resulting plasmid, named pHMPCAT, was confirmed by DNA sequencing.

**Transfection Analysis**—LNCaP cells, grown in 12.5-cm flasks, were transfected (10 μg of plasmid/flask) using Lipofectin (5 μl/ml; Life Technologies, Inc.) in 1 ml of serum-free RPMI 1640 medium according to the manufacturer's instructions. Plasmids were isolated using QiaPrep columns (Qiagen Inc., Chatsworth, CA) according to the manufacturer's instructions. Following transfection, the cells were washed once with serum-free RPMI 1640 medium and then incubated in treatment medium. Cell lysates were collected and analyzed for chlorphenicol acetyltransferase (CAT) enzyme activity as described previously (31). The cell lysate added to each CAT enzyme assay was normalized for equal protein as determined by the Bio-Rad protein assay. The percent butylation of $[^{14}C]$chloramphenicol by cell lysates was determined by TLC, followed by exposure of the TLC plates to a storage phosphor screen and analysis of the digital images obtained as described above for Northern analyses.

**RESULTS**

**Monocyties Secrete a Factor That Induces Matrilysin Expression in LNCaP Cells**—The monocyte cell line THP-1 (32) was used as a source of monocyte-derived factors to test the hypothesis that these factors induce matrilysin expression in prostate epithelial cells. The human prostate carcinoma cell line LNCaP was used because these cells express matrilysin protein in cell culture and have retained some features of normal prostate epithelial cells including androgen responsiveness and secretion of prostate-specific antigen. LNCaP cells were incubated in serum-free RPMI 1640 medium alone, in serum-free RPMI 1640 medium plus LPS, or in THP-1 CM. After a 48-h incubation, the amount of matrilysin protein secreted into the medium was determined. Western analysis for matrilysin protein revealed that THP-1 CM dramatically induced the expression of matrilysin protein by LNCaP cells (Fig. 1A). Nearly all of the matrilysin protein present was in the 28-kDa proenzyme form, with only a slight band corresponding to the 19-kDa activated form (Fig. D). THP-1 cells did not secrete any matrilysin protein in response to LPS activation (lane B), and LPS alone did not induce matrilysin protein expression in LNCaP cells (lane C). An ELISA was used to better quantitate and follow the induction of LNCaP matrilysin protein expression by THP-1 cell-secreted factors. Quantitation of promatrilysin by ELISA demonstrated an ∼70-fold increase in secreted matrilysin protein in response to LPS activation (lane B), and LPS alone did not induce matrilysin protein expression in LNCaP cells (lane C).
IL-1 induces the expression of matrilysin by LNCaP cells. LNCaP cells (75,000 cells/cm²) were incubated with 0.5 ml of serum-free RPMI 1640 medium alone (Control) or with 50 pg IL-1b, TNF-α, or IL-6. Media were collected after 48 h of incubation with LNCaP cells. The quantity of promatrilysin protein in the media was determined by ELISA. Results represent the means and 95% confidence intervals for least three experiments run in triplicate.

Data strongly implicate IL-1 as being a factor in THP-1 CM that induces a significant change in matrilysin expression. These data therefore used to determine if one of these proteins was responsible for THP-1 CM induction of matrilysin expression in LNCaP cells. As shown in Fig. 3, preincubation of THP-1 CM with anti-IL-1β antibody prior to incubation with LNCaP cells completely abrogated the ability of THP-1 CM to induce matrilysin expression in LNCaP cells, while preincubation with anti-IL-1α antibody had no effect. The neutralization observed with anti-IL-1β antibody was specific as preincubation with anti-IL-1α or a monoclonal antibody to mouse IL-2 did not alter the ability of THP-1 CM to induce LNCaP matrilysin expression. Anti-IL-1α antibody was able to neutralize the induction of LNCaP matrilysin expression by a 50 pg dose of recombinant IL-1α, demonstrating that the antibody was active (data not shown).

The effect of THP-1 CM on steady-state matrilysin mRNA levels in LNCaP cells was also studied. LNCaP cells were treated for 20 h with THP-1 CM with or without antibody preincubation. At the end of the treatment period, total RNA was collected from LNCaP cells and analyzed by Northern hybridization. Treatment with THP-1 CM resulted in a substantial increase in steady-state matrilysin mRNA (Fig. 4A, lane B) over that observed in untreated control cells (lane A). Quantiﬁcation by digital image analysis revealed that, following glyceraldehyde-3-phosphate dehydrogenase correction for loading and transfer, this increase was 50-fold over untreated LNCaP cells (Fig. 4B, column 1). Preincubation of THP-1 CM with IL-1β neutralizing antibody completely blocked its capacity to induce steady-state matrilysin mRNA levels (lane C and column 2), while the irrelevant antibody against mouse IL-2 had no effect (lane D and column 3).
Interleukin-1β Induces Matrilysin Expression in LNCaP Cells

We have demonstrated that IL-1β secreted from the THP-1 monocyte cell line induces expression of the matrix metalloprotease matrilysin by the prostate carcinoma cell line LNCaP. This is the first time to our knowledge that IL-1β has been demonstrated to induce matrilysin in an epithelial cell line. THP-1 cells are induced to secrete inflammatory cytokines including TNF-α, IL-1, and IL-6 by treatment with LPS (33). Although LNCaP cells have been reported to express receptors for all three of these cytokines (34–36), and TNF-α has been shown to be an important regulator of matrix metalloprotease expression in non-epithelial cells (37–39), only IL-1 induced matrilysin protein expression in LNCaP cells. Both IL-1α and IL-1β induced matrilysin expression in LNCaP cells; however, IL-1α antibody treatment did not affect matrilysin induction by THP-1 CM. We can therefore conclude that THP-1 cells secrete little or no IL-1α, which is in agreement with published observations of IL-1 expression by these cells (40). Unlike IL-1β, IL-1α exists primarily as an intracellular and membrane-bound protein and is not normally secreted (41).

Monocytes have been reported to express matrilysin in vitro (5), and this expression is reportedly enhanced by LPS treatment. Therefore, one might expect that the THP-1 cells would express matrilysin. However, we observed no matrilysin expression by THP-1 cells even after LPS treatment. The expression of matrilysin by monocytes has been determined to be developmentally regulated as fully differentiated macrophages do not express matrilysin (5). It is possible then that THP-1 cells, which are a leukemic cell line of unknown passage number, have not retained the ability to express matrilysin.

The increase of steady-state matrilysin mRNA in LNCaP cells induced by THP-1 cell-secreted IL-1β was comparable to that observed for matrilysin protein induction, suggesting that regulation of the matrilysin mRNA level is the major mechanism by which IL-1β treatment increased matrilysin protein expression by LNCaP cells. This result is in agreement with reports that IL-1β is a transcriptional regulator of other matrix metalloprotease genes including stromelysin-1 (16, 42, 43). Transient transfection experiments with the reporter plasmid pHMPCAT in LNCaP cells revealed a significant IL-1β-induced increase in CAT transcription, although the magnitude of this increase does not account for the total increase in steady-state matrilysin mRNA observed in IL-1β-treated LNCaP cells. This could be due to problems inherent to transient transfection analysis, or the matrilysin gene may contain additional IL-1β response elements not present in pHMPCAT.

The known enhancer elements in the portion of the matrilysin promoter present in pHMPCAT include an AP-1-binding site, two PEA-3 elements, and a number of NF-IL-6 consensus sequences (TYTG/NNNGAA/TG) (1). There are also three putative transforming growth factor-β inhibitory elements. We are now performing deletion analysis of the human matrilysin promoter in pHMPCAT to determine the regions responsible for IL-1β transcriptional regulation in LNCaP cells. IL-1β may also have additional effects on matrilysin mRNA stability in LNCaP cells, and we are conducting experiments to address this possibility.

Although we cannot rule out the possibility that other factors could be necessary to permit a similar matrilysin induction in prostate epithelial cells in vivo, our finding that IL-1β induces the expression of matrilysin in a prostatic cell line offers a potential explanation for the matrilysin overexpression observed in inflamed dilated ducts and atrophic glands of the normal prostate. Saarialho-Kere et al. (44) reported that normal prostate glands constitutively express matrilysin; however, this basal expression must be very low as we have not observed strong matrilysin expression in normal, non-inflamed prostate glands and ducts (11, 12). We propose that infiltrating macrophages present near inflamed ducts and glands secrete IL-1β, which induces transcription of the matrilysin gene in ductule and glandular epithelial cells. This hypothesis is supported by results from a limited number of experiments with normal human prostate epithelial cells. These cells secrete very low levels of promatrilysin protein in vitro, and treatment with THP-1 CM or IL-1β (50 pM) results in a 2–3-fold increase in promatrilysin protein expression (data not shown).

The pathological significance of dilated ducts and atrophic glands in the human prostate is not known; however, it is likely that a substantial amount of extracellular matrix remodeling occurs at these sites. The presence of macrophage infiltration near areas of epithelial matrilysin expression is not limited to the prostate. For example, the number of macrophages present in endometrial tissue increases substantially in the late secretory/premenstrual endometrium (45), correlating with a reported increase in matrilysin expression in the late secretory and menstrual endometrial epithelium (2). During inflammation, macrophages secrete a number of matrix-degrading enzymes and are capable of inducing stromal fibroblasts to express matrix metalloproteases. IL-1β induction of matrilysin expression by epithelial cells may be another important component of inflammation-associated tissue remodeling in the prostate as well as in other glandular epithelial tissues.

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