REVIEW

Stromal Androgen Receptor Roles in the Development of Normal Prostate, Benign Prostate Hyperplasia, and Prostate Cancer

Simeng Wen,* Hong-Chiang Chang,† Jing Tian,‡ Zhiqun Shang,* Yuanjie Niu,* and Chawnshang Chang†‡

From the Chawnshang Chang Sex Hormone Research Center,* Tianjin Institute of Urology, The Second Hospital of Tianjin Medical University, Tianjin, China; the Departments of Pathology and Urology,† George Whipple Lab for Cancer Research, Wilmot Cancer Center, University of Rochester Medical Center, Rochester, New York; and the Sex Hormone Research Center,‡ China Medical University, Taichung, Taiwan

Accepted for publication October 20, 2014.

Address correspondence to Yuanjie Niu, Ph.D., or Chawnshang Chang, Ph.D., Box 626 601 Elmwood Ave. Rochester, NY 14642. E-mail: niuyuanjie@tijmu.edu.cn or chang@urmc.rochester.edu.

The prostate is an androgen-sensitive organ that needs proper androgen/androgen receptor (AR) signals for normal development. The progression of prostate diseases, including benign prostate hyperplasia (BPH) and prostate cancer (PCa), also needs proper androgen/AR signals. Tissue recombination studies report that stromal, but not epithelial, AR plays more critical roles via the mesenchymal-epithelial interactions to influence the early process of prostate development. However, in BPH and PCa, more attention has been focused on epithelial AR roles. However, accumulating evidence indicates that stromal AR is also irreplaceable and plays critical roles in prostate disease progression. Herein, we summarize the roles of stromal AR in the development of normal prostate, BPH, and PCa, with evidence from the recent results of in vitro cell line studies, tissue recombination experiments, and AR knockout animal models. Current evidence suggests that stromal AR may play positive roles to promote BPH and PCa progression, and targeting stromal AR selectively with AR degradation enhancer, ASC-J9, may allow development of better therapies with fewer adverse effects to battle BPH and PCa. (Am J Pathol 2015, 185: 293–301; http://dx.doi.org/10.1016/j.ajpath.2014.10.012)

The prostate contains mainly the stromal cells and epithelial cells that are separated by base members and merged in extracellular matrix. Stromal cells include fibroblasts, smooth muscle cells (SMCs), and other minor inflammatory cells, nerve cells, and endothelial cells.

The prostate is developed from the endodermal urogenital sinus1 that contains an outer layer of embryonic connective tissue urogenital sinus mesenchyme (UGM) and an inner layer of urogenital sinus epithelium (UGE).1 The initial step of prostate development in UGM involves the differentiation of fibroblasts and SMCs,1 and in response to the UGM androgen/androgen receptor (AR) signals, UGE can grow into the surrounding stromal cells and develop into the prostate epithelial cells as part of the normal prostate development.

The ability of the UGM to induce epithelial development and the developed epithelial cells, in return, to direct UGM to undergo differentiation, suggesting that the reciprocal developmental interactions between UGM and UGE might be governed by androgen/AR signals, which are essential for the development of normal prostate, benign prostate hyperplasia (BPH), and prostate cancer (PCa). Prostate development factors, including its proliferation, differentiation, morphogenesis, and functional maintenance, are all influenced by androgen/AR signals.2 Androgen/AR signals also play vital roles in the initiation and progression of BPH and PCa,3,4 which may require the proper interaction with various AR coregulators.5

AR is a member of the nuclear receptor superfamily that can be activated and translocated from cytoplasm to nucleus after binding the testosterone or dihydrotestosterone.5–7 In prostate, AR is expressed in both epithelial and stromal tissues. The

Supported by NIH grant CA156700 (C.C.), George Whipple Professorship Endowment (C.C.), and Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence grant DOH102-TD-B-111-004 (C.C.).

S.W. and H.-C.C. contributed equally to this work.

Disclosures: ASC-J9 was patented by the University of Rochester, University of North Carolina, and AndroScience, and then licensed to AndroScience. Both the University of Rochester and C.C. own royalties and equity in AndroScience.
transactivated AR in nucleus may then function through modulation of various downstream target genes to influence the development and maintenance of the prostate. In addition to influencing cell growth directly, epithelial AR and stromal AR can also function through epithelial-mesenchymal transition (EMT) to influence prostate development. EMT is a process by which epithelial cells lose their cell-cell adhesion and gain migratory properties to become mesenchymal-like and/or mesenchymal stem cells. These potent mesenchymal cells may then differentiate into different cell types to influence the progression of BPH and PCa.

This review will focus on the discussion of the roles of stromal AR in the development of normal prostate and prostate diseases.

AR Roles in Normal Prostate Development

Accumulating evidence suggests that androgens through AR in embryonic stromal cells, but not in epithelial cells, direct the development of the prostate via mesenchymal-epithelial interactions. Early studies suggested that during the embryonic stage, UGM may promote prostate development via inducing epithelial bud formation, eliciting prostatic bud growth, and regulating ductal branching, as well as promoting epithelial differentiation and determining the secretory protein expressions. More important, these UGM-mediated functions may be through androgens/AR signals to influence the normal prostate development. This conclusion is further strengthened from immunostaining data showing detection of AR only in the early UGM and not in the UGE. The stromal androgens/AR signals may function through modulation of different growth factors, including fibroblast growth factors (FGFs), keratinocyte growth factor, insulin-like growth factor (IGF), and vascular endothelial growth factor, to promote adjacent epithelium growth and differentiation in a temporal and spatial manner. However, so far no single growth factor was able to completely replace the stromal AR roles, suggesting stromal AR may need to modulate multiple factors to influence the mesenchymal-epithelial interactions for the proper prostate development.

Evidence from in Vitro Studies

In the prostate, cell proliferation and differentiation are influenced by many AR-modulated growth factors, including transforming growth factor (TGF), IGF, FGF, and epidermal growth factor. In established primary cell lines from human prostatic stroma, androgen influences the proliferation, differentiation, and regression of stromal cells by regulating the expression of TGF-β, basic FGF, AR, and SMC-specific proteins. Dihydrotestosterone has a significant stimulatory effect on stromal cell growth via increasing the production and/or secretion of growth factor(s), including basic FGF-like human pituitary growth factor in human prostatic fibroblasts isolated from fetal prostate. Similar phenomenon in stromal cells derived from primary culture of explanted human normal or benign prostatic tissue is also observed.

Androgens can induce stromal-derived keratinocyte growth factor to stimulate prostate epithelial cell growth. In rat ventral stromal cells, androgen/AR signals can stimulate myodifferentiation of stromal cells, and stromal AR can modulate Ca2+ metabolism through the direct regulation of the Stim1 gene or stimulate epidermal growth factor receptor signaling to influence the prostate development.

Knocking down AR in prostate stromal cells (PrSCs) may affect the expression of growth factors resulting in the repression of prostate growth. In primary cultured cells isolated from fibroblast specific protein 1-Cre AR knockout (FSP-ARKO) mice, the loss of AR in stromal fibroblasts decreases prostate development. Co-culturing these ARKO stromal fibroblasts with the prostate epithelial BPH-1 cells can then decrease the growth of BPH-1 cells, with decreased expression of various growth factors, including IGF-1, FGF-2, FGF-7, FGF-9, FGF-10, vascular endothelial growth factor-β, and placental growth factor in the stromal fibroblasts. Knocking down AR in primary cultured cells suppresses prostate growth in primary cultured cells isolated from mice with AR knocked out in the stromal SMCs (SM-ARKO). However, instead of functioning through modulation of many growth factors, AR in the SMC is more specific and modulates only IGF-1 signaling. In studies with immortalized PrSCs from wild-type (WT) mice and selective double-knockout AR (dARKO) mice, PrSCs from WT mice promote prostate epithelium growth significantly compared with those from dARKO mice. Stromal AR might function through the modulation of IGF-1, placental growth factor, and secreted phosphoprotein-1 to influence epithelial cell growth. Together, results from various stromal cell lines studies conclude that stromal AR may play essential roles for the prostate development.

UGM-UGE Tissue Recombination Approaches in Prostate Development

Tissue recombination techniques have been used for >50 years to study the cellular biological features of both developing and adult organs. The earlier studies for the prostate recombination technique were conducted by Cunha et al., who evaluated the mesenchymal induction of prostatic epithelium. By using renal capsule implementation of tissue recombinants, it was demonstrated that AR in stromal, but not in epithelial, cells plays essential roles for the prostate development via influence of ductal morphogenesis, epithelial differentiation, apoptosis, and proliferation. In tissue recombinants of mesenchyme and epithelial cells from WT and AR-deficient testicular feminization (Tfm) mice, tissue recombinants composed of Tfm-UGM + Tfm-epithelium fail to form prostate even in the presence of androgens. However, WT-UGM + WT-epithelium tissue recombinants form prostate in response to androgens. More important, Tfm-UGM + WT-epithelium tissue
recombinants fail to develop prostate in the presence of androgens, suggesting a critical role of mesenchymal AR, but not epithelium AR, in prostate development. This conclusion was further confirmed in the reciprocal WT-UGM + Tfm-epithelium tissue recombinant study in which AR-deficient Tfm epithelium underwent androgen-dependent ductal morphogenesis, epithelial proliferation, and columnar cytodifferentiation, thus forming glandular epithelium resembling the prostate.  

Together, results from tissue recombinant experiments concluded that many androgenic effects on prostatic epithelial development require the paracrine action of AR-positive mesenchyme. Even later analysis of Tfm/WT tissue recombinants also revealed that epithelial AR might also play some roles to induce some AR downstream secretory proteins.  

Evidence from in Vivo Mouse Models

AR KO mouse models with selective knockout of AR in either prostate epithelial or stromal cells also help us better understand the specific roles of stromal AR in prostate development.

By using the Cre-loxP system to generate the floxed AR mice, and then mating with FSP1 Cre mice, Yu et al successfully generated male mice with the AR gene selectively deleted in prostate stromal fibroblasts (named FSP-ARKO), and reported the ventral prostate lobes of FSP-ARKO mice to be lighter than WT littermates. Tissue histological analysis of ventral prostate lobe shows changed epithelial cells with more cuboidal and flattened shapes in prostate ducts of FSP-ARKO mice; the WT prostate epithelial cells remain columnar. These results suggested that knocking out AR in prostate stromal fibroblasts might reduce epithelial differentiation in prostate. Proliferation reduces with increased apoptosis in the FSP-ARKO ventral prostates. These results suggest that AR in prostate stromal fibroblasts plays positive roles to stimulate the prostate development.

In SM-ARKO mice, the prostates of SM-ARKO mice have no significant difference in gross appearance and branching morphogenesis compared to WT mice. However, hematoxylin and eosin staining shows defective structures in the SM-ARKO mice prostates, suggesting that knocking down AR might result in fewer epithelial in-foldings into the lumens. The morphological changes of SM-ARKO mouse prostates are due to the defective epithelium proliferation, which is mainly mediated by stromal SMC-secreted IGF-1. IGF-1 is a key AR-modulated growth factor in prostate for proliferation and morphogenesis. Knocking down AR in the SM-ARKO mice significantly suppresses IGF-1 expression in anterior and ventral prostates.

In double-stromal AR knockout mice (with selectively deleted AR in both stromal fibroblasts and SMCs, named dARKO), the size of the anterior prostate lobes is significantly reduced. Decreased proliferation and increased apoptosis in the epithelial cells of dARKO mouse anterior prostates are also observed. Dissection of the mechanism in the PrSCs, isolated from dARKO mice, confirms that IGF-1 is the key modulator of stromal AR function for normal prostate growth. Together, results from various ARKO mice conclude that AR in prostate stromal fibroblasts or SMCs plays positive roles to stimulate normal prostate development (Figure 1).

AR Roles in BPH

Human prostate consists of three distinct histological zones: central, peripheral, and transition. Nearly all clinically significant BPH develops in the transition zone of the prostate. Macroscopic growth of the transition zone can cause narrowing of the urethra as it passes through the prostate, leading to a bladder outlet obstruction, which may affect the flow of urine. BPH is the most common benign neoplasm in American men and affects almost three-quarters of men during the seventh decade of life. BPH-induced lower urinary tract symptoms, including bladder outlet obstruction, contribute to a spectrum of urinary voiding problems that can significantly affect quality of life. The etiology of BPH remains unclear. An early study indicated that BPH contains mainly stromal cells (88.4%), with only 9.0% epithelial cells, suggesting the stromal cells may play more important roles in the development of BPH, even though both the stromal and epithelial components are involved in the development of BPH. McNeal hypothesized that the reversion of the stroma to an embryonic phenotype and the formation of hyperplastic stromal nodules are the earlier events in BPH, and the de novo formation of epithelial glands in BPH is a later event, which is induced by paracrine factors from the stromal nodules, emphasizing that stroma may play an important role in influencing BPH development.

The stromal androgens/AR signals may influence the initiation and progression of BPH via alteration of the various growth factors in the paracrine and/or autocrine manner. For example, factors involved in alteration of cell proliferation/differentiation, or stem cell population, as well as factors involved in the EMT or inflammation/immune tolerance, have been suggested to be directly or
indirectly linked to the AR. Therefore, targeting androgens/AR signals continue to play key roles in battling the progression of BPH.47,48

Evidence from in Vitro Studies

There are three reported mechanisms by which prostate AR promotes the development of BPH. The first mechanism is to influence the proliferation of prostate cells directly from stromal AR. AR tissue compartment assays indicate that BPH tissue has much higher AR expression compared to adjacent normal glandular tissue.47,48 In epithelial cells and BPH tissue has much higher AR expression compared to stromal AR. AR tissue compartment assays indicate that to in

Evidence from Tissue Recombination Approaches

Because several key factors from BPH microenvironment and interactions between epithelium and stroma are not easy to study via the in vitro cell line system, the tissue recombination approaches were developed to better evaluate the AR roles in the BPH microenvironment for their impact on epithelial-stromal interactions.

Use of tissue recombination approaches to compare the stromal cells from the peripheral zone of BPH versus normal prostate to induce the growth of epithelial BPH-1 cells revealed that BPH-1 cells mixed with stromal cells isolated from BPH, and not from normal prostate, can generate the grafts with proper development.53 Histological examination of these grafts revealed densely packed, well-organized, tubular epithelium with minimal stroma, sharply demarcated from the surrounding renal tissue. Stromal AR, and not epithelium AR, is critical in BPH development.58

Evidence from ARKO Mouse Models

By using prostate stromal double-ARKO (AR was knocked out in both fibroblasts and SMCs) mice to mate with the prolactin transgenic mice, Lai et al59 generated the first BPH mouse model (dARKO/prolactin transgenic) that selectively deleted AR in stromal fibroblasts and SMCs. They showed that loss of AR in stromal fibroblasts and SMCs can result in the development of the smaller prostates with a lower proliferative index, better urination function, and normal bladder volume.59

Prolactin-induced hyperplastic prostate growth involves the epithelial-stromal interaction. Epithelial autonomous prolactin/prolactin receptor—granulocyte macrophage colony stimulating factor signaling in a paracrine manner to facilitate stromal cell growth, and stromal AR, can modulate granulocyte colony stimulating factor—STAT3 signaling to control epithelium cell growth. These findings were confirmed using single AR knockout from fibroblasts or SMC mouse models. Previous findings that the stromal AR might play positive roles to promote BPH development were further validated in specific SMC ARKO mice; knocking out SMC AR in adult male mouse prostate results in dramatically decreased anterior prostate lobe, dorsolateral prostate lobe, and ventral prostate lobe weights.

Together, results from in vivo mice studies confirm the data from in vitro cell lines and tissue recombination studies showing that the AR in stromal smooth muscle and fibroblasts is the key player in promoting BPH development via modulating the epithelial-stromal interaction (Figure 2).

Clinically, the most inconvenient symptoms induced by BPH are lower urinary tract symptoms that may be treated by either α-blockers or 5α-reductase inhibitors to suppress testosterone conversion to more potent dihydrotestosterone. However, not all of the patients are sensitive to these therapies and some still need surgery. Further clinical trials to prove the above conclusion showing AR in stromal and
epithelial cells may play key roles in promoting development of BPH, which may help us develop new and better therapies via targeting AR in stromal and epithelial cells.

Stromal AR Roles in PCa

PCa is the leading cancer in men in the United States, and it may affect one-sixth of men. PCa was proved to originate from epithelial cells. Since the discovery of Huggins and Hodges in 1941, the vital roles of androgens/AR signals have been realized well, and androgen deprivation therapy to prevent or reduce androgen binding to AR, which may suppress tumor progression in most of the cases in the first 1 to 2 years, has been the standard therapy to treat the advanced PCa.

Prostate tumorigenesis has been regarded as a largely cell-autonomous process that may involve genetically transformed epithelial cells. Interestingly, although the epithelial AR roles in the influence of PCa development have been well studied, the stromal AR roles in the development of PCa remain relatively unclear.

PCa stroma is composed of fibroblasts, SMCs, extracellular matrix, and other infiltrating cells in the prostate tumor microenvironment. Normal prostate stromal compartment has the inherent plasticity to respond rapidly to emerging situations, including disrupted homeostasis with tumor development. During emerging situations, stromal cells may alter the phenotypic and genotypic changes to become the so-called reactive stroma, which mainly includes the changes of SMA and activation of carcinoma-associated fibroblasts (CAFs) or myofibroblasts.

SMCs, one of the main components of stromal cells, express AR and respond to androgens to maintain the highly differentiated secretory epithelium via homeostatic stromal-epithelial interactions in PCa. The fibroblasts, another main component of stromal cells, can be influenced/activated by the surrounding cancer epithelial cells, and in return, these fibroblasts can then potentially promote the growth and invasion of PCa. Interestingly, the phenotypes of these activated fibroblasts (named CAFs) are more closely related to the myofibroblasts, and may function through their AR to promote the PCa cell growth and invasion.

Evidence from in Vitro Studies

To analyze the stromal AR roles in PCa development, the immortalized CAFs were co-cultured with the PCa epithelial cells; the capability of CAFs to promote PC-3 cell proliferation and invasion is interrupted by knocking down AR, which involves the modulation of the expression of IGF-1, FGF7, FGF10, stromal derived factor 1, hepatocyte growth factor, and TGF-β2. These data suggested that the AR in CAFs might be able to promote PCa epithelial growth and invasion via regulating the expression of the growth factors.

Via transfecting a functional AR-cDNA into the immortalized human Prostate PCa cell line studies, recombination experiments, and AR knockout animal models demonstrates that stromal AR can promote PCa growth, metastasis, and tumorigenesis. FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; MIP, macrophage inflammatory protein; SDF, stromal derived factor; TGF, transforming growth factor.

Evidence from the Tissue Recombination Approaches

The concept that stromal cells may play a role in carcinogenesis was also proved by the tissue recombination studies. By using tissue recombination models in rats, Wang et al demonstrated that nontumorigenic human prostatic epithelial BPH-1 cells with prostate UGM recombinants would develop...
the invasive carcinomas in the presence of testosterone pro-
pionate (T) and 17-β-estradiol (E2). In contrast, the epithelial
cells might lead to cell apoptosis when the recombinants are
not treated with T + E2 or host mice are castrated. These re-
sults suggest that the nontumorigenic BPH-1 cells can undergo
hormonal carcinogenesis in response to T + E2 stimulation.
However, although BPH-1 cells can survive and grow in the
absence of UGM, they could not form the tumors or organized
structures, suggesting that the PrSCs play an important role in
mediating hormonal carcinogenesis.77 Because BPH-1 cells
express little AR and ER, whereas rat UGMs express both AR
and ERα, it is likely that T + E2 may function through the
stromal AR and ERα to promote prostate tumorigenesis.78

Interestingly, T + E2 treatment promotes the metastases of
murine UGM1 and BPH-1 recombinants, leading to
carcinoma.79 Tissue recombinants with AR-negative stro-
mal cells derived from mouse UGM and AR-negative
human benign prostatic epithelial cells fail to develop into
tumors. In contrast, tissue recombinants composed of WT
stromal cells and WT epithelial cells develop into much
larger and invasive tumors.79

In tissue recombination of human prostate WPMY1
stromal cells with human PCa epithelial PC-3 cells, the
stromal AR might function as a stimulator in PCa cell
growth and metastases in the orthotopic xenografted
prostate tumors. These data suggest that stromal AR
might play important roles in the PCa initiation and
progression.

Evidence from in Vivo Mouse Models

Tissue-specific AR knockout mouse models80 were also
applied to prove the essential roles of stromal-epithelial
interaction for the PCa development. Niu et al7 generated
inducible ARKO-TRAMP and prostate epithelial-specific
ARKO TRAMP mouse models, in which the AR was
knocked out in both, or separately, in prostate epithelial and
stromal cells. The results showed that in inducible ARKO-
TRAMP mice, knocking out AR in both epithelial and stro-
mal cells at earlier stages results in smaller primary prostate
tumors with lower proliferation rates. And in prostate
epithelial-specific ARKO-TRAMP mice, knockout of prostate
epithelium AR results in larger primary prostate tumors with
higher proliferation rates. These results indicate that the
prostate stromal AR might play more important roles than the
epithelial AR to promote primary tumor proliferation at the
early stages of tumor development.

In the established animal model with AR deletion in
stromal fibromuscular cells (dARKO; AR knockout in fi-
broblasts and SMCs), loss of stromal fibromuscular AR
suppresses prostate tumorigenesis development.85 Stromal
AR plays roles in the alterations of the tumor microenvi-
ronments, such as extracellular matrix remodeling, angio-
genesis, and immune cell infiltration. By comparing the
stromal cells isolated from WT mice and stromal cells from
ARKO mice, they further proved that stromal AR was able to
regulate proinflammatory cytokine/chemokine expression
[eg, macrophage inflammatory protein (Mip)-1a, Mip-1b,
Mip-2, and Il-10] to affect immune cell recruitment and
modulate inflammatory responses in mouse prostate. For
example, AR may cooperate with NF-κB to activate MIP-1b
promoter (Ccl4) after Il-1b stimulation, instead of directly
binding to Mip-1b promoter80 (Figure 3).

Conclusions and Perspective

Some studies demonstrated that epithelial AR in PCa
functions can be opposite and complicated.81,82 These
opposite epithelial AR roles might lead to different func-
tions, which explains why androgen deprivation therapy
cannot completely suppress PCa.81 In contrast, stromal AR
seems to play more consistent roles. At the embryonic
phase, stromal AR may promote prostate development via
inducing epithelial bud formation, eliciting prostatic bud
growth, and regulating ductal branching, as well as pro-
moting epithelial differentiation and determining the secre-
tory protein expressions.11–13 Stromal AR also can promote
the initiation and progression of BPH through many
mechanisms.49,55 Similar to BPH, the positive roles of
stromal AR in PCa are well demonstrated.4,83

The conclusion that stromal AR plays key roles in pro-
moting the development of BPH and PCa suggests that tar-
geting stromal AR can provide a potential therapeutic
approach to suppress the progression of BPH and PCa. ASC-
J9, a newly developed AR degradation enhancer, degrades AR
in selective cells via interruption of interaction between AR
and selective AR coregulator ARAS55 in stromal cells.84 Early
studies suggest that AR coregulator ARAS55 can bind to WT
AR and mutant AR (named mART877S; point mutation
threonine to serine at codon 877) in a ligand-dependent
manner to enhance their transcriptional activities85 and in-
fluence the progression of PCa.86 ASC-J9 has been well proved
to suppress the progression of BPH via degradation of WT AR
and mutant AR in the prostate. Multiple mechanisms are
involved, including the suppression of macrophage-induced
PrScs proliferation,35 EMT-induced BPH,44 prolactin-driven
BPH,89 and alteration of branching morphogenesis.18 Simi-
larly, the effect of targeting stromal AR-ARA55 interaction to
suppress PCa via ASC-J9 might involve the interruption of
TGF-β—Smad3—matrix metallopainase 9 signals,87 infil-
trating macrophage-chemokine ligand 2-STAT3 signals.88
In conclusion, results from above studies suggest that
targeting stromal AR may help us develop some new ther-
apeutic approaches to better suppress prostate diseases.

References

1. Hayward SW, Baskin LS, Haughney PC, Foster BA, Cunha AR,
   Dahiya R, Prins GS, Cunha GR: Stromal development in the ventral
   prostate, anterior prostate and seminal vesicle of the rat. Acta Anat
   (Basel) 1996, 155:94–103

2. Mastroianni CJ, Baskin LS, Paro J, Brannan DJ, Burt RW, Cunha AR:
   Stromal proliferation in rat prostate, anterior prostate and seminal

3. Togashi K, Maekawa T, Terada N, Aoki S, Yamamoto Y, Nishida H:
   Stromal proliferation in rat seminal vesicle. Acta Anat (Basel) 1996,
   155:27–32

   Stromal proliferation in rat seminal vesicle. Acta Anat (Basel) 1996,
   155:13–19

5. Kato K, Takahashi M, Togashi K, Maekawa T, Nishida H, Yamamoto Y:
   Stromal proliferation in rat seminal vesicle. Acta Anat (Basel) 1996,
   155:5–12

6. Shibata T, Aoki S, Terada N, Nishida H, Yamamoto Y: Stromal prolifera-
32. Donjacour AA, Cunha GR: Assessment of prostatic protein secretion in tissue recombinants made of urogenital sinus mesenchyme and urothelium from normal or androgen-insensitive mice. Endocrinology 1993, 132:2342–2350


