Growth Inhibition of Prostate Cancer by an Adenovirus Expressing a Novel Tumor Suppressor Gene, pHyde

Mitchell S. Steiner, Xiongwen Zhang, Ying Wang, and Yi Lu

University of Tennessee Urologic Research Laboratories, Department of Urology, University of Tennessee-Memphis [M. S. S., X. Z., Y. W., Y. L.], and Genotherapeutics, Inc., [M. S. S., Y. L.] Memphis, Tennessee 38163

ABSTRACT

It has been estimated that there will be >180,400 new cases of prostate cancer and 31,900 prostate cancer deaths in the United States this year. New therapeutic strategies against locally advanced prostate cancer are desperately needed. A novel gene (pHyde) was identified by an improved cDNA competition hybridization technique for Dunning rat prostate cancer cell lines. A recombinant replication-deficient E1/E3-deleted adenovirus type 5 containing a pHyde gene under the control of a truncated Rous sarcoma virus (RSV) promoter (AdRSVpHyde) was generated. In vitro, AdRSVpHyde significantly inhibited growth of human prostate cancer cell lines DU145 and LNCaP in culture. In vivo, a single injection of AdRSVpHyde (5 x 10⁹ plaque-forming units) reduced DU145 tumors in nude mice remarkably compared with untreated control or viral control-treated DU145 tumors. Moreover, AdRSVpHyde induced apoptosis and stimulated p53 expression. These results together suggest that pHyde is a tumor suppressor gene that inhibits growth of prostate cancer and that this inhibition is at least in part due to the induction of apoptosis.

INTRODUCTION

Prostate cancer formation is a multistep process involving tumor initiation, transformation, conversion, and progression (1, 2). This process is driven by multiple factors, including chromosomal instability, spontaneous mutations, and carcinogen-induced genetic and epigenetic changes. Although several genes, including IGF-1 (3, 4), DOC-2 (5), and pp32 (6, 7), have been implicated in prostate carcinogenesis, the exact mutational events responsible for this progression of prostate cancer are unknown. A better understanding of the molecular mechanisms responsible for prostate cancer may lead to new therapies to combat prostate cancer.

Several tumor suppressor genes, including PTEN (8), DOC-2 (5), E-cadherin (9), and C-CAM (10), have been shown to suppress prostate cancer growth. Gene therapy strategies that use critical tumor suppressor genes have been shown to be effective against many cancers. Adenoviral-mediated p53 tumor suppressor gene therapy is efficacious against colorectal cancer (11), prostate cancer (12, 13), breast cancer (14, 15), cervical cancer (16), ovarian carcinoma (17), and melanoma (18). Recently, retrovirus LXSNC, which expresses BRCA1 tumor suppressor gene, was used in phase I human clinical trials for advanced prostate cancer (19). An adenovirus that expresses p16 tumor suppressor gene significantly inhibited prostate cancer growth and prolonged survival in an animal model (20). As such, the finding of novel tumor suppressor genes will have a therapeutic potential for gene therapy for prostate cancer as well as other cancers.

Using an improved cDNA competition hybridization technique, we isolated a novel cDNA, designated as pHyde, and sequenced it from cDNA libraries derived from two Dunning rat prostate cancer cell lines that have different metastatic phenotypes (21, 22). The isolated pHyde cDNA gene comprises 2713 nucleotides with an open reading frame of 1467 nucleotides coding for a polypeptide of 489 amino acid residues (21). A database search showed that there was no homology between pHyde and any known full-length cDNA sequences, except that it showed a significant homology (76%) to a 154-bp partial cDNA sequence, named TSAP-6, that was isolated from murine cDNA libraries by differential display and was claimed to be associated with p53-induced apoptosis (16). Interestingly, TSAP-6 has been shown to be an untranslated 3′ region of pHyde. Therefore, pHyde is a novel cDNA gene with a complete open reading frame and coding sequence. The similarity with TSAP-6 implies that pHyde may be the rat homologue of murine TSAP-6 or a member of the TSAP-6-like family, which plays roles in apoptosis and is involved in a p53-associated pathway.

To characterize the novel gene pHyde, we generated a replication-defective recombinant E1/E3-deleted adenovirus containing a truncated RSV promoter and the rat pHyde cDNA gene (AdRSVpHyde) to investigate the effects of pHyde on prostate cancer cells both in vitro and in vivo. Our study revealed that pHyde is able to suppress prostate cancer through apoptosis.

MATERIALS AND METHODS

Cell Lines and Tissue Culture Conditions. Human prostate cancer cell lines DU145, LNCaP, TSU, and PC-3 (all obtained from American Type Culture Collection, Rockville, MD) were grown in RPMI 1640 (Cellgro, Herndon, VA) containing 10% fetal bovine serum (HyClone Laboratories, Logan, UT) at 37°C and 5% CO₂. The human embryonic kidney cell line 293 (American Type Culture Collection) was grown in DMEM (Cellgro) containing 10% heat-inactivated fetal bovine serum at 37°C and 5% CO₂.

Construction of AdRSVpHyde. A rat pHyde cDNA gene was isolated as described previously (21). After digestion with EcoRI, a 2.6-kb fragment that contained the 1467-bp full-length coding sequence of pHyde cDNA was subcloned under the control of a truncated RSV promoter (395 bp) into an E1-deleted adenoviral shuttle vector, pAsv09a (Genetic Therapy, Inc., Gaithersburg, MD). The resultant adenoviral shuttle vector was cotransfected into 293 cells with pM17 (23), an adenoviral type 5 genome plasmid, by the calcium phosphate method (24). Individual plaques were screened for recombinant AdRSVpHyde by PCR, using specific primers for both the RSV promoter and pHyde cDNA sequences. Single viral clones were propagated in 293 cells. The culture medium of the 293 cells showing the completed cytopathic effect was collected, and the adenovirus was purified and concentrated twice by CsCl gradient ultracentrifugation. The viral titration and transduction were performed as described previously (25). The schematic diagram of AdRSVpHyde is illustrated in Fig. 1.

Northern Blot Analysis. Total RNA was isolated by the RNasey Kit (Qiagen, Santa Clarita, CA). Total RNA was loaded on a 1.2% polyacrylamide gel and electrophoresed. The standard Northern blot transfer to a nylon membrane (Hybond-N⁺; Amersham Life Science, Buckinghamshire, United Kingdom) was performed as described previously (26). The cDNA probes (pHyde or p53) were layered by α-3²P]dCTP using a random primer method (Prime-II Kit; Stratagene, La Jolla, CA). The membrane was hybridized with

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2 To whom requests for reprints should be addressed, at Department of Urology,
College of Medicine, University of Tennessee-Memphis, 936 Court Avenue, Memphis,
TN 38163. Phone: (901) 448-5436; Fax: (901) 448-5496; E-mail: ylu@utmem.edu.

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Each well was loaded with 10 μl in vitro infected with control virus AdRSVlacZ or AdRSVpHyde primary antibody. 125 I-labeled antirabbit antibody was used as the secondary antibody. The size of the pHyde protein was 54-kDa, as expected.

**Western Blot Analysis.** Cells were extracted as described previously (27). Cell extract lysates (100 μg) were loaded on 12% polyacrylamide gels and electrophoresed on a 2% agarose gel. The membrane was treated with RNase A (50 μg/ml) at 37°C for 1 h, followed by treatment with proteinase K (100 μg/ml) in 0.5% SDS at 50°C for 2 h. The residual material was extracted with phenol/chloroform, precipitated in ethanol, and electrophoresed on a 2% agarose gel.

**TUNEL Staining.** For the in vitro TUNEL assay, the slide flasks (NUNC, Roskilde, Denmark) were precoated with 50 μg/ml poly-L-lysine (Sigma, St. Louis, MO) for 15 min and washed twice with PBS. DU145 cells (1.0 × 10^5)

**DNA Extraction and Gel Electrophoretic Analysis of DNA Fragmentation.** Soluble DNA was extracted as described previously (28). Briefly, the suspended cells in medium were collected 48 h post transduction by centrifugation. The pellet was resuspended in Tris-EDTA buffer (pH 8.0). The cells were lysed in 10 mM Tris-HCl (pH 8.0), 10 mM EDTA, 0.5% Triton X-100 on ice for 15 min. The lysate was centrifuged at 12,000 × g for 15 min to separate soluble (fragmented) DNA from pellet (intact genomic) DNA. Soluble DNA was treated with RNase A (50 μg/ml) at 37°C for 1 h, followed by treatment with proteinase K (100 μg/ml) in 0.5% SDS at 50°C for 2 h. The residual material was extracted with phenol/chloroform, precipitated in ethanol, and electrophoresed on a 2% agarose gel.

**t-test for Significance.** The Student t-test was performed to determine the significance of the differences between the means of the experimental groups and the control group. The significance level was set at p < 0.05.

**Fig. 1.** Schematic presentation of the structure of AdRSVpHyde. The 2664-bp inserted fragment contains a 1467-bp full-length pHyde cDNA gene and 1166-bp 3'-untranslated downstream region (GenBank Accession No. AF238865).

**Fig. 2.** Expression of pHyde by AdRSVpHyde. DU145 cells transduced by AdRSVpHyde at MOI = 200 were harvested 48 h post transduction. Either mRNA or protein was then extracted. A, expression of pHyde at the mRNA level in DU145 cells. Each well was loaded with 10 μg of total RNA. Samples were electrophoresed in a 12.5% agarose gel, transferred to nylon membrane, and hybridized with 32P-labeled pHyde cDNA (which showed an ~3.0-kb transcript). The Northern blot was then stripped and rehybridized with GAPDH cDNA (which showed a 1.2-kb transcript) to assess RNA integrity and gel loading. Cells transduced by control virus (AdRSVlacZ) did not show an overexpression of pHyde mRNA (not shown); AdpHyde (AdRSVpHyde). B, expression of pHyde at the protein level in DU145 cells. Protein extracts (100 μg/well) were loaded on a 12% SDS-PAGE gel. Rabbit antirat pHyde polyclonal antibody was used as the primary antibody. 125I-labeled antirabbit antibody was used as the secondary antibody. The size of the pHyde protein was 54-kDa, as expected.

**Fig. 3.** Inhibitory effects of pHyde on growth of prostate cancer cell lines DU145 and LNCaP. DU145 (A) and LNCaP (B) cells were transduced with or without adenoviral vectors (control virus or AdRSVpHyde) at MOI = 100. Cell numbers were counted at day 5 after viral transduction. The data represent the results from two independent experiments, each performed in duplicate. Bars, SD; *, error bars too small to see.
were plated on slide flasks and grown for 24 h before viral transduction. The cells were then either left untreated or transduced with control virus or AdRSVpHyde at a MOI of 200. The cell monolayers grown on slides were rinsed twice with PBS at 72 h after transduction and subjected to TUNEL staining. For the in vivo TUNEL assay, the xenograft DU145 tumors (untreated control tumors, control virus-, or AdRSVpHyde-treated tumors 21 days after viral injection) growing in nude mice were harvested at necropsy, fixed with freshly prepared 10% buffered neutral formalin (Fisher Scientific, Fair Lawn, NJ) overnight at room temperature, dehydrated in a gradual series of ethanol, and embedded in paraffin. Tissue sections were cut 4 μm thick, mounted on Superfrost Plus glass slides (Fisher Scientific, Pittsburgh, PA), deparaffinized with xylene, rehydrated in a gradual series of ethanol, washed in H2O, and subjected to TUNEL staining. Both in vitro and in vivo TUNEL assays use the In Situ Cell Death Detection Kit (Boehringer Mannheim, Indianapolis, IN) according to the manufacturer’s instruction. Cells were visualized by fluorescence microscopy. In some cases, the TUNEL-stained cells were counterstained with propidium iodide (Sigma).

RESULTS

Exogenous pHyde Is Expressed in DU145 Cells. To determine whether AdRSVpHyde was able to successfully transfer and express rat pHyde, DU145 cells were transduced by AdRSVpHyde at MOI = 200. The cell extracts were harvested 48 h after viral transduction, and both mRNA and protein were isolated. Endogenous human pHyde mRNA was detectable in DU145 cells by Northern blot analysis (Fig. 2A) but not by Western blot analysis (Fig. 2B), suggesting that there is no detectable cross-reactivity between the generated rat pHyde antibody and human pHyde. After AdRSVpHyde transduction, however, there was high exogenous pHyde mRNA expression (Fig. 2A) and pHyde protein expression (Fig. 2B). The Western blot (Fig. 2B) showed a 54-kDa protein product, which is consistent with the expected protein size deduced by the amino acid sequence of pHyde cDNA open reading frame.

AdRSVpHyde Inhibits Prostate Cancer Proliferation in Vitro. To determine the effects of pHyde on prostate cancer cell growth, human prostate cancer DU145 and LNCaP cells were treated in vitro with AdRSVpHyde, AdRSVlacZ (control viral vector), or no virus. Cell growth was determined by counting the number of cells at day 5 post viral transduction. AdRSVpHyde significantly inhibited the growth of DU145 and LNCaP cells, with 76.9% (Fig. 3A) and 83.1% (Fig. 3B) inhibition, respectively, compared with untreated control cells. Viral control-treated cells had no inhibition (Fig. 3).

AdRSVpHyde Suppresses Prostate Tumor Growth in Vivo. To evaluate the effects of AdRSVpHyde treatment on prostate cancer cell growth in vivo, DU145 human prostate tumors were established in nude mice by injecting 1.4 × 10^7 PPC-1 cells s.c. into the flanks of
nude mice. When mice developed tumors averaging 80 mm$^3$ volume, the mice were divided into three groups: AdRSVPHyde-treated ($n = 7$), AdRSVlacZ control virus-treated ($n = 7$), and untreated ($n = 7$). A single dose of $5 \times 10^9$ pfu of either the control virus or AdRSVPHyde was injected into the treated tumors. As shown in Fig. 4, untreated and control virus-treated DU145 tumors grew rapidly relative to the AdRSVPHyde-treated tumors. By day 53 after viral injection, the tumor burden in nude mice bearing untreated and control virus-treated DU145 tumors reached 5953 and 4777 mm$^3$, respectively. In contrast, DU145 tumors transduced by AdRSVPHyde had a significant reduction in tumor volume (1515 mm$^3$) compared with untreated and control virus-treated DU145 tumors, i.e., 25.4% of untreated and 31.7% of control virus-treated DU145 tumor volume (Fig. 4).

**pHyde Induces Apoptosis.** To demonstrate whether pHyde could directly induce apoptosis in human prostate cancer cell lines, DU145 and LNCaP were transduced with either AdRSVPHyde or control virus AdRSVlacZ. Five days after transduction, AdRSVPHyde-transduced cells showed typical apoptotic morphology, i.e., cells became rounded and detached (Fig. 5, C and F), whereas control and control virus-transduced cells did not exhibit apoptotic morphology (Fig. 5, A, B, D, and E).

To confirm that apoptosis indeed occurred in the cells transduced by AdRSVPHyde, cell suspensions were collected from untreated control DU145 cells and DU145 cells transduced by either control virus AdRSVlacZ or AdRSVPHyde. DNA was extracted from the suspensions and subjected to a DNA fragmentation assay. As shown in Fig. 6, an apparent DNA laddering pattern, a hallmark of apoptosis, was observed in AdRSVPHyde-transduced cells, with apoptosis increased to the higher MOI of the AdRSVPHyde used. In contrast, untreated control cells and control virus-transduced cells had no detectable DNA laddering. Thus, this suggests that overexpression of pHyde induced apoptosis.

**Fig. 6.** AdRSVPHyde induces apoptosis in DU145 cells. Cells were untreated or transduced by either control virus AdRSVlacZ (control virus) or AdRSVPHyde (AdpHyde) at different MOI values as shown. Supernatants were collected 72 h post transduction. Soluble DNA was extracted from cell suspensions and electrophoresed on a 2% agarose gel.

**Fig. 7.** TUNEL assay of DU145 cells in vitro. DU145 cells were either untreated (A and D), or transduced with control virus AdRSVlacZ (B and E) or AdRSVPHyde (C and F) at MOI = 200. Three days after transduction, the cells were fixed and processed for TUNEL assay. The cells were then visualized by fluorescence microscopy. The arrows indicated some of the apoptotic cells. Magnification: A–C, ×20; D–F, ×40.
Interestingly, AdRSVpHyde-transduced DU145 cells had a stimulation of p53 at the mRNA level (Fig. 9), suggesting that pHyde may induce apoptosis via the p53 pathway.

DISCUSSION

Previous studies using the Dunning rat prostate cancer cell lines AT-1 and AT-3 stably transfected with pHyde expression vector have shown that pHyde has the ability to act as an intrinsic factor for apoptosis. The rat prostate cancer cells stably expressing pHyde were more sensitive to UV DNA damage, driving these cells into cell-programmed death (22). In this study, overexpression of pHyde mediated by a recombinant adenovirus expressing pHyde, AdRSVpHyde, strongly inhibited human prostate cancer cell growth both in vitro and in vivo. Moreover, pHyde directly induced apoptosis in human prostate cancer cells, suggesting that induction of apoptosis accounts for at least in part for the pHyde-mediated growth inhibition. We are studying nonprostate cancer cells with different origins to determine whether pHyde is a tumor suppressor gene in a more global manner.

The TUNEL assay of AdRSVpHyde-transduced DU145 cells did not show numbers of apoptotic cells (~10% stained cells; Fig. 7) comparable to those found in the growth inhibition study (76.9% inhibition; Fig. 3A). One explanation is that the cell growth inhibition was measured 5 days after AdRSVpHyde transduction (Fig. 3A), whereas the in vitro TUNEL staining was performed on cells 3 days after AdRSVpHyde transduction (Fig. 7). pHyde-mediated apoptosis may take longer to reach peak values, so that at day 3 after viral transduction, peak values might not be reached in the cells; in vivo TUNEL staining of the AdRSVpHyde-treated DU145 xenograft tumor sections that were derived 21 days after AdRSVpHyde transduction showed significantly higher numbers of apoptotic cells (Fig. 8) compared with the in vitro TUNEL staining performed on day 3 after transduction (Fig. 7). In addition, cells undergoing apoptosis might detach from the plate and go to suspension, whereas the in situ TUNEL staining was performed only on the cells attached to the plates. Therefore, TUNEL staining might underestimate the numbers of apoptotic cells.

The other classical method for detecting apoptosis, the TUNEL assay, was also used to demonstrate that AdRSVpHyde indeed caused DU145 cells to enter apoptosis. Seventy-two h after viral transduction, DU145 cells growing on culture dishes were subjected to the TUNEL assay. There were more fluorescence-stained cells in the AdRSVpHyde-transduced cells (Fig. 7, C and F) than in the untreated control (Fig. 7, A and D) or control virus-transduced cells (Fig. 7, B and E), indicating that there were more apoptotic cells in AdRSVpHyde-treated cells than the latter two kinds. In addition, tumor sections from DU145 xenograft tumors growing in nude mice showed that there was a significant apoptosis occurring in AdRSVpHyde-treated tumors (Fig. 8A) compared with untreated tumors (Fig. 8A) and control virus-treated tumors (not shown).

**pHyde Induces p53 Expression.** The concurrent inhibition of cell proliferation and induction of apoptosis by another tumor suppressor gene, p53 (12, 18, 29, 30), may represent a common inhibitory mechanism. To explore the possible mechanism by which pHyde may modulate apoptosis via the p53 pathway, the apoptosis-associated gene p53 was evaluated before and after AdRSVpHyde transduction. Interestingly, AdRSVpHyde-transduced DU145 cells had a stimulation of p53 at the mRNA level (Fig. 9), suggesting that pHyde may induce apoptosis via the p53 pathway.

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**Fig. 8.** TUNEL assay of DU145 cells in vivo. DU145 xenograft tumors (~80 mm³) growing on nude mice were either untreated (A) or injected with 5 × 10⁹ pfu AdRSVpHyde (B). Tumors were harvested after 21 days. Tumor sections were fixed and processed for TUNEL assay. The sections were counterstained with propidium iodide (red) to show the nuclei of cells. The bright yellow indicates the apoptotic cells. Tumor sections from control virus AdRSVlacZ-treated DU145 tumor showed results similar to those in A (not shown). Magnification: A and B, ×20.

**Fig. 9.** AdRSVpHyde induced p53 expression in DU145 cells. The same Northern blot as in Fig. 2A was used. In detail, untreated control DU145 cells or DU145 cells transduced by AdRSVpHyde at MOI = 200 were harvested 48 h post transduction for mRNA extraction. Each sample well was loaded with 10 μg of total RNA, and samples were electrophoresed in a 12.5% agarose gel, transferred to nylon membrane, and hybridized with ³²P-labeled pHyde cDNA (which showed a ~3.0 kb transcript). The Northern blot was stripped and rehybridized with ³²P-labeled p53 cDNA probe (which showed a 2.5 kb transcript size). The Northern blot was stripped again and rehybridized with ³²P-labeled GAPDH cDNA (which showed a 1.2-kb transcript size) to assess RNA integrity and gel loading. Cells transduced by control virus did not show increased p53 mRNA expression (not shown).
of the actual apoptotic cells. Another explanation is that apoptosis may account for only part of the pHyde-mediated growth inhibition; in other words, pHyde-mediated growth inhibition may involve apoptosis and some other unknown mechanisms. As described below, AdRSVpHyde was able to inhibit cell growth of another human prostate cancer cell line, TSU; however, no apoptosis was observed in AdRSVpHyde-transduced TSU cells.

One important finding of this study was that AdRSVpHyde induced p53 expression in DU145 cells. This suggests that one mechanism by which pHyde induces apoptosis is to stimulate the p53 pathway. This result is consistent with the notion that pHyde has a sequence homology with TSAP-6, a murine partial cDNA sequence that has been claimed to code for a protein involved in p53-induced apoptosis pathway (16). Thus, the ability of pHyde to up-regulate p53 expression suggests that pHyde may be a new class of protein. p53 exerts various physiological functions through transactivation of downstream genes. p53 acts as a transcriptional factor (31) and activates genes by binding to DNAs in a sequence-specific manner (32–39). However, there have been few, if any, cellular proteins identified to date that have been shown to be upstream regulators of p53. Consequently, continued elucidation of the biological functions of pHyde as it relates to p53 may provide important molecular insights into p53 and apoptosis pathways. Whether pHyde regulates p53 expression directly at the transcriptional level is under investigation.

To determine whether there is an association between p53 status and susceptibility to apoptosis by pHyde, four different human prostate cancer cell lines, PC-3, TSU, LNCaP, and DU145, were screened for endogenous expression of p53, and their sensitivities to pHyde-mediated growth inhibition and apoptosis were compared. Northern blot analysis showed that PC-3 and TSU cells did not express p53 at the mRNA level, whereas both LNCaP and DU145 cells expressed p53 mRNA. In contrast, all four cell lines expressed comparable Rb at the mRNA level (Fig. 10). Consistent with this, another group, using Western blot analysis, has shown that DU145 and LNCaP cells, but not PC-3 cells, express p53 protein (40).

To determine the sensitivity of these four cell lines to pHyde-mediated growth inhibition and apoptosis, cells were transduced with AdRSVpHyde and the growth was monitored. AdRSVpHyde strongly inhibited the growth of DU145 and LNCaP cells (76.9% and 83.1% inhibition compared with the untreated control, respectively; Fig. 3), two cell lines that express p53. Interestingly, for PC-3 and TSU, two cell lines that do not express p53, AdRSVpHyde had no inhibitory effect on the growth of PC-3 cells, but had a minor inhibitory effect (24.5% inhibition compared with the untreated control) on the growth of TSU cells (Fig. 11). However, both AdRSVpHyde-transduced PC-3 and TSU cells did not show any apoptosis as detected by DNA fragmentation and TUNEL assays (data not shown). These results suggest that there may be an association between the presence of p53 and the susceptibility of cells to pHyde-mediated apoptosis. p53 may be required for pHyde-mediated apoptotic induction. At this time, we do not know what the difference is between the two p53-nonexpressing cell lines that allows TSU cell growth, but not that of PC-3, to be inhibited by pHyde, probably through an unknown mechanism other than apoptosis.

In the normal prostate epithelium, cell proliferation is balanced by an equal rate of programmed cell death (apoptosis); therefore, there is neither involution nor overgrowth. In prostate cancer, however, this balance is lost so that there is greater proliferation than death, producing continuous net growth. Thus, an imbalance in programmed cell death must occur during prostatic cancer progression. For exam-
ple, high-level expression of bcl-2, an apoptosis-suppressing protein, was observed in prostate cancer cells (41), and its degree of expression correlated to the malignant stage (42) and the resistance to chemotherapy (43). Therefore, the goal of effective therapy for prostatic cancer is to correct this imbalance, either by suppressing bcl-2 and other antiapoptosis proteins or by promoting apoptosis by mechanisms such as introduction of pHyde overexpression in prostate cancer cells. Induction of apoptosis has been widely used in the treatment of cancer, including chemotherapy and radiation adjuvant therapy (44).

Gene therapy strategies have used adenoviruses that express proapoptotic genes, including p53 (11–14, 18, 29, 30) and Fas ligand (45, 46). This study has demonstrated that pHyde is a novel tumor suppressor gene that induces growth inhibition both in vitro and in vivo and apoptosis in prostate cancer cells, suggesting that AdRSVpHyde may have a therapeutic potential for the treatment of prostate cancer.

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Growth Inhibition of Prostate Cancer by an Adenovirus Expressing a Novel Tumor Suppressor Gene, pHyde

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