Loss of Caspase-1 and Caspase-3 Protein Expression in Human Prostate Cancer

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ABSTRACT

Activation of the caspase cascade is involved in the execution of apoptosis in a variety of cellular systems. Recent studies demonstrated that caspase-1 activation was required for human prostate cancer cells to undergo apoptosis in response to transforming growth factor-\(\beta\) (Y. Guo and N. Kyprianou, Cancer Res., 59: 1366–1371, 1999). In the present study, to identify the significance of caspases in prostate cancer progression, we examined the expression of three key caspases, caspase-1, caspase-3, and caspase-9, in normal and malignant human prostates. Caspase-1, -3, and -9 expression was examined at the mRNA and the protein level in a series of normal human and malignant prostate specimens. No significant differences were observed in the mRNA expression in prostatic tumors relative to the normal gland for any of the three caspases. Immunohistochemical analysis revealed that the pattern of protein expression and distribution was uniformly homogeneous in the normal prostate, with the epithelial cells exhibiting a diffuse cytoplasmic staining for caspase-1 and caspase-3. Significantly, the majority of primary prostate cancer specimens (80%) had total lack of caspase-1 immunoreactivity, whereas the remaining showed a significantly reduced expression compared with the normal prostate (\(P < 0.05\)). Caspase-3 expression was also reduced in moderately and poorly differentiated prostatic tumors compared with well-differentiated prostate adenocarcinomas and the normal prostate (\(P < 0.05\)). No significant correlation was found between the apoptotic index or Gleason grade and the pattern of caspase protein expression in the primary prostatic tumors analyzed. Western blot analysis revealed constitutive expression of the proenzyme forms of caspase-1, -3, and -9 in the human prostate cancer cell lines PC-3, DU-145, TSU-Pr1m and LNCaP, but caspase-1 expression was low in the less tumorigenic Pr1m and LNCaP. These findings implicate the loss of caspase-1 protein as a potential step in the loss of apoptotic control during prostate tumorigenesis. This study suggests that the pattern of caspase-1 and -3 expression in prostatic tumors may have prognostic significance in disease progression.

INTRODUCTION

Prostate cancer is the second highest cause of cancer death in males after lung cancer. As the age of the American population increases, an estimated 178,300 American men will be diagnosed with prostate cancer in 2000. The probability of developing prostate cancer is 1 in 55 in males ages 40–59 and 1 in 6 in males ages 60–79 (1). Prostate cancer mortality results from metastasis to the bone and lymph nodes and progression from androgen-dependent to androgen-independent prostatic growth (2). Prostate cancer patients, although initially responsive to hormone-ablation therapy, often relapse with androgen-independent disease that is resistant to further therapeutic interventions. Apoptosis is the physiologically relevant mode of programmed cell death that counterbalances cell proliferation (3). Tissue homeostasis in the normal prostate gland is maintained by the quantitative relationship between the rate of cell proliferation and the rate of apoptotic cell death (4). Recent kinetic studies on the dynamics of prostate growth by this laboratory and other investigators suggest that disruption of the molecular mechanisms that regulate apoptosis and cell proliferation among the epithelial cells is responsible for the abnormal growth of the gland during neoplastic development (5). Identification and targeting of cellular modifiers of apoptosis for implementing effective therapeutic strategies for advanced prostate cancer has been the focus of intense efforts.

The mechanism of apoptosis is remarkably conserved across species, and is executed with a cascade of sequential activation of initiator and effector caspases (6). Caspases, members of the cysteine protease family, are synthesized as inactive proenzymes and are selectively cleaved after an aspartate residue to produce the active enzyme (7, 8). Once activated, the effector caspases can cleave a broad range of cellular targets and ultimately cause apoptosis in diverse cell types, including prostate cancer cells (3, 9). This processing leads to cleavage of various death substrates, which in turn lead to morphological changes typical of apoptosis. There are two families of caspases based on the lengths of their NH\(_2\)-terminal prodomains. Caspase-1, -2, -4, -5, -8, -9, and -10 have long prodomains and function in targeting and regulating apoptosis. Caspase-3, -6, and -7 have short prodomains and are responsible for the execution of apoptosis by operating at the downstream end of the DNA repair enzyme poly(ADP-ribose) polymerase, whose cleavage is essential for apoptosis induction (3, 10). Caspase activation involves a distinct, temporal cascade demonstrating a complex hierarchy within the caspase family. Mitochondria also play a key part in the regulation of apoptosis (11). Cytochrome \(c\), which usually is present in the mitochondrial intermembrane space, is released into the cytosol after induction of apoptosis by different stimuli, including chemotherapeutic and DNA-damaging agents. The release of cytochrome \(c\) from mitochondria and its subsequent binding to caspase-9 (resulting in transactivation of procaspase-9 by Apaf 1) can trigger the sequential activation of caspase-3, an apoptosis executioner (12).

Caspase 1, also known as interleukin \(\beta\)-converting enzyme, is required for apoptosis (7, 13). Caspase-1 is an initiator caspase that was originally characterized as cleaving inactive prointerleukin \(\beta\) to generate the active proinflammatory cytokine interleukin 1 \(\beta\) (13). Overexpression of caspase-1 has been found to induce apoptosis in mammalian and insect cells (10). Caspase-9 is another initiator caspase that is dependent on cytosolic factors for expression of its activity (14). Apoptotic signals release cytochrome \(c\) from the mitochondria where it associates with Apaf-1 in the presence of dATP. Apaf-1 recognizes the inactive procaspase-9 and forms the apoptosome, which triggers autocatalytic processing of procaspase-9 (12, 15). Caspase-3 is the ultimate executioner caspase that is essential for the nuclear changes associated with apoptosis, including chromatin condensation (4). An expanding body of recent evidence suggests that the caspase cascade is involved in the execution of apoptosis in prostate cancer cells in response to diverse stimuli, including lovastatin and Fas-mediated signaling (16, 17). TGF-\(\beta\)1 (18), and ocadica.
acid (19). In addition, blockade of caspases activity by the inhibitor CrmA has been shown to suppress androgen-ablation-induced apoptosis in LNCaP prostate cancer cells in vitro and in vivo (20). Furthermore, caspase-3 activation plays a role in apoptotic induction of other human cancers, such as osteosarcoma (21) and ovarian cancer (22), gastric, and breast cancer (23).

Considering the evidence gathered in this laboratory that activation of TGF-β signaling suppresses prostate tumorigenicity via induction of caspase-1-mediated apoptosis (18, 24) and concerning the central role of caspase cascade in the execution of apoptosis of prostate cancer cells in response various agents (15, 16, 19), we examined the pattern of caspase-1, -3, and -9 expression in normal and malignant human prostate. Our findings indicate that the immunoreactivity of caspase-1 and -3 (but not caspase-9) is significantly decreased in prostate cancer, whereas no significant changes in mRNA expression were observed.

MATERIALS AND METHODS

Immunohistochemical Analysis. Formalin-fixed, paraffin-embedded tissue sections (6 μm) from human prostate tissue were obtained from the Department of Pathology Archives at the University of Maryland Medical Center. Specimens included 42 primary prostate adenocarcinomas from patients undergoing radical prostatectomy for localized disease. Prostatic tumors were characterized for pathological grade using the Gleason scoring system prior to immunohistochemical analysis (A. B.). Six normal prostates were obtained from age-matched patients undergoing cytoprostatectomy for bladder cancer.

Expression of caspase-1 was determined using rabbit polyclonal antibody against human caspase-1 from Santa Cruz Biotechnology (San Diego, CA). Expression of caspase-3 was determined using the antibody from PharMingen (San Diego, CA). Both antibodies recognize the precursor and the active subunits of caspase-1 and -3, respectively. The bcl-2 mouse monoclonal antibody was obtained from DAKO (Carpinteria, CA). The proliferative index was determined on the basis of Ki-67 immunostaining using the mouse monoclonal MIB1 antibody (AMAC, Westbrook, ME), as described previously (6, 25). Prostate tissue sections were incubated 30 min at room temperature with the appropriate secondary antibody (Santa Cruz Biotechnology), and color development was accomplished using the ABC kit (Santa Cruz Biotechnology) and the chromogen 3,3-diaminobenzidine tetrahydrochloride solution. Negative controls were processed in the absence of primary antibody. Sections were counterstained with hematoxylin, and cells were reviewed at three fields randomly selected at ×400 by three independent observers (R. N. W., A. K., and N. K.) who were blinded to the clinicopathological characteristics of the patients and disease outcome. Scoring of immunoreactive cells was based on the distribution of positive cells in three different fields (with ~300 cells per field) within the same section, and the percentage of positive immunoreactivity was expressed as the percentage of the number of stained cells over the total number of cells.

Apoptosis Detection. Detection of apoptosis in situ was performed in paraffin-embedded sections using the ApoTag Kit (Intergen, Purchase, NY), based on the TUNEL assay as described previously (25). Sections of rat ventral prostate after castration were used as biologically positive controls. Negative controls consisted of consecutive sections of each case in which the terminal deoxynucleotidyl transferase enzyme was omitted. Sections were counterstained with methyl green.

RT-PCR Analysis. RNA was isolated from cells by the TRIZol method (18). The four human prostate cancer cell lines used, PC-3, DU-145, TSU-Pr1, and LNCaP, were obtained from the American Tissue Culture Collection (Rockville, MD) and were maintained in RPMI 1640 (Life Technologies, Gaithersburg, MD) supplemented with 10% FCS (Hyclone, Logan, UT). RNA was extracted from prostate cancer tissue as described previously (26). The specimens included 15 normal prostates (from patients undergoing cytoprostatectomy for bladder cancer), 23 primary prostate adenocarcinoma specimens, 8 lymph nodes negative for metastatic deposits of prostate cancer, 15 lymph nodes positive for metastatic prostate cancer (obtained from patients undergoing laparoscopic lymph node dissection), and 3 specimens with histological evidence of BPH. RT-PCR was performed using 2 μg of total cellular RNA and the Ribo Clone cDNA synthesis kit (Promega Corp., Madison, WI) in a Perkin-Elmer amplification cycle (Wellesley, MA). The sequence of the primers used for RT-PCR was as follows:

Caspase-1: sense, 5'-ATCCGTTCCATGGAAGCCGGCA-3'; antisense, 5'-CAATGGCTCCAGCTGTCTAACA-3'.
Caspase-2: sense, 5'-TTCAAGGCGGATCGTGTGAGTACG-3'; antisense, 5'-AAAGCCCTTGGCCATACCTGTTCAG-3'.
Caspase-3: sense, 5'-ATGAGGAACGGCCGGATCGGCTCC-3'; antisense, 5'-GCACCCTGCGGTGAAAGTTTCTAG-3'.

The primers for human GAPDH were obtained from Clonetech (Palo Alto, CA), and the sequences were as described previously (18). The conditions used for the RT-PCR for each caspase were as follows: for caspase-1, 94°C for 5 min, 60°C for 5 min, 40 cycles of 94°C for 1 min, 60°C for 2 min, and 72°C for 2 min, with final extension of 72°C for 10 min; for caspase-3, 94°C for 5 min, 35 cycles of 68°C for 1 min and 94°C for 1 min, with final extension of 72°C for 10 min; for caspase-9, 94°C for 5 min, 30 cycles of 68°C for 1 min and 95°C for 1 min, with final extension of 72°C for 10 min. The integrity of the RNA used for RT-PCR was confirmed using GAPDH synthesis as a positive control reaction as described previously (18). The amplified RT-PCR products were analyzed electrophoretically through 1% agarose gels, visualized by ethidium bromide staining, and photographed under UV illumination.

Western Blot Analysis. Cell lysates from the human prostate cancer cell lines were lysed as described previously (18). Cell lysates were subjected to SDS-PAGE (12.5%) followed by Western blotting, using the following antibodies: the antibody against human caspase-1 from Santa Cruz Biotechnology; the antibody against caspase-3 from PharMingen; the antibody against caspase-9 from New England Biolabs (Beverly, MA); and antibody against α-actin (Oncogene Research, Boston, MA). Protein expression was detected using the ECL detection kit (Amersham Int., Arlington Heights, IL). The expression of α-actin was used as a normalizing control.

Statistical Analysis. Statistical analysis was conducted using the t test for analysis of significance between the different values. Values were expressed as the mean values ± SE. Statistical significance was established at values of P < 0.05.

RESULTS

The expression of caspase-1, -3, and -9, three key caspases previously implicated in the execution of apoptosis in prostate cancer cells (16, 18, 20), was determined in human prostate specimens by immunohistochemical analysis. Fig. 1 shows a characteristic caspase-1 immunoreactivity pattern in normal, benign, and malignant human prostate tissue. Uniformly intense cytoplasmic immunoreactivity for caspase-1 was observed among epithelial cells in the normal prostate (Fig. 1). A significant decrease in caspase-1 immunostaining was detected in epithelial cells from a BPH prostate (Fig. 1), whereas malignant prostatic tissue exhibited a heterogeneous pattern of dramatically reduced caspase-1 immunoreactivity among the tumor cell populations (Fig. 1, C and D). A similar pattern of heterogeneous immunoreactivity in prostate cancer tissue was observed for caspase-3 (data not shown).

Quantitative analysis of the data (summarized in Table 1) revealed a dramatic loss of caspase-1 protein expression in primary prostatic tumors compared with the normal gland (P < 0.01). In the prostate cancer specimens, a significant decrease in caspase-1 and -3 (P < 0.01) was paralleled by a significant increase in bcl-2 levels (P < 0.05). As shown on Table 1, the proliferative index/apoptotic index ratio was more than 2-fold higher (1.8) in the malignant prostate compared with the normal gland (0.7), indicating the higher number of proliferating epithelial cells in prostate cancer. Surprisingly, our analysis documented that the TUNEL-positive prostate cells are not...
necessarily high caspase-1- or caspase-3-expressing cell populations because linear regression revealed no correlation between a high caspase immunoreactivity and elevated apoptotic index. Also shown on Table 1 is the significant increase in bcl-2 protein expression in the prostatic tumor epithelial cells (23.5%) compared with the normal prostate (4.5%; \( P < 0.05 \)).

Table 2 shows the association of clinicopathological characteristics with the expression levels of caspase-1, caspase-3, and bcl-2 in the prostatic tumors analyzed. A relatively high caspase-1 expression, relative to the low apoptotic index, was detected in the normal human prostate (60%). In prostatic adenocarcinoma specimens, there was a dramatic decrease in caspase-1 levels to 11% (Gleason 3–5) and 21% (Gleason 6–7; Table 2). For caspase-3 expression, there was a statistically significant decrease (\( P < 0.05 \)) in the moderately differentiated tumor group (Gleason 6–7; 58%) as well as the poorly differentiated tumors (Gleason 8–9; 51%) compared with the normal human prostate (82%; Table 2).

Using linear regression analysis, we found no direct correlation between loss of caspase-1 and -3 expression and apoptotic index or proliferative index of the prostatic tumor cell populations (\( r = 0.233 \)). Although a trend was clearly detected toward higher levels of caspase-1 expression with increasing Gleason grade, the differences failed to reach statistical significance (\( P > 0.05 \)).

In Fig. 2, Western analysis reveals the presence of the proenzyme forms of caspase-1, -3, and -9 in the androgen-independent PC-3, TSU-Pr1, and DU-145 and the androgen-responsive LNCaP human prostate cancer cell line. The weak presence of the activated form of caspase-3 probably reflects constitutive activation in all of the cell lines analyzed. Although caspase-3 and -9 proteins were detected in all four cell lines, the LNCaP and DU-145 cell lines had very low expression of both the proenzyme and active form of caspase-1 (Fig. 2).

To examine whether the loss of protein expression in prostatic tumors as detected by immunohistochemistry was a result of down-regulation of mRNA expression, semiquantitative RT-PCR analysis was performed. A total of 64 samples (15 normal prostate, 8 negative lymph nodes, 15 positive lymph nodes, 23 prostate cancer, and 3 BPH samples) were analyzed for caspase-1, -3, and -9 expression. The human prostate cancer cell lines were also analyzed. Fig. 3 shows

<table>
<thead>
<tr>
<th>Specimens</th>
<th>% Caspase-1 expression(^a)</th>
<th>% Caspase-3 expression(^b)</th>
<th>% Bcl-2 expression(^c)</th>
<th>Proliferative index/Apoptotic index(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal prostate</td>
<td>59.9 ± 8.1</td>
<td>82.1 ± 3.1</td>
<td>4.5 ± 1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>20.8 ± 3.0(^e)</td>
<td>60.7 ± 3.2(^e)</td>
<td>23.5 ± 4.7(^e)</td>
<td>1.8(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Values represent the percentage of positive cells over the total number of cells/section. Values represent mean ± SE.

\(^b\) Proliferative index is defined as the percentage of Ki-67-positive cells over the total number of cells (as described in ‘Materials and Methods’).

\(^c\) Apoptotic index is defined as the percentage of TUNEL-positive cells over the total number of cells.

\(^d\) Values statistically significant from the normal prostate (\( P < 0.05 \)).

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Fig. 1. Photomicrographs of caspase-1 immunoreactivity patterns in normal (A), benign (BPH; B), and malignant (C and D) human prostate. A, abundant immunostaining is detected in the normal prostate (magnification, ×50). B, a BPH section with moderate immunoreactivity for caspase-1 among the benign epithelial cells. C and D, two different prostatic adenocarcinoma sections, with characteristically extensive loss of caspase-1 immunoreactivity. The Gleason scores of the cancer foci indicated were 4 and 7 for C and D, respectively (magnification, ×100).
represents the percentage of positive cells over total number of cells/section (mean ± SE).

Table 2 Association of caspase-1, caspase-3, and bcl-2 protein expression with the apoptotic status and tumor grade of prostate cancer

<table>
<thead>
<tr>
<th>Specimens</th>
<th>% Caspase-1 expression</th>
<th>% Caspase-3 expression</th>
<th>Proliferative index (%)</th>
<th>Apoptotic index (%)</th>
<th>% Bcl-2 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal prostate (n = 6)</td>
<td>59.9 ± 8.1</td>
<td>82.1 ± 3.1</td>
<td>2.4 ± 0.5</td>
<td>3.6 ± 1.1</td>
<td>4.5 ± 1.2</td>
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<tr>
<td>Prostate cancer</td>
<td></td>
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<tr>
<td>Gleason 3-5 (n = 6)</td>
<td>11.5 ± 4.0</td>
<td>79.9 ± 7.9</td>
<td>1.7 ± 0.8</td>
<td>1.8 ± 0.9</td>
<td>23.5 ± 4.7</td>
</tr>
<tr>
<td>Gleason 6-7 (n = 31)</td>
<td>21.6 ± 3.7</td>
<td>58.7 ± 3.5</td>
<td>3.6 ± 0.3</td>
<td>5.2 ± 0.7</td>
<td>38.7 ± 3.3</td>
</tr>
<tr>
<td>Gleason 8-9 (n = 5)</td>
<td>26.6 ± 5.8</td>
<td>51.6 ± 5.4</td>
<td>10.4 ± 1.3</td>
<td>7.5 ± 2.2</td>
<td>26.9 ± 7.6</td>
</tr>
</tbody>
</table>

DISCUSSION

Activation of the caspase cascade has been correlated with the onset of apoptosis, and caspase inhibition attenuates apoptosis in prostate cancer cells in response to diverse apoptotic stimuli, including androgen ablation (8, 16, 17, 19, 20). In this study, we demonstrate a diminished detection of caspase-1 and -3 protein in human prostate cancer compared with the normal gland with no significant changes in the mRNA expression. Caspase-1 and -3 immunoreactivity was predominantly localized to the secretory epithelial cells of the prostate. This is similar to an earlier report indicating expression of caspase-3 to the prostatic epithelium of the normal gland (27). Our data indicate a high degree of variation in the immunostaining and pattern of expression of caspase-1 and -3 in prostatic tumor epithelial cells that was not correlated with the incidence of apoptosis in situ. Moreover, there was no statistically significant correlation between either caspase-1 or caspase-3 expression with Gleason grade of the prostatic adenocarcinomas examined. The possibility that analysis of a larger group of tumors with more cases in the low and high histological grade categories may yield differences that achieve statistical significance cannot be ruled out. Conceptually, the present findings are in contrast with a recent report indicating a correlation between caspase-3 expression and elevated apoptosis and histological aggression in breast cancer (28). On the other hand, the high proliferative capacity and reduced apoptosis, which correlated with the elevated bcl-2 expression of the epithelial cells in prostatic tumors, are in full accord with previous studies on the kinetics of prostate cancer growth (5, 25, 29).

The relatively high caspase-1 and -3 immunoreactivity detected in the human prostate tissue compared with the low apoptotic indices of the same tumor cell populations probably reflects the recognition of both the active and inactive (constitutively expressed) forms of the enzyme by the antibody in paraffin-embedded sections. This possibility is somewhat challenged by the results of the Western analysis in prostate cancer cells not actively undergoing apoptosis, which revealed endogenous expression of only the proenzyme form of caspase-1, whereas the active caspase-1 was not detected. Cell lysates from prostatic tumors are currently being analyzed to investigate the expression of the active as well as the inactive forms of the caspases (caspase-1, -3, and -9) in clinical prostate cancer specimens from patients treated with hormonal ablation and radiotherapy.

The present data indicating no significant changes at the mRNA level, although based on semiquantitative analysis, are consistent with the possibility that changes in the levels of inactive caspases, rather than down-regulation of the active enzymes are responsible for the reduced caspase-1 immunoreactivity detected. Although this evidence may point to a potential posttranscriptional deregulation of caspase expression, RNase protection assays will provide a better insight into the level of control. Furthermore, our observations indicating that the androgen-responsive LNCaP and the androgen-independent DU-145 prostate cancer cells both lack expression of caspase-1 at the mRNA and protein levels highlight the functional significance of caspase-1 in the development of prostate tumorigenic phenotype. In accord with this concept is existing evidence that LNCaP cells are resistant to radiation-induced apoptosis (30). The effect of genetic restoration of caspase-1 expression on the tumorigenic potential and apoptotic “sensitivity” of these cells is currently being investigated.

The active role of caspase-1 (originally thought to be involved only in the proinflammatory response) in the apoptotic program is evolving rapidly. Although studies with caspase-1-deficient mice indicated no
differences in their apoptotic response to Fas/CD95 signaling (31). Evidence from this laboratory indicated that TGF-β1-mediated apoptosis induction in prostate cancer cells proceeds via caspase-1 activation (18). The concept was further supported by a recent study demonstrating the functional significance of caspase-1 in enhancing Fas-mediated apoptosis potentially through facilitation of caspase-8 activation (32). The mechanism of potential synergy between caspase-1 and cytochrome c is unknown at present, but it may well require active caspase-8 to amplify a caspase-9 cascade. Because prostatic tumors overexpress bcl-2 oncoprotein (Refs. 25, 29, and present data), which restricts cytochrome c release and consequent activation of caspase-9, thus incapacitating apoptosis activation in prostate cancer, identification of the effect of high bcl-2 levels on caspase-9 expression/activation pattern in malignant prostate epithelial cells might be worth pursuing.

The present study provides the first evidence to indicate a significant loss of caspase-1 and -3 protein expression in human prostatic tumors compared with the normal gland and to implicate deregulated expression of caspases in prostate tumorigenesis. Indirect support for this concept stems from a report that documented deregulation of interleukin 1β-converting enzyme-like caspase expression in prostate cancer patients treated with antiandrogens (33). In accord with our results in prostate cancer, recent studies by Jarry et al. (34) demonstrated significant down-regulation of caspase-1 expression in human colon cancer. In contrast, an up-regulation of caspase-1 protein has been reported in pancreatic tumors (35). The apparent discrepancy may reflect specific differences in the molecular mechanisms underlying the development of various human malignancies, or alternatively may be attributable to the different origin of the antibody used in the latter study. The diversity of mechanisms involved in the regulation and implementation of apoptosis, which is indicative of a rich variety of targets for its inhibition during tumorigenic development, must also be considered (36).

Growing evidence implicates deregulation of caspase-1 and -3 in the pathophysiology of other human diseases. A potentially important role for caspase-1 has been suggested in the pathogenesis of Huntington’s disease (37), whereas caspase-3 has been functionally implicated in the ultimate death of neurons by apoptosis in Alzheimer’s disease (38). Mice deficient in caspase-3 exhibit specific defects in the apoptotic pathway, including delayed kinetics, and lack of DNA fragmentation during brain development (4). Furthermore, caspase-2 and -3 are expressed in Hodgkin’s and non-Hodgkin’s lymphomas, chronic lymphocytic leukemias, and reactive lymph nodes (39, 40), and more recent evidence supports a predictive role for caspase-3 localization in the clinical outcome of B-cell lymphoma (41).

In conclusion, our observations provide a rationale for the involvement of a deregulated caspase cascade in prostate tumorigenesis. As might be predicted, loss of expression of key caspases would confer protection against apoptosis in malignant prostate cells. The present findings may have high clinical relevance by identifying a potentially significant value for caspases not only as markers of disease progression, but also as therapeutic targets for effective activation of the apoptotic process in advanced prostate cancer. Prospective studies involving a large number of clinical tissue specimens from patients with advanced disease before and after hormonal therapy are required to establish the potential use of caspases in the development of therapeutic modalities for advanced prostate cancer.

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REFERENCES


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