Engineered IGF-I expression induces glandular enlargement in the murine prostate

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Abstract

IGF-I has been implicated as a factor that may predispose one to prostate cancer and to benign prostatic hypertrophy (BPH). We established murine IGF-I transgenic mice under the control of rat probasin promoter and analysed the histology of the murine IGF-I-overexpressing prostate.

Immunohistochemically, IGF-I was expressed in prostatic epithelial cells or basement membranes of the ventral, dorsal and lateral lobes in a line of IGF-I transgenic mice, but not in their control littermates. The anterior lobe did not express IGF-I. IGF-binding protein-3 (IGFBP-3), inhibitory to the mitogenic action of IGF-I, was detected in epithelial cells of prostatic ventral lobes, but not in those of the dorsal, lateral or anterior lobes of IGF-I transgenic mice. In controls, IGFBP-3 was not detected in epithelial cells of any prostatic lobe. Macroscopic prostatic size and the appearance of IGF-I transgenic mice were comparable with those of their control littermates of the same age. With a computed morphometric analysis, epithelial glands and intraglandular lumens in the prostatic lobes except the

ventral lobe were smaller at 17 months of age than at 14 months both in IGF-I transgenic mice and controls. Glands and intraglandular lumens in the ventral prostatic lobes of IGF-I transgenic mice expressing more IGF-I protein in the prostate than controls were dense and enlarged similar to cysts compared with those of non-transgenic littermates without showing epithelial growth. Glands and lumens in the dorsal and lateral lobes of the IGF-I transgenic mice were also larger than controls at 14 and/or 17 months of age. Glands in the anterior prostatic lobe of the IGF-I transgenic mice were not morphologically or morphometrically different from those of non-transgenic littermates.

In conclusion, IGF-I transgenic mice under the control of rat probasin promoter showed more dense and enlarged epithelial glands in their prostatic ventral, dorsal and lateral lobes.

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Introduction

Insulin-like growth factors IGF-I and IGF-II are 7 kDa mitogenic polypeptides involved in the regulation of cell proliferation, differentiation and apoptosis. There are two transmembrane IGF receptors, both of which have a similarity to the insulin receptor (Djavan *et al.* 2001). The type 1 IGF receptor (IGF-1R) is expressed in prostatic epithelial and stromal cells (Djavan *et al.* 2001). The IGF-binding proteins (IGFBPs) 1–6 were reported to be involved in the modulation of the proliferative and mitogenic effects of IGFs on cells. Most IGF-I and IGF-II (99%) are bound to IGFBPs in serum. The interaction of IGF-I and IGF-II with IGF-1R is regulated by IGFBPs, which are expressed by prostatic epithelial cells and to a lesser extent by stromal cells (Djavan *et al.* 2001). IGFBP-3 decreases the mitogenic effects of IGF-I in normal prostatic epithelial cells in culture, and cleavage of the binding

protein by prostate-specific antigen decreases its affinity for IGF-1R, thus reversing this inhibitory effect (Djavan *et al.* 2001).

IGF-I has been implicated as a factor that may predispose one to prostate cancer and to benign prostatic hypertrophy (BPH). In humans, elevated serum IGF-I was reported to be a potent risk factor of carcinogenesis of the prostate (Chan *et al.* 1998). Glands from 44-day-old IGF-I-deficient animals were not only smaller than those from wild-type mice, but also had fewer terminal duct tips and branch points, and deficits in tertiary and quaternary branching, indicating a specific impairment in gland structure (Ruan *et al.* 1999). In the transgenic adenocarcinoma of the mouse prostate model (TRAMP) that expresses SV40 T antigen specifically in the epithelium of the prostate, prostate-specific IGF-I and fibroblast growth factor-2 (FGF-2) axis mRNA expression increased during prostatic cancer progression similar to the accompanying

metastatic lesions (Foster *et al.* 1998, Kaplan *et al.* 1999). Both prolactin and growth hormone transgenic mice elevated IGF-I levels, the former developed marked prostatic enlargement while the latter showed slight enlargement, thus the direct action of IGF-I on prostatic growth is still controversial (Wennbo *et al.* 1997).

It is necessary to introduce IGF-I in the prostate epithelium to delineate the prostatic growth induced by IGF-I. Recently, DiGiovanni *et al.* (2000) reported that IGF-I transgenic mice under the control of BK5 promoter expressing human IGF-I in the basal epithelium of mouse prostate formed spontaneous neoplasia in the tissue. We have also established murine IGF-I transgenic mice under the control of rat probasin promoter and analysed the histology of the murine IGF-I-overexpressing prostate. Probasin (prostate basic protein) is an androgen-dependent and prostate-specific secretory protein produced in differentiated prostatic epithelial cells. Short rat probasin promoter (−426 to +34) is used to establish transgenic mice expressing genes in the prostatic epithelial cells (Rennie *et al.* 1993).

Materials and Methods

Construction of murine IGF-I expression vector

pBH500 vector containing the 5′-flanking region of the rat probasin gene was digested with HindIII, blunted with Klenow DNA polymerase, digested with BamHI, then electrophoresed. The 454 bp fragment of pBH500 including the rat probasin promoter region was gel-purified, and ligated between the KpnI site blunted with Klenow and the cohesive BamHI site of the pUC18 vector, resulting in the pUC18–probasin vector. Murine IGF-I cDNA was excised with EcoRI from pmigf1 purchased from the American Tissue Culture Collection, gel-purified, and ligated into the EcoRI site of the mammalian expression vector pCAGGS (Niwa *et al.* 1991) yielding pCmIGFI. The XbaI–HindIII fragment of pCmIGFI, containing murine IGF-I cDNA and the rabbit β-globin polyA signal, was ligated between the XbaI and HindIII sites of pUC18–probasin, yielding the pBH-IGFI vector, which expresses murine IGF-I under the control of rat probasin promoter.

Establishment of murine IGF-I transgenic mice

Transgenic mouse lines were generated by microinjection of fertilized eggs as described previously (Takeuchi *et al.* 1999). The purified inserts of the SacI–HindIII fragment of pBH-IGFI were injected into the male pronucleus of fertilized eggs from the C57BL/6 L (Japan SLC, Inc., Hamamatsu, Japan) mouse strain. The manipulated eggs were cultured and transferred into the oviducts of ICR mice (Japan SLC, Inc.) pseudopregnant recipients. New-

born mice and their descendants were screened for genomic integration of the murine IGF-I transgene as described below. Tail genomic DNA purified as described previously (Takeuchi *et al.* 1999) was amplified by 35 cycles (95 °C for denaturing, 55 °C for annealing and 72 °C for extension) of PCR, using a thermal cycler with 1 mM sense and antisense primers (5′-CAGGCATTGGGCATTGTCCA-3′/5′-CTCGGTCCACACACGAACTG-3′) taken from the rat probasin promoter region upstream from the inserted cDNA and murine IGF-I cDNA respectively, 10 mM dNTPs, 2.5 U of *Taq* polymerase (Roche Diagnostics Corp.), and the buffer supplied with the enzyme. Amplified products (10 µl) were resolved by electrophoresis in 1.5% agarose gels containing ethidium bromide. Transgene-positive founder (F0) mice (C57BL/6 L) were crossed with naive C57BL/6 L and naive C3H/HeN mice (Nihon Clea, Tokyo, Japan). The studies were approved by the authors' institutional committees on animal care.

RT-PCR

RT-PCR was performed as described previously (Takeuchi *et al.* 1999) using 2 µg of total RNA. Sense/antisense PCR primer for murine IGF-I and β-actin were 5′-TCGTCTTCACACCTCTTCTACCTGG-3′/5′-TGCTTTTGTA GGCTTCAGTGGGGCA-3′ and 5′-TGGAATCCTGTGGCATCCATGGAAAC-3′/5′-TAAACGCAGCTCA GTAACAGTCCG-3′ respectively.

Western blotting

Protein was extracted from IGF-I transgenic and control F1 (C57BL/6 L × C3H/HeN) prostates in a Triton X-100 homogenization buffer containing 1 mmol/l PMSF, 2 µg/ml leupeptin, and 2 µg/ml aprotinin. After centrifugation for 20 min at 4 °C, the cleared supernatant was used for immunoprecipitation. Three hundred micrograms of each protein extract were pre-cleaned with protein A agarose beads (Roche Diagnostics Corp.) for 1 h at 4 °C in the Triton-X 100 cell lysis buffer. The extracts were then incubated with 2 µg anti-IGFI antibody for 1 h at 4 °C and with protein A agarose beads for another hour at 4 °C with constant rocking. After centrifugation, the pellets were washed twice with the Triton-X cell lysis buffer and then three times with a kinase buffer (50 mmol/l Tris-HCl, pH 8.0, 10 mmol/l MgCl₂, 1 mmol/l dithiothreitol, 1 mmol/l PMSF, 2 µg/ml leupeptin, and 2 µg/ml aprotinin). The immunoprecipitations were terminated by the addition of 30 µl 2X SDS loading buffer with boiling for 5 min. Fifty micrograms of each protein extract were separated on 10% SDS-polyacrylamide gels and transferred onto nylon membranes (Millipore, Bedford, MA, USA) with a semi-dry blotting system (Pharmacia Biotech). After blocking in 1X PBS/5% non-fat dry milk/0.2% Tween-20 at 4 °C

overnight, the membranes were incubated with anti-human IGF-I rabbit polyclonal antibody (H-20, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) at a dilution of 1:200 in a blocking buffer (1X PBS/2% non-fat dry milk/0.2% Tween-20) for 1 h at room temperature. The membranes were washed three times with the blocking buffer and incubated with a secondary antibody, which was conjugated with horseradish peroxidase (Amersham, Buckinghamshire, UK) at a final dilution of 1:7000. After final washes with 1X PBS/0.2% Tween-20, the signals were detected with ECL chemiluminescence reagents (Amersham, Buckinghamshire, UK).

Serum IGF-I measurement

Sera were collected when the mice were killed. Serum IGF-I was measured using a rat IGF-I RIA kit (DSL-2900, Diagnostic Systems Laboratories, Inc., Webster, TX, USA).

Histology

Ventral, dorsolateral and anterior lobes of the prostate were separated when the mice were killed.

Haematoxylin-eosin staining Cryospecimens were fixed with 4% paraformaldehyde in PBS (pH 7.4), then stained with haematoxylin and eosin.

Immunocytochemistry Cryostat sections were fixed in 4% paraformaldehyde in PBS for 5 min, rinsed with PBS (pH 7.4), then incubated with anti-human IGF-I rabbit polyclonal antibody (Santa Cruz Biotechnology, Inc.) at a dilution of 1:100, anti-mouse IGFBP-3 goat polyclonal antibody (M-19, Santa Cruz Biotechnology, Inc.) at a dilution of 1:50 or control serum overnight at room temperature. Labelling was visualized using the avidin-biotin complex method.

Morphometric analysis

Morphometry of prostatic sections was performed using a biological microscope (BX51-34, Olympus, Tokyo, Japan) with a digital camera (DP50, Olympus, Tokyo, Japan). Morphometric data were analysed using WINROOF software (Mitani Corporation, Fukui, Japan). Areas of gland, intraglandular lumen and epithelium (glandular area minus intraglandular luminal area) were measured for each gland. Area of a given lobe minus the sum of areas of each gland in the lobe in the section was regarded as the area of the interstitium. The numbers of measured individual glands in the morphometric analysis are listed in Table 1. Histograms of data of individual prostatic glands in prostatic lobes are shown in Figs 6-9.

Table 1 Numbers of measured glands in the morphometry

	Ventral	Dorsal	Lateral	Anterior
14-month-old line 1				
Non-transgenic	52	37	37	10
Transgenic	72	81	62	6
17-month-old line 1				
Non-transgenic	68	73	16	7
Transgenic	58	67	17	26

Figure 1 IGF-I transgene screening by PCR using mouse tail genomic DNA. Ladder, λ HindIII ladder; P, positive control (the pBH-IGF1 vector); Non Tg, negative transgene; Tg, positive transgene.

Table 2 Transgene transmission into F1

Line	Transmission (%)
Line 1	19.5
Line 2	37.5
Line 3	30.0
Line 4	Died before mating

Results

Establishment of murine IGF-I transgenic mice

Among 39 newborn C57BL/6 L mice, seven (four males and three females) were positive for the murine IGF-I transgene (Fig. 1). Transgene transmission when F0 was crossed with normal C57BL/6 L or C3H/HeN mice was as shown in Table 2. IGF-I transgenic and control littermates F1 (C57BL/6 L $\times$ C3H/HeN) prostates of IGF-I transgenic lines 1 and 2 were used for histological analysis.

Expression of IGF-I and IGFBP-3 in murine IGF-I transgenic mice

In 4-week-old IGF-I transgenic mouse lines 1 and 2 and their controls, IGF-I mRNA (RT-PCR) and IGF-I

Figure 2 IGF-I protein expression in IGF-I transgenic prostates. mo, months; Tg, IGF-I transgene; line, transgenic line.

protein (immunohistochemistry) were not detected in the prostate ($n=2$). At this age, IGF-I mRNA was detected by RT-PCR in the lung, liver and heart, but not in the intestine, kidney or testis both in IGF-I transgenic mice and in control littermates (data not shown).

As shown in Fig. 2, the level of IGF-I protein expression in the prostate of the IGF-I transgenic mouse line 1 assessed by Western blotting analysis was similar to controls at the age of 2 months, while it was enhanced compared with controls at the age of 8 months. In IGF-I transgenic mouse line 2, prostatic IGF-I protein expression was similar to controls at the age of 6 months. Serum IGF-I levels in IGF-I transgenic mice line 1 were comparable with those in controls (Fig. 3), thus IGF-I production and its action in this model could be local but not systemic.

Immunohistochemically, IGF-I was expressed in prostatic epithelial cells of ventral lobes and in epithelial basement membranes of dorsal lobes and lateral lobes of IGF-I transgenic mice (line 1), but not in those of their control littermates at 14 and 17 months of age ($n=3$ for each age, Fig. 4a). IGF-I was not detected in the anterior

lobes in IGF-I transgenic mice or controls. IGF-I was slightly expressed in prostatic stromal fibroblasts of IGF-I transgenic mice (line 1) and controls. IGFBP-3 was detected in epithelial cells of prostatic ventral lobes, but not in those of dorsal, lateral or anterior lobes of IGF-I transgenic mice (Fig. 4b). In control littermates, IGFBP-3 was not detected in epithelial cells of any prostatic lobe (Fig. 4b). With respect to prostatic stroma, IGFBP-3 was observed in fibroblasts of IGF-I transgenic mice, but not in those of controls.

The morphology of the prostate in murine IGF-I transgenic mice

Macroscopic size and the appearance of prostatic lobes of IGF-I transgenic mouse lines 1 and 2 were comparable with those of their control littermates of the same age (14 and 17 months), as shown in Table 3 and Fig. 5. As shown in Fig. 4c, glands in ventral prostatic lobes of IGF-I transgenic mouse line 1 expressing more IGF-I than controls were more dense and enlarged similar to cysts compared with those of non-transgenic littermates. Glands and intraglandular lumens in the dorsal and lateral lobes of IGF-I transgenic mice were slightly larger than those of controls. In contrast, glands in the anterior prostatic lobe of IGF-I transgenic mouse line 1 were not morphologically different from those of non-transgenic littermates. Epithelial hyperplasia and atypism in the prostatic glands were not observed. Glands in ventral prostatic lobes and the dorsal, lateral and anterior lobes of IGF-I transgenic mouse line 2 expressing a similar amount of IGF-I as controls were not morphologically different from those of control littermates ($n=2$, data not shown).

With morphometric analysis, the areas of the lobe, gland and interstitium of IGF-I transgenic mice were not significantly different from those of controls (Table 3). Epithelial glands and intraglandular lumens in the prostatic

Figure 3 Serum IGF-I level in IGF-I transgenic mice line 1. Tg, transgenic; Non-Tg, non-transgenic.

Figure 4 Histological analysis of IGF-I transgenic prostate (line 1). (a) IGF-I expression of IGF-I transgenic prostate by immunohistological staining, $\times 100$. (b) IGFBP-3 expression of IGF-I transgenic prostate by immunohistological staining, $\times 100$. (c) Haematoxylin–eosin staining of IGF-I transgenic prostate; $\times 50$ for AL, DL and LL, and $\times 20$ for VL. AL, anterior lobe; DL, dorsal lobe; LL, lateral lobe; VL, ventral lobe; Cont, control (non-transgenic); Tg, transgenic. Representative findings of mice at 17 months of age are shown.

Table 3 Areas of prostatic lobes. Median values are shown

		Lobal area	Glandular area	Interstitial area
Lobe				
14-month-old line 1				
Ventral	Non-Tg	6.3	4.6	1.7
	Tg	9.1	6.2	2.9
Dorsal	Non-Tg	1.6	1.1	0.9
	Tg	4.6	3.2	1.4
Lateral	Non-Tg	9.0	8.7	8.7
	Tg	9.0	6.0	3.0
Anterior	Non-Tg	5.9	3.8	2.1
	Tg	5.2	5.1	0.2
17-month-old line 1				
Ventral	Non-Tg	3.9	2.5	1.4
	Tg	7.3	5.8	1.4
Dorsal	Non-Tg	2.9	1.9	0.9
	Tg	2.8	2.2	0.6
Lateral	Non-Tg	2.5	1.6	1.0
	Tg	2.7	2.2	0.6
Anterior	Non-Tg	7.5	2.4	5.1
	Tg	7.8	2.9	4.9

Non-Tg, non-transgenic; Tg, transgenic.

There was no significant difference between controls and transgenic mice by nonparametric Mann–Whitney *U* test.

Figure 5 Haematoxylin–eosin staining of IGF-I transgenic prostate (17 months), $\times 10$. Upper panel, control; lower panel, transgenic; left, anterior lobe; middle, dorsolateral lobe; right, ventral lobe.

lobes, except the ventral lobe, were smaller at 17 months of age than at 14 months both in IGF-I transgenic mice and controls. The glandular and luminal sizes of individual glands in the ventral lobe of the IGF-I transgenic mouse line 1 were significantly larger than those of controls at 14 and/or 17 months of age, but the area of the individual

Table 4 Areas of individual prostatic gland. Values are means ± s.e.

		Ventral	Dorsal	Lateral	Anterior	
14-month-old line 1	Individual gland	Non-Tg	0.15 ± 0.02	0.09 ± 0.01	0.24 ± 0.05	0.75 ± 0.38
		Tg	0.20 ± 0.04	0.12 ± 0.01*	0.30 ± 0.05	0.86 ± 0.45
	Intraluminal	Non-Tg	0.09 ± 0.02	0.05 ± 0.01	0.21 ± 0.05	0.58 ± 0.33
		Tg	0.15 ± 0.02*	0.05 ± 0.01	0.25 ± 0.05	0.66 ± 0.36
	Epithelium	Non-Tg	0.06 ± 0.00	0.07 ± 0.01	0.04 ± 0.00	0.18 ± 0.06
		Tg	0.05 ± 0.00	0.07 ± 0.00	0.05 ± 0.00	0.20 ± 0.09
17-month-old line 1	Individual gland	Non-Tg	0.20 ± 0.02	0.04 ± 0.00	0.10 ± 0.02	0.29 ± 0.15
		Tg	0.29 ± 0.03**	0.06 ± 0.00*	0.18 ± 0.01*	0.23 ± 0.03
	Intraluminal	Non-Tg	0.10 ± 0.02	0.01 ± 0.00	0.06 ± 0.02	0.06 ± 0.03
		Tg	0.20 ± 0.03*	0.02 ± 0.00*	0.15 ± 0.01*	0.07 ± 0.02
	Epithelium	Non-Tg	0.11 ± 0.01	0.03 ± 0.00	0.04 ± 0.01	0.27 ± 0.15
		Tg	0.09 ± 0.01	0.04 ± 0.00	0.03 ± 0.00	0.15 ± 0.02

Non-Tg, non-transgenic; Tg, transgenic.
P*<0.01 compared with non-transgenic, *P*<0.03 compared with non-transgenic by unpaired t-test.

Figure 6 Histograms of individual glandular, luminal and epithelial areas in the prostatic ventral lobe. Tg, transgenic; Non-Tg, non-transgenic; vertical axis, %; horizontal axis, area (μm^2).

Figure 7 Histograms of individual glandular, luminal and epithelial areas in the prostatic dorsal lobe. Tg, transgenic; Non-Tg, non-transgenic; vertical axis, %; horizontal axis, area (μm^2).

glandular epithelium was similar to the controls (Table 4 and Fig. 6). The individual glandular size of the dorsal and lateral lobes of IGF-I transgenic mouse line 1 was also larger than that of controls at 14 and/or 17 months (Table 4 and Figs 7 and 8). The individual glandular size, luminal size and epithelial area in the anterior lobe of IGF-I transgenic mouse line 1 were similar to the controls. The glandular size, luminal size and epithelial area of individual glands in the ventral lobe of IGF-I transgenic mouse line 2 were comparable with those of control mice (data not shown).

Statistical analysis

Unpaired *t*-test and Mann-Whitney U test were used for statistics. $P < 0.05$ was taken as significant.

Discussion

In the present IGF-I transgenic prostate overexpressing IGF-I protein, the epithelial glands and their lumens

were more dense and enlarged in prostatic ventral lobe microscopically and by morphometric analysis. Epithelial glands of the prostatic dorsal and lateral lobes of the transgenic line were slightly larger than those of controls microscopically. Morphometric analysis also found that their glandular and luminal sizes were significantly larger than those of controls.

In the IGF-I transgenic prostate of line 2, which did not overproduce IGF-I compared with control non-transgenic prostate, epithelial glands of the prostatic lobes were microscopically similar to controls. Thus, the changes observed in the ventral, dorsal and lateral lobes of line 1 mice overproducing IGF-I in the prostate may be because of overproduced IGF-I. There may be no morphological changes in the anterior lobe, as the glandular epithelium in the anterior lobe did not produce IGF-I.

Most significant morphological changes were observed in the prostatic ventral lobes of IGF-I transgenic mice. Since we did not perform precise quantitation of IGF-I in individual lobes, there may have been differences in the IGF-I levels among individual prostatic lobes. IGFBP-3 was detected only in the ventral lobes, not in the

Figure 8 Histograms of individual glandular, luminal and epithelial areas in the prostatic lateral lobe. Tg, transgenic; Non-Tg, non-transgenic; vertical axis %; horizontal axis, area (μm^2).

dorsal, lateral or anterior lobes of IGF-I transgenic mice. Considering that IGFBP-3 is inhibitory to the mitogenic action of IGF-I in some circumstances, IGFBP-3 expression in the transgenic ventral lobes alone may be compensatory for more IGF-I expression in the transgenic ventral lobes than the transgenic dorsal, lateral or anterior lobes. Another possibility may be that the ventral lobe may be more sensitive to IGF-I than other lobes and may modulate expression of IGFBP-3. There is also a possibility that IGF-I and IGFBP-3 expression in the ventral lobe of IGF-I transgenic mice are independent.

The morphology of a prostatic duct changes markedly between the tip and the urethral opening, and there is a possibility that glands close to or far from the urethra can be chosen in one section. Histograms (Figs 6–9) created with glands in these sections may be appropriate for showing the rightward-shift pattern of individual glandular and luminal size in the ventral, dorsal and lateral lobes.

DiGiovanni *et al.* (2000) reported that transgenic IGF-I expression led to activation of the IGF-I receptor and spontaneous tumorigenesis in prostate epithelium such as hyperplasia, atypical hyperplasia, prostatic intraepithelial

neoplasia, and finally adenocarcinoma in prostatic dorso-lateral and ventral lobes in mice by 6 months of age. Differences between the present findings and those reported by DiGiovanni may be due to the extent of IGF-I production in the transgenic prostate. IGF-I production in the present IGF-I transgenic mouse line 1 was two- to threefold greater than that in controls. This may not be enough to lead to more profound epithelial hyperplasia and malignancy. In the present study, prostatic glands in the ventral, dorsal and lateral lobes did not show enhanced epithelial growth or epithelial neoplastic changes, but prostatic glandular enlargement was obvious. Thus, IGF-I might have stimulated fluid secretion into intraglandular lumens from prostatic glandular epithelium of the prostatic ventral lobes and to a lesser extent the lateral dorsal lobes in IGF-I transgenic mice. The follicle of polycystic ovary syndrome has characteristic IGF family expression, supporting an intraovarian role for IGF family in ovarian follicle growth, steroidogenesis and atresia (Giudice 1999).

According to our unpublished findings, FGF-2 (basic FGF) transgenic mice under the control of rat probasin

Figure 9 Histograms of individual glandular, luminal and epithelial areas in the prostatic anterior lobe. Tg, transgenic; Non-Tg; non-transgenic; vertical axis, %; horizontal axis, area (μm^2).

promoter expressing FGF-2 in the prostate showed simple epithelial hyperplasia in the dorsal lobe of the prostate, but not in the lateral and anterior lobes. This may also support a prostatic lobal difference in the sensitivity to given growth factors. In conclusion, IGF-I transgenic mice under the control of rat probasin promoter showed more dense and enlarged epithelial glands in their prostatic ventral, dorsal and lateral lobes.

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