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Identification and characterization of the novel human prostate cancer-specific *PC-1* gene promoter

Jian Wang [1], Hui Zhang [1], Rui-Xia Liang, Bo Pang, Qing-Guo Shi, Pei-Tang Huang, Cui-Fen Huang, Jian-Guang Zhou *

Beijing Institute of Biotechnology, Beijing 100850, PR China

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Abstract

Human prostate and colon gene-1 (*PC-1*, also known as *PrLZ*) is an androgen-regulated, prostate tissue and prostate cancer cells specifically expressed novel gene. The increased expression of *PC-1* gene appears to promote prostate cancer cells androgen-dependent (AD) and androgen-independent (AI) growth. To clone and investigate the expression and regulation elements of *PC-1* gene may provide insight into the function of PC-1 and develop a new promoter that targets therapeutic genes to the AD and AI prostate cancer cells. The goal of the present study is cloning and characterization of the *PC-1* promoter. A series of luciferase constructs that contain various fragments of the *PC-1* 5′-genomic region were transfected into human prostate cancer cells for promoter transactivation analysis. 5′ deletion analysis identified the −1579 bp promoter region was required for the maximal proximal promoter activity; two transcriptional suppression and a positive regulatory region were identified; −4939 bp promoter fragment of the *PC-1* gene retained the characteristic of prostate cancer-specific expression and exhibited higher transcription activity than PSA-6 kb promoter in the medium supplemented with steroid-depleted FBS. An androgen response element (ARE) was located in between −345 and −359 bp of the *PC-1* 5′-untranslated region relative to the translation initiation site. Thus, our studies not only provide molecular basis of *PC-1* transcription regulation, but also define a new regulatory sequence that may be used to restrict expression of therapeutic genes to prostate cancer in the prostate cancer gene therapy.

Keywords: *PC-1* gene; Promoter; Prostate cancer; Gene therapy

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in North American men [1]. To study the molecular mechanism underlying the development and progression of prostate cancer, LNCaP/C4-2 human prostate cancer progression model was established. The LNCaP cell line, which represents AD status of prostate cancer, was isolated and established as a stable prostate specific antigen (PSA)-producing and androgen receptor (AR)-positive cell line from a patient with lymph node metastases [2]. C4, C4-2 and C4-2B sublines were established from the lineage-related LNCaP parent line through tumor–stroma interaction and xenograft selection and obtained the ability of sustainable growth in castrated hosts and metastasis to the lymph nodes and bone [3,4]. Because this model mimics the progression of clinical prostate cancer, gene differential expression analysis between the LNCaP and lineage-related sublines may provide clues to the molecular mechanism of prostate cancer progression.

PC-1 was isolated from 1500 arrayed genes for gene differential expression in LNCaP and C4-2 cells. The full-length cDNA of *PC-1* was 2573 bp and contained an ORF of 224 amino acid residues [5]. With marked homology to the Tumor Protein D52 gene, *PC-1* belongs to TPD52 family [6]. *PC-1* is primarily expressed in human prostate tissue, while TPD52 is expressed in a variety of human tissues without evidence of tissue specificity [6–8]. The expression of *PC-1* is regulated by androgen not only

* Corresponding author. Fax: +86 10 68248045.
E-mail address: zhou.jianguang@yahoo.com.cn (J.-G. Zhou).
[1] These authors contributed equally to this work.

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in LNCaP cells, but also in its sublines C4-2 and C4-2B cells [5].

The biological function of PC-1 is still not very clear, but this protein is associated with prostate cancer progression and possesses some oncogenic properties [5,9–11]. *PC-1* gene is located at chromosome 8q21.1, while the amplification of 8q is the most frequent genomic abnormality in clinical prostate cancer [12]. Immunohistochemical staining showed that PC-1 was highly expressed in the majority of high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer specimens compared with the normal prostate tissues [5]. Elevated expression of PC-1 in prostate cancer may represent a gain of function favoring prostate tumor cells transformation and malignancy.

The prostate-specific expression and higher expression in the AI prostate cancer cell lines suggested that *PC-1* has a unique transcriptional regulation mechanism. To clone *PC-1* promoter and investigate the regulation mechanism may provide insight into the function of PC-1. Here, we describe the isolation and characterization of the *PC-1* promotor. The *cis*-regions are identified to mediate the transcription of the *PC-1* gene. In addition, we also present evidence that the 5-kb promoter of *PC-1* maintains the prostate-specific transcription and contains an androgen response element (ARE) that mediates transactivation in response to androgen.

Materials and methods

Cell culture. The prostate cancer LNCaP, C4-2, C4-2B, PC-3; the breast cancer MCF-7, T47D; the chronic myeloid leukemia K562 cells were cultured in RPMI1640 supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 μg/ml streptomycin. The cervix adenocarcinoma HeLa, african green monkey kidney COS-7, epithelial mouse melanoma B16 and human lung giant cell carcinoma PLA801 were cultured in DMEM with 5% FBS and 100 U/ml penicillin and 100 μg/ml streptomycin.

Cloning of the PC-1 promoter. The *PC-1* promoter was cloned with PCR method. The 323 base pairs of the 5′-untranslated region of *PC-1* cDNA (GenBank Accession No. AF202897) was used for a DNA homology search at the Nation Center for Biotechnology Information (NCBI) using standard nucleotide–nucleotide basic local alignment search tool (BLASTN). The genomic chromosome 8 clones (GenBank Accession No. AC009686) complementary to this sequence was used for cloning of the *PC-1* promoter. Oligonucleotides (5′-CGACGCGTTACACTGA CATATTTGAG) with the sequence from the 4939 bp upstream of the *PC-1* translation initiation site was designed as a forward sense primer and oligonucleotide (5′-GGACTCGAGTCCAGACAAACGCAG-3′) complementary to the 20 bp upstream of the *PC-1* translation initiation site was used as a reverse anti-sense primer for PCR. Prostate cancer LNCaP cell genomic DNA was used as a template for PCR.

Plasmid constructs. The luciferase vector p4939 was created by inserting the 4939 bp DNA fragment into the *Xho*I and *Mlu*I sites of a pGL3-Basic. Deletion constructs were created with PCR using p4939 as the template and cloned into the same sites of pGL3-Basic. For deletion constructs, anti-sense primer for PCR was used as above and forward sense primers were the following: for 3845 bp deletion construct, forward primer was: 5′-CGACGCGTAGATCTGAAGCA CAGGC-3′; for 2831 bp construct: 5′-CGACGCGTTATGCCTG CAGTGCATC-3′; for 1831 bp construct: 5′-CGACGCGAAGAAG CCAGACAATCCA-3′; for 1579 bp construct: 5′-CGACGCGTAG TTGAGACCAGCCTG-3′; for 1336 bp construct: 5′-CGACGCGT AGAGTACAACATGAGAC-3′; for 1099 bp construct: 5′-CGACG CGTTAGATTAGAACACTGCCT-3′; for 757 bp construct: 5′-CGACG CGTTCTCCTTTGAGTGCATG-3′; for 340 bp construct: 5′-CGA CGCGTGCCATATTGCAGAACCCTG-3′. For pmini-CMV construct, we used pTRE-LUC as template for PCR to get 118 bp minimal CMV promoter fragments and cloned into the *Xho*I and *Hin*dIII sites of pGL3-Basic vector. The forward primer and anti-sense primer were used to amplify this fragment as blow, respectively: 5′-C CGCTCGAGG TAGGCGTGTACGGTGGGAGGC-3′; 5′-GCCAAGCTTGGCTTGG ATCGGTCCCGGTGTC-3′. Constructs pARE–miniCMV and pmtARE–miniCMV were generated by inserting three copies of AREpc and AREpc mutate into pmini-CMV, respectively. The 3*AREpc oligonucleotides: 5′-CGCGTTGAACTGTTTGTACCTGAACTGTTTGTACCTG AACTGTTTGTACCC-3′ and 5′-TCGAGGGTACAAACAGTTCAGG TACAAACAGTTCAGGTACAAACAGTTCAA-3′; the 3*mtAREpc oligonucleotides: 5′-CGCGTGAACTGTTTGTTGAACTGTTTGTTG AACTGTTTGTC-3′; 5′-TCGAGACAAACAGTTCACAAACAGTTC ACAAACAGTTCA-3′. To generate a 4939 bp PC-1 upstream promoter with a deletion of AREpc (p4939del2), the two pairs of primers (pair1: 5′-CGACGCGTTACACTGACATATTTGAG-3′, 5′-GGCAAACATCAG ACACTGG-3′; pair 2: 5′-CAGTGTCTGATGTTTGCCTCTGGGCC ATATTGCAGAACCCTG-3′, 5′-GGACTCGAGTCAGACAAACGC AG-3′) and p4939 vector as a template was used in PCR to produce a 4939 bp fragment which deleted the AREpc element and cloned into the *Xho*I and *Mlu*I sites of pGL3-Basic vector.

Transient transfections and luciferase assay. Cells were transiently transfected using Lipofectamine2000 (Invitorgen) with constructs described above together with a pRL-TK plasmid used as an internal control of the transfection efficiency. The pGL3-Basic was used for background luciferase activity. After transfection, cells were grown either in fresh culture medium or steroid-depleted culture medium in the presence or in the absence of 1 nm R1881. After 48 h, cells were harvested for the luciferase activity assays. Luciferase activity was assayed using the Dual luciferase assay system (promega). All transfections were performed at least three times in triplicates.

Electrophoretic mobility-shift assays. Cell nuclear extract was obtained from LNCaP cells as described previously [13]. The digoxigenin (DIG) gel shift kit (Roche Applied Science) for 3′-end labeling of double-stranded oligonucleotide probes was used for protein-DNA binding assays. The 25 bp oligonucleotides containing a *PC-1* AREpc element were synthesized and purified by HPLC. The oligonucleotides were annealed, labeled, and used in the gel shift reactions according to the manufacturer's instructions. A non-denaturing 8% polyacrylamide gel in 0.25× TBE (Tris–borate–EDTA buffer) was prepared and used for electrophoresis to separate the protein-DNA complexes. Blotting was performed using a Bio-Rad electro-blotting system according to the manufacturer's instructions. Chemiluminescence detection of DIG-labeled DNA-protein complexes on the nylon membranes was detected using Hyperfilm ECL (Amersham Pharmacia). For supershift and competition studies, we pre-incubated 20 vg nuclear extract with 1 *vg* AR antibody or 250-fold excess cold double-stranded oligonucleotides before adding DIG-labeled oligonucleotides.

Results

Cloning and analysis of a series of putative human PC-1 gene promoters

In order to investigate the expression and regulation of human *PC-1* gene at the transcriptional level, we first cloned the complete 1831 bp DNA fragment, as well as a series of truncated 5′-flanking regions upstream of translation initiation site of *PC-1* gene into a promoterless luciferase expression vector pGL3-Basic and transfected into LNCaP cells for promoter transactivation analysis. As shown in Fig. 1A, the p1579 exhibited the highest promoter

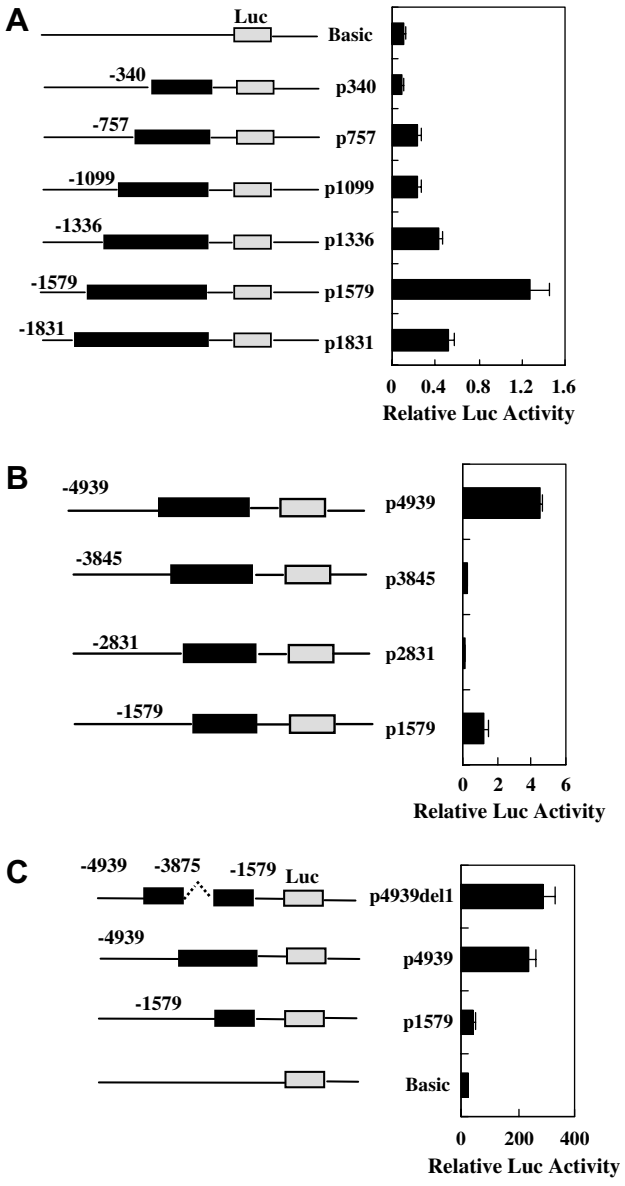

Fig. 1. (A) *PC-1* gene proximal promoter activity in the human prostate cancer LNCaP cells. On the left, a schematic representation of the 1831 bp PC-1 promoter and its deleted variants inserted upstream of the luciferase gene reporter vector pGL3-Basic. The numbers indicated the 5′ end of the promoter inserts DNA, in relation to the translation initiation site of *PC-1*. LNCaP was transfected with the *PC-1* reporter constructs and assayed for luciferase activity as described under Materials and methods. Relative luciferase values were normalized for co-transfection with pRL-TK. (B,C) Various trunctions and deletion of the 5′ upstream region of PC-1 gene were inserted into the pGL3-Basic reporter vector and co-transfected with pRL-TK. Relative luciferase activity were presented as the ratio of the *Firefly* luciferase activity to *Renilla* luciferase activity. Average activities with SD from three independent experiments with duplicate samples are shown.

activity among the six constructs examined. As we know that lots of *cis*-elements exhibiting their transcription regulatory effect are far away from the proximal promoter. In order to seek these kinds of *cis*-elements and look for a higher promoter activity, the longer DNA fragments about 4939, 3845 and 2831 bp relative to *PC-1* translation initiation site were further cloned into pGL3-Basic. We found that the p4939 had the higher activity than the construct p1579, while the p3845 and p2831 almost lost the promoter activity (Fig. 1B). The construct of p4939del1 in which the DNA fragment between −3845 and −1579 was deleted gained more transcription activity than that of the p1579 and the p4939 (Fig. 1C). So our results showed that at least two important negative regulatory regions are located in between −1579 and −3845 and a positive region between −3845 and −4939 of the *PC-1* gene promoter.

The prostate cancer cell-specific regulation effect of the PC-1 4939 bp promoter

PC-1 is predominantly expressed in normal human prostate tissue with only a minimal expression in a few other glandular organs [5], we therefore examined whether the 4939 bp promoter of *PC-1* displayed the prostate cancer cell-specific regulation. The p4939 construct was transiently transfected into a variety of cancer cell lines from different tissue origins. The 4939 bp promoter dominatively displayed its activity in the LNCaP and C4-2 prostate cancer cells, though in the T47D breast cancer cells this promoter also exhibited a moderate activity (Fig. 2), this result indicated that the 4939 bp *PC-1* promoter retains the characteristic of the prostate cancer cell-specific transcriptional regulation.

Identification of an androgen response element in the PC-1 gene 5′-untranslated region

Androgen can regulate the expression of the *PC-1* gene, so there should have androgen response element (ARE) in the *PC-1* regulatory region. Bioinformatics analysis of the 757 bp fragment revealed that a putative ARE (TGAA CTgttTGTACC, designated as AREpc) located in −345/−359 region, which has highly homology with the consensus ARE (GGTACAnnnTGTTCT) and two other ARE (AGAACAgcaAGTGCG; GGAACAtatTGTATC) found in the PSA promoter [14,15]. To identify this putative ARE function, we deleted this AREpc from the p4939

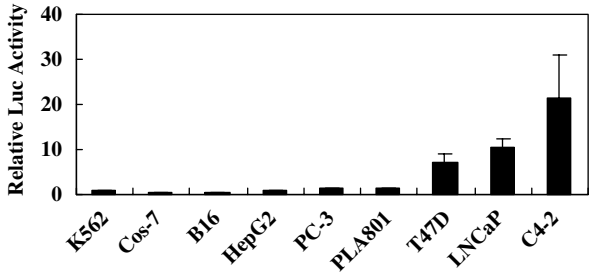

Fig. 2. Cell-specific expression of *PC-1* promoter. Various cell lines of different tissue origin were transiently transfected with a reporter vector p4939 and pRL-TK was co-transfected as an internal control. We also co-transfected pGL3-Basic and pRL-TK reporter vector into various cell lines. Luciferase activities were expressed in relation to background activity of pGL3-Basic.

and got the construct p4939del2. We analyzed the activities of the p4939 and p4939del2 in different culture conditions by transiently transfected into LNCaP cells. In absence of androgen R1881, transcriptional activity of the p4939 and p4939del2 were about the same, while in presence of androgen R1881, the p4939del2 totally lost the ability to be induced by androgen (Fig. 3A). Three copies of AREpc or three copies of mtAREpc which deleted the A, G and C from the AREpc were inserted in front of the minimal CMV promoter in pmini-CMV and transfected into LNCaP cells. The results showed that AREpc displayed 10-fold induction upon R1881 stimulation, while mutation AREpc lost the respond to the R1881 stimulation (Fig. 3B). Gal retardation experiment was performed with labeled ds-oligonucleotides encompassing this element. As shown in Fig. 3C, nuclear extract from LNCaP cells bound to this element and a specific band was observed, while the androgen receptor antibody addition destroyed the binding band. From above investigation, we concluded that the AREpc is an androgen response element which can bind to AR and is responsible for androgen induction of *PC-1* gene expression.

Comparison of the transcription activity between PC-1 4939 bp promoter and PSA 6 kb promoter

Among the genes that express specifically by human prostate, *PSA* gene 6 kb promoter has been widely studied for controlling therapeutic gene expression [16–18]. Because *PC-1* gene 4939 bp promoter displayed the characteristic of the prostate cancer cell-specific expression, we want to know whether this promoter will have the promise future in the prostate cancer gene therapy. LNCaP cells and C4-2B cells were transiently transfected with luciferase reporter constructs containing either *PC-1* promoter p4939 or *PSA* 6 kb promoter PSA-61. The results demonstrated that the transcription activity of PSA 6 kb promoter was higher than that of the *PC-1* 4939 bp promoter when transfected cells were cultured in the regular FBS, while lower than that of the *PC-1* promoter when transfected cells were

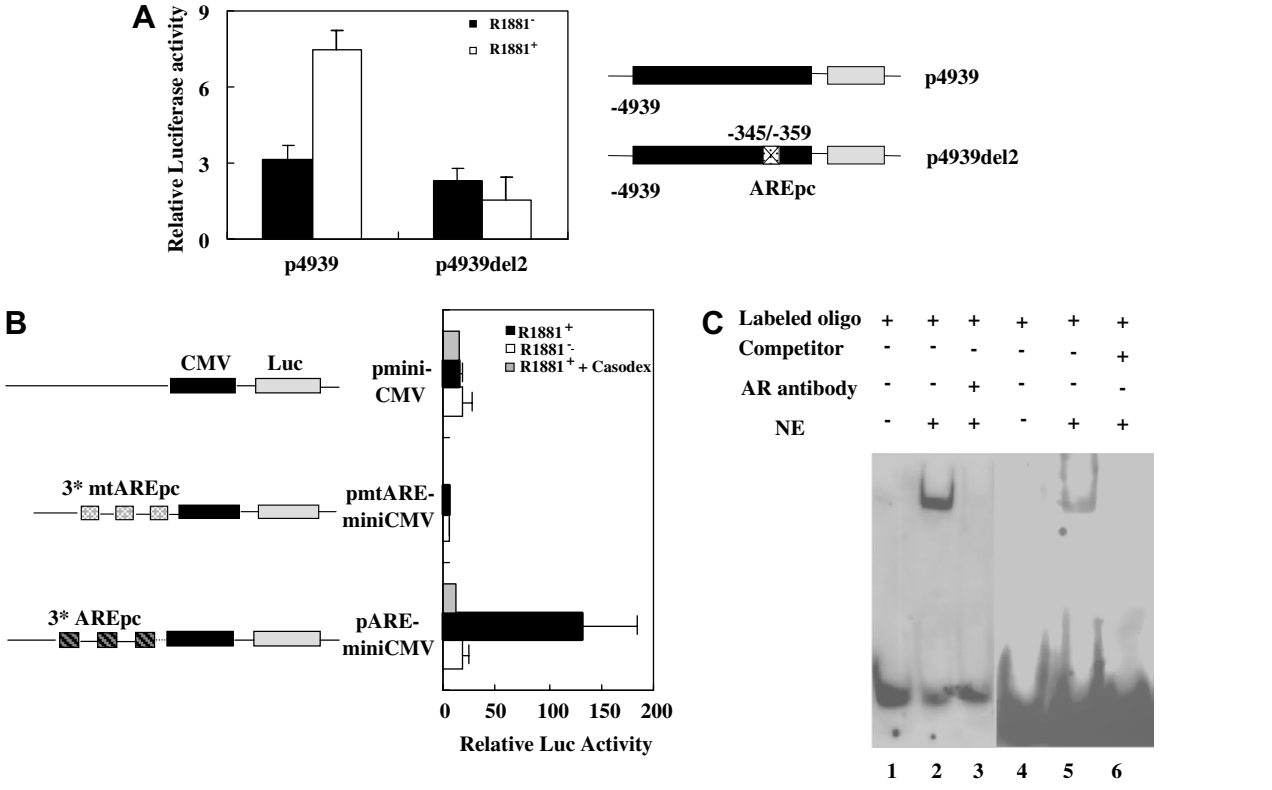

Fig. 3. Identification of an ARE in the *PC-1* promoter. (A) Mutation of *PC-1* promoter with AREpc deletion abolished the androgen-mediated promoter activity. The wide-type and mutant *PC-1* 4939 bp promoter constructs were inserted upstream of the pGL3-Basic luciferase gene. LNCaP cells were transiently transfected with reporter vectors and 6 h later the transfected cells were cultured in RPMI1640 supplemented steroid-depleted FBS in the absence or in the presence of 1 nm R1881. (B) Effect of AREpc and AREpc mutation on minimal CMV promoter activity. Three copies of AREpc or AREpc mutation were inserted upstream of the minimal CMV promoter on the pmini-CMV and transiently transfected LNCaP cells. Six hours later, LNCaP cells were cultured in RPMI1640 supplemented with 5% steroid-depleted FBS in the absence R1881 or in the presence of 1 nm R1881 or 1 nm R1881 plus 10 vM Casodex. pRL-TK was co-transfected with the reporter vector as an internal control of transfection efficiency and average activities with SD from three independent experiments with duplicate samples are shown. (C) Interaction of LNCaP cell nuclear extract (NE) with AREpc by Electrophoretic mobility-shift assay. The DIG-labeled *PC-1* promoter fragment containing putative AREpc was incubated with 20 μg LNCaP cell nuclear extract which had been preincubated without (lane 2; lane 5) or with 250-fold of designated cold double-stranded oligonucleotides (lane 6) or preincubated with 1 μg AR antibody (land 3) on ice for 30 min. Electrophoresis and detection was performed as described in Materials and methods. Lanes 1 and 4, free probe only.

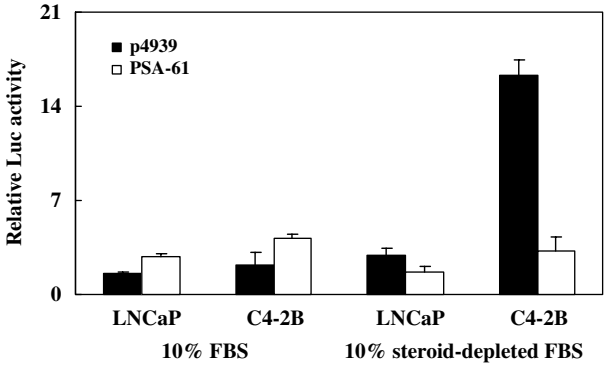

Fig. 4. Comparison of *PC-1* and *PSA* promoter activity. LNCaP and C4-2B were transiently transfected with a reporter vector p4939 containing 4939 bp *PC-1* promoter and a reporter vector PSA-61 containing 5.8-kb PSA promoter, respectively. pRL-TK was co-transfected as an internal control. Transfected cells were cultured in RPMI1640 completed with normal FBS or steroid-depleted FBS. Forty eight hours later, luciferase activity was assayed with dual luciferase assay kit as described in Materials and methods. Average activities with sd from three independent experiments with duplicate samples are shown.

grown in the medium supplemented with steroid-depleted FBS (Fig. 4).

Discussion

PC-1 was firstly isolated from the LNCaP/C4-2 progression model for its differential expression [5]. According to the *PC-1* cDNA sequence in the Genbank, the *PC-1* transcription at least started at the nucleotide position 332 bp upstream of the translation initiation site, so we cloned 340 bp sequence and other longer sequences upstream of the translation initiation site into the reporter vector pGL3-Basic, respectively. As we expected, no transcription activity in 340 bp segment was found, while the construct p1579 showed the highest transcription activity though the absolute transcription activity was still low. The reason may be that there are other regulation elements existing far away from the proximal promoter. After we cloned the 4939 bp length segment into the pGL3-Basic, we found that the transcription activity increased 4-fold compared with that of the p1579. The further investigation showed the *cis*-regulatory regions were located between the −1579 and −4939 region. More detailed characterization of these regions will help us understand the transcriptional regulatory mechanism of *PC-1* promoter.

Northern blot hybridization and RT-PCR both confirmed that *PC-1* expression was regulated by androgen [5]. Androgen receptor is activated by androgen and binds to ARE in the promoter region of target genes triggering their transcription activation. [19]. Our research found a putative ARE at −345/−359 site upstream of the translation initiation site of *PC-1*. Because the transcriptional initiate site is located upstream of this element, the ARE we have found is in the 5′-untranslated region of *PC-1*. This kind of arrangement of regulatory element is not unprecedented, as a variety of transcriptional factors (including steroid receptors) act via regulatory elements that are downstream of the transcription initiate site or separated from the promoter by many kilobases. For example, multiple AREs in the AR coding region are involved in androgen-mediated up-regulation of AR mRNA [20], and multiple AREs regulating the *c-FLIP* genes have been identified within the region of +50/+150 downstream of the transcriptional initiate site [21]. Though AREpc plays a very important role in the androgen-induced transcription, we still can not exclude the possibility that additional AREs or non-ARE elements exist and contribute to the androgen induction in *PC-1* gene regulation. It is generally true that androgen regulation of target gene expression involves cooperativity among multiple nonconsensus AREs [22].

Our research found that the 4939 bp promoter retained the ability to direct prostate cancer cell-specific expression. Among the gene products that specifically express in human prostate, the transcriptional regulation of the *PSA* gene has been widely studied. *PSA* promoter activity is tightly regulated by androgen, while a major of the patients with advanced, hormone-refractory prostate cancer are under androgen deprivation therapy, which may compromise the activity of the *PSA* promoter [23]. In this paper, we reported that the *PC-1* promoter activity was higher than that of the PSA when the transfected LNCaP and C4-2B cells were cultured in the medium with steroid-depleted FBS. This result implicated that *PC-1* gene 4939 bp promoter may be a useful transcription regulation element to control the therapeutic gene expression in the androgen ablation prostate cancer gene therapy.

The differential expression of PC-1 in the prostate cancer are partly ascribed to the amplification of this gene on the 8q chromosome region [5], partly ascribed to the modification of the promoter activity. In this article we report the expression of *PC-1* is regulated by upstream negative and positive element in its promoter region. Further studies are required to identify the *trans*-acting factors that are involved in the transcriptional regulation of the *PC-1* gene. This work may facilitate our understanding the mechanism of *PC-1* expression and the relation to the prostate cancer progression.

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