Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) and MMP-2 Immunolocalization in Human Prostate: Change in Cellular Localization Associated with High-Grade Prostatic Intraepithelial Neoplasia

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ABSTRACT

Membrane type 1-matrix metalloproteinase (MT1-MMP) is a known activator of latent MMP-2 (pro-MMP-2), and increased MMP-2 expression has been associated with tumor aggressiveness in prostate cancer. However, expression of MT1-MMP in human prostate tissue has not been described. We investigated the expression and immunolocalization of MT1-MMP and MMP-2 in the epithelial components of benign prostate epithelium, high-grade prostatic intraepithelial neoplasia (HGPIN), and prostate cancer. Tissue sections from the peripheral zone of 50 prostates (radical prostatectomy specimens) were chosen based on their containing benign glands, HGPIN, and prostate cancer glands. All 50 sections were immunostained for MT1-MMP and MMP-2 and were evaluated for staining pattern, uniformity, and intensity. Western blotting and gelatin zymography were done to confirm expression of MT1-MMP and activity of MMP-2, respectively. Comparisons were made between benign epithelium, HGPIN, and cancer. In benign glands, basal cells (BCs) uniformly stained intensely for MT1-MMP, whereas secretory cells (SCs) were rarely positive (P < 0.001). Conversely in HGPIN, SCs showed consistent cytoplasmic staining (P < 0.0001). In cancer cells, staining was heterogeneous and varied from no staining to very intense staining in select glands. MMP-2 in normal tissue stained both BCs and the apical region of SCs, whereas in HGPIN, staining was observed in the SC in a predominantly cytoplasmic pattern. Similar to MT1-MMP, staining in cancer tissue for MMP-2 was heterogeneous; however, there was a significant association between the pattern of MMP-2 and MT1-MMP staining within the epithelial components of the cancer glands in individual specimens (P < 0.001). Finally, MMP-2 and MT1-MMP were confirmed to be expressed in the prostate tissues by gelatin zymography and Western blotting. In conclusion, we found that consistent changes in localization and intracellular distribution of MMP-2 and MT1-MMP were associated with the transition from benign prostate epithelium to HGPIN, suggesting that regulation of these enzymes is altered during the earliest stages of prostate cancer.

INTRODUCTION

MMPs are a family of enzymes that degrade extracellular matrix and basement membrane components. These enzymes have been shown to play a critical role in physiological and pathological processes (1). One class of MMPs are the gelatinases, including MMP-9 (gelatinase B) and MMP-2 (gelatinase A), which have been shown to degrade basement membrane type IV collagen, a major structural barrier for malignant tumor cells (2). Thus, gelatinase expression in human tumors has been associated with tumor invasion and metastasis (3). The MT-MMPs are a subfamily of MMPs that contain a transmembrane domain and therefore are inserted in the outer side of the plasma membrane (4). Because MMP-2 is secreted from cells in an inactive form (zymogen), activation of this proenzyme is necessary for its biological function. This activation appears to be mediated at least in part by MT1-MMP on the cell surface (5). Recently, the expression of MT1-MMP in various human cancer tissues has been associated with pro-MMP-2 activation (6, 7). In prostate cancer, in vivo studies have shown that high expression of MMP-2 by in situ hybridization was associated with aggressive behavior and metastasis (8). However, the expression and localization of MT-MMPs in human prostate tissues has not been studied.

Here, we have characterized the expression and localization of MT1-MMP and MMP-2 by immunohistochemistry in areas of benign epithelium, HGPIN, and carcinoma in the peripheral zone of human prostate specimens. We found colocalization of MT1-MMP and MMP-2. We also found consistent

Received 7/8/99; revised 9/16/99; accepted 9/27/99.

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1 Supported by Wayne State University Prostate Cancer Initiative and in part by NIH Grant CA-61986 (to R. F.) and ACS Grant CRTG-97-044-01-EDT (to M.C.).

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3 The abbreviations used are: MMP, matrix metalloproteinase; MT, membrane type; HGPIN, high-grade prostatic intraepithelial neoplasia; RP, radical prostatectomy; BC, basal cell; SC, secretory cell.
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Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Total no.</th>
<th>No. of patients</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>62 (39–74)</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16 (32%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>34 (68%)</td>
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</tr>
<tr>
<td>Median PSA (range)</td>
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</tr>
<tr>
<td>Clinical stage</td>
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<td></td>
</tr>
<tr>
<td>T1c</td>
<td>11 (22%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>39 (78%)</td>
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</tr>
<tr>
<td>Pathological stage</td>
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<tr>
<td>OC</td>
<td>33 (66%)</td>
<td></td>
</tr>
<tr>
<td>SM+</td>
<td>8 (16%)</td>
<td></td>
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<td>EPE</td>
<td>6 (12%)</td>
<td></td>
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<tr>
<td>SV+</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>LN+</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Gleason distribution</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>28 (56%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1 (2%)</td>
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</tbody>
</table>

* OC, organ confined; SM+, organ confined with positive surgical margin; EPE, extraprostatic extension; SV+, seminal vesicle invasion; LN+, lymph node metastasis.

changes in localization and intracellular distribution of MMP-2 and MT1-MMP associated with HGPIN, suggesting that altered regulation of these enzymes occurs during the early stages of prostate cancer development.

MATERIALS AND METHODS

Tissue Samples. A representative tissue block containing areas of benign epithelium, HGPIN, and tumor was selected from the peripheral zone of 50 RP specimens for histopathological analysis. These patients underwent RP for clinically localized prostate cancer. Patient and specimen characteristics are shown in Table 1. No patient had preoperative hormonal or radiation therapy. The RP specimens were processed according to an institutional protocol described previously (9). Briefly, the prostate gland was sectioned fresh at 3–4 mm intervals. These sections were then fixed in 10% neutral buffered formalin and embedded in paraffin. Pathological staging was assigned as described previously (9).

Immunohistochemistry. The polyclonal rabbit anti-serum to MT1-MMP antibody was raised against a synthetic peptide (RFNEELRAVDSEYPNIK) derived from the amino acid sequence of human MT1-MMP as described (10). The anti-MMP-2 monoclonal antibody (CA-1004) was raised against a synthetic peptide (APSPIKFPGDVAPKTD) from the NH2-terminal domain of pro-MMP-2 as described previously (11).

Serial adjacent sections (4–5 μm) were mounted on poly-L-lysine-coated slides. The tissue was deparaffinized and rehydrated through graded alcohols, and one section was stained by H&E for routine histological examination. For MT1-MMP staining, antigen retrieval was performed as described previously (10). Slides were placed in 10 mM citrate buffer (pH 6.0) and boiled by microwave heating for 5 min. Nonspecific sites were blocked by incubation with Superbloc (ScyTek, Logan, UT). Sections were incubated with the polyclonal antiserum to MT1-MMP at a 1:20 dilution. Immunoreactive sites were detected using a biotin/avidin enzyme system and the Vectastain alkaline phosphatase kit (Vector, Burlingame, CA). For MMP-2 staining, no microwave treatment was used. Nonspecific binding was blocked by incubation with Superbloc. Sections were then incubated with the monoclonal antibody (CA-4001) against MMP-2 at a 1:1000 dilution. The sections were then incubated with rabbit antimouse immunoglobulin at 1:20 dilution, followed by alkaline phosphatase anti-alkaline phosphatase (Sigma Chemical Co.) at a dilution of 1:40. Immunoreactive sites for both staining protocols were developed using Sigma Fast Red substrate, and nuclei were counterstained with hematoxylin. Duplicate sections were stained in the absence of primary antibody to serve as a control for nonspecific staining.

Preliminary evaluation showed that prostatic smooth muscle stained with uniform staining intensity for both MT1-MMP and MMP-2. This allowed standardization of intensity of epithelial staining using smooth muscle as an internal reference. Sections were evaluated for comparison of staining between the epithelial cells of benign, HGPIN, and cancerous tissue simultaneously by two observers (D. J. G. and J. U.). Also, serial adjacent sections were used for evaluation of colocalization of MT1-MMP and MMP-2. Three features were scored across the entire section for each antibody and for each tissue type separately: intensity, proportion of epithelial cells staining, and the pattern or location of staining. For intensity, a scoring system of 0–3 was used: 0, no staining; 1, intensity less than smooth muscle; 2, intensity equal to smooth muscle; and 3, intensity greater than smooth muscle. The proportion of the epithelial components that stained for each tissue type in each section was defined as: 0, none; 1, 0%–25%; 2, 26%–50%; 3, 51%–75%; and 4, 76%–100%. The staining pattern was defined as uniform or heterogeneous, depending on variability of intensity within or between glands for benign, HGPIN, or cancerous epithelium evaluated individually.

Western Blot Analysis. For confirmation of the presence of MT1-MMP protein, fresh frozen prostate cancer tissue was taken from the peripheral zone of identical RP specimens and homogenized in lysis buffer [25 mM Tris-HCl (pH 7.5), 100 mM NaCl, and 1% IGEPAL] containing protease inhibitors (10 μg/ml aprotinin, 2 μg/ml leupeptin, 1 mM phenylmethylsulfonyl fluoride, and 4 mM benzamidide). For these analyses, samples were prepared from frozen tissues with similar histological features to their corresponding paraffin-embedded counterparts used for immunohistochemistry. Homogenized samples were centrifuged, and the protein content of the supernatants was measured using the DC protein assay (Bio-Rad, Hercules, CA) using BSA as a standard. Aliquots of the homogenized tissues containing equal amounts of protein were used for Western blotting. As a positive control for MT1-MMP production, HT1080 human fibrosarcoma cells were used.

Aliquots of tissue homogenates (100 μg of protein) were denatured by boiling in SDS sample buffer containing 5% 2-mercaptoethanol and electrophoresed on 10% SDS-polyacrylamide gels. After transfer to nitrocellulose, membranes were probed with the MT1-MMP antibody. A peroxidase-conjugated antirabbit immunoglobulin (Vector, Burlingame, CA) was used.
as a secondary antibody. The membranes were developed using the enhanced chemiluminescence system (ECL; Amersham).

Gelatin Zymography. For confirmation of MMP-2 and MMP-9 enzymatic activity, fresh frozen specimens of prostate cancer tissue, taken from the peripheral zone of identical RP specimens, were homogenized as above in lysis buffer and centrifuged, and the protein content of the supernatants was measured as described above. Aliquots containing equal amounts of protein were used for gelatin zymography. As a positive control for MMP-2 and MMP-9 expression, medium conditioned by HT1080 human fibrosarcoma cells was used.

Samples (20 μg of protein) were electrophoresed in 10% SDS-polyacrylamide gels containing 0.1% gelatin as described (10). After electrophoresis, the gels were incubated 30 min in a solution of 2.5% Triton X-100 in H2O and then washed in distilled water. The gels were then incubated for 17 h at 37°C in 50 mM Tris-HCl, 5 mM CaCl2 (pH 8) and stained with 0.25% Coomassie Blue in a solution of 10% methanol and 5% acetic acid. Clear bands of gelatinolytic activity were detected by destaining the gels with 10% methanol-5% acetic acid.

RESULTS

MT1-MMP Localization in Benign Epithelium, HGPIN, and Cancer. Representative photomicrographs demonstrating the intensity and pattern of MT1-MMP staining in benign, HGPIN, and cancer tissues are shown in Fig. 1. In benign tissue, BCs stained intensely (A, arrow and inset). Conversely, in HGPIN, SCs stained intensely (B, arrow), and in cancer, staining varied from intense (C, arrow) to negative (C, arrowhead). MMP-2 staining in benign tissue was concentrated at the luminal surface of SCs (E, arrow). BCs stained uniformly as well (E, arrowhead and inset). In contrast, a cytoplasmic staining pattern was seen in HGPIN (F, arrow). Similar to MT1-MMP staining in cancer tissue, MMP-2 staining was heterogeneous and varied from none (G, arrowhead) to very intense staining (G, arrow). D (MT1-MMP) and H (MMP-2) show staining within adjacent tissue sections containing areas of normal (arrow), HGPIN (asterisk), and cancer (arrowhead). A–H, ×120; A and E insets, ×320.

Fig. 1 MT1-MMP and MMP-2 immunostaining in benign epithelium, HGPIN, and cancer. MT1-MMP staining (A–C) and MMP-2 staining (E–G) of benign epithelium, HGPIN, and cancer, respectively, are shown. In benign epithelium, BCs stained intensely for MT1-MMP (A, arrow and inset). Conversely, in HGPIN, SCs stained intensely (B, arrow), and in cancer, staining varied from intense (C, arrow) to negative (C, arrowhead). MMP-2 staining in benign tissue was concentrated at the luminal surface of SCs (E, arrow). BCs stained uniformly as well (E, arrowhead and inset). In contrast, a cytoplasmic staining pattern was seen in HGPIN (F, arrow). Similar to MT1-MMP staining in cancer tissue, MMP-2 staining was heterogeneous and varied from none (G, arrowhead) to very intense staining (G, arrow). D (MT1-MMP) and H (MMP-2) show staining within adjacent tissue sections containing areas of normal (arrow), HGPIN (asterisk), and cancer (arrowhead). A–H, ×120; A and E insets, ×320.
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In prostate cancer tissue, MT1-MMP was expressed in a greater proportion of the cancer epithelium (25%) at variable intensities. In 21 of 50 (42%) cases, MT1-MMP showed strong staining, with a wide range of intensities within and between glands. Finally, in 18 of 50 (36%) cases, all of the malignant epithelium (100%) stained strongly.

In cancer cells, staining for MT1-MMP was heterogeneous and varied from no staining to very intense staining in select glands (Fig. 1C). In 11 of 50 (22%) cases, we found either none or minimal proportions of the cancer epithelium staining (<25%) at variable intensities. In 21 of 50 (42%) cases, MT1-MMP was expressed in a greater proportion of the cancer epithelium (25% but <100%), with a wide range of intensities within and between glands. Finally, in 18 of 50 (36%) cases, all of the malignant epithelium (100%) stained strongly.

MMP-2 Staining in Benign Epithelium, HGPIN, and Cancer. Unlike MT1-MMP staining, which was negative in SCs in benign epithelium, immunostaining for MMP-2 showed equal intensity of staining in both SCs and BCs (Figs. 1E and 2B). In HGPIN, the SCs stained uniformly as well (Fig. 1F). There were no significant differences in intensity of staining of SCs in HGPIN compared with benign tissue (Fig. 2B). The cellular distribution of MMP-2, however, was different compared with MT1-MMP. In benign epithelium, the MMP-2 in the SCs was luminal in pattern rather than cytoplasmic. In contrast, HGPIN and cancer demonstrated a cytoplasmic staining pattern (Fisher exact test, $P < 0.001$; Fig. 1, F and G), although a few cases of HGPIN showed luminal staining. Similar to MT1-MMP, intensity and proportion of staining in cancer tissue for MMP-2 was heterogeneous in a predominantly cytoplasmic pattern (Fig. 1G). In 13 (26%) cases, only a minimal proportion of cancer epithelium ($\leq 25\%$) expressed MMP-2 weakly. Twenty (40%) cases had variability in cancerous tissue staining ($>25\%$ and $<100\%$), whereas in the remaining 17 (34%) cases, all of the malignant epithelium (100%) stained with moderate intensity.

Association of MT1-MMP and MMP-2 Staining. As described above, benign epithelium and HGPIN stained with uniform patterns and intensities for both MMP-2 and MT1-MMP. Although cancer epithelium stained heterogeneous for both enzymes within and between specimens and within and between individual cancer glands in individual specimens, there was a consistent staining pattern when comparing MMP-2 and MT1-MMP. For example, if a particular portion of a gland stained intensely for MMP-2, the same portion of the same gland stained intensely for MT1-MMP in adjacent tissue sections. Statistically, for benign epithelium, HGPIN, and cancer, there was a significant association between the overall intensity score of MMP-2 and MT1-MMP ($P < 0.001$ for all, Fisher’s exact test).

As described above, for benign epithelium and HGPIN, a uniform proportion (100%) of each section stained for both MMP-2 and MT1-MMP, and for cancer epithelium, the proportion of each section staining varied between specimens. However, within specimens, there was a significant association in the proportion of cancer epithelium staining for each enzyme ($P < 0.001$, Fisher’s exact test). For example, in adjacent sections (Fig. 1, D and H), cancer glands with positive staining for MT1-MMP were also positive for MMP-2 staining, and in areas with no staining for MT1-MMP, no staining for MMP-2 was seen.

MT1-MMP and MMP-2 by Zymography and Western Blotting. To confirm both the presence of MT1-MMP in prostate tissue and the specificity of our antibody, we carried out Western blot analysis of human prostate cancer tissue. As shown in Fig. 3A, the antibody detected a major protein of 63 kDa in cancer tissues, consistent with the molecular mass of human MT1-MMP (Fig. 3A, Lanes 2 and 3). A specific band of 57 kDa was also detected. The 57-kDa form represents a processed form of MT1-MMP (10). This study demonstrates that the major proteins in prostate tissue extracts recognized by the anti-MT1-MMP antibody are the 63- and 57-kDa forms of MT1-MMP. Gelatin zymography demonstrated the presence of MMP-2, a 72-kDa protein, in human prostate cancer tissue specimens (Fig. 3B).

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Fig. 2 Analysis of MT1-MMP and MMP-2 immunostaining in benign epithelium, HGPIN, and prostate cancer. A, MT1-MMP immunostaining. In benign areas, BCs stained on average more intensely than SCs (+, $P < 0.0001$). HGPIN also stained intensely compared with benign SCs (#, $P < 0.0001$). B, MMP-2 immunostaining.
DISCUSSION

MMPs have been associated with tumor invasion and metastasis in various human cancers. MMP-2 is secreted from the cells in an inactive form (pro-MMP-2; Ref. 5). Unlike other MMPs, the activation of pro-MMP-2 has been shown to occur at the cell surface. MT-MMPs, especially MT1-MMP, have been suggested to be the main activator of pro-MMP-2. This process appears to be fundamental to the regulation of MMP-2 activity and its role in matrix degradation (5).

To our knowledge, no prior studies on MT1-MMP localization and its association with MMP-2 expression in the prostate are available. For MT1-MMP, we found uniform staining of BCs in benign prostate glands, whereas the SCs were rarely positive. Conversely, in HGPIN the SCs showed consistent cytoplasmic staining, which was significantly different from benign glands. Finally, cancerous tissue showed a heterogeneous pattern of staining.

Recently, MT1-MMP expression and immunolocalization have been reported in various tumor tissues including lung, gastric, colon, breast, and bladder cancer (6, 7, 12–15). According to immunohistochemical studies of gastric carcinoma, MT1-MMP showed predominantly cytoplasmic localization in carcinoma cells similar to our data. Conversely, MMP-2 was immunolocalized on the cell membrane of the carcinoma cells (6). Vascular invasion was observed more frequently in MT1-MMP-positive cases with colocalization of MMP-2. Immunostaining of benign tissue for MT1-MMP was weak or not present in the stomachs of patients with gastric cancer (6). In cervical cancer, MT1-MMP was detected in stromal and endothelial cells surrounding the neoplastic tissue at both the protein and the mRNA level, indicating a possible cooperation between stromal and tumor cells in the invasion process (13). In squamous cell lung cancer, MT1-MMP localization by immunostaining and in situ hybridization was in carcinoma and stroma cells (14). In urothelial cancer, MT1-MMP was localized to the carcinoma cell membrane in both superficial and invasive carcinomas and was absent in normal mucosa, indicating the production of MT1-MMP predominantly in carcinoma tissue. However, the level of mRNA was identical in superficial and invasive cancers, indicating that MT1-MMP may play a role in early stages of invasion (15).

HGPIN is a putative precursor of adenocarcinoma that shows some of the morphological features of cancer but lacks stromal invasion (16). It is characterized by an abnormal proliferation of cells within architecturally normal glands and ducts. However, increasing grades of prostatic intraepithelial neoplasia are associated with progressive disruption of the BC layer and patchy loss of the type IV collagen-immunoreactive basement membrane (16). Because the basement membrane is a critical barrier to tumor cell dissemination, invasion of this barrier may represent an early step in tumor spread. Therefore, collagen degradation and MMP expression may be involved in the transition from HGPIN to carcinoma. The relatively intense staining for MT1-MMP and MMP-2 in the SCs of HGPIN compared with no staining of the SCs for MT1-MMP and weak luminal staining for MMP-2 of the benign epithelium suggests a role for these enzymes during the early stages of neoplasia.

We did not find a significant difference in intensity of staining for MMP-2 comparing benign SCs and BCs, HGPIN, and cancer tissue. However, similar to previous studies (17–20), the pattern of staining was different comparing benign tissue to HGPIN and cancer. In benign tissue, the staining in the SCs was concentrated at the apical surface. In contrast, HGPIN and cancer demonstrated cytoplasmic staining. These observations suggest a change in intracellular distribution of the enzyme. In this sense, our results agree with previous studies that characterized MMP-2 immunostaining in PIN and prostate cancer (17–20). Boag and Young (17) found that in adenocarcinoma, malignant cells stained strongly for MMP-2 in a cytoplasmic pattern. Stearns and Wang (18) showed that in the tumor tissue, malignant cells stained strongly for MMP-2 compared with normal prostate to invasive cancer. A change in the pattern of staining from apical to cytoplasmic was also observed. Intense cytoplasmic staining was seen in the periphery of the tumor, where the stroma was more abundant. It should be noted that because the MMPs are secreted proteins, immunoreactive MMPs associated with epithelial cells could have been synthesized by neighboring stromal cells and translocated after secretion. In a previous report, results of in situ hybridization experiments demonstrated that MMP-2 was synthesized primarily in the stromal cells in human prostate cancer specimens (8). We also saw positive immunostaining of stromal cells; however, our data suggest synthesis by prostate cancer cells as well. In addition, because MT1-MMP is not a secreted protein, positive immunostaining of epithelial cells in our study suggests synthesis by those cells.

Immunostaining of adjacent sections revealed some similarities and differences in the patterns of staining between MMP-2 and MT1-MMP. The intensity scores and proportions of the tissue staining for MMP-2 and MT1-MMP were correlated with each other within individual sections for all three types of tissue. In benign epithelium, MT1-MMP uniformly localized to BCs, and SCs were rarely positive. In contrast, MMP-2 was found in both BCs and SCs, and the pattern of staining in the SCs was luminal. In HGPIN, SCs showed consistent cytoplasmic staining for both MT1-MMP and MMP-2. Finally, in cancer
MT1-MMP in Prostate Cancer

cells, MT1-MMP and MMP-2 staining was heterogeneous and varied from no staining to very intense staining in select glands. Importantly, within and between cancer glands, we found a significant spatial association between the patterns of MMP-2 and MT1-MMP immunostaining. The correlation between MT1-MMP and MMP-2 immunostaining supports the role of MT1-MMP as an activator of pro-MMP-2 in human prostatic cancer tissue.

In conclusion, we report the first characterization of MT1-MMP expression in human prostate tissue. Consistent changes in localization and intracellular distribution of MMP-2 and MT1-MMP were associated with HGPIN, suggesting that altered regulation of these enzymes may play a role in the earliest stages of prostate cancer. Further studies are necessary to elucidate the roles of these enzymes in the invasion and metastasis of prostate cancer.

REFERENCES


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