Published in final edited form as:

Differentiation. 2011 ; 82(0): 168–172. doi:10.1016/j.diff.2011.04.002.

A historical perspective on the role of stroma in the pathogenesis of benign prostatic hyperplasia

Gerald R. Cunha^{1,3} and William A. Ricke²

¹Department of Urology, University of California, San Francisco, CA 94143

²Department of Urology, UWCCC, 1111 Highland Ave, 7107 WIMR, Madison, WI 53705

Abstract

This review summarizes the concept that the neo-formation of ductal-acinar architecture in the pathogenesis of benign prostatic hyperplasia (BPH) is due to the reactivation of embryonic inductive activity by BPH stroma, an idea enunciated by John McNeal. The concept is the synthesis of McNeal's astute pathological inference based upon developmental biology and supported by the mesenchyme-epithelial interaction studies. In a broader context, McNeal's concept of framing epithelial pathogenesis in terms of developmental biological principals has been extended more recently into the field of carcinogenesis under the umbrella of tumor microenvironment.

One of the pioneers of prostatic research is John McNeal. I had the pleasure of following his studies and knowing him over a period of many years, and I am sorry that he is no longer with us. I became acquainted with his work as a result of reading his ground-breaking paper published in the NIH Monograph on Benign Prostatic Hyperplasia (BPH) in 1976 in which he proposed the idea that the neo-formation of prostatic ductal-acinar tissue in the pathogenesis of BPH was due to the reawakening of embryonic inductive activity by adult prostatic stroma (McNeal, 1976; McNeal, 1978). At that time I was an Associate Professor at the University of Colorado, and McNeal was a pathologist in a small local hospital in Berkeley, California. After a brief phone conversation, we agreed to meet in Berkeley the next time I returned to the Bay Area where my family resided. In 1977 we met and had a long discussion on prostatic anatomy and the pathogenesis of BPH. McNeal was then using the meager resources available to him in a small hospital to make his seminal discoveries, since in the 1970's he was not affiliated with an academic institution.

One of the foremost discoveries made by McNeal was to redefine the anatomy of the prostate by challenging the decades old concept of prostatic lobes. The idea of prostatic lobes emerged early in the 1900s as a result of studies of human embryos in which individual prostatic lobar sub-divisions were evident (Lowsley, 1912). Even though such lobar sub-divisions are not apparent in the adult human prostate, lobe-based descriptions of the adult human prostate continued to be accepted for decades. McNeal proposed the idea of zonal sub-division of the human prostate (McNeal, 1981; 1983). McNeal was an astute biologist and recognized that patterns of ductal organization observed in sections through

© 2011 International Society Of Differentiation. Published by Elsevier B.V. All rights reserved.

³Corresponding Author: Department of Urology, University of California, San Francisco, CA 94143; cunha@urology.ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the prostate were contingent upon the plane of section. Transverse, longitudinal, and coronal sections gave very different “lobar” patterns that were inconsistent with the lobar pattern of prostatic anatomy. The reason for these discrepancies was that the prostatic urethra, which traverses through the human prostate, does not pass straight through the gland, but instead undergoes about a 60 degree bend about half way through the prostate (McNeal and Bostwick, 1984). By preparing sections through the prostate at precise angles, McNeal revealed a new organizational pattern termed “zonal anatomy” in which 3 zones were recognized: the peripheral zone (the common site of prostatic adenocarcinoma); the central zone through which the ejaculatory ducts traverse; and the transitional zone located around the urethra and which is the site of BPH (McNeal, 1984; 1983). Ducts of each zone were shown by McNeal to arise from the urethra in specific areas and to arborize into zone-specific patterns. Subtle zonal differences in epithelial histodifferentiation were also noted (McNeal et al., 1988). McNeal's zonal anatomy of the human prostate was not initially accepted by the prostatic community, as lobar anatomy was an entrenched idea that continued to be held by many pathologists. Fortunately, McNeal was given the opportunity to present his novel idea of prostatic anatomy in national and international meetings. I had the good fortune to witness these debates on several occasions. To get a sense of these heated discussions see the articles by McNeal versus Tisell in the book, “New Approaches to the Study of Benign Prostatic Hyperplasia” (Kimball et al., 1984). For these meetings McNeal was extraordinarily well prepared and masterfully persuasive. Over the course of several meetings McNeal's zonal anatomy of the prostate became accepted and is universally used throughout the world to this day.

The zonal anatomy of the prostate espoused by McNeal had important pathological implications. The peripheral zone, located mostly in the posterior aspect of the gland is the primary site of prostate cancer development and is not involved in BPH. In contrast, the transition zone, located near the upper portion of the prostatic urethra develops cancer less frequently (~20%), but instead is the site of BPH (McNeal, 1983).

Another important prostatic investigator and a contemporary of McNeal was L. M. Franks. Franks also published a most important paper on BPH in the 1976 NIH Monograph on Benign Prostatic Hyperplasia, in which he emphasized the idea that BPH is a nodular disease and that BPH nodules were of several types: stromal, fibromuscular, muscular (leiomyoma), fibroadenomatous, and fibromyoadenomatous (Franks, 1976). Both Franks and McNeal emphasized the idea that BPH is a nodular disease (McNeal, 1990; Franks, 1954). McNeal interjected a note of caution concerning the idea of equating trans-urethral resection chip (TURP) specimens arising from “BPH” surgery with real BPH. The idea is that if one cannot confirm that a chip actually is part of a nodule, how can one say it is BPH. TURP chip specimens undoubtedly contain bona fide BPH nodules derived from the transitional zone, but also non-nodular prostatic tissue from other zones.

In regard to BPH, McNeal was particularly interested in the fibroadenomatous or so-called “epithelial” nodules, which are not pure epithelial, but instead contain both epithelial and stroma tissues with the epithelial component being particularly abundant. In fortuitous sections of human BPH, McNeal noted that areas interpreted to be newly formed ductal-acinar tissue appeared to be emerging from a pre-existing duct and in turn encroaching or invading into an adjacent purely stromal nodule. Based upon general principles of ductal branching morphogenesis derived from other types of embryonic glands (salivary gland, lung, pancreas, mammary gland), McNeal proposed the idea that the adult stromal nodule had re-acquired embryonic activity and was inducing the formation of a new duct that was invading and arborizing into the adjacent stromal nodule. This idea was based upon (1) the demonstration that embryonic prostatic development is induced by urogenital sinus mesenchyme (Cunha, 1972), and (2) McNeal's intuition and knowledge of ductal branching

morphogenesis. Taken together McNeal's proposal was an interesting idea, and a personal challenge for me to see if it was possible to provide laboratory support for this idea. In order for BPH stroma to be the inducer of new ductal-acinar development in the adult prostate, 2 requirements must be satisfied: (1) that BPH stroma is actually inductive in either a directive or permissive sense, and (2) that adult prostatic epithelium is actually responsive to inductive stromal influences.

In 1976, the responsiveness of adult epithelia to embryonic induction was unknown. Serendipitously, in the late 1970's we carried out a most unusual experiment by combining embryonic urogenital sinus mesenchyme (UGM) with non-glandular adult urinary bladder epithelium (BLE) and growing the resultant UGM+adult BLE tissue recombinant for 4 weeks in adult male hosts (Cunha et al., 1980b). When the UGM+adult BLE tissue recombinants were analyzed, fully differentiated prostatic tissue was observed. Seeing this extraordinary result for the first time, my initial interpretation was that it was an artifact due to a technical error (UGM contaminated with epithelium). My second thought was that Beth Melloy, my technician, did not make such mistakes. Clearly, if the results were true, we had made an extraordinary finding. Subsequently the experiment was repeated many times, and there is no doubt that non-glandular adult urinary bladder epithelium can be induced by UGM to undergo prostatic morphogenesis and differentiation (Cunha et al., 1987; Cunha et al., 1983a). In subsequent studies, we showed that the ability of UGM to induce adult urinary bladder epithelium to undergo prostatic differentiation can occur across species lines between rat, mouse and rabbit tissues (Cunha et al., 1983b). Finally, we showed that both human fetal as well as adult human bladder epithelium, when combined with a rodent prostatic mesenchymal inducer, was induced to undergo prostatic development and differentiation, including the expression of human prostate specific antigen (PSA) (Cunha et al., 1983b; Aboseif et al., 1999). These studies on prostatic induction in adult bladder epithelium emphasized in a generic sense the idea that adult urogenital epithelium is indeed responsive to embryonic induction. There are two likely interpretations for the induction of prostatic differentiation in adult bladder epithelium. One is based upon the idea that adult bladder epithelium contains pluripotent stem cells capable of responding in the inductive activity of UGM. The other interpretation is that differentiated adult bladder epithelial cells underwent transdifferentiation in response to UGM, a possibility supported by recent studies from the Bhowmick laboratory (Li et al., 2009).

To specifically address the issue of responsiveness of adult prostatic epithelium (PrE) to mesenchymal induction, Jill Norman, a member of the Cunha lab, was the first to analyze tissue recombinants composed of embryonic UGM+adult mouse prostatic epithelium (UGM+PrE) (Norman et al., 1986). In these studies, a small (~300µm) segment of an adult prostatic duct was combined with embryonic UGM, and the resultant tissue recombinants were grown for 1 month in a male host. The result was the formation of ~40mg of fully differentiated prostatic tissue. The initial 300µm segment of adult prostatic duct contained ~5000 epithelial cells, whereas that resultant 40mg of fully differentiated prostatic tissue contained ~20,000,000 epithelial cells (Cunha, 2008). In comparable experiments by Leland Chung, the in situ surgical implantation of embryonic UGM into adult mouse prostate stimulated considerable growth of the adult mouse gland (Chung et al., 1984b; Chung et al., 1984a). When the mesenchyme utilized was a specific inducer of dorsal-lateral prostate and the target epithelium was derived from the adult ventral prostate, the dorsal-lateral prostatic inducer re-programmed the lobar identity of the adult prostatic epithelium changing ventral prostate into dorsal-lateral prostate based upon secretory protein gene expression (Hayashi et al., 1993). Thus, adult prostatic epithelium is indeed responsive to prostatic induction. To explore this idea in regard to human prostatic epithelium, Simon Hayward (also from the Cunha lab) isolated small segments of adult human prostatic ducts from TURP chip specimens. Small unbranched human prostatic ductal segments were combined with rat

UGM, and the resultant tissue recombinants grown in male athymic mouse hosts (Hayward et al., 1998). Such rat UGM+human prostatic epithelial tissue recombinants exhibited epithelial growth, ductal branching morphogenesis, and expressed differentiation markers (including PSA) appropriate for human prostate. Thus, adult human prostatic epithelium is indeed responsive to prostatic induction.

Over the years, the Cunha laboratory and others explored the role of mesenchyme in prostatic development. The record shows that androgens elicit prostatic epithelial development and growth through interacting with androgen receptors within the UGM (Cunha and Lung, 1978; Cunha et al., 1980a; Sugimura et al., 1986). Urogenital sinus mesenchyme induces prostatic morphogenesis in target epithelium such as from the urinary bladder through the initial generation of prostatic epithelial buds and subsequent ductal elongation and branching morphogenesis, processes that are dependent upon UGM-induced epithelial proliferation. UGM or sub-divisions thereof induce the expression of several specific genes in the epithelium, such as Nkx3.1, the androgen receptor, and lobe-specific secretory protein genes. UGM elicits within the epithelium a specific program of epithelial cytodifferentiation that culminates in the differentiation of the set of epithelial cells (luminal, basal, and neuroendocrine) appropriate for the prostate each expressing their characteristic set of marker proteins. Thus, UGM induces prostatic epithelial morphogenesis and differentiation, a process involving androgen action mediated primarily through androgen receptors in the UGM (paracrine pathways) (Cunha et al., 1983a; Cunha et al., 1987; Cunha et al., 2004). The effect of UGM on prostatic development is one aspect of one of the most basic developmental mechanisms, namely the mesenchymal-epithelial interaction. Such interactions are involved in organogenesis of all 3 germ layers within the embryo. Organs of male and female urogenital tracts develop via mesenchymal-epithelial interactions that are in turn regulated or influenced by steroid sex hormones acting through mesenchymal and epithelial steroid receptors (Cunha et al., 2004). Table 1 is a compilation of mesenchymal effects on epithelial development taken from studies on hormone-responsive organs of male (mostly prostate) and female urogenital tracts. These studies emphasize the broad range of regulatory influences of mesenchyme on epithelial morphogenesis, differentiation and gene expression.

Demonstration of inductive activity in adult prostatic stroma has not been achieved for a variety of reasons. Due to the architectural complexity and interdigitation of adult prostatic ducts within adult prostatic stroma, it is difficult (if not impossible) to directly isolate epithelium-free adult prostatic stroma. Adult prostatic stroma can be isolated as a result of differential culture, but this requires long periods of cell culture during which inductive activity (if present) may be lost. Furthermore, recreating a complex adult stroma containing the appropriate ratio of stromal cells, including fibroblasts, smooth muscle cells, endothelium, lymphocytes, and other cells has not been achieved. For these reasons, we have not pursued such experiments. Furthermore, it must be recognized that normal adult prostatic stroma may not be inductive under certain physiologic conditions, and thus experimental design may be paramount in exploring inductive activity of adult prostatic stroma. First, one must consider when adult prostatic stroma might be inductive? Under steady state homeostatic conditions (intact adult males), the prostate is growth-quiescent, and thus under such conditions adult prostatic stroma is unlikely to be inductive. However, after a period of androgen deprivation elicited by castration, androgen replacement stimulates considerable prostatic epithelial growth and ductal branching morphogenesis. Thus, adult prostatic stroma during periods of androgen-induced prostatic regeneration may be inductive. Specific hormonal conditions may have to be satisfied in order for adult prostatic stroma to be inductive. For example, as men age their serum sex hormone profiles change. Aging men have an increased estradiol-17- β (E2) to testosterone (T) ratio, which is associated with age-related diseases such as BPH. Stroma associated with BPH is exposed to

an altered E2:T ratio, which may be critical for inductivity of BPH stroma. In support this concept, Barclay and colleagues demonstrated that stroma associated with BPH nodules enhanced prostate epithelial proliferation (Barclay et al., 2005).

While it has not yet been possible to formally demonstrate that BPH stroma induces the neo-formation of ductal-acinar tissue during the pathogenesis of BPH, McNeal's idea, that stroma may play a pivotal role in epithelial pathogenesis, is supported by studies of carcinogenesis. In a general sense this concept states that carcinomas (epithelial cancers) arise in part as a result of interactions with an abnormal stroma. This is an idea that has been debated for years, and which now receives considerable experimental support. A milestone in the field of tumor microenvironment was an NIH workshop in 2001 entitled, *Epithelial-stromal interactions and tumor progression*, organized by Suresh Mohla, Lynn Matrisian and Jerry Cunha, which ultimately culminated in a special issue of the journal *Differentiation* published in 2002 and containing 15 articles dedicated to this topic. Within that issue of *Differentiation* is a review article from the Cunha laboratory, which is relevant to McNeal's idea that stroma plays a pivotal role in prostatic epithelial pathogenesis (Cunha et al., 2002; Olumi et al., 1999). We demonstrated that fibroblasts associated with human prostatic carcinomas (CAF, carcinoma-associated fibroblasts) stimulate tumor progression of initiated, but non-tumorigenic human prostatic epithelial cells (BPH-1 cells) to become fully tumorigenic (Olumi et al., 1999). Subsequent studies led to a model of hormonal carcinogenesis in which tissue recombinants composed of mouse UGM+BPH-1 were grown under the kidney capsule of male athymic mice treated with testosterone and estradiol to recreate the hormonal environment of aging men. Under such conditions, the non-tumorigenic human prostatic BPH-1 epithelial cells became fully and irreversibly tumorigenic and metastatic (Ricke et al., 2006; Wang et al., 2001; Phillips et al., 2001; Hayward et al., 2001). The effect requires treatment with both testosterone and estradiol, and the tumor-promoting effect of testosterone on progression of the non-tumorigenic BPH-1 cells to tumorigenesis and metastasis is mediated through paracrine mechanisms via AR within the UGM, thus emphasizing the role of stromal in prostatic epithelial pathogenesis (Ricke et al., 2006). The role of AR and stroma in human BPH has yet to be elucidated but may be orchestrated in a manner similar to that of prostatic organogenesis.

Two of the major monographs on benign prostatic hyperplasia were proceedings of NIH symposia published in 1976 and 1986. In the 1976 NIH monograph on BPH John McNeal announced the concept of re-awakening of inductive activity by BPH stroma as a mechanism of the neo-formation of new ductal-acinar tissue in adult human prostatic during the etiology of BPH. By 1986 much of the experimental underpinning of this idea had been established through studies on stromal-epithelial interactions during an era before the advent of molecular biology. In the intervening 25 years molecular biology has come to the fore and the genomes of many species (including man) have been ascertained. Advances in molecular mechanisms directed upon the etiology and prevention of BPH now give us a better appreciation of the systemic, tissue and cell biology and cell-cell interaction involved in this complex disease.

Acknowledgments

This work was supported by NIH grants CA123199, 1RC2 ESO18764 (WAR).

References

- Aboseif S, El-Sakka A, Young P, Cunha G. Mesenchymal reprogramming of adult human epithelial differentiation. *Differentiation*. 1999; 65:113–118. [PubMed: 10550544]

- Barclay WW, Woodruff RD, Hall MC, Cramer SD. A system for studying epithelial-stromal interactions reveals distinct inductive abilities of stromal cells from benign prostatic hyperplasia and prostate cancer. *Endocrinology*. 2005; 146:13–18. [PubMed: 15471963]
- Chung LW, Matsuura J, Rocco AK, Thompson TC, Miller GJ, Runner MN. A new mouse model for prostatic hyperplasia: induction of adult prostatic overgrowth by fetal urogenital sinus implants. *Prog Clin Biol Res*. 1984a; 145:291–306. [PubMed: 6201880]
- Chung LWK, Matsuura J, Runner MN. Tissue interactions and prostatic growth. I. Induction of adult mouse prostatic hyperplasia by fetal urogenital sinus implants. *Biol of Reprod*. 1984b; 31:155–165. [PubMed: 6205700]
- Cunha GR. Epithelio-mesenchymal interactions in primordial gland structures which become responsive to androgenic stimulation. *Anat Rec*. 1972; 172:179–196. [PubMed: 5012433]
- Cunha GR. Mesenchymal-epithelial interactions: past, present, and future. *Differentiation*. 2008; 76:578–586. [PubMed: 18557761]
- Cunha GR, Chung LWK, Shannon JM, Reese BA. Stromal-epithelial interactions in sex differentiation. *Biol Reprod*. 1980a; 22:19–43. [PubMed: 6991009]
- Cunha GR, Cooke PS, Kurita T. Role of stromal-epithelial interactions in hormonal responses. *Arch Histol Cytol*. 2004; 67:417–434. [PubMed: 15781983]
- Cunha GR, Donjacour AA, Cooke PS, Mee S, Bigsby RM, Higgins SJ, Sugimura Y. The endocrinology and developmental biology of the prostate. *Endocrine Rev*. 1987; 8:338–362. [PubMed: 3308446]
- Cunha GR, Fujii H, Neubauer BL, Shannon JM, Sawyer LM, Reese BA. Epithelial-mesenchymal interactions in prostatic development. I. Morphological observations of prostatic induction by urogenital sinus mesenchyme in epithelium of the adult rodent urinary bladder. *J Cell Biol*. 1983a; 96:1662–1670. [PubMed: 6853597]
- Cunha GR, Hayward SW, Wang YZ. Role of stroma in carcinogenesis of the prostate. *Differentiation*. 2002; 60:473–485. [PubMed: 12492490]
- Cunha GR, Lung B. The possible influences of temporal factors in androgenic responsiveness of urogenital tissue recombinants from wild-type and androgen-insensitive (Tfm) mice. *J Exp Zool*. 1978; 205:181–194. [PubMed: 681909]
- Cunha GR, Lung B, Reese B. Glandular epithelial induction by embryonic mesenchyme in adult bladder epithelium of Balb/c mice. *Invest Urol*. 1980b; 17:302–304. [PubMed: 6153176]
- Cunha GR, Sekkingstad M, Meloy BA. Heterospecific induction of prostatic development in tissue recombinants prepared with mouse, rat, rabbit, and human tissues. *Differentiation*. 1983b; 24:174–180. [PubMed: 6884617]
- Franks LM. Benign nodular hyperplasia of the prostate: A review. *Ann R Coll Surg*. 1954; 14:92–106.
- Franks, LM. Benign prostatic hyperplasia: gross and microscopic anatomy. In: Grayhack, JT.; Wilson, JD.; Scherbenske, MJ., editors. *Benign Prostatic Hyperplasia*. US Govt. Printing Office; Washington, DC: 1976. p. 63-90.
- Hayashi N, Cunha GR, Parker M. Permissive and instructive induction of adult rodent prostatic epithelium by heterotypic urogenital sinus mesenchyme. *Epithelial Cell Biol*. 1993; 2:66–78. [PubMed: 8353595]
- Hayward S, Wang Y, Cao M, Hom Y, Zhang B, Grossfeld G, Sudilovsky D, Cunha G. Malignant transformation in a non-tumorigenic human prostatic epithelial cell line. *Cancer Research*. 2001; 61:8135–8142. [PubMed: 11719442]
- Hayward SW, Haughney PC, Rosen MA, Greulich KM, Weier HU, Dahiya R, Cunha GR. Interactions between adult human prostatic epithelium and rat urogenital sinus mesenchyme in a tissue recombination model. *Differentiation*. 1998; 63:131–140. [PubMed: 9697307]
- Kimball, FA.; Buhl, AE.; Carter, DB. *New Approaches to the Study of Benign Prostatic Hyperplasia*. A.R. Liss; New York: 1984.
- Li X, Wang Y, Sharif-Afshar AR, Uwamariya C, Yi A, Ishii K, Hayward SW, Matusik RJ, Bhowmick NA. Urothelial transdifferentiation to prostate epithelia is mediated by paracrine TGF-beta signaling. *Differentiation*. 2009; 77:95–102. [PubMed: 19281768]
- Lowsley OS. The development of the human prostate gland with reference to the development of other structures at the neck of the urinary bladder. *Am J Anat*. 1912; 13:299–349.

- McNeal J. Pathology of benign prostatic hyperplasia. Insight into etiology. Urol Clin North Am. 1990; 17:477–486. [PubMed: 1695776]
- McNeal, JE. Developmental and comparative anatomy of the prostate. In: Grayhack, JT.; Wilson, JD.; Scherbenske, MJ., editors. Benign Prostatic Hyperplasia. US Govt. Printing Office; Washington, DC: 1976. p. 1-7.
- McNeal JE. Origin and evolution of benign prostatic enlargement. Invest Urol. 1978; 15:340–345. [PubMed: 75197]
- McNeal JE. The zonal anatomy of the prostate. Prostate. 1981; 2:35–49. [PubMed: 7279811]
- McNeal JE. The prostate gland: morphology and pathobiology. Monogr Urology. 1983; 4:3–37.
- McNeal JE. Anatomy of the prostate and morphogenesis of BPH. Prog Clin Biol Res. 1984; 145:27–53. [PubMed: 6201879]
- McNeal JE, Bostwick DG. Anatomy of the prostatic urethra. JAMA. 1984; 251:890–891. [PubMed: 6694288]
- McNeal JE, Leav I, Alroy J, Skutelsky E. Differential lectin staining of central and peripheral zones of the prostate and alterations in dysplasia. Am J Clin Pathol. 1988; 89:41–48. [PubMed: 3337051]
- Norman JT, Cunha GR, Sugimura Y. The induction of new ductal growth in adult prostatic epithelium in response to an embryonic prostatic inductor. Prostate. 1986; 8:209–220. [PubMed: 3703742]
- Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Res. 1999; 59:5002–5011. [PubMed: 10519415]
- Phillips J, Hayward S, Wang Y, Vasselli J, Pavlovich C, Padilla-Nash H, Pezullo J, Ghadimi B, Grossfeld G, Rivera A, Linehan W, Cunha G, Ried T. The consequences of chromosomal aneuploidy on gene expression profiles in a cell line model for prostate carcinogenesis. Cancer Research. 2001; 61:8143–8149. [PubMed: 11719443]
- Ricke WA, Ishii K, Ricke EA, Simko J, Wang Y, Hayward SW, Cunha GR. Steroid hormones stimulate human prostate cancer progression and metastasis. Int J Cancer. 2006; 118:2123–2131. [PubMed: 16331600]
- Sugimura Y, Cunha GR, Bigsby RM. Androgenic induction of deoxyribonucleic acid synthesis in prostatic glands induced in the urothelium of testicular feminized (Tfm/y) mice. Prostate. 1986; 9:217–225. [PubMed: 2946028]
- Wang Y, Sudilovsky D, Zhang B, Haughney PC, Rosen MA, Wu DS, Cunha TJ, Dahiya R, Cunha GR, Hayward SW. A human prostatic epithelial model of hormonal carcinogenesis. Cancer Res. 2001; 61:6064–6072. [PubMed: 11507055]

Table 1
Mesenchymal Effects On Epithelial Development In Male And Female Urogenital Tracts

Mesenchymal Effect	Reference
Induces epithelial morphogenesis	(Cunha et al., 1983a; Cunha, 1976)
Specifies epithelial cytodifferentiation	(Cunha et al., 1983a; Cunha, 1976)
Specifies epithelial hormone receptor profile	(Cunha et al., 1980c; Kurita et al., 2001a)
Species epithelial secretory protein expression	(Donjacour and Cunha, 1993; Donjacour and Cunha, 1995; Hayashi et al., 1993; Higgins et al., 1989)
Specifies epithelial cytokeratin profile	(Kurita et al., 2001a)
Specifies epithelial heparan sulfate expression	(Boutin et al., 1989)
Induces epithelial expression of Nkx3.1	(Bhatia-Gaur et al., 1999)
Determines epithelial expression of Hox genes	(Pavlova et al., 1994)
Specifies epithelial regulation of steroid hormone receptors	(Kurita et al., 2001b; Kurita et al., 2000)
Determines hormonal regulation of epithelial proliferation	(Sugimura et al., 1986b)
Induces prostatic ductal elongation	(Norman et al., 1986)
Regulates epithelial apoptosis	(Kurita et al., 2001c)
Promotes carcinogenic progression	(Olumi et al., 1999; Ricke et al., 2006)
Specifies expression of p63	(Kurita and Cunha, 2001)