ORIGINAL ARTICLE

Relationship among expression of basic-fibroblast growth factor, MTDH/Astrocyte elevated gene-1, adenomatous polyposis coli, matrix metalloproteinase 9,and COX-2 markers with prognostic factors in prostate carcinomas

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Abstract

Background: The etiopathogenesis of prostate cancer (PC) is still not clear, but hormonal, genetic, and environmental factors are thought to play a role in the tumor pathogenesis. Astrocyte elevated gene-1(AEG-1) as a novel transmembrane protein is predominantly located in the perinuclear region and endoplasmic reticulum. It has been found that AEG-1 upregulation increases the invasive ability of glioma and prostate cancer. Basic fibroblast growth factor (bFGF), matrix metalloproteinase-9 (MMP-9), cyclooxygenases-2 (COX-2), and adenomatous polyposis coli (APC) are very important in tumor progression as well. **Materials and Methods:** This study included 97 radical prostatectomy specimens. IHC stains for bFGF, MMP-9, COX-2, APC, and AEG-1 were performed on the tissue microarray using standard procedures. For each patient, the age, Gleason score, tumor volume, lymphovascular invasion, lymph node metastasis, surgical margin, and the invasion of vesiculoseminalis areas were assessed. Analyses were performed using the statistical PASW (ver. 18). **Results:** Statistically significant positive relationships were found MMP-9 and COX-2 (r = 0.242 and *P* = 0.017), between MMP-9 and APC (r = 0.207 and *P* = 0.043), and between bFGF and AEG-1 (r = 0.295 and *P* = 0.004). However, the relationships between age and staining results and tumor volume and staining results were not found to be significant. Although a positive correlation was found between the Gleason score and tumor volume and the Gleason score and age (r = 0.415 and *P* = 0.0001; r = 0.246 and *P* = 0.015, respectively), we did not find a statistically significant relationship between other stains and other prognostic parameters (lymphovascular invasion, lymph node metastasis, surgical margin, or vesiculoseminalis invasion). **Conclusion:**The relationships we found between MMP-9 and COX-2, between MMP-9, and APC and between bFGF and AEG-1 as independent prognostic parameters could be helpful in the development of new therapeutic procedures.

Key words: Adenomatous polyposis coli, astrocyte elevated gene-1, basic fibroblast growth factor, cyclooxygenases-2, matrix metalloproteinase-9, prognostic parameters, prostate adenocarcinomas

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Introduction

Prostate cancer (PC) is the second most frequent cause of cancer deaths in men in the United States. The role of many of the changes in PC initiation and progression remains unclear. The biology of human PC is complex, although

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many genetic and epigenetic alterations have been detected in human PC.[1]

Basic fibroblast growth factor (bFGF), also known as FGF2 is a member of the FGF family, a group of more than 20 structurally related proteins that control a multitude of cellular processes in different contexts, including proliferation, differentiation, survival, and motility.[2-9] bFGF is expressed in human prostate cancer, as well as in many other malignant neoplasms including melanomas, astrocytomas, and carcinomas of the breast, lung, bladder, pancreas, and head and neck.[2-8] It also plays a critical role in cancer development due to its role in angiogenesis.[9]

Cancer cells invade during metastasis and migrate through the normal molecular constraints, such as the extracellular matrix (ECM).[10] Cancer cells are capable of degrading the ECM barrier by using enzymes, resulting in dissolution of the basement membrane (BM). Most prominent among these enzymes are the matrix metalloproteinases (MMPs).[11] MMPs have long been known to be associated with pathological and physiological processes such as wound healing, tissue remodeling, angiogenesis, and cancer progression.[11-14] Matrix metalloproteinase-9 (MMP-9) has long been recognized as a key enzyme for the proteolytic degradation of ECM during tumor invasion and metastasis.[15] These varied functions of MMP-9 have made it an extremely promising target for preventing metastasis in cancer patients.[16] Its expanding roles include regulating cancer progression, activating angiogenesis, and recruiting macrophages or other bone marrow-derived myeloid cells to the preexisting metastatic niche.[17]

AEG-1, a novel gene, is known to be a potent mediator in the development of malignancies. It is a component of oncogenic signaling pathways and has been demonstrated to play a role in several significant stages of tumor progression and initiation of apoptosis, including angiogenesis, invasion metastasis, transformation, and chemoresistance. Following its initial identification, AEG-1 was thought to be a potential focus for targeted therapy, based on its multi-faceted role in regulating cancer progression.[18]

Cyclooxygenases-2 (COX-2) may play a key role in the tumorigenesis of a variety of human malignancies by stimulating cell proliferation and angiogenesis, tumor metastasis, inhibiting apoptosis, mediating immune suppression and inhibiting epithelial differentiation, enhancing cell invasiveness, and increasing the production of mutagens. The COXs are a family of enzymes that catalyze the rate-limiting step of prostaglandin biosynthesis.[19-21] The expression of COX-2 in PC tissues has been the subject of many recent studies.[22-24] Several of these have examined the expression of COX-2 in postatrophic hyperplasia, proliferative inflammatory atrophy, and prostate intraepithelial neoplasia, but the results are still controversial.[24-28]

Several studies have also evaluated the potential role of adenomatous polyposis coli (APC) protein in colorectal and other cancers, including prostate cancer. Alterations in APC have been identified in both primary and metastatic prostate cancers, including both somatic alterations.[29,30]

In this study, we evaluated AEG-1, bFGF, COX-2, MMP-9, APC, and the other prognostic parameters such as tumor grade, stage, tumor volume, metastasis, and age of the patient in 97 radical prostate specimens.

Materials and Methods

This retrospective study used formalin-fixed tumor samples taken from patients who were diagnosed between 2005 and 2011 with prostatic adenonarcinomas in the Department of Pathology, Medical Faculty. The study protocol was reviewed and approved by the Ethics Committee.

The samples were comprised 97 radical prostatectomy specimens and did not include tru-cut biopsy. All of the hematoxylin and eosin sections of the cases were examined retrospectively. PC cases were graded histopathologically using the Gleason system, and were grouped using other prognostic parameters. Sections were examined by light microscopy (Olympus BX50).

Immunohistochemistry

Immunohistochemical staining was performed on the 3-μm sections of formalin-fixed, paraffin-embedded material. The sections were deparaffinized with xylene and rehydrated with ethanol. Nonenzymatic antigen retrieval was performed on each slide and they were washed with 10 mM phosphate-buffered saline (PBS), pH 7.5. Immunohistochemical staining was performed manually using the standard avidin–biotin peroxidase complex technique (Neomarkers, Thermo Fisher Scientific, Fremont, CA, USA). Briefly, the slides were incubated at 37°C for 60 min with the following primary antibodies: AEG-1 [Polyclonal] Conc. 0.1ml (1:600), code: HPA010932, Atlas, bFGF (1-24)) [Polyclonal] Conc. 0.1 ml (1:100). code: F3393, Sigma Aldrich, MMP-9 [15W2] Conc. 1 ml (1:40-80), code: MMP9-439, Leica/Novocastra, APC [EMM43] Conc. 1 ml (1:20-40), Leica/Novocastra.

The slides were then washed twice for 5 min with 10 mM PBS and incubated with biotinylated rabbit antigoat immunoglobulin G (1:200 dilution; Dako, Carpinteria, CA, USA) for 1 h at room temperature. After final washing, the color reaction was developed using 0.5% diaminobenzidine and 0.01% hydrogen peroxide. The

sections were counterstained with hematoxylin and eosin before being mounted.

Immunohistochemistry evaluation

Immunoreactivity for AEG-1, bFGF, COX-2, Ki-67 MMP-9, and APC was scored using a semi-quantitative scale for intensity of staining: 0 = negative, no staining; 1+ = weak positive; 2+ = moderately positive; 3+ = strongly positive [Figures 1-4].

Statistical analysis

Descriptive statistics were computed as mean ± SD and percent frequency. The Spearman's correlation analysis or likelihood Chi-square test analysis (whichever was deemed appropriate in each case) was used to evaluate the relationship between prognostic factors and the degree of staining, and the relation of staining results to each other. The level of significance was determined to be 0.05. Statistical analyses were performed using the PASW (ver. 18).

Results

The age range of the cases was between 44 and 79 years (63.7 ± 7.2 years). Tumor volume ranged between 0.5 and 90% (14.4 ± 14.1). In 32 cases (33%), the tumors were Gleason score 6, in 53 cases (54,6%) Gleason score 7, in 5 cases (5.2%) Gleason score 8, and in 7 cases (7.2%) the Gleason score was 9. There were 85 cases PT2 and 12 cases PT3. Statistically significant positive relationships were found only between MMP-9 and COX-2 ($r = 0.242$ and $P = 0.017$), between MMP-9 and APC ($r = 0.207$ and $P = 0.043$) and between bFGF and AEG-1 ($r = 0.295$ and $P = 0.004$). However, the relationships between age and staining results and tumor volume and staining results were not found to be significant, although positive correlations were found between the Gleason score and tumor volume and the Gleason score and age ($r = 0.415$ and $P = 0.0001$; $r = 0.246$ and $P = 0.015$, respectively). We did not find a statistically significant relationship between other stains and other prognostic parameters such as lymphovascular

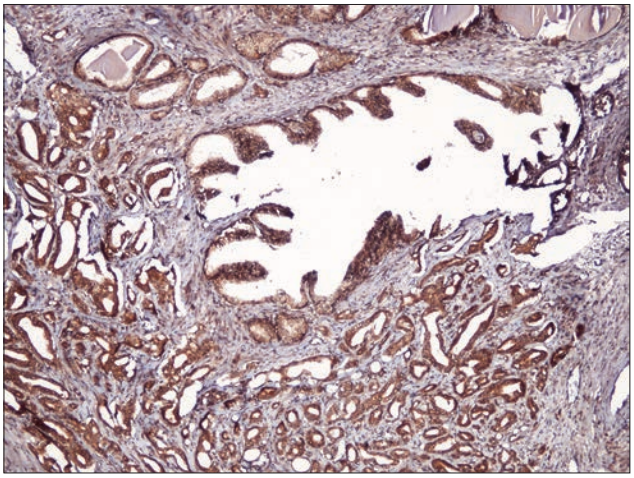

Figure 1: AEG-1 expression was more intense in malignant glands than in benign glands (AEG-1×100)

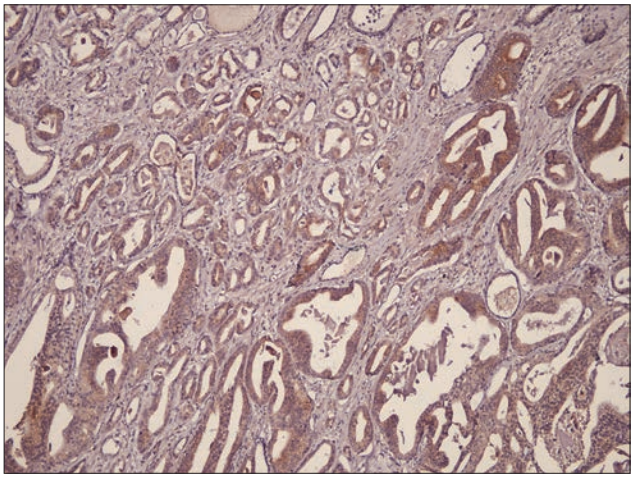

Figure 2: COX-2 expression seen in malignant glands (COX-2×100, grade 2, cytoplasmic)

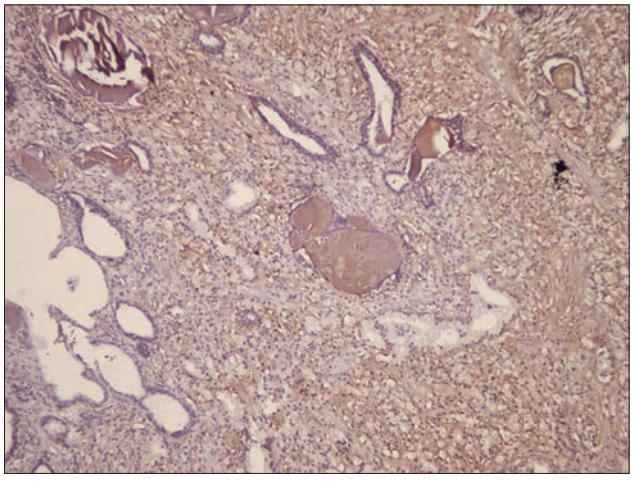

Figure 3: APC expression seen in malignant glands, but not in benign glands (APC×100)

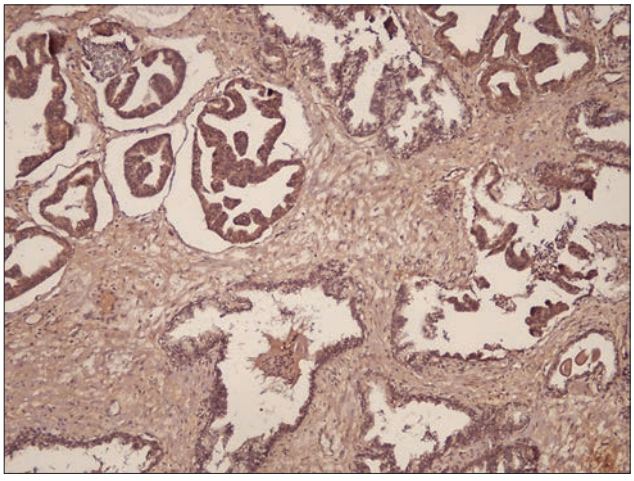

Figure 4: bFGF expression was more intense in malignant glands than in benign glands (bFGF×100)

invasion, lymph node metastasis, surgical margin, or vesiculoseminalis invasion [Table 1].

Discussion

Studies have found that clinical examination alone cannot predict the pathological outcome, and therefore this is not the ideal method to decide the mode of treatment.[31] Overexpression of COX-2 has been demonstrated to contribute to carcinogenesis by stimulating cell proliferation, inhibiting apoptosis, and enhancing angiogenesis; all of these effects are thought to be mediated via PGE2.[32-34]

COX-2 overexpression has been identified in many tumor tissues. In addition to COX-2, overexpression is well established in PC.[33] Madaan *et al.*, found expression of COX-2 in 74% of 82 cases of PC.[22] Kirschenbaum *et al.*, reported expression of COX-2 in 63% of 31 cases.[23] Yoshimura *et al.*, found increased expression in 28 cases of PC.[24] However, research on the expression of COX-2 in human PC is still controversial. Zha *et al.*, conducted a large study analyzing 144 samples of PC as large sections or tissue-microarray cores and found them to be negative for COX-2.[25] Denkert *et al.*, observed an overexpression of COX-2 in PC (44.7%) and prostate intraepithelial neoplasia (72.1%) samples when compared with benign prostatic tissue.[28] In the present study, we found overexpression of COX-2 in PC (65.9%). We found more overexpression of COX-2 in prostate intraepithelial neoplasia than in benign prostatic hyperplasia [Figure 2].

Table 1: (*N*:97)

	APC	AEG-1	FGF	MMP-9	COX-2
Spearman's rho					
APC					
Correlation coefficient	1.000	0.019	−0.151	0.207	0.013
Sig. (2-tailed)	0	0.853	0.144	0.043	0.901
AEG-1					
Correlation coefficient	0.019	1.000	0.295	0.131	0.120
Sig. (2-tailed)	0.853	0	0.004	0.203	0.243
FGF					
Correlation coefficient	−0.151	0.295	1.000	−0.107	−0.0036
Sig. (2-tailed)	0.144	0.004	0	0.307	0.731
MMP-9					
Correlation coefficient	0.207	0.131	−0.107	1.000	0.242
Sig. (2-tailed)	0.043	0.203	0.307	0	0.017
COX-2					
Correlation coefficient	0.013	0.120	−0.036	0.242	1.000
Sig. (2-tailed)	0.901	0.243	0.731	0.017	0
Age					
Correlation coefficient	−0.116	0.037	−0.013	−0.058	−0.068
Sig. (2-tailed)	0.257	0.718	0.904	0.575	0.511
Volume					
Correlation coefficient	−0.0001	0.055	0.177	−0.128	0.006
Sig. (2-tailed)	0.995	0.596	0.086	0.213	0.951
Score					
Correlation coefficient	−0.019	0.085	0.171	−0.122	−0.027
Sig. (2-tailed)	0.855	0.406	0.097	0.237	0.796

MMP=Matrix metalloproteinase, APC=Adenomatous polyposis coli, AEG=Astrocyte elevated gene, FGF=Fibroblast growth factor, COX=Cyclooxygenases

There are multiple mechanisms by which loss of bFGF could inhibit tumorigenesis. bFGF is a potent growth factor for both normal and neoplastic prostatic epithelial cells.[35]

Ropiquet *et al.*, have studied the effects of bFGF expression under the control of a strong promoter on immortalized but nontumorigenic human prostatic epithelial cells.[36] Thus, bFGF signaling may potentially promote proliferation, survival, invasion, metastasis, and angiogenesis in prostate cancer, and loss of all these activities could inhibit cancer progression. bFGF released by epithelial cells could also act as autocrine and paracrine factors on endothelial and fibroblastic cells to promote angiogenesis or to stimulate secretion of other tumor-promoting factors by these mesenchymal cells. At the same time, bFGF released by fibroblastic and endothelial cells could act as a paracrine factor on the epithelial cells or as an autocrine factor promoting angiogenesis. Such effects could occur either in the primary site or at sites of distant metastasis.[35,36]

AEG-1 is abundantly expressed in about 44 to 47% of primary tumors and is significantly correlated with the clinical stage, tumor size, lymph node spread, distant metastasis, and poor survival.[37-39] AEG-1 is overexpressed in PC samples and cell lines compared with benign prostatic hyperplasia tissue samples and normal prostate epithelial cells.[40,41] AEG-1 inhibition reduces cell viability and promotes apoptosis of PC cells, but not normal prostate epithelial cells.[41] Interestingly, decreased nuclear staining of AEG-1 was associated with an increased Gleason grade and shorter survival of patients.[38] AEG-1 may have a nuclear function in normal prostate tissue and is lost in tumorigenesis. AEG-1 overexpression enhances anchorage-independent growth, matrigel invasion, *in vivo* tumorigenicity, and angiogenesis through the enhancement of PI3K/Akt, MAPK, and Wnt/β-catenin pathways.[42] In this case, AEG-1 was stained cytoplasmic. We found overexpression of AEG-1 in PC (66.6%).

In addition to studies suggesting a role for APC in prostate cancer, two studies have looked specifically at APC and the risk of prostate cancer. An increase in PC risk associated with APC was observed in a community-based study of Ashkenazi Jews (Washington Ashkenazi Study), although the confidence limits were wide due to the small number of prostate cancers reported.[43] A second study using a case-only design was not able to directly estimate the risk conferred by the mutation; however, APC was reported to modify the association between body mass index (BMI)

and PC risk.[44] The implications of this study are unclear, because it seems unlikely that APC was considered *a priori* as an effect modifier of BMI and risk of prostate cancer. However, Poynter *et al*., said that APC is unlikely to play a clinically meaningful role in susceptibility to prostate cancer.[44] In this study, a significant relationship was found between MMP-9 and APC ($r = 0.207$ and $P = 0.043$). This result could be the relationship of tumor progression.

Whether MMP-9 has pro-tumorigenic or anti-tumorigenic effects depend on the environment and stage in tumor progression. For example, in neuroblastoma and orthotopically injected human pancreatic cancer cells, loss of MMP-9 results in decreased microvessel size and decreased vascularization. Deficiency of MMP-9 led to an increased dependence on perivascular invasion and a reduction in vasculature-independent invasion.[45,46] Several MMPs are overexpressed in PC progression, and androgen ablation or castration increases levels of MMPs.[45-49] Moreover, a synthetic MMP inhibitor reduces expression of MMP-9 in prostatic carcinoma cells and results in reduced lung metastases, but does not affect the tumor growth rate and decreases in tumor growth and metastases in a rat PC model.[50,51] The MMP-9 deficient tumors developed similar survival, and both tumor and metastatic burdens compared with controls. Hence, the same MMP has quite different outcomes in different tumors.[52]

In this study, significant relationships were found between MMP-9 and COX-2, MMP-9 and APC, and bFGF and AEG-1. We found significant relationships between MMP-9 and COX-2 and between MMP-9 and APC, but no significant relationship with prognostic parameters. This outcome is similar to others found in the literature.[53]

Conclusion

In this study, significant relationships were found between MMP-9 and COX-2, MMP-9 and APC, and bFGF and AEG-1. These relationships could be poor prognostic parameters and independent prognostic parameters of prostate adenocarcinomas. They may be important for understanding tumor progression and developing therapies.

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