Castration-Induced Apoptotic Cell Death in the Brown Norway Rat Prostate Decreases as a Function of Age*

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ABSTRACT

Growth and differentiation of the prostate gland depends upon androgens, yet overgrowth of the human prostate occurs later in life when serum levels of testosterone are declining. We have reported a similar phenomenon in the Brown Norway rat, but the age-dependent overgrowth of the prostate is confined to the dorsal and lateral lobes and, hence, is lobe specific. Because tissue growth depends upon the balance between proliferation and death of cells, the present study was designed to investigate whether cell death differed in the various prostatic lobes of Brown Norway rats as a function of age. Apoptosis of cells in the ventral, dorsal, lateral, and anterior lobes of the prostate was examined in young (4-month-old) and old (24-month-old) Brown Norway rats after castration. Whereas castration caused tissue weights of all four prostatic lobes to decrease over the course of 10 days, this occurred more rapidly and to a greater magnitude in the ventral than in the dorsal, lateral, and anterior lobes. Tissue DNA content, a measure of cell number, decreased only in the ventral lobe after castration. DNA fragmentation, indicative of apoptotic cell death, was detected by in situ labeling using the terminal deoxynucleotidyltransferase-mediated dUTP nick end-labeling (TUNEL) method and as intranucleosomal cleavage of genomic DNA analyzed by agarose gel electrophoresis. Both methods demonstrated the correlation between specific overgrowth of the prostate occurs spontaneously as a function of age (8) and can be further enhanced by administration of pharmacological doses of testosterone (9). Investigation of overgrowth and its mechanisms in the rodent prostate gland is complicated because of the heterogeneous cell population and regional structural differences that exist within each lobe (10, 11). In rodents, most studies of cell death have focused on the ventral lobe (2, 12–16) considering this lobe as representative of the entire prostate gland, with little attention directed to the dorsal, lateral and anterior lobes. However, we previously demonstrated that apoptotic cell death is specific to the ventral lobe in prostates from young adult Sprague Dawley rats (7). Because overgrowth of the prostate in Brown Norway rats is specific to the dorsal and lateral lobes and is age dependent, our objective was to determine whether androgen-sensitive cell death in prostates from Brown Norway rats was lobe specific and was altered as a function of age.

In the present study we have compared the effects of castration on apoptotic cell death in all four lobes of the prostate from young and old Brown Norway rats, in part to determine the extent to which cells in each lobe are sensitive or resistant to androgen withdrawal. We show that castration causes loss of tissue weight and a reduction in cell size for all lobes, but that apoptosis in response to androgen withdrawal occurs predominantly in the ventral lobe; castration had little...
effect on the DNA content or apoptotic index in the dorsal, lateral, and anterior lobes. Although the apoptotic index was low in the dorsal, lateral, and anterior lobes compared with that in the ventral lobe, the percentage of apoptotic cells observed in all four prostatic lobes was significantly reduced as a function of age.

Materials and Methods

Animals

Young (4-month-old) and old (24-month-old) male Brown Norway rats were purchased from Charles River Laboratories, Inc., Breaclng Laboratory (Wilmington, MA) under special arrangement with the NIA (NIH, Bethesda, MD). The rats were housed in an air-conditioned room and fed Purina laboratory chow (Ralston Purina Co., St. Louis, MO) and water ad libitum. Castration was performed via the abdominal route under ether anesthesia. Epididymides were removed along with the testes. Animal protocols were approved by the animal care and use committee of The Johns Hopkins University School of Hygiene and Public Health. Rats were killed at 1, 2, 3, 4, 7, 10, and 30 days after castration.

Serum testosterone concentrations

Trunk blood was collected and allowed to clot for 2 h at room temperature. The serum was then separated by centrifugation and stored frozen (–20°C) until assayed. Serum aliquots of 1 ml were extracted twice with 5 ml anhydrous ethyl ether, and combined extracts were taken to dryness under nitrogen. Testosterone concentration was determined by RIA (Diagnostics Systems Laboratories, Inc., Webster, TX). The sensitivity of this assay was 0.05 ng/ml.

Dissection of prostatic lobes

Prostates were immersed in ice-cold HBSS (Life Technologies, Inc., Grand Island, NY), pH 7.4, and the ventral, dorsal, lateral, and anterior lobes were separated under a dissection microscope, blotted onto filter paper, weighed, and divided into three representative portions, each containing distal and proximal aspects. Two portions of each lobe were snap-frozen in liquid nitrogen for subsequent determination of protein and DNA contents and for isolation of genomic DNA. The third portion was fixed in neutral buffered paraformaldehyde and embedded in paraffin for in situ labeling of fragmented DNA (7) and morphological analysis (8).

Determination of DNA content

Frozen portions of ventral, dorsal, lateral, and anterior prostatic lobes from intact control and castrated young and old rats were homogenized in ice-cold saline (0.9% NaCl, pH 7.4; 1:20, wt/vol). DNA was extracted and precipitated with perchloric acid from each tissue homogenate. After its hydrolysis at 70°C in 1 ml 0.8 M perchloric acid, DNA (500 μl) was assayed by the diphenylamine method of Burton (17), with calf thymus DNA as standard. Total DNA contents per ventral, dorsal, lateral, and anterior prostatic lobes were determined by multiplying the amount of DNA per aliquot by the dilution factor and adjusting for the total volume of tissue homogenate and tissue weight.

Analysis of genomic DNA internucleosomal cleavage

Genomic DNA was prepared from ventral, dorsal, lateral, and anterior lobes of young and old rat prostates as described by Gross-Bellard et al. (18) and later modified by Tilly and Hsueh (19). After extraction, purification, and quantitation, DNA was labeled at the 3′-end with [α-32P]dideoxy-ATP (3000 Ci/mmol; Amersham Pharmacia Biotech, Arlington Heights, IL) using terminal transferase (Roche Molecular Biochemicals, Mannheim, Germany) reaction (19). Radiolabeled DNA samples (500 ng) were resolved by electrophoresis through 2% agarose gels at 50 V for 3–3.5 h. For autoradiographic analyses, dried gels were overlaid with Kodak X-OMat film (Eastman Kodak Co., Rochester, NY) at –70°C, overnight. After autoradiography, low mol wt (<15 kb) DNA fragments were excised from the gels, mixed with 3 ml scintillation fluid (Scintiverse BD, Fisher Scientific, Pittsburgh, PA), and counted in a β-counter (Beckman Coulter, Inc., Mountain View, CA) to provide a quantitative estimate of the internucleosomal DNA cleavage among samples (19).

In situ localization of fragmented DNA

Individual cells containing fragmented DNA were visualized by a nonisotopic DNA end-extension system containing digoxigenin-deoxy-UTP, terminal deoxynucleotidyl transferase (20), and antidigoxigenin fragment-conjugated reporter system (Oncor, Gaithersburg, MD). Briefly, slides containing tissue sections were deparaffinized, rehydrated through graded alcohols and PBS (10 mM phosphate buffer, pH 7.4, containing 0.9% NaCl; PBS), digested with 20 μg/ml proteinase K (Roche Molecular Biochemicals, Indianapolis, IN) for 15 min at room temperature, and washed with PBS. Slides were then incubated successively in a humidified incubation chamber with equilibration buffer (10 min, room temperature), working terminal transferase enzyme containing digoxigenin-labeled deoxy-UTP (1 h, 37°C), and anti-digoxigenin-peroxidase (30 min, room temperature). Sections were then stained with 3,3′-diaminobenzidine substrate solution (Vector Laboratories, Inc., Burlingame, CA). Rat small intestine was used as a positive control, as negative controls, sections of small intestine and of the prostate from castrated rats were stained after incubation in distilled water rather than terminal deoxynucleotidyl transferase enzyme.

The percentages of apoptotic epithelial and stromal cells in prostatic ducts of distal and proximal segments were determined by enumerating labeled and unlabeled cells in randomly selected areas, with 2,000–3,000 cells counted for each of 4 rats/group. Thus, at least 10,000 cells were counted for each group of rats. Distal and proximal segments were distinguished readily by the columnar and cuboidal epithelial cells, respectively, lining the prostatic ducts and by the position of the urethra.

Morphological analysis

A portion of each ventral, dorsal, lateral, and anterior prostatic lobe from intact control and castrated rats was fixed in paraformaldehyde and embedded in paraffin as described previously (8). For each tissue section, three to five blocks were randomly selected. Longitudinal sections of 5 μm thickness were cut, stained with eosin and hematoxylin, and viewed under a light microscope.

Statistical analysis

Data are expressed as the mean ± sem. Statistical differences within treatment groups were determined by one-way ANOVA. Differences between individual groups were determined with Scheffe’s F test (P < 0.05). Statistical differences between young and old groups were compared by Student’s t test (P < 0.05).

Results

The serum testosterone concentration in intact 4-month-old Brown Norway rats was 1.45 ± 0.08 ng/ml and decreased to 0.92 ± 0.02 ng/ml in 24-month-old rats. In both young and old rats, serum testosterone levels were at the lower limit of assay sensitivity (–0.05 ng/ml) by 1 day after castration. By the second day after castration, serum testosterone concentrations in both young and old rats reached undetectable levels (<0.05 ng/ml).

The effects of castration on the tissue weights of the ventral, dorsal, lateral, and anterior prostatic lobes from young and old rats are shown in Fig. 1. In young rats, a significant loss of tissue weight was observed in all four lobes as early as 1 day after castration and continued to decline over time. By 10 days after castration, the loss of tissue weight was 86% in the ventral lobe, whereas the dorsal, lateral, and anterior lobes lost 50–60% of their weights. Compared with young rats, tissue weights of the four lobes in old rats declined more...
slowly and were not significantly decreased until 7–10 days postcastration. In old rats, tissue weight decreased by 50% in the ventral lobe and only 30–40% in the dorsal, lateral, and anterior lobes by 10 days after castration. Tissue weights of the prostatic lobes did not decline further in young or old rats examined 30 days after castration (data not shown).

Figure 2 shows the effect of castration on the DNA contents of the ventral, dorsal, lateral, and anterior prostatic lobes from young and old rats. Values are the mean ± SEM (n = 8 rats/group). *, Significantly different from intact control (P < 0.05).

**FIG. 1.** Effect of castration on the tissue weights of the ventral, dorsal, lateral, and anterior prostatic lobes from young and old rats. Values are the mean ± SEM (n = 8 rats/group). *, Significantly different from intact control (P < 0.05).
The dorsal, lateral, and anterior lobes from old rats showed no significant loss of DNA content even 10 days after castration.

To extend the measurements of DNA content and to confirm that the loss of DNA content was due to apoptotic cell death, a DNA laddering technique was used to analyze the effect of castration on the integrity of genomic DNA. Figure 3 shows the internucleosomal cleavage of DNA that occurred in the ventral lobes from young and old rats between 1–10 days after castration. In young rats, DNA fragmentation of genomic DNA was evident by 1 day after castration. The magnitude of castration-induced DNA fragmentation was maximal by 3 days and then decreased between 4–10 days (Fig. 3, A and B). Similarly, in the ventral lobe of old rats, DNA fragmentation also peaked by 3 days after castration and decreased between 4–10 days (Fig. 3, C and D). Quantitatively, the level of low mol wt DNA fragments was approximately 50% lower in the ventral lobes from old compared with young rats (Fig. 3, B and D). In contrast, DNA fragmentation was not seen in the dorsal lobes from young rats.

**Fig. 2.** Effect of castration on the DNA contents of the ventral, dorsal, lateral, and anterior prostatic lobes from young and old rats. Values are the mean ± SEM (n = 8 rats/group). *, Significantly different from intact control (P < 0.05).
or old rats (Fig. 4). Similarly, DNA fragmentation was not evident in either the lateral or anterior lobes of young and old rats at any time up to 10 days after castration (data not shown).

To identify the individual cell types, the numbers of cells that were undergoing apoptosis after castration and their regional localization within each lobe, an in situ DNA end-labeling (TUNEL) system was used. Only a few apoptotic cells were observed in the ventral lobe of young and old intact control rats before castration (Fig. 5, A and G); however, observation of such cells confirms the existence of a low, but constant, level of cell death. As soon as 1 day after castration, the numbers of apoptotic cells increased in the ventral lobes of both young and old rats (Fig. 5, B and H). Greater numbers of apoptotic cells were evident on days 2, 3, and 4 after castration in young (Fig. 5, C, D, and E, respectively) and old (Fig. 5, I, J, and K, respectively) rats. Subsequently, by days 7 (data not shown) and 10 (Fig. 5, F and L) after castration, the numbers of apoptotic cells decreased in the ventral lobes from young and old rats. In contrast, little apoptotic cell death was observed in the dorsal (Fig. 5, M and N), lateral (Fig. 5, O and P), and anterior (Fig. 5, Q and R) lobes from young and old rats on day 3 after castration; this did not differ from observations of these lobes from intact rats or from rats at any other time point after castration (data not shown).

The number of cells in the ventral lobe undergoing apoptosis in young and old rats was also determined (Fig. 6). The percentage of apoptotic cells was quite low (0.4%) in young intact rats, increased to 0.9% by 1 day postcastration, then increased significantly by day 2 and reached a maximum of 5.5% by day 3 after castration. By day 4 after castration, the percentage of apoptotic cells had decreased to 3.2%, and this was followed by a gradual further decline. In the ventral lobe from old rats, the percentage of apoptotic cells was also low (0.2%) before castration, but increased to 0.4% on the first day after castration, peaked on day 3 (2.4%), and then gradually decreased by day 10 (0.5%) postcastration. Because the percentage of apoptotic cells in the ventral lobe of old rats was still higher on day 10 after castration than it was before
castration, we examined tissue weight, DNA content, and the percentage of apoptotic cells in the ventral lobe from young and old rats 30 days after castration. The values obtained for these parameters at the later time point were not different from those observed at 10 days after castration for either age group (data not shown).

As might be predicted from the above results, morphological analyses revealed a decrease in epithelial cell size and the loss of infolding for the epithelial lining within the ducts of the ventral lobe from young rats on days 10 (Fig. 7A) and 30 (Fig. 7B) after castration compared with those in intact control rats (Fig. 7C). In the ventral lobe from old rats, epithelial cell size also decreased by days 10 (Fig. 7D) and 30 (Fig. 7E) after castration compared with that in intact control rats (Fig. 7F), but the infoldings of the epithelial ducts remained, even 30 days after castration. In the dorsal, lateral, and anterior lobes from young and old rats, epithelial cell size also decreased after castration, but, in a manner similar to that in the ventral lobe from old rats, the infoldings of the epithelial lining within the ducts were not altered after castration in either young or old rats (data not shown).

Because the prostatic lobes are populated by different cell types, and their distributions along the prostatic ducts are heterogeneous, with columnar epithelial cells along the more distal branches and cuboidal epithelial cells along the proximal branches, we were interested in determining whether apoptotic cells are localized to a particular region within the ventral lobe, whether apoptosis involves only epithelial cells, and whether the localization of apoptotic cells is affected by age. Figure 8 shows the percentages of epithelial cells undergoing apoptosis in the distal and proximal segments of the ventral lobe from young and old rats. In both young and old rats, apoptotic epithelial cells, both columnar and cuboidal, were observed throughout the glandular ducts, although at significantly higher percentages in the distal than in the proximal segments on day 3 after castration when apoptotic cell death is maximal. We also found both epithelial and stromal cells (Fig. 9) undergoing apoptosis throughout the ventral prostatic ducts, with the percentages of epithelial cells greatly exceeding those of stromal cells at both ages. Similar results were observed for epithelial and stromal cells in the other three lobes (data not shown). In contrast to that in the ventral lobe, the percentages of apoptotic cells in the dorsal, lateral, and anterior lobes were much lower and did not change significantly at any time throughout the 10 days after castration (data not shown). In addition, no significant differences in the percentages of epithelial cells undergoing apoptosis were observed between the distal and proximal...
FIG. 5. Apoptotic cell death in the ventral, dorsal, lateral, and anterior lobes after castration of young and old rats as detected by in situ DNA end labeling (TUNEL). Ventral lobe: A, Young control; B, young 1 day castrate; C, young 2 day castrate; D, young 3 day castrate; E, young 4 day castrate; F, young 10 day castrate; G, old control; H, old 1 day castrate; I, old 2 day castrate; J, old 3 day castrate; K, old 4 day castrate; L, old 10 day castrate. Dorsal lobe: M, young 3 day castrate; N, old 3 day castrate. Lateral lobe: O, young 3 day castrate; P, old 3 day castrate. Anterior lobe: Q, young 3 day castrate; R, old 3 day castrate. Micrographs are all at the same magnification (×200). Arrows indicate apoptotic cells.
segments of the dorsal, lateral, and anterior lobes (data not shown). However, as shown in Fig. 10, the percentage of cells undergoing apoptosis is significantly less in old rats compared with young rats in all four prostatic lobes when the cells were counted in random sections throughout the prostatic ducts of each lobe 3 days after castration.

Discussion

Apoptosis or programmed cell death is a physiological process critical for organ development, tissue homeostasis, and elimination of defective or potentially dangerous cells in complex organisms (21–24). Defects in normal programmed cell death mechanisms play a major role in the pathogenesis of various cancers, and attempts to activate apoptosis provide a therapeutic approach to the treatment of these malignancies (24–28). Androgen ablation forms a cornerstone in the clinical management of prostate cancer (29–30), but tumors that initially are sensitive to hormonal therapy eventually progress to androgen independence (31–33). Presently, our understanding of cell death or survival following androgen ablation, in a tissue that is normally androgen responsive, is inadequate. The results presented herein demonstrate that apoptotic cell death in the Brown Norway rat prostate gland induced by castration is lobe specific, thus suggesting that survival of some cells in the androgen-responsive rat prostate is androgen dependent, but is androgen independent in others. Furthermore, the sensitivity of cells to undergo apoptosis after androgen ablation changes with age, most dramatically in the ventral lobe. As we showed, castration of Brown Norway rats caused tissue weight and protein content (data not shown) to decrease in all four prostate lobes, but these events occurred more rapidly and profoundly in the ventral lobe than in the dorsal, lateral, and anterior lobes. Morphologically, the effect of androgen ablation was also apparent in all four lobes as epithelial cell size decreased. These findings are consistent with our earlier report in young Sprague Dawley rats, where tissue weights, protein contents, and cell size in the ventral, dorsal, and lateral lobes decreased in response to androgen ablation by castration, but DNA content decreased as a consequence of apoptotic cell death only in the ventral lobe (7).

The present study considered cell death in the context of aging as relates to our previous observations of an age-dependent, lobe-specific overgrowth of the prostate in Brown Norway rats (8). Overall, we observed a decrease in castration-induced cell death as a function of age, suggesting an age-related increase in androgen independence within all four prostatic lobes.

Prostatic overgrowth in the form of benign prostatic hyperplasia or carcinoma that occurs during aging is believed to be due to an imbalance in the normal rates of cell death compared with cell proliferation. In fact, recent studies have implicated not only increased rates of cell proliferation, but also decreased rates of cell death in determination of tumor size. We reported earlier that lobe-specific spontaneous overgrowth occurs in the prostate of Brown Norway rats as a function of age (8). At that time, we did not know whether the age-dependent overgrowth of the dorsal and lateral lobes was related to a decrease in the rate of cell death, as demonstrated in the present study. Based upon our examination of the castration-induced cell death in each prostatic lobe, the approximately 50% reduction in apoptosis that occurs in old compared with young rats is likely to contribute to a significant accumulation in the number of cells in each prostatic lobe over time. Therefore, one can conclude that the age-dependent overgrowth of the dorsal and lateral lobes in Brown Norway rats could be at least partially accounted for by an age-dependent decrease in cell death. Additional studies of cell proliferation after androgen replacement in castrated Brown Norway rats will be necessary to access the rates of cell proliferation in each prostatic lobe from young and old animals. However, the question remains as to why overgrowth does not occur in the ventral lobe with increasing age when cell death also decreases in this lobe as a function of age after castration. This may be partly explained by our morphological observation that significant age-associated atrophy occurs within the intermediate ductal segment of the ventral lobe from old rats (8). Age-related atrophy within the intermediate ductal segment of the ventral lobe may be a reflection of substantial cell loss, such that even a 50% re-

![Fig. 6. Percentages of cells undergoing apoptosis in the ventral lobe of young and old rats after castration. Values are the mean ± SEM (n = 4 rats/group). * Significantly different from intact control (P < 0.05).](https://academic.oup.com/endo/article-abstract/141/2/821/2988402)
duction in the rate of cell death within this lobe may not affect the total number of cells per ventral lobe, and hence, no age-dependent overgrowth would be observed.

An intriguing aspect of this study as well as our earlier study with Sprague Dawley rats (7) is the failure of cells in the dorsal, lateral, and anterior lobes of the prostates from young and old rats to die despite androgen ablation by castration. Androgen-dependent differentiation, growth, and maintenance of glandular secretory activity of these prostatic lobes have been well established (34–40). Androgens regulate gene expression in these prostatic lobes (41–43), and as shown by the present studies, androgen ablation decreases cell size and cellular protein contents in all prostatic lobes. In addition, we previously showed that administration of exogenous androgen to both young and old Brown Norway rats caused a dose-dependent increase in tissue weights, protein contents, and cell size in the ventral, lateral, and dorsal lobes (9). A number of earlier studies (44, 45), including our recent observations (unpublished results), show that cells in all four prostatic lobes express androgen

Fig. 7. Changes in morphology of the ventral lobe of young and old rats after castration. A, Young, intact; B, young, 10 days postcastration; C, young, 30 days postcastration; D, old, intact; E, old, 10 days postcastration; F, old, 30 days postcastration. Micrographs are all at the same magnification (×200).

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receptors. Therefore, it is curious that cell death occurs in the ventral lobe but not in other prostatic lobes after castration. Our results suggest that survival of cells in the dorsal, lateral, and anterior lobes does not require androgen, whereas survival of the majority of cells within the ventral lobe is dependent upon androgen. Androgens appear to play a dual role in each prostatic lobe with regard to androgen-dependent cell survival, on the one hand, and androgen-regulated protein synthesis and secretion, on the other.

The factors and pathways responsible for cell death in the absence of androgen are likely to be complex and, based upon our results, differ dramatically between the individual prostatic lobes and are influenced by age. The differences could arise at the level of the androgen receptor or further downstream in the apoptotic regulatory pathway. Prins et al. reported that androgen receptor levels decreased in the ventral and dorsal lobes of young adult rats after castration, but did not change in the lateral lobe (45). Similarly, we confirmed by immunocytochemical staining intensity these same lobe-specific changes in androgen receptor levels for epithelial cells in both young and old Brown Norway rats immediately (1–4 days) after castration (unpublished observations). However, by 7–10 days after castration, nuclear androgen receptor immunostaining is increased compared with the level observed immediately after castration (1–4 days), but is still less than that in intact animals. We also observed age-dependent and lobe-specific differences in the level of androgen receptor expression in intact rats (unpublished observations). The level of androgen receptor expression in epithelial cells decreases with age in the ventral lobe, but actually increases with age in the lateral and dorsal lobes. These changes need to be considered in the context of decreasing serum testosterone levels in aging Brown Norway rats that diminish ligand availability. These findings suggest that lobe-specific sensitivity to androgens may be dependent upon the availability of the ligand as well as its receptor, that androgen receptor levels are regulated differently in the various lobes, and that both ligand-dependent and -independent activities may vary between lobes and may change with age.

Recent studies have shown that androgen receptors can be activated not only by androgens, but also by a number of polypeptide growth factors, including epidermal growth factor, keratinocyte growth factor, and insulin-like growth factor I; cytokines such as interleukin-6; and second messengers such as cAMP (46–48). Work in our laboratory has revealed that the mitogenic growth factor, transforming growth factor-α (TGFα), is constitutively expressed at low levels in the ventral lobe, but at much higher levels in the dorsal and
lateral lobes of Brown Norway rats (unpublished observations). We previously showed that TGFα expression is repressed by androgen in columnar epithelial cells in the ventral lobe of young adult Sprague Dawley rats, but its level increases dramatically after castration (49). Therefore, it is possible that any of several growth factors, including the mitogenic factor, TGFα, may activate androgen receptors or alternative pathways and thereby act as a survival factor(s) for prostatic cells and provide protection against apoptotic cell death. Such an action for TGFα would be consistent with our observations that apoptosis occurs in the ventral lobe, but does not occur in the dorsal and lateral lobes after castration.

The balance between expression of apoptotic (Bcl family proteins, caspases, and nucleases) and antiapoptotic (Bcl family proteins, caspase inhibitors, and mitogenic growth factors) factors may also differ between lobes of the rat prostate and might change as a function of age. The differential regulation of Bcl-2 expression observed in our recent work represents one such factor (unpublished results). The antiapoptotic factor, Bcl-2, is constitutively expressed at much higher levels in cells of the dorsal and lateral lobes than in the ventral lobe of intact Brown Norway rats. Moreover, its expression appears to increase with age in the dorsal and lateral lobes, thus providing increased protection against castration-induced cellular apoptosis.

Taken together, our studies provide the basis for further examination of the pathways that determine androgen-dependent and -independent cell death and survival. Although the molecular basis for the lobe-specific and age-dependent cell death and survival in the rat prostate remains elusive at present, the aging Brown Norway rat will provide a model for such studies.

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