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Regressive Changes in Finasteride-Treated Human Hyperplastic Prostates Correlate With an Upregulation of TGF-β Receptor Expression

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BACKGROUND. Prostatic atrophy has been documented histologically as a consequence of finasteride action on human hyperplastic prostates. An increase in apoptotic rates has also been reported in androgen-deprived hyperplastic prostates. Transforming growth factor beta (TGF-β) signaling is implicated in apoptotic cell death. TGF-βs have been detected in normal and diseased human prostate. In the normal prostate, TGF-β acts as a predominantly negative growth regulator. TGF-β signaling receptors TβRI and TβRII have been shown to be negatively regulated by androgens.
METHODS. We studied the histological changes in 9 selected finasteride-treated patients with benign prostatic hyperplasia (BPH), and analyzed the levels of expression and localization of TGF-β receptor types TβRI and TβRII in these patients as compared to selected BPH controls.
RESULTS. The prostatic epithelial compartment seemed to be a primary target site for finasteride action, since we observed moderate to severe glandular atrophy after 4–6 months of treatment. TGF-β receptors were upregulated in treated cases. We assessed a twofold increase in TβRII mRNA levels in treated cases as compared to controls. An increase in both TβRI and TβRII at the protein level by immunostaining was observed, which also provided a helpful means for detecting glands undergoing regression.
CONCLUSIONS. We conclude that finasteride may modulate the TGF-β signaling system to promote changes leading to apoptosis of epithelial cells and prostatic glandular atrophy. *Prostate 37:84–90, 1998.* © 1998 Wiley-Liss, Inc.

KEY WORDS: **prostate; benign prostatic hyperplasia; TGF-β; TGF-β receptors; finasteride**

INTRODUCTION

Development of benign prostatic hyperplasia (BPH) appears to be dependent on the conversion of testosterone to dihydrotestosterone (DHT), which is enzymatically mediated by a steroid 5α-reductase [1]. Finasteride (Proscar®, Merck & Co., West Point, PA) is a potent and specific inhibitor of human type II 5α-reductase and consequently produces with oral administration a significant decrease in the circulating and intraprostatic levels of DHT [2,3]. In BPH patients, finasteride has proved to be effective in reducing prostate size and improving clinical symptoms [4,5]. These clinical effects occur particularly in prostates that are 40 g or larger [6]. Recently, prostatic atrophy has been reported histologically in men receiving finasteride [7]

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and demonstrated in experimental models [8,9]. The role of the complex stromal-glandular interactions in BPH development and regression following antiandrogen therapy is under extensive investigation, but is not yet fully characterized. Growth factors are a major class of molecules implicated in the regulation of those interactions [10,11]. The transforming growth factor beta (TGF-β) family is composed of a series of isoforms which regulate very distinct cellular functions, including proliferation and differentiation [12]. TGF-βs have been detected in normal and diseased human prostate [13,14]. TGF-β1 seems to be a potent inhibitor of prostatic epithelial cell proliferation and has been shown to mediate apoptotic epithelial cell death in vitro [15]. Signaling by TGF-β is dependent on binding to cell surface receptors, three of which, designated TβRI, -II, and -III, have been cloned. Receptors types I and II are serine/threonine kinases [16]. In a proposed model, TGF-β binds to the type II receptor, and then the type I receptor is recruited and phosphorylated by the type II receptor. Phosphorylation propagates the signal to unknown downstream effector molecules [17]. Sex steroids appear to be involved in modulating TGF-β systems, since androgen ablation upregulates both TGF-β and TGF-β receptors in castrated rats [18]. To assess whether finasteride-induced atrophic changes in BPH could be mediated by TGF-β, we examined the level of expression and cellular localization of TGF-β receptors in BPH tissue from men treated with finasteride as compared to untreated control BPH tissue. We also addressed the question of whether TGF-β receptor detection could be a sensitive indicator in monitoring an early treatment response.

SUBJECTS AND METHODS

Patients and Tissue Samples

Open prostatectomy was performed on 9 selected BPH patients under current finasteride protocols and 8 BPH control patients. These protocols were approved by the Ethical and Research Committees of our institution (H.U.V.R.). Major inclusion criteria in these protocols were prostate volume over 40 cm^3, clinical and/or flowmetric criteria for surgical indication, no permanent urinary catheterization, no lithiasis or other concomitant vesico-prostatic pathology, and no previous treatment for BPH. Duration of finasteride treatment (5 mg per day) was from 120–168 days. Clinical response to finasteride was evaluated according to the American Urological Association Symptom Index [19], also known as the International Prostate Symptom Score (I-PSS), serum prostate-specific antigen (PSA), prostate volume measured by transrectal ultrasonography, and urinary flow rates. All of these parameters were determined before finasteride treatment and immediately before surgery. In accordance with current criteria, open prostatectomy was indicated over transurethral resection, due to the large prostate volumes of the selected patients. For the purposes of this study, open prostatectomies were preferred as a source of tissue for more accurate sampling. Following resection, the specimens were measured in length and weight, and representative tissue blocks were frozen in liquid nitrogen and stored until use. Immediately adjacent tissue blocks were formalin-fixed and paraffin-embedded for histological examination.

Histology and Immunohistochemistry

Routine hematoxylin-eosin histological sections were submitted for double-blinded observation by two independent pathologists. Epithelial changes were evaluated semiquantitatively (+–+++), considering glandular volume and shape, height and loss of lining epithelial cells, and hyperplasia of basal cells. Polyclonal antibodies anti-human TβRI and anti-human TβRII were obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). For immunohistochemistry, sections from paraffin tissue blocks were incubated overnight with primary antibodies (0.5–1 μg/ml) at 4°C. Biotinylated secondary antibody and avidin-biotin-peroxidase complex were applied according to the manufacturer's instructions (LSAB2 Kit, Dako A/S, Glostrup, Denmark). Diaminobenzidine (DAB) was used as the chromogenic substrate for visualization (Biomeda Corp., Foster City, CA). Appropriate negative and positive controls were used in every experimental procedure.

Immunoblotting

Total protein was obtained from tissue homogenates as follows. Frozen tissue slices were disrupted in ice-cold homogenization buffer (phosphate-buffered saline (PBS), 1% Nonidet P40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate, 10 μg/ml phenylmethylsulfonyl fluoride, and 30 μg/ml aprotinin) with a Dounce homogenizer. Cell lysates were centrifuged (15,000*g*) for 20 min at 4°C, and protein concentration in the supernatant was determined with a colorimetric method (BCA Protein Assay, Pierce Chemical Co., Rockford, IL). One hundred micrograms of total protein were electrophoresed through 4–16% tris-glycine gradient gels and electroblotted onto nitrocellulose membranes (Hybond-ECL, Amersham International plc, Little Chalfont, UK). Membranes were treated with a blocking reagent (Boehringer Mannheim GmbH, Mannheim, Germany) to avoid nonspecific binding, and incubated overnight

TABLE I. Results of Clinical Evaluations in Patients Treated With Finasteride*

Case no.	Treatment (days)	I-PSS[a]			Prostate volume (cm^3)			Serum PSA (ng/ml)		
		Before	After	% reduction	Before	After	% reduction	Before	After	% reduction
1	133	29	22	24.1	58.2	46.2	20.9	3.1	1.3	58.1
2	132	27	23	14.8	44.0	37.6	30.3	1.7	1.3	23.5
5	139	23	25	–8.7	48.6	37.0	23.8	3.0	2.3	23.3
7	125	28	26	7.1	50.9	49.0	3.7	5.4	4.2	22.2
8	124	17	15	11.7	89.5	66.9	25.7	4.9	2.4	51.6
10	168	29	23	20.7	45.7	35.2	23.0	2.0	1.3	34.5
12	154	30	26	13.3	77.1	65.2	15.4	8.3	6.5	21.7
14	120	21	17	19.0	54.2	52.6	3.1	3.4	2.1	38.2
16	140	31	22	29.0	112.9	90.6	19.8	7.8	5.2	33.0

*Raw values are indicated before and after finasteride treatment.
[a]International prostate symptom score: 0–7, mild; 8–19, moderate; and 20–35, severe symptoms.

with primary antibodies at 4°C. Reactivity was detected by a chemoluminiscent system (Boehringer Mannheim).

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

PolyA+ RNA was isolated from frozen prostate samples using the MicroFast-Track Kit system (Invitrogen BV, Leek, The Netherlands). Double-stranded templates for PCR were prepared using the cDNA Cycle Kit (Invitrogen). Primers for TβRII gene transcript amplification were designed from the reported human sequence [20] and were as follows: forward primer, 5′-TAT AAA TCT CCC CTC CCC-3′; reverse primer, 5′-CGT AAT ATG CTC CAT CCC-3′. Thirty-five PCR cycles were run in a thermal cycler (Mastercycler, Eppendorf-Netheler-Hinz GmbH, Hamburg, Germany) under the following conditions: 94°C, 1 min; 55°C, 2 min; and 72°C, 3 min. PCR product size was 178 bp. β_2-microglobulin was amplified as an internal standard for quantitation under the same PCR conditions. Primers used were as follows: forward primer, 5′-ACC CCC ACT GAA AAA GAT GA-3′; reverse primer, 5′-ATC TCC AAA CCT CCA TGA TG-3′. PCR products were electrophoresed on 3% NuSieve 3:1 agarose gels (FMC BioProducts-Europe, Vallensbaek Strand, Denmark). Relative ethidium bromide-stained band intensities were assessed densitometrically with the aid of NIH-Image software.

RESULTS

Results of the Clinical Evaluations

Table I shows the duration of finasteride treatment and the percent changes obtained in the I-PSS, serum PSA levels, and prostate volume estimated by transrectal ultrasonography in each individual case when comparing determinations before and after finasteride treatment. Although the sample size (n = 9) does not allow statistically significant conclusions, the results are in accordance with previously reported large series [4–6]. With regard to flowmetric data (not shown), no relevant differences were observed, as expected from the surgical criteria in these patients.

Regressive Epithelial Changes Observed in Finasteride-Treated BPH

All of the selected cases corresponded to the mixed glandular/stromal form of BPH. Histologically, control untreated prostates were made up of nodules with complex glands, in which tall columnar cells and papillary infoldings were prominent (Fig. 1a). In general, treated cases showed moderate to marked regressive histological changes in the epithelial compartment (Fig. 1b). Glandular complexity as defined by gland size and infolding was reduced, with a relative increase of the stromal component. Epithelial lining cells, usually columnar in hyperplastic glands, were cuboidal to flat or even lost in the numerous glands undergoing atrophy in those cases treated with finasteride. Basal-cell proliferation was evident to prominent, in inverse correlation to the atrophic changes seen in treated cases. Table II compares results of histological changes in the prostate of control and finasteride-treated patients.

Immunodetection and Localization of TβRI and TβRII in Untreated and Finasteride-Treated BPH

The expression of TβRI and TβRII at the protein level was analyzed by both Western blot and immunohistochemistry on representative tissue samples.

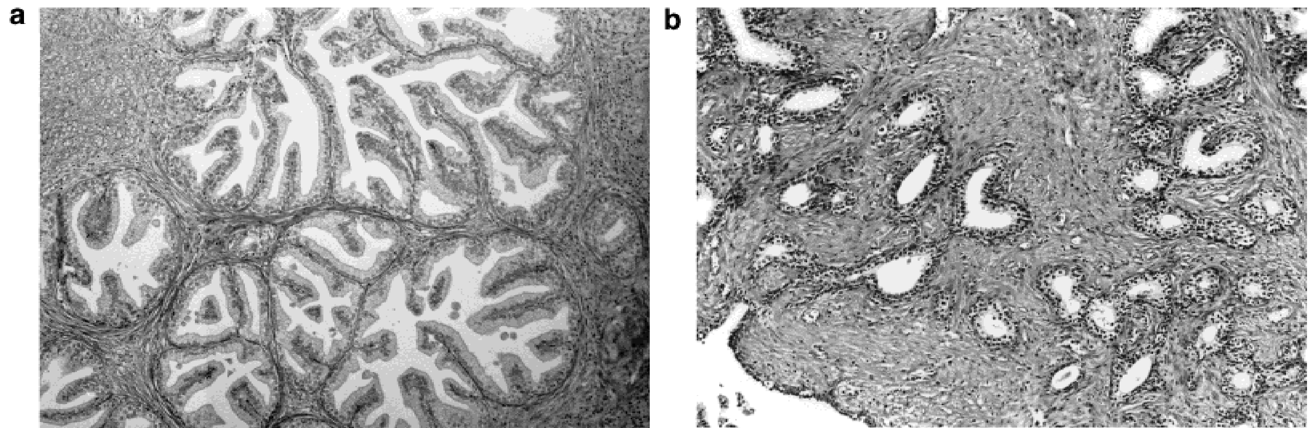

Fig. 1. Histological changes induced by finasteride treatment. **a:** Control case with typical morphological features of BPH (original magnification, ×25). **b:** Finasteride-treated case, showing a marked degree of gland atrophy and epithelial flattening. There is a relative increase of the stromal compartment (original magnification, ×25).

TABLE II. Results of Histological Evaluation

Finasteride-treated cases				Control BPH cases			
Case no.	Glandular complexity[a]	Epithelial height[b]	Basal-cell hyperplasia[c]	Case no.	Glandular complexity[a]	Epithelial height[b]	Basal-cell hyperplasia[c]
1	+	++	++	3	+++	++	+
2	+	+	+++	4	++	++	−
5	+	+	+++	6	+++	+++	−
7	++	++	+	9	+++	++	+
8	++	++	++	11	+++	+++	−
10	+	+	+++	13	++	++	+
12	++	++	+	15	+++	++	−
14	+	++	+++	17	+++	++	−
16	+	+	++				

[a]Predominant glands were +++, large with dilated lumina and prominent papillary infoldings; ++, medium-sized with small papillary infoldings; or +, small with narrow lumina and no papillary infoldings.
[b]Surface epithelial cells were predominantly +++, tall columnar; ++, columnar to cuboidal; or +, cuboidal to flat.
[c]Basal-cell hyperplasia was scored as +++, marked; ++, moderate; +, slight; or −, none.

For adequate comparative analysis, a careful selection of samples with similar epithelial/stromal ratios was made. On Western blots, the specific immunoreactive bands for TβRI (50–55 kDa) and TβRII (70–80 kDa) were more intense in those cases treated with finasteride (Fig. 2). On immunohistochemistry, changes were notably more pronounced in the epithelial rather than the stromal compartment between the two groups of patients. In finasteride cases, intense TβRII immunoreactivity in hyperplastic basal cells was observed, and this became more intense with increasing grades of gland atrophy (Fig. 3). Luminal cells in complex hyperplastic glands were negative, whereas cells in

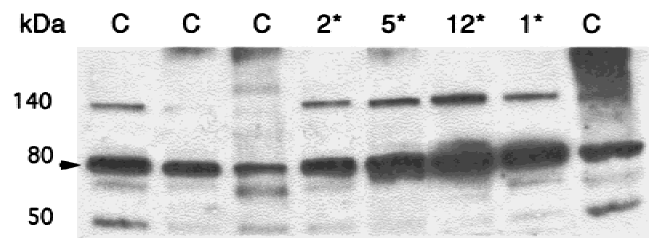

Fig. 2. Immunoblot analysis of TβRII. In general, finasteride-treated cases showed higher intensities for the 70–80-kDa-specific band (arrowhead) than control cases. Case numbers marked with an asterisk correspond to finasteride-treated cases. C, control cases.

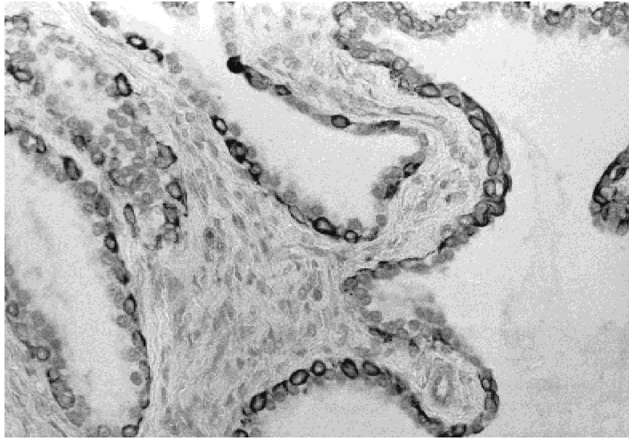

Fig. 3. Immunohistochemical demonstration of TβRII in atrophic glands. In finasteride-treated cases, the presence of proliferated basal cells in response to gland atrophy was the most salient feature after TβRII immunostaining (original magnification, ×100).

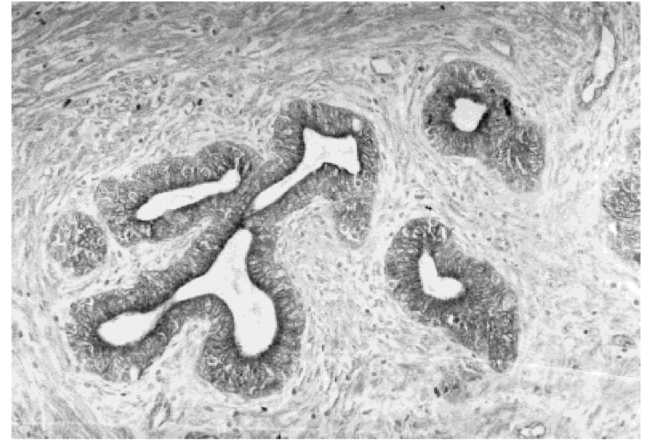

Fig. 4. TβRI immunostaining in a finasteride-treated case. Only secretory cells in atrophic glands were immunoreactive for TβRI. Hyperplastic glands in control BPH cases were negative (original magnification, ×50).

less complex intermediate glands undergoing atrophy showed nuclear and weak cytoplasmic TβRII immunostaining. TβRI was detected only in the cuboidal or flat luminal cells of the atrophic glands (Fig. 4). Basal cells and luminal cells in hyperplastic glands showed no TβRI immunostaining. In untreated cases, TβRII-positive basal cells and TβRI-positive cuboidal luminal cells were mainly seen in atrophic and compressed internodular areas (Fig. 5). In the stroma, immunostaining for both TβRI and TβRII was more variable but slightly more marked for TβRII in the treated cases.

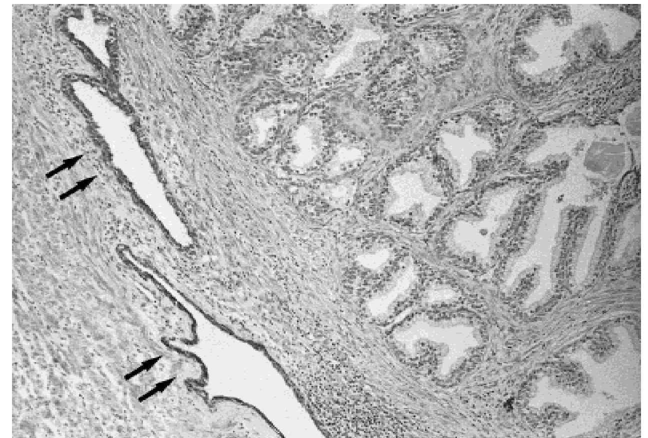

Fig. 5. TβRII immunostaining in control BPH. TβRII-immunoreactive basal cells were mostly seen in the atrophic internodular glands (arrows) (original magnification, ×25).

Quantitative Analysis of TβRII mRNA Levels in Finasteride-Treated BPH vs. Control Untreated BPH

Figure 6 shows the results of analysis by agarose gel electrophoresis of RT-PCR products from treated and untreated cases. Band intensity of the 178-bp TβRII-specific product obtained by scanning densitometry was divided by the intensity of the 110-bp β_2-microglobulin-specific band. The TβRII/β_2-microglobulin value in each individual sample is given in Table III. In the finasteride-treated cases, a more than twofold increase was observed in TβRII mRNA levels in treated cases (mean value 1.75, range 0.92–2.59) compared to controls (mean value 0.80, range 0.50–1.16).

DISCUSSION

Until recently, surgery was the only effective treatment for BPH. Advances in hormone therapy have changed the urologist's approaches to BPH. Finasteride has proved effective in improving both clinical symptoms and urinary flow rates, as well as in reducing prostate size, in BPH patients with prostates that are 40 g or larger. There are only a few reports documenting histologic regressive changes induced by finasteride in men or animal models. Rittmaster et al. [7] recently described regressive changes after finasteride treatment in men. The authors documented morphometrically a shrinkage of epithelial cells and a decreased infolding of prostate ducts, with maximum changes occurring by 4 months of treatment. Albeit semiquantitatively, we also found an obvious time-dependent reduction in the epithelial parameters analyzed as compared to controls. Glands showed less complexity, with flattened epithelial cells and proliferating basal cells. Basal-cell hyperplasia was a particularly prominent observation. As has been pointed

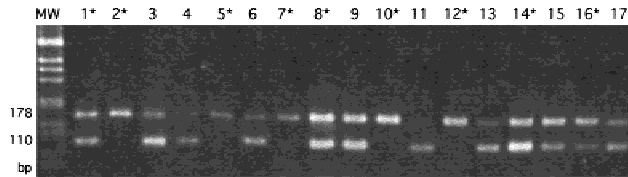

Fig. 6. Analysis of TβRII mRNA levels by RT-PCR. Coamplification of TβRII (178 bp) and β_2-microglobulin (110 bp) RT-PCR products was analyzed on ethidium bromide-stained agarose gels. Case numbers marked with an asterisk correspond to finasteride-treated cases. Bands were examined by scanning densitometry. TβRII/β_2-microglobulin value for each individual case is given in Table III. MW, molecular weight ladder.

TABLE III. Results of TβRII mRNA Levels Estimated by RT-PCR*

Finasteride-treated		Control BPH	
Case no.	TβRII/β_2m value	Case no.	TβRII/β_2m value
1	1.04	3	0.79
2	2.59	4	0.64
5	2.05	6	0.83
7	1.92	9	1.02
8	0.96	11	0.52
10	2.53	13	0.50
12	2.51	15	1.16
14	0.92	17	0.91
16	1.27		

*TβRII and β_2-microglobulin (β_2m) mRNA-specific bands on agarose gel, as shown in Figure 6, were scanned and quantitated by densitometry. Values represent ratios of TβRII mRNA-specific band to β_2-microglobulin mRNA-specific band used as internal standard.

out, the ability of basal cells to proliferate is not likely to be influenced by antiandrogens or castration [21,22]; alternatively, their proliferation could represent a regenerative process in response to secretory-cell involution or loss [23]. A reduction in stroma volume has been described in dogs treated with finasteride [9]. In men, changes in stroma volume have not been assessed morphometrically, but this compartment seems to be less affected than the glandular compartment by finasteride treatment [7].

Apoptotic cell death has been proposed as a mechanism to explain involution in androgen-deprived prostates. In the rat, castration triggers apoptosis in epithelial and stromal cells throughout the ventral lobe [24,25]. To a lesser extent, an increase in apoptosis has been observed by a quantitative DNA end-labeling technique in finasteride-treated rats [8]. In humans, finasteride-induced apoptosis seems to explain at least partially the involutive changes in treated prostates [7].

The TGF-β signaling system plays an established role in apoptotic cell death in different transformed and nontransformed epithelial cell types [26–28]. In the prostate, TGF-β1 has been detected only in the secretory cells and in the basal cells by some authors [29], and also in the stroma by others [30]. Undoubtedly, the TGF-β system is regulated by androgens. Castration increases the levels of TGF-β1 mRNAs, which return to normal after androgen replacement [14]. TGF-β receptors are also upregulated by castration. Kim et al. [18] documented a 6–8-fold increase in TβRI and -II mRNA levels shortly after castration in the rat ventral prostate. Our observation of a significant twofold increase in TβRII mRNA levels in those prostates treated with finasteride is a further confirmation of this androgen regulation and points out a mediation of finasteride action by the TGF-β system. Our immunostaining results show that both TβRI and TβRII localize most abundantly in glands showing moderate to severe atrophic changes, which were more extensive in treated prostates. Basal-cell immunostaining for TβRII was a striking feature, previously unreported to our knowledge. TGF-β receptor immunostaining helped us to define gradual changes in the regression of prostate glands sequentially, as follows: hyperplastic negative glands, intermediate (±) glands, and atrophic positive glands. We are unable to explain the nuclear staining obtained with the TβRII antibody, but it was observed exclusively in the secretory cells of glands of the intermediate type. In the stroma, a low intensity of immunostaining for both TβRI and TβRII was seen, and no obvious changes in treated cases vs. controls were observed. It appears that although 5α-reductase is more abundant in the stromal components of the human prostate, the epithelial compartment in BPH is more likely the primary target of finasteride treatment. In the male rat, apoptosis has not been detected in the ventral prostate stroma after finasteride treatment [8], although it was observed after castration [25]. Although TGF-β1 inhibits the proliferation of prostate-derived fibroblasts in vitro [31], participation of TGF-β signaling in the modulation of stromal proliferative activity in vivo has not been elucidated.

In summary, our report documents histological regressive epithelial changes in human hyperplastic prostates after treatment with finasteride for 4–6 months. TβRI and TβRII were upregulated and localized in the glands undergoing involution. The upregulation of these receptors could be one of the earliest changes observed in the responsive secretory cells as a result of inhibitory signals. In basal cells, the upregulated TGF-β receptors could mediate a proliferative rather than an inhibitory signal. TGF-β-mediated apoptosis and glandular atrophy could explain at least

partially the involution of hyperplastic prostates treated with 4-azasteroids. Finasteride might exert its action by altering the negative regulation by androgens on the TGF-β signaling system.

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