Prostate Carcinoma

Prostate carcinoma is the most common malignancy in men and the second leading cause of cancer death in Western countries. A number of genetic changes have been shown to occur in prostate carcinogenesis, yet it is difficult to translate the molecular knowledge into diagnostic and prognostic criteria widely applicable to the management and treatment of the disease. Recent molecular studies have shown several candidate genes important in hereditary prostate cancer (1, 2), but few specific molecular markers for this tumor have as yet been found. At present, determination of prostate-specific antigen values in sera is primarily used in the identification and prognostication of prostate cancer. Although valuable, this biochemical marker has interpretative restrictions; for instance, serum prostate-specific antigen levels are regularly elevated in both benign prostatic hyperplasia and prostatitis (3). Using cDNA subtraction and microarray analyses, recent molecular searches for differentially expressed genes have shown higher expressions of P504S protein, the α-methylacyl-CoA rasemase (AMACR) gene product, in prostate cancers, with little expression in benign prostate tissue (4–6). Differential display analysis of mRNA expression is also particularly useful in analyzing the expression of large numbers of genes and their potential relationship with different grades of tumors (7); some novel and/or interesting genes have been reported in the evaluation of prostate carcinoma using this method (8–10). However, the need remains for one or more sensitive specific markers for the detection and monitoring of prostate neoplasias.

The genome is continuously subjected to harmful stimuli, such as ionizing radiation and nucleic acid-modifying compounds, and errors in transcription are not uncommon during its replication. Mechanisms have evolved in all organisms for tight protection against and reliable repair of this kind of damage. However, disorders or defects of these mechanisms in a cell can lead to tumor development. Alkylation is one of the mechanisms by which nucleic acids can be altered. Alkylating agents are ubiquitous in our environment and are endogenously produced during cellular metabolism. They introduce the base modifications 7-methylguanine, 3-methyladenine, and O6-methylguanine in double-stranded DNA and...
1-methyladenine and 3-methylcytosine in ssDNA (11). DNA alkylation induces mutations, inhibits replication, and is implicated in carcinogenesis, in the development of neurodegenerative diseases, and in aging. These harmful modifications are repaired by demethylation. All organisms are known to possess sophisticated defense mechanisms involving such agents as 3-methyladenine glycosylase (MAG; ref. 12) and O6-methylguanine methyltransferase (AGT; ref. 13) that protect them against alkylating agents. MAG excises cytotoxic 3-methyladenine from duplex DNA by a base-excision-repair pathway, whereas AGT transfers the methyl group from O6-methyguanine to a nucleophilic cysteine residue in the active site of the protein.

DNA alkylation damage repair mechanisms are best studied in Escherichia coli and are known to be controlled by six genes (14). The tag and ogt genes are expressed constitutively, but the other four genes, ada, alkA, aidB, and alkB, are induced upon exposure to a sublethal dose of alkylating agents, called the adaptive response. The alkB gene was discovered to sensitivity control of E. coli to N2-methylating reagents (15). The Tag and AlkA proteins are methyladenine glycosylases, and Ogt and Ada proteins are methylguanine methyltransferases. The exact function of the AidB protein remains unknown, but two important findings regarding the AlkB protein have recently been reported. AlkB evidently repairs both ssDNA and RNA modifications generated by S2-methylating reagents (16, 17), and AlkB is a member of the α-ketoglutarate-Fe2+-dependent dioxygenase superfamily, which uses an active iron-oxo intermediate to hydroxylate 1-methyladenine and 3-methylcytosine in DNA (18–20). 1-Methyladenine and 3-methylcytidine occur in ssDNA and are critical to the constitution of hydrogen bonds. Damaged repair mechanisms, therefore, would lead to cell death or carcinogenesis.

In our search for potential gene markers for prostate carcinoma, we have molecularly identified genes showing differential expression between prostate carcinomas and normal tissues using fluorescent differential display (FDD) analysis. In the process, we have identified a new gene, designated prostate cancer antigen-1 (pca-1), that shows increased mRNA expression in cancer tissues compared with normal or noncancerous tissues. pca-1 was found to have high homology to E. coli alkB. Immunohistochemical analysis using anti-PCA-1 antisera indicated that PCA-1 is highly expressed in human prostate cancer. PCA-1 cDNA transfection partially reversed the cell death of COS-7 cells exposed to alkB alkylation agent, methylmethane sulfonate (MMS). This is the first report that pca-1, the human counterpart of alkB, reverses alkylation-induced cell death in mammalian cells and seems to be an immunohistochemical marker for prostate carcinoma.

Materials and Methods

**Tumor samples and cell lines.** All primary tumor samples were obtained with informed consent from radical prostatectomy patients who had not undergone any previous hormonal treatments or chemotherapy. The prostate cancer cell lines DU 145 and PC-3, obtained from the American Type Culture Collection (Manassas, VA), were grown at 37°C under a 5% CO2 atmosphere in appropriate medium (Sigma, St. Louis, MO) supplemented with 10% heat-inactivated FCS (Nichirei, Tokyo, Japan) and 100 μg/ml kanamycin.

**RNA extraction and fluorescent differential display.** Tissues selected for FDD were homogenized in Trizol reagent (Invitrogen, Rockville, MD), and total RNAs were isolated according to the Trizol protocol. Possible DNA contamination was removed by treatment with RNase-free DNase I (Wako Pure Chemical, Ltd., Osaka, Japan). FDD analysis was done using a fluorescence differential display kit (Takara Biochemicals, Shiga, Japan); in brief, total RNAs (200 ng) were reverse transcribed with an FITC-labeled 3′-anchored oligo-dT primer and avian myeloblastosis virus reverse transcriptase (Invitrogen). Aliquots of synthesized cDNA were added to each PCR reaction mixture containing 0.5 unit of LA Taq DNA polymerase (Takara Biochemicals), 0.1 μM of each deoxynucleotide triphosphate, 1.35 mmol/l MgCl2, and a combination of the FITC-labeled downstream primers and 24 upstream primers (each 0.5 μmol/l) in 20 μl of 1× PCR buffer. Thermal cycling was done using a DNA thermal cycler (GeneAmp PCR system 2400, Perkin-Elmer, Wellesley, MA) under the following program: 94°C for 2 minutes, 38°C for 5 minutes, and 72°C for 5 minutes following by 34 cycles of 94°C for 30 seconds, 38°C for 2 minutes, and 72°C for 1 minute, and a final extension segment at 72°C for 5 minutes. Following a 2-fold dilution with sample buffer (25% glycerol, 5 mmol/l EDTA, 0.5% SDS, 1.25 mg/ml bromophenol blue, and 1.25 mg/ml xylene cyanol) and heat denaturation, each sample was loaded onto a 4% to 6% polyacrylamide/7 mol l urea gel, electrophoresed, and the bands of interest excised.

**Molecular cloning of products identified by fluorescent differential display.** The band regions corresponding to the differentially displayed gene products were excised from the gels and the cDNAs extracted in boiling water. After reamplification, using the same primer pairs used in the FDD analyses, the amplified cDNA was subcloned into pT7 blue-vector following a 2-fold dilution with sample buffer (25% glycerol, 5 mmol/l EDTA, 0.5% SDS, 1.25 mg/ml bromophenol blue, and 1.25 mg/ml xylene cyanol) and heat denaturation, each sample was loaded onto a 4% to 6% polyacrylamide/7 mol l urea gel, electrophoresed, and the bands of interest excised.

**Preparation of antisera.** Anti-PCA-1 antisera were raised against the synthetic peptide of PCA-1 (amino acids 64-76) as an antigen. The peptide sequence was chosen based on the following criteria which favor peptide immunogenicity: (i) a sequence rich in hydrophilic amino acids, indicating that it may be surface-exposed in the native protein and (ii) a sequence suitable as an antigen as determined by homology and secondary structure prediction. A cysteine residue was added at the NH2 terminus to facilitate conjugation of the peptide to keyhole limpet hemocyanin. Briefly, preimmune sera were prepared from blood collected from each of two naive female New Zealand White rabbits (Japan SLC, Inc., Shizuoka, Japan); 0.5 mg of the peptides was emulsified in an equal volume of Freund's complete adjuvant and then injected s.c. at several sites in each rabbit. Freund's incomplete adjuvant was used for all subsequent immunizations. Antiserum was prepared from each sample of blood we collected via the marginal ear veins at 2-week intervals for a total of five collections from each rabbit. We evaluated the relative reactivity of the antisera against the synthetic peptide by ELISA, and those antisera with high titers were affinity purified using SulfoLink (Pierce Biotech, Rockford, IL).

**Immunoblot analysis and immunohistochemistry.** Western blotting was done as previously described (21). Briefly, cell lysates were resolved by 10% SDS-PAGE and then transferred to a nitrocellulose membrane (Schleicher & Schuell, Keene, NH). The membrane was blocked with 3% bovine serum albumin in TBS-T (20 mmol/l Tris-HCl [pH 8.0], 137 mmol/l NaCl, and 0.1% Tween 20), incubated with 0.2 μg/ml anti-PCA-1 antisera at room temperature for 1 hour, and washed thrice with TBS-T. To detect antibody binding, the membrane was exposed to horseradish peroxidase–conjugated anti-rabbit IgG (Santa Cruz Bio-tech, Santa Cruz, CA) diluted in TBS-T and incubated at room
temperature for 1 hour. After three washings in TBS-T, bound horseradish peroxidase conjugates were visualized with the enhanced chemiluminescent reagent (Wako Pure Chemical).

Immunohistochemical analysis of the expression of PCA-1 protein in paraffin-embedded sections of benign prostatic hyperplasia and prostate tumor samples was done as described previously (22). The relative degree of immunostaining was recorded as (−) when <20% of tumor cells were positive, (+) when >20% but <50% of tumor cells were positive, and (++) when over 50% of tumor cells were positive. Appropriate positive and negative controls were also included.

Methylymethane sulfonate–induced alkylation damage in PCA-1-transfected COS-7 cells. COS-7 cells were transfected with either 10 μg of pEGFP-PCA-1 expression vector or pEGFP-N1 (BD Clontech) by the DEAE-dextran method, as previously described (21). After a 48-hour incubation, the transfected cells were replated at 10⁵ cells in a 12-well plate and treated with MMS for 1 hour. The numbers of viable cells were counted 48 hours post-MMS exposure.

Quantitative reverse transcription-PCR. We analyzed the relative mRNA quantity in a panel of normalized cDNAs derived from 15 human tissues (Human MTC Panels I and II; BD Clontech) by real-time reverse transcription (RT-PCR) using LightCycler-FastStart DNA master SYBR Green I (Roche Applied Science, Mannheim, Germany). The primers and the protocol for RT-PCR amplification of a 104-bp fragment within the open reading frame of pca-1 were as follows: PCA-1-F (5'-TACCACCTGCTAAAGACCCATCTCC-3') and PCA-1-R (5'-ACC-TGCTGAGGTTCTTTGAACAC-3'); a predenaturation step (10 minutes at 95°C) and 40 amplification cycles (15 seconds at 95°C, 30 seconds at 62°C, and 10 seconds at 72°C). We normalized the pca-1 transcript number to the quantity of β-actin transcripts, which we quantified by using the primers of β-actin-F (5'-CTAGGAGCTTCGCTCGGCG-3') and β-actin-R (5'-GGGACAGGCTCTGAGCC-3') and applying the same PCR protocol as used for amplification of pca-1. Serial dilutions of plasmid DNA containing pca-1 and β-actin were used to make standard curves and each determination was carried out thrice for each cDNA sample as independent PCR runs. Data from each PCR were normalized by dividing the quantity of pca-1 by the quantity of β-actin to correct for differences in each sample.

Results

Identification of pca-1 by fluorescent differential display analysis and its molecular cloning. In this study, we prepared mRNA from three samples obtained from radical prostatectomies done on patients (Table 1) who had had no previous chemotherapy or hormonal treatments; the samples were representative of cancerous foci large enough to isolate without contamination with normal or noncancerous adjacent tissues based on H&E evaluation. One gene fragment showing higher mRNA expression only in cancerous tissues was detected by RT-PCR analysis using a primer pair made up of an upstream primer (GATGGCGATTG) and a downstream primer (Tn-AC, n = 13-15; Fig. 1). After cloning and sequencing, this gene fragment was found to have high homology to one EST sequence (U38442.1) by National Center for Biotechnology Information BLAST search. We then cloned the cDNA, which was 1,520 nucleotides in length and including an open reading frame of 286 amino acids based on a combination of EST information and data obtained from the 5'-RACE method (Fig. 2), and submitted the sequence to the DDBJ data base as PCA-1 (accession no. AB042029). The National Center for Biotechnology Information human genome resources database indicates that the pca-1 gene is located in chromosome region 11p11.12 and has a 60.9% probability of being localized in the nucleus based on the k-nearest neighbor algorithm. An National Center for Biotechnology Information conserved domain search (http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi) indicates that PCA-1 belongs to the 2-oxoglutarate and Fe(II)-dependent oxygenase superfamily and shows high similarity to E. coli AlkB, an alkylated DNA repair protein.

Production of anti-PCA-1 antiserum. To examine the expression of PCA-1 in prostate cancer at the protein level, we raised an anti-PCA-1 polyclonal antibody against a unique 13-amino-acid peptide localized in the NH₂-terminus (KRRR) in the NH₂ terminus and has a 60.9% probability of being localized in the nucleus based on the k-nearest neighbor algorithm. An National Center for Biotechnology Information conserved domain search (http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi) indicates that PCA-1 belongs to the 2-oxoglutarate and Fe(II)-dependent oxygenase superfamily and shows high similarity to E. coli AlkB, an alkylated DNA repair protein.

![Fig. 1. FDD analysis of changes in mRNA transcripts between cancerous and noncancerous prostate tissues. RT-PCR analysis was performed using a pair of the upstream primer (GATGGCGATTG) and the downstream primer (Tn-AC, n = 13-15). An arrow indicates the pca-1 gene fragment, which showed higher mRNA expression in three prostate cancer tissues than in three corresponding noncancerous tissues of the prostate. Clinical characteristics of the indicated specimen numbers are described in Table 1.](image-url)
Immunohistochemical staining of PCA-1 in prostate cancer with anti-PCA-1 antiserum. We found that 90% (63 of 70) of our prostate cancer specimens were immunohistochemically positive for PCA-1 (Fig. 4A). Positive staining was confined to cancerous cells in the prostate tissue sample and was not seen either in adjacent normal epithelium (0 of 70) or in benign prostatic hyperplasia (0 of 63; Fig. 4B). In some prostate carcinoma specimens, obvious nuclear staining of PCA-1 was detected (Fig. 4C); nuclear localization of PCA-1 was further confirmed in HeLa cells transfected with an expression vector of EGFP-PCA-1 fusion protein (data not shown), suggesting an important function of PCA-1 in nuclei. Little or no PCA-1 immunostaining was observed in samples of glioma, thyroid carcinoma, gastric cancer, colon cancer, lung cancer, and breast cancer (data not shown), suggesting expression of PCA-1 is specific to prostate cancer. Interestingly, of the 22 high-grade prostatic intraepithelial neoplasias (PIN) found in this series of prostate specimens, fully 50% (11 of 22) of the PIN samples were found to be positive for PCA-1 staining. Whereas not all of the cells of the lesions were positive, PCA-1 staining was most often exhibited by atypical epithelia in high-grade PIN (Fig. 4D). The relationship between immunohistochemical staining of PCA-1 and the assigned Gleason score or pathologic T stage (pT) is summarized in Table 2. PCA-1 expression was strongly positive in 31% of tumors (22 of 70) and moderately positive in ~59% of tumors (41 of 70); the remaining 10% of the tumors examined showed little to no immunoreactivity. Of the 31 samples given Gleason scores of 8 to 10, 87% (27 tumors) were strongly or moderately positive, whereas of those assigned scores of 7 and 5 to 6, 95% (19 of 20) and 89% (16 of 18) showed strong to moderate immunoreactivity, respectively. There was no significant correlation between PCA-1 expression and the pT stage, but tumors at pT2 (i.e., those confined within the prostate) tended to show comparatively less expression than did tumors at other stages.

PCA-1 rescued methylmethane sulfonate–induced cell damage in transfected COS-7 cells. During our examinations of PCA-1 function, we found that PCA-1 has the ability to complement the defective reactivation of both MMS-treated ssDNA bacteriophage (23) and ssRNA bacteriophage (17) in AlkB-deficient E. coli. We then examined whether PCA-1, as a homologue of E. coli AlkB, had any protective activity against MMS-induced cell death in mammalian cells. COS-7 cells were transiently transfected with either pEGFP-PCA-1 or a mock vector and treated with MMS at concentrations of 0.25, 0.5, and 1 mmol/L for 1 hour. After washing, we cultured the cells for 48 hours and counted the number of viable cells. As shown in Fig. 5, 0.25 and 0.5 mmol/L MMS treatment induced a decrease of 40% and 65% in cell number, respectively, in mock-transfected cells. This was not seen in cells transfected with pEGFP-PCA-1, indicating a protective function for PCA-1.
COS-7 cells, whereas, in contrast, pca-1-transfected COS-7 cells showed obvious resistance against cell death induced by MMS, decreasing by only 13% at 0.25 mmol/L and by 41% at 0.5 mmol/L, indicative of demethylation activity. We also confirmed pca-1-mediated demethylation in alkB-deficient HK82/F E. coli treated with MMS (data not shown).

Expression of PCA-1 in normal human tissues. We determined the level of pca-1 mRNA expression in various normal human tissues using quantitative real-time PCR on a normalized panel of 15 human tissue samples. Assays were done with a specific primer pair that amplifies the 104-bp fragment within pca-1 open reading frame and the 102-bp fragment within β-actin as a housekeeping gene. The results are expressed as a relative fold increases over β-actin. As shown in Fig. 6, PCA-1 transcripts are most highly expressed in pancreas and testis, although it was ubiquitously observed in all human tissues examined. We confirmed the expression of a full-length transcript of pca-1 open reading frame in the pancreas and testis by RT-PCR and then by nucleotide sequencing (data not shown).

Discussion

FDD analysis is a powerful technique for identifying new genes or specific gene isoforms expressed differentially among distinct tissues or organs that are hard to detect by gene chip analysis. Using this method, we identified a new target molecule that may prove useful in the diagnosis and treatment of prostate carcinoma. We have cloned pca-1, which, by FDD, shows higher mRNA expression specifically in prostate carcinomas, rather than in normal prostatic tissues or benign prostatic hyperplasia. Moreover, our preliminary experiments showed lack of PCA-1 expression in cancers of several other tissues. The overexpression of PCA-1 in prostate carcinoma was also confirmed immunohistochemically in 90% of the human prostate carcinomas specimens examined using a direct anti-PCA-1 antibody; in 31% of tumors stained, virtually all cancer cells were strongly immunopositive for PCA-1, whereas the remainder showed varying degrees of expression. It is well known that the biological behavior of prostate cancer varies widely, ranging from apparently innocuous latent tumors to rapidly disseminating and lethal disease. This clinical diversity is thought to be a consequence of histologic heterogeneity and multifocal origin (24, 25). The varying levels of PCA-1 expression in prostate carcinomas may reflect this characteristic heterogeneity. Characterization of precursor lesions is extremely important both for clinical diagnosis and management of prostate cancer and to the investigative process of prostate carcinogenesis. Therefore, the identification of a new molecular marker to detect putative premalignant lesions is invaluable. Recent studies have focused on PIN, which is generally regarded the precursor of prostate carcinoma; high-grade PIN is now
generally accepted to be a premalignant lesion (26). Whereas PCA-1 was not detected by immunohistochemistry in either benign prostatic hyperplasia or normal prostatic tissue, many but not all atypical cells in high-grade PIN do frequently overexpress PCA-1. PIN has been well-described using microdissection techniques (27, 28), with the hope that any genetic alterations developing in a continuum from normal epithelium to malignant tumor will provide a clearer understanding of the molecular history and clinical future. Whereas it remains to be proven, it is possible that these atypical PIN cells expressing PCA-1 have a higher potential to undergo malignant progression and that expression of PCA-1 may correlate to the earlier stages of prostate cancer development; however, we found no significant correlation between PCA-1 expression and tumor grades or pathologic stages.

PCA-1, which is also designated as hABH3 in the literature, has a high homology to the COOH-terminal domain of the E. coli –alkylated DNA repair protein, AlkB, leading us to hypothesized that PCA-1 would also show repair of alkylated DNA in human cells. Several findings concerning PCA-1/hABH3 have been reported, notably that PCA-1/hABH3 is a member of the \( \alpha \)-ketoglutarate-dioxygenase superfamily which includes AlkB and two other human homologues, ABH1 and ABH2 (23). Although ABH2 apparently demethylates alkylated DNA by oxidative demethylation, the functional activity of ABH1 is controversial (23, 29). PCA-1/ABH3 complements the defective reactivation of an MMS-treated ssDNA phage in the AlkB-deficient E. coli strain and removes 1-methyladenine and 3-methylcytosine from methylated polynucleotides in an \( \alpha \)-ketoglutarate-dependent manner in vitro; furthermore, PCA-1/ABH3 may also reactivate methylated RNA bacteriophage in AlkB-deficient E. coli (17).

We noted the obvious but partial rescue of MMS-induced alkylation damage in COS-7 cells by PCA-1 expression. MMS is a direct-acting DNA methylating agent, acting primarily at the N7-position of guanine and the N3-position of adenine (30). Although PCA-1 also induces demethylation of alkylated DNA in human cells, it can not completely repair the damaged cells. The role of PCA-1 in repairing damaged RNA in human cells also requires further examination. Many tRNAs and rRNAs have both 1-methyladenine and 3-methylcytosine bases as natural, enzyme-mediated modifications (31). It would seem likely that PCA-1 is involved in the regulation of this naturally existing modification of RNAs. We found the expression of some point mutants and splice variants in pca-1 in the prostate carcinomas (data not shown). The demethylation activity of the pca-1 mutants remains to be determined, although its clarification might provide important information for both

![Fig. 5. Effect of PCA-1 on MMS-induced cell death in transfected COS-7 cells. COS-7 cells were transfected with 10 \( \mu \)g of pEGFP-PCA-1 expression vector or a mock vector pEGFP-N1. After cultivation for 48 hours, the transfected cells were treated at the indicated concentrations of MMS for 1 hour. Viable cells were counted 48 hours after MMS stimulation and expressed as a control %. Representative of three independent experiments done with triplicate.

![Fig. 6. Real-time PCR analysis of pca-1 mRNA expression in normal human tissues. The tissue-specific expression of pca-1 mRNA was determined by an SYBR Green I – based quantitative PCR assay in normalized cDNA samples derived from 15 different human tissues. The expression levels of PCA-1 transcript in the human tissues were normalized for the expression levels of the \( \beta \)-actin transcripts in the same cDNAs. 1, brain; 2, thymus; 3, heart; 4, lung; 5, liver; 6, spleen; 7, pancreas; 8, small intestine; 9, colon; 10, kidney; 11, prostate; 12, testis; 13, ovary; 14, peripheral blood leukocyte; 15, placenta. Columns, averages of three independent measurements per tissue.

Table 2. PCA-1 expression in prostate cancer according to Gleason score and pathologic stage

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NOTE: Immunoreactivity was expressed as (–). (<20% of cells immunopositive: (+), 20% to 50% of cells immunopositive; and (++), >50% of cells immunopositive.

Abbreviation: pT, tumor stage.
prostate cancer research and for studies of RNA methylation and demethylation.

PCA-1 has a putative NLS in the NH2 terminus, and the transfection experiments by us and at least one other group (17) have shown the nuclear localization of PCA-1. Our immunohistochemical analyses indicate that the nuclear localization of PCA-1 is specific to prostate carcinoma. This raises the possibility that the overexpression of PCA-1 and/or intracellular localization of PCA-1 in prostate epithelial cells is associated with tumorigenesis. Similar findings regarding nuclear localization and protein overexpression in cancer cells have been reported for other alkyl repair enzymes; for example, MAG immunostaining has been observed in the nuclei of normal ovary cells and in benign epithelial ovarian tumors, although its nuclear localization in malignant ovarian tumors seems to disappear (32). MAG expression and glycosylase activity have also been found to be increased in breast cancers compared with normal breast epithelium.

Overexpression of MAG seems to contribute to the formation of sister chromatid exchanges, chromosomal aberrations, and gene mutations, possibly due to incomplete excision repair (33). AGT is localized in the nucleus as well as the cytoplasm in tumor cell lines (34). Compared with corresponding normal tissue, higher AGT activity has been observed in cancers of the colon, lung, breast, and pancreas, as well as in non-Hodgkin’s lymphoma, myeloma, and glioma (13). Other human DNA repair enzymes, MAG (35) and AGT (36), are also known to be ubiquitously expressed in human cell lines and in normal tissues. However, among tissues, the activities of these repair enzymes are somewhat different. For example, the highest activity of AGT is detected in the liver, followed by the lung and kidney, with much lower activity in the pancreas, hematopoietic cells, and lymphoid tissues (37, 38). In normal human tissues, the expression of pca-1 mRNA is also ubiquitous and variable, with the highest expression being in the testis, pancreas, and ovary. It is quite reasonable to assume that PCA-1, as a DNA repair enzyme, exists in all organs. One could suggest that the differing levels of expression of repair enzymes among tissues may be related to various types and degrees of carcinogen exposure. If so, high expression of PCA-1 in the testis and ovary is very interesting in terms of protection and repair systems.

In summary, we found for the first time that PCA-1 is overexpressed in prostate carcinoma as well as high-grade PIN and that PCA-1 repairs MMS-induced alkylation damage in human cells. Although more studies are needed to determine the targets of PCA-1 in human cells and the relationship between prostate carcinogenesis and the overexpression, localization, and/or mutations of pca-1, the present study strongly supports the possibility of PCA-1 as a potential new protein marker that can be used for earlier detection and better management of prostate carcinoma.

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References

High Expression of a New Marker PCA-1 in Human Prostate Carcinoma

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