

Overexpression of Ornithine Decarboxylase in Prostate Cancer and Prostatic Fluid in Humans¹

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ABSTRACT

Prostate cancer (PCA), the most commonly diagnosed cancer in males in the United States, is the second leading cause of cancer-related deaths of males in this country. Because of the poor success rate in the treatment of PCA, an intervention at an early stage may reduce the progression of small carcinoma to large metastatic lesion, thereby reducing PCA-related deaths. Concerted efforts are needed to establish mechanism-based approaches to develop: (a) the markers for early detection of the disease as well as toward monitoring the efficacy of treatment(s); and (b) novel chemopreventive strategies against PCA. Using unique samples of pair-matched benign and cancer tissue obtained from the same PCA patient, we showed that ornithine decarboxylase (ODC) activity is significantly ($P < 0.001$) elevated in PCA (1142 ± 100 ; mean \pm SE) than in paired benign tissue (427 ± 51 ; mean \pm SE). The immunoblot analysis also showed a significant elevation in the protein expression of ODC in the PCA tissues as compared with the paired benign tissue. Furthermore, our data showed that the ODC activity in the prostatic fluid obtained by a digital rectal massage from the patients with PCA (3847 ± 162 ; mean \pm SE) was significantly higher than in the patients with benign prostatic hyperplasia (2742 ± 167 ; mean \pm SE) or normal individuals (1244 ± 67 ; mean \pm SE). This observation might

be of significance because the prostatic fluid could be obtained noninvasively by digital rectal massage. We suggest that ODC could serve as a target for early detection of human PCA as well as for monitoring the efficacy of treatment(s). The development of ODC as a target for novel chemopreventive strategies against PCA is an intriguing possibility.

INTRODUCTION

PCA⁴ ranks as the most common cancer of males in the United States and, next only to lung cancer, is the second biggest cause of cancer-related deaths in American males (1).⁵ According to estimates and projections by the American Cancer Society, a total of 184,500 men will be diagnosed with PCA in the United States in the year 1998. Of this vast population, 39,200 PCA-related deaths are predicted.⁵ Because of limited treatment options and diagnostic approaches, presently PCA accounts for 29% of all cancers diagnosed in American males, with 13% of the total cancer-related deaths in men.⁵ The development of PCA in humans has been viewed as a multistage process, involving the onset as small, latent carcinoma of low histological grade to large, metastatic lesion of higher grade (2–4). Because of the poor success rate in the treatment of PCA, an intervention at an early stage appears to be a practical approach. This may also reduce the progression of small carcinoma to metastatic lesion, thereby reducing PCA-related deaths. For this reason, concerted efforts are required to establish mechanism-based approaches to develop: (a) the markers for early detection of the disease as well as toward monitoring the efficacy of treatment(s); and (b) novel chemopreventive strategies against PCA. These efforts may be valuable for proactive intervention of patients with localized prostate cancer.

ODC is the first and the rate-limiting enzyme ($M_r \sim 53,000$ protein) in the biosynthesis of polyamines (putrescine, spermidine, and spermine) in mammalian cells (5). Although the precise intracellular functions of polyamines remain incompletely defined, the accumulation of cellular polyamines has been shown to be essential for the growth, proliferation, and differentiation of mammalian cells (6, 7). A considerable body of research has provided convincing evidence for a role of polyamines in tumor cell growth and in the biological response of tumor promoters and growth factors (8, 9). Studies have demonstrated that the levels and/or the biosynthesis of polyamines increase in a variety of tumors other than in normal tissues (7, 10). Much of this information has emanated from studies on mouse skin (11, 12), where this enzyme is tightly

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⁴ The abbreviations used are: PCA, prostate cancer; ODC, ornithine decarboxylase; BPH, benign prostatic hyperplasia.

⁵ American Cancer Society—Cancer Facts and Figures. Graphical data: 1998 (available at website <http://www.cancer.org>).

regulated in normal tissues at the mRNA and protein levels and is dysregulated in papillomas and carcinomas (13). The "basal" levels of ODC activity in mouse skin papillomas are significantly elevated as compared with the normal epidermis (11–15). A number of studies conducted in rodent models have established, beyond doubt, the importance of ODC in tumor progression (Refs. 16–19 and references therein). This led to the hypothesis that an uncontrolled regulation of ODC may contribute to the development of tumors in different organ types, especially in the epithelial tissues. In humans and experimental animals, ODC is ubiquitously expressed in most of the tissues (20, 21). In humans, among all tissues, the highest concentration of polyamines and polyamine synthetic enzymes, especially ODC, occurs in the prostate (22, 23).

We hypothesized that ODC could serve as a biomarker for the diagnosis or monitoring the therapeutic efficacy of PCA in humans, and possibly as a target for intervention of the disease, through chemoprevention. In this communication, we provide evidence that ODC enzyme activity as well as protein expression is significantly higher in human PCA than in paired benign tissue. Furthermore, ODC enzyme activity was also detectable in prostatic fluid collected through digital rectal massage and was significantly higher in the patients with PCA than in BPH patients or normal volunteers.

MATERIALS AND METHODS

Tissue Sample Collection. The paired benign (or normal) prostate tissue and prostate cancer tissue specimens were obtained from the same patients who underwent radical prostatectomy performed at Mayo Clinic (Rochester, MN). Immediately after surgery, tissues were snap frozen and shipped in dry ice to University Hospitals of Cleveland, where all biochemical studies were performed. The resectability of benign and prostate cancer could be determined through medical records of serum preoperative PSA concentration and Gleason grade for estimation of clinical stage of prostate cancer. Each PCA and paired benign tissue was histologically verified for its pathological condition. The benign tissue attached to the cancerous tissue was carefully removed by an experienced human prostate pathologist before further processing.

Prostatic Fluid Collection. Prostatic fluid was obtained from the urethra after digital rectal massage from normal individuals and patients with BPH and PCA undergoing treatment at the University Hospitals of Cleveland. The samples were collected in microfuge tubes and were stored at -70°C .

Preparation of Tissue Supernatant for ODC Enzyme Activity. Frozen tissues were ground to a fine powder with a mortar and pestle with occasional addition of liquid nitrogen, which prevents the tissue from thawing (24). The powder was homogenized at 4°C in a glass-to-glass homogenizer in 10 volumes of ODC buffer [50 mM Tris-HCl buffer (pH 7.5), containing 0.1 mM EDTA, 0.1 mM DTT, 0.1 mM pyridoxal-5-phosphate, 1 mM 2-mercaptoethanol, and 0.1% Tween 80 (all from Sigma Chemical Co. St. Louis, MO)]. The tissue homogenate thus obtained was centrifuged at $100,000 \times g$ at 4°C in an ultracentrifuge (model L7-70; Beckman). The supernatant was carefully aspirated and used for enzyme determination. For prostatic fluids, the equal amount of ODC buffer was added to

the samples that were kept over ice for 30 min and centrifuged at $14,000 \times g$ for 15 min, and the supernatant was collected. Protein concentration was determined by Bradford assay, using a Bio-Rad protein detection kit per the manufacturer's protocol.

Measurement of ODC Enzyme Activity. ODC activity in the supernatant and prostatic fluid was determined by measuring the release of $^{14}\text{CO}_2$ from DL-[1- ^{14}C]ornithine hydrochloride, as described earlier (25). Briefly, 100 μl of the supernatant obtained from tissue or prostatic fluid were added to 0.25 ml of the assay mixture [35 mM sodium phosphate (pH 7.2), 0.2 mM pyridoxal phosphate, 4 mM DTT, 1 mM EDTA, and 0.4 mM L-ornithine containing 0.5 μCi of DL-[1- ^{14}C]ornithine hydrochloride] in 15-ml Corex centrifuge tubes equipped with rubber stoppers and central well [containing ethanolamine and methoxyethanol (0.2 ml; 2:1, v/v)] assemblies (26). After incubation at 37°C for 60 min, the reaction was terminated by the addition of 0.5 ml of 2 M citric acid, using a 21-gauge needle/syringe. The incubation was continued for another 1 h to ensure complete absorption of $^{14}\text{CO}_2$ into the absorption mixture in the central well. Finally, the central well containing the ethanolamine:methoxyethanol mixture (to which $^{14}\text{CO}_2$ has been trapped) was transferred to a vial containing 10 ml of toluene-based scintillation fluid and 2 ml of ethanol. The radioactivity was measured in a liquid scintillation counter (model LS 6000 SC; Beckman). Assays were carried out in triplicate using a blank sample containing no enzyme.

Immunoblot Analysis. Frozen tissues (benign or PCA) were homogenized in lysis buffer (50 mM Tris-HCl, 150 mM NaCl, 1 mM EGTA, 1 mM EDTA, 20 mM NaF, 100 mM Na_3VO_4 , 0.5% NP40, 1% Triton X-100, 1 mM PMSF, 10 $\mu\text{g}/\text{ml}$ aprotinin, and 10 $\mu\text{g}/\text{ml}$ leupeptin, pH 7.4) at 4°C and left over ice for 30 min to prepare $\sim 10\%$ homogenate. The homogenate was centrifuged at 14,000 rpm for 20 min, the supernatant was collected, and protein content was determined using DC Bio-Rad protein assay kit using the vendor's protocol. For Western blot analysis, the cell lysates containing 10–20 μg of protein were denatured by boiling over water with $2\times$ or $5\times$ sample buffer and then subjected to electrophoresis on 12% SDS-polyacrylamide gel (Novex, San Diego, CA). The protein was then transferred onto a nitrocellulose membrane. The nonspecific sites were blocked by incubating the block with the blocking buffer (5% nonfat dry milk and 0.1% Tween 20 in TBS, pH 7.6) for 1 h at room temperature. The blot was washed twice with wash buffer (10 mM Tris, 100 mM NaCl, and 0.1% T-20) for 10 min and then incubated with mouse monoclonal antibody that recognizes $M_r \sim 53,000$ ODC protein [with epitope of MP16-2 monoclonal antibody that localizes in amino acids 355–360 (-IWGPTC-) of ODC] in blocking buffer overnight at 4°C . The antibody was obtained from Neomarkers (Fremont, CA) and was used at 1:500 dilution. The blot was washed for 2×10 min and then incubated with antimouse secondary antibody HRP conjugate (1:2000 dilution; Amersham Life Science, Inc., Arlington Heights, IL) for either 1 h at room temperature or overnight at 4°C . The blot was washed for 2×10 min and 4×5 min, and the protein was detected by chemiluminescent detection with ECL Plus kit and autoradiography using Hyperfilm ECL (Amersham).

Statistical Analysis. Statistical significance of the data obtained was analyzed by the Wilcoxon rank sum test or Student's *t* test (Statworks; Cricket Software, Philadelphia, PA).

RESULTS

ODC Enzyme Activity Is Elevated in PCA Tissue. The ODC activities in paired benign and prostate cancer specimens from 31 individuals who underwent prostatectomy is shown in Fig. 1A. A wide interindividual variation in ODC enzyme activity was observed among the 31 individuals examined. As shown in Fig. 1B, the ODC-specific activity in benign tissue was 427 ± 51 (mean \pm SE), whereas it was elevated to 1142 ± 100 (mean \pm SE) in the PCA tissue, which represents a 2.7-fold increase ($P < 0.001$).

ODC Protein Expression Is Higher in PCA Tissue. To further confirm the differential expression of ODC in PCA versus benign tissue, the immunoblot analysis was performed on benign and PCA specimens of randomly selected individuals. Data in Fig. 2 show that the protein expression of ODC was elevated in PCA tissues of each individual as compared with the paired benign tissue.

ODC Enzyme Activity Is Elevated in the Prostatic Fluids of Patients with PCA. Data in Fig. 3 show that the ODC activity was measurable in the prostatic fluid collected by digital rectal massage in 15 individuals. Among these 5 were normal volunteers, and the remaining 10 were from patients with prostate abnormalities. ODC activity in the patients with PCA (3847 ± 162 ; mean \pm SE) was significantly higher than in the patients with BPH (2742 ± 167 ; mean \pm SE) or normal individuals (1244 ± 67 ; mean \pm SE).

DISCUSSION

Because of the increasing incidences of PCA and PCA-related deaths in humans in recent years, there has been an increasing attention for understanding pathophysiology of this disease and to develop novel approaches for its therapy and prevention. PSA is regarded as a sensitive and specific marker available for PCA in the clinical practice today (27–29). The role of PSA in the screening of population for early detection of PCA is not certain. Recently, there has been uncertainty about its specificity (30, 31). The debate emanates from the fact that PSA production is influenced by the volume of benign epithelium, the grade of adenocarcinoma, inflammation status of the tissue, androgen levels of individuals, growth factors, extracellular matrix, and racial differences (28–32). Furthermore, it is reported that a decline in PSA levels may not correlate with decrease in tumor growth *in vivo* (33). An important consideration toward intervention and prevention of prostate cancer is the development of surrogate biochemical markers that can detect early premalignant changes along the tumor development pathway. It is desirable that a biomarker should also be able to monitor the efficacy of the treatment.

Using unique samples of pair-matched benign cancer tissue obtained from the same PCA patient, we investigated whether ODC, which is the rate-limiting and terminal enzyme in the polyamine biosynthetic pathway, could be used as a biomarker for the detection of PCA in humans. ODC catalyzes the decarboxylation of ornithine to form putrescine, which is then me-

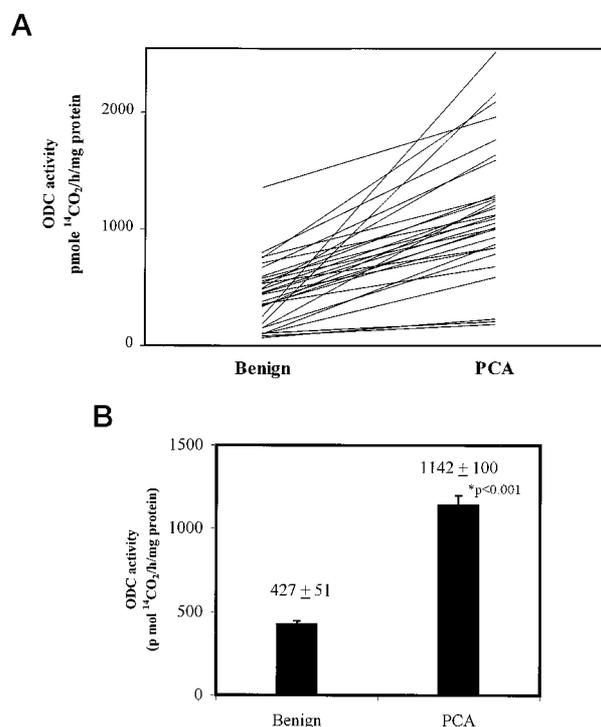


Fig. 1 ODC enzyme activity in paired benign and cancer tissue obtained from patients with PCA. The ODC enzyme activity was measured in the benign and PCA tissue obtained during prostatectomy of same patient. The details are described in "Materials and Methods." **A**, ODC activity in the benign and cancer tissue of all of the 31 patients. **B**, means of the ODC activity, from all of the 31 patients; bars, SE.

tabolized to spermine and spermidine (9, 34). ODC is a member of the early response gene family that must be activated if cells are to move from G1 to S phase in the cell cycle (35). Its expression is very tightly regulated, with little, if any, activity being detected in the quiescent cells (35). In a mouse skin tumor model, it has been shown that most, if not all, of the tumor promoters induce ODC in a transient fashion with a good correlation between promotion potency and magnitude of ODC induction (11, 15). In addition, the epidermal growth factor has been shown to stimulate ODC transcription in SV40-transformed keratinocytes (36), and conversely, overexpression of ODC in NIH 3T3 cells increases both the basal and ligand-stimulated tyrosine kinase activity in epidermal growth factor receptors (37). High levels of all these growth factors are known to be present in the prostate (38) and are able to stimulate prostatic epithelial cell growth (39). On the basis of these facts, ODC could also be regarded as a marker for cell growth and proliferation, which if dysregulated may result in uncontrolled cell growth and proliferation that is a hallmark of the development of cancer.

It is important to emphasize here that many studies are under way to investigate the prevention of cancer by agents such as DFMO, which is a potent suicide substrate inhibitor of ODC (40). Recently, one polyamine-based chemopreventive trial in human skin has yielded positive results, where the topical application of DMFO caused a significant reduction in the number

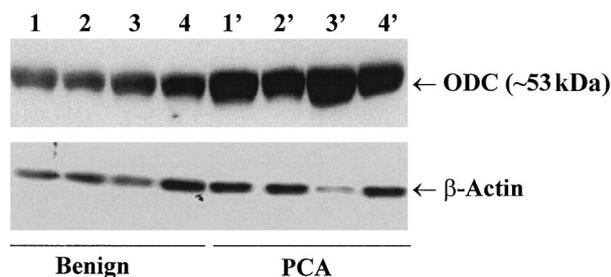


Fig. 2 ODC protein expression in paired benign and cancer tissue obtained from patients with PCA. The protein expression was measured by immunoblot analysis in the tissue obtained from the benign and cancer tissue of the same patient. Total cell lysates were prepared from the benign and PCA tissues obtained from four randomly selected representative patients. Protein (10–20 μ g) was subjected to SDS-PAGE, followed by immunoblot analysis and the detection of protein. The protein expression in the benign and PCA tissue from the same patients is represented as 1,2,3,4 and 1',2',3',4', respectively. For normalization of protein loading, the membrane was stripped and reprobed with β -actin primary antibody and appropriate secondary HRP conjugate. The details are given in "Materials and Methods." This figure represents results obtained only from four patients.

of actinic keratoses and total polyamine content (Ref. 41 and references therein). It is important to emphasize here that DFMO is presently at the most advanced stage among the drugs that are being assessed for the prevention of cancer at many sites in the clinical trials (42).

In this study, we have demonstrated that the ODC enzyme activity as well as its protein expression is significantly elevated in the cancerous tissue as compared with the paired benign tissue of the prostate in patients with PCA. In this study, the benign and cancerous tissues were obtained from the same individual, which minimized the chance of error due to inter-individual variation. It is important to emphasize here that ODC is constitutively expressed at fairly high levels in normal human prostate and shows a further significant elevation in the prostate cancer. This suggests that the overexpression of ODC may be a target for detecting/monitoring the growth and development of latent to metastatic lesions of PCA in humans.

Because the prostate is known to secrete ODC and polyamines into RBCs (43), it is likely that the prostate secretes ODC into the prostatic fluid. We, therefore, measured the level of ODC enzyme activity in the prostatic fluids obtained from the patients with PCA after digital rectal massage and compared it with the prostatic fluid obtained from patients with BPH and normal individuals. In prostatic fluid, the ODC activity in the PCA patients was significantly higher than in normal individuals. The ODC activity in the patients with BPH was intermediate between PCA patients and normal individuals. This observation could be of significance because the prostatic fluid could be obtained by digital rectal massage, which is essentially a non-invasive method. Therefore, in prostatic fluid, the ODC activity could be used to follow tumor proliferation and tumor aggressiveness during subsequent follow-up of the patients. The drawback of using this noninvasive method is that the amount of protein secreted into the prostatic fluid largely depends on the part of tissue massaged. This could account for the variation observed in ODC activity in the prostatic fluid from the same

Normal	BPH	PCA
1244 \pm 67	2742 \pm 167	3847 \pm 162

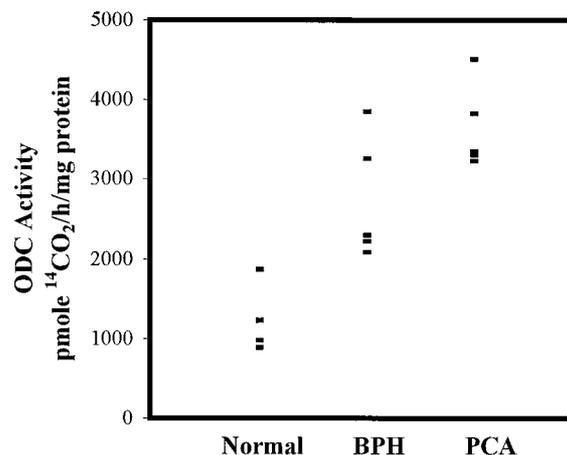


Fig. 3 ODC activity in prostatic fluid obtained by digital rectal massage from normal individuals and patients with BPH and PCA. The ODC activity was measured in the prostatic fluid as described in "Materials and Methods."

individual. The improvement in techniques for fluid collection could increase the sensitivity of ODC in proving a viable adjuvant marker for staging of prostate cancer.

Also, ODC may prove to be an efficient marker because it is regarded that for a biomarker to be useful, it should be: (a) expressed in early stage lesions; (b) associated with early invasive tumors; and (c) modulated by the chemopreventive agents so that it could predict the reduction of invasive tumors. Our data demonstrated a significant increase in ODC activity in prostatic fluid of the patients with BPH that could be regarded as an early stage lesion. It is tempting to suggest that ODC could also serve as a target to develop novel chemopreventive strategies against PCA.

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