The Reviewing of Prostate Tumors Growing with Emphasized on Molecular Genetics

Mohammadhossein Bahrami

MSc in Applied Biomolecular Technology, The University of Nottingham, Faculty of Medicine & Health Sciences, School of Clinical Sciences, Division of Preclinical Oncology, Cancer Genetics & Stem Cells Group, Queen's Medical Centre
bahmanimohammadhossein14@yahoo.com

Abstract: Early detection through serum examining for prostate specific antigen (PSA) and improved procedures for surgical intervention and radiation therapy have significantly decreased the number of fatalities; however, there is still no main cure for men with advanced disease. Prostate tumors growing afflict one man in nine over the age of 66 and represent the often frequently diagnosed cancer in American men. Therefore, much evidence has been dedicated to identifying prognostic markers that distinguish indolent versus aggressive forms of prostate tumors growing. Indeed, less evidence has been devoted to understanding the molecular mechanisms that underlie real prostate growth and development or cancer initiation and progression significantly. We think on key regulatory molecules that have been implicated by result of patterns of allelic loss in man prostate tumors growing and/or by reverse genetic approaches in the mouse. In this review, we address recent expansion due to the central objectives of understanding parameters of real versus unreal prostatic development and of elucidating a molecular pathway for prostate tumors growing progression.
[Mohammadhossein Bahrami. **The Reviewing of Prostate Tumors Growing with Emphasized on Molecular Genetics.** *Cancer Biology* 2014;4(3):95-99]. (ISSN: 2150-1041). http://www.cancerbio.net. 10

Keywords: key regulatory molecules, Tumors growing, radiation therapy

1. Introduction

Most prostate tumors are adenocarcinomas, sharing numerous common features with other prevalent epithelial cancers, such as breast and colon cancer. Here, we introduce certain salient aspects of prostate tumors growing that are relevant for investigation of the disease process. The prostate gland is an organ that is located at the base or outlet (neck) of the urinary bladder. The gland surrounds the first part of the urethra. The urethra is the passage through which urine drains from the bladder to exit from the penis. One function of the prostate gland is to help control urination by pressing directly against the part of the urethra that it surrounds. The main function of the prostate gland is to produce some of the substances that are found in normal semen, such as minerals and sugar. Semen is the fluid that transports the sperm to assist with reproduction. A man can manage quite well, however, without his prostate gland.

In a young man, the normal prostate gland is the size of a walnut (<30g). During normal aging, however, the gland usually grows larger. This hormone-related enlargement with aging is called benign prostatic hyperplasia (BPH), but this condition is not associated with prostate cancer. Both BPH and prostate cancer, however, can cause similar problems in older men. For example, an enlarged prostate gland can squeeze or impinge on the outlet of the bladder or the urethra, leading to difficulty with urination. The resulting symptoms commonly include slowing of the urinary stream and urinating more frequently, particularly at night. Patients should seek medical advice from their urologist or primary-care physician if these symptoms are present.

A distinguishing feature of prostate tumors growing is its intimate association with aging; indeed, aging is the single often significant risk factor for prostate tumors growing. Although preneoplastic lesions known as prostatic intraepithelial neoplasia (PIN) can be found in men in their twenties and are fairly common in men by their fifties (Sakr et al. 1993), clinically detectable prostate tumors growing is not generally manifest until the age of 61 or 73. Furthermore, the occurrence of precancerous lesions is significantly more prevalent (~1 in 3 men) than the incidence of carcinoma (~1 in 9 men). Therefore, whereas the morphological changes associated with initiation are relatively common and occur early in life, progression to invasive carcinoma is a significantly less common event that occurs in a more limited population as a consequence of aging.

The incidence of prostate tumors growing in the United States is significantly higher than in often other countries, particularly Asian countries, even though the incidence of histological pre-neoplastic lesions has been reported to be similar worldwide (Dhom 1983). Dietary and environmental factors have therefore been presumed to play a key role in prostate carcinogenesis (Carter et al. 1990a), similar to their role in other common epithelial cancers. Recent evidence, however, has thrown into question

whether there actually are differences in the relative incidence of preneoplastic lesions in Asian versus American men (Miller 2000).

Hereditary factors account for a relatively small percentage (~10%) of prostate tumors growing and are generally associated with early onset disease (Cannon et al. 1982; Carter et al. 1992, 1993). To date, two familial susceptibility loci have been mapped to the X chromosome and to a region of chromosome 1q (Smith et al. 1996; Xu et al. 1998), although the respective candidate genes have not yet been identified. In addition, several studies have identified a statistical association between breast and prostate tumors growing (Thiessen 1974; Anderson and Badzioch 1992; Tulinius et al. 1992), but the molecular basis for such a link is unresolved.

Steroid hormone receptor signaling plays a pivotal role in all stages of prostate carcinogenesis. In particular, there is a characteristic age-related decrease in the ratio of androgens to estrogens in men, which may represent a contributing factor in prostate tumors growing initiation (Mawhinney and Neubauer 1979; Dai et al. 1981; Prehn 1999). In addition, the transition to androgen independence that is a hallmark of advanced prostate tumors growing has been a think of numerous investigations. Deciding on treatment can be difficult, partly because the options for treatment today are far better than they were 10 years ago but also because not enough reliable data are available on which to base the decisions. Accordingly, scientifically controlled, long-term studies are still needed to compare the benefits and risks of the various treatments.

To decide on treatment for an individual patient, doctors categorize prostate cancers as organ-confined (localized to the gland), locally advanced (a large prostate tumor or one that has spread only locally), or metastatic (spread distantly or widely). The treatment options for organ-confined prostate cancer or locally advanced prostate cancer usually include surgery, radiation therapy, hormonal therapy, cryotherapy, combinations of some of these treatments, and watchful waiting. A cure for metastatic prostate cancer is, unfortunately, unattainable at the present time. The treatments for metastatic prostate cancer, which include hormonal therapy and chemotherapy, therefore, are considered palliative. By definition, the aims of palliative treatments are, at best, to slow the growth of the tumor and relieve the symptoms of the patient.

The staging of a cancer refers to determining the extent of the disease (where in the body have the prostate cancer cells spread). Once a prostate cancer is diagnosed on a biopsy, additional tests are done to assess whether the cancer has spread beyond the gland.

Radionuclide bone scans can determine if there is a spread of the tumor to the bones. The radioactive substance highlights areas where the cancer has affected the bones. This test is usually reserved for men with prostate cancer who have deep bone pain or a fracture or who have biopsy findings and high PSA values (>10-20 ng/ml) suggestive of advanced or aggressive disease.

Chest X-ray can be used to detect whether or not cancer has spread to the lungs. Ultrasound tests can be used to look for the effects of a urinary blockage on the kidneys. This study can also be used to assess the bladder for any sign of urinary obstruction due to prostate enlargement by looking at the thickness of the bladder wall as well as the amount of urine remaining within the bladder after an attempt at passing urine.

Additionally, CT scans (coaxial tomography) and MRIs (magnetic resonance imaging) can determine if the cancer has spread to adjacent tissues or organs such as the bladder or rectum or to other parts of the body such as the liver or lungs. Newer scanning using a method called PET scan can sometimes help to detect hidden locations of cancer that has spread to various areas of the body.

Cystoscopy is usually performed in selected situations. A thin, flexible, lighted tube with a tiny camera on the end is inserted through the urethra to the bladder. The camera transmits images to a video monitor. This may show whether the cancer has spread to the urethra or bladder and may be utilized to take a biopsy from these organs.

2. Methodology

With regard to multifocality, individual neoplastic lesions within a given section of prostate tumors growing tissue have been described as genetically distinct (nonclonal), even those in close proximity (e.g., Bostwick et al. 1998; Macintosh et al. 1998). This observation suggests that multiple neoplastic foci may emerge and evolve independently, which has significant implications for the molecular mechanisms of disease progression. From a practical standpoint, the heterogeneity and multimodality of prostatic lesions, combined with the relatively small size of the prostate, make it difficult to obtain reasonably homogeneous material in sufficient quantities for molecular result. The heterogeneous and multifocal nature of prostate tumors growing lesions poses significant difficulties for evidences. In recent years, these difficulties have been partially circumvented by microdissection and laser-capture microscopy approaches that facilitate result of individual neoplastic foci (Emmert- Buck et al. 1995, 1996; Macintosh et al. 1998), and by cell-sorting approaches that permit the isolation of

relatively pure populations of carcinoma cells (Liu et al. 1997, 1999). With regard to heterogeneity, histological inspection of prostate tumors growing tissue typically reveals a juxtaposition of benign glands, preneoplastic (PIN) foci, and neoplastic foci of varying severity To account for this heterogeneity, Gleason proposed a grading system that is now the predominant system used by pathologists, since it is an excellent prognostic indicator. In this system, a score is given based on the sum of the two often prevalent grades of neoplastic foci (e.g., 3 + 3; 3 + 4); a higher Gleason grade indicates a more advanced carcinoma (Gleason 1992). These factors represent significant limitations in identifying regulatory genes associated with prostate carcinogenesis, as well as in defining a molecular pathway for the initiation and progression of prostate tumors growing.

3. Results

This restriction implies that numerous conclusions in the literature are based on studies of a small repertoire of cell lines, even though the relevance of these cell lines for prostate carcinogenesis in vivo is uncertain. Prostate tumors growing evidence has also been hampered by difficulties in generating permanent cell lines for in vitro studies. This limitation is undoubtedly related to the inherently slow growth of often prostate tumors and the low proliferation rate of the real prostatic epithelium (e.g., Isaacs and Coffey 1989; Berges et al. 1995). Despite numerous attempts to obtain cell lines (discussed in Bright et al. 1997; Navone et al. 1999), only a handful of man prostate lines have been generated, of which the often commonly used (LNCaP, PC3, DU145, and TSUPr1) were isolated from metastatic lesions rather than primary tumors.

Indeed, it is intriguing to note that malignant prostatic tumors are among the often common neoplasia in men, whereas other ductal organs of the male urogenital system, such as the seminal vesicles and bulbourethral (Cowper's) glands, are virtually immune to neoplasia. The prostate gland surrounds the urethra at the base of the bladder and functions by contributing secretory proteins to the seminal fluid. Found exclusively in mammals, the prostate is not required for viability or even basal levels of fertility; therefore, its primary significance stems from its relevance for man disease.

The significance of this architecture is based upon the relationship of these zones to prostatic disease. Benign prostatic hyperplasia (BPH), a nonmalignant overgrowth that is fairly common among aging men, occurs mainly in the transition zone, and prostate carcinoma arises primarily in the peripheral zone. In adult mans, the prostate is a small acorn-shaped tissue, with ductal–acinar histology, that lacks discernible lobular organization. In his classic work, McNeal defined three distinct morphological regions within the man prostate: the peripheral zone, the transition zone, and the central zone (McNeal 1969, 1988).

There is no clear analogy between the lobular structure of the rodent prostate and the zonal architecture of the man prostate; indeed, although several studies assert that the dorsolateral lobe is often similar to the man peripheral zone, the evidence supporting this assertion is primarily descriptive. Indeed with mans, the rodent prostate gland consists of four distinct lobes: anterior (also known as the coagulating gland), dorsal and lateral (collectively referred to as the dorsolateral lobe), and ventral. These lobes are arranged circumferentially around the bladder and display characteristic patterns of ductal branching and secretory protein production (Sugimura et al. 1986; Hayashi et al. 1991).

So, the dissimilar anatomy and morphology of the rodent prostate, together with the absence of spontaneous prostate tumors growing in laboratory rodents, has led to concerns about the relevance of rodent models for man prostate disease. Recent studies, however, strongly support the validity of rodent models for prostate tumors growing, as discussed below.

During midgestation, the primitive urogenital sinus is separated from the terminal region of the hindgut through the division of the cloaca by the urorectal septum. Formation of the prostate occurs during embryogenesis through epithelial budding from the urogenital sinus, a hindgut derivative that is of endodermal origin. The often rostral region (vesiculo-urethral part) of the primitive urogenital sinus forms the urinary bladder, whereas the often caudal region (phallic part) forms the penile urethra.

So, although ductal morphogenesis is androgen dependent, the early postnatal period is marked by low levels of circulating androgens (Barkley and Goldman 1977; Jean-Faucher et al. 1978). Although the overall process is similar in mans, the time course of prostate maturation differs significantly, since ductal morphogenesis largely occurs in response to high levels of androgen stimulation during puberty. The prostate gland originates from the intermediate region, known as the pelvic part (generally referred to as the urogenital sinus). In the mouse, the prostatic buds first emerge at the rostral end of the urogenital sinus at approximately 17.5 days of gestation, due to the end of pregnancy. Subsequently, the prostatic epithelial buds undergo extensive ductal outgrowth and branching into the surrounding mesenchyme during the first three weeks of postnatal development (Sugimura et al. 1986; Timms et al. 1994). The result

of the Nkx3.1 homeobox gene has recently provided insights into the earliest stages of prostate formation in the mouse (Sciavolino et al. 1997; Bhatia- Gaur et al. 1999). Within the urogenital system, Nkx3.1 expression is first detected in the lateral aspects of the urogenital sinus epithelium prior to prostate formation, and subsequently marks all stages of prostate development. So, Nkx3.1 expression precedes formation of the prostatic buds by two days, and appears to correspond to the regions where prostatic buds will emerge, suggesting that regions of the urogenital sinus epithelium may have a differential capacity to form prostate (Bhatia-Gaur et al. 1999). This idea is distinct from the previous view that the mesenchyme is solely responsible for inducing a passive epithelium.

The identification of additional regulatory genes and pathways expressed during prostate development represents an important avenue of future evidence. Current candidates for such regulatory genes include components of the Sonic hedgehog and BMP signaling pathways. Given that carcinogenesis often involves deregulation of developmental regulatory genes, elucidation of the molecular pathways of prostate development should provide fresh insights into prostate tumors growing.

As with many other tissues, prostate formation is initiated as a consequence of interactions between epithelial and mesenchymal tissues. The role of epithelial–mesenchymal interactions in prostate formation has been defined through elegant tissue recombination studies performed by Cunha and colleagues (Cunha et al. 1987; Cunha 1996; Hayward et al. 1997). These tissue recombinations employ dissection and enzymatic isolation of epithelium and mesenchyme from embryonic urogenital sinus and/or from other tissues, which are then recombined in vitro and transplanted under the kidney capsule of adult male nude mouse hosts. The formation of prostate tissue in these recombinants can subsequently be assessed by their histological appearance and by production of prostatic secretory proteins. These tissue recombination studies have led to the following principal conclusions:

- Man epithelium and rodent mesenchyme can be recombined to form prostate, supporting the validity of rodent prostate as a model for the man gland.
- Specificity for the mesenchymal component is relatively stringent, because prostate will only form using mesenchyme from embryonic urogenital sinus (and under certain conditions, from seminal vesicle).
- Prostatic differentiation requires both epithelial and mesenchymal components; in the absence of either, mature cell types fail to differentiate.
- During prostate development, androgens initially act on the mesenchyme, because prostate does not form when urogenital sinus mesenchyme that is defective in androgen receptor (from a Testicular-feminization [Tfm] mutant) is combined with wild-type urogenital sinus epithelium. Subsequently, androgens act on the epithelium, for urogenital sinus epithelium defective in androgen receptor combined with wild-type mesenchyme forms prostatic ducts that lack production of prostatic secretor proteins. These results indicate that androgen signaling is required in the mesenchyme to produce signals for prostate induction and growth, and later in the epithelium for the secretor function of differentiated cell types.
- Specificity for the epithelial component is relatively broad, because a wide range of epithelia of endodermal origin, including those from differentiated male or female adult tissues, can form prostate when combined with urogenital sinus mesenchyme.

4. Conclusion

The signals that mediate such mesenchymal–epithelial interactions in carcinogenesis have not been identified, but may include members of the fibroblast growth factor (FGF) and transforming growth factor- (TGF) families (Cunha 1996; Djakiew 2000). Interactions between the epithelial and stromal components are essential for all stages of real prostate growth and development; it is likely that aberrant interactions play a significant role in carcinoma. Although neoplastic foci arise in the epithelial compartment, the role of the stromal compartment in carcinogenesis has been relatively neglected. So, however, tissue recombination experiments have suggested that aberrant growth factor signaling from stromal components plays an integral role in cancer progression (Hayward et al. 1997; Olumi et al. 1999).

Corresponding Author:
Mohammadhossein Bahrami
MSc in Applied Biomolecular Technology, The University of Nottingham, Faculty of Medicine & Health Sciences, School of Clinical Sciences, Division of Preclinical Oncology, Cancer Genetics & Stem Cells Group, Queen's Medical Centre
bahmanimohammadhossein14@yahoo.com

References

1. Aumuller, G., Leonhardt, M., Janssen, M., Konrad, L., Bjartell, A., and Abrahamsson, P.A. 1999. Neurogenic origin of man prostate endocrine cells. Urology 53: 1041–1048.
2. Bandyk, M.G., Zhao, L., Troncoso, P., Pisters, L.L., Palmer, J.L., von Eschenbach, A.C., Leland, L.W.K., Leland, L.W.K., and Liang, J.C. 1994. Trisomy 7: A potential cytogenetic marker of man prostate tumors growing progression. Genes Chromosomes Cancer 9: 19–27.
3. Bui, M. and Reiter, R.E. 1998. Stem cell genes in androgenindependent prostate tumors growing. Cancer Metastasis Rev. 17: 391–399.
4. Cannon, L., Bishop, D.T., Skolnick, M., Hunt, S., Lyon, J.L., and Smart, C.R. 1982. Genetic epidemiology of prostate tumors growing in the Utah mormon genealogy. Cancer Surveys 1: 47–69.
5. Dunn, N.R., Winnier, G.E., Hargett, L.K., Schrick, J.J., Fogo, A.B., and Hogan, B.L. 1997. Haploinsufficient phenotypes in Bmp4 heterozygous null mice and modification by mutations in Gli3 and Alx4. Dev. Biol. 188: 235–247.
6. Eagle, L.R., Yin, X., Brothman, A.R., Williams, B.J., Atkin, N.B., and Prochownik, E.V. 1995. Mutation of the MXI1 gene in prostate tumors growing. Nat. Genet. 9: 249–255.
7. Guo, Y., Sklar, G.N., Borkowski, A., and Kyprianou, N. 1997. Loss of the cyclin-dependent kinase inhibitor p27(Kip1) protein in man prostate tumors growing correlates with tumor grade. Clin. Cancer Res. 3: 2269–2274.
8. Haggman, M.J., Macoska, J.A., Wojno, K.J., and Oesterling, J.E. 1997a. The relationship between prostatic intraepithelial neoplasia and prostate tumors growing: Critical issues. J. Urol. 158: 12–22.
9. Kyprianou, N. and Isaacs, J.T. 1988. Activation of programmed cell death in the rat ventral prostate after castration. Endocrinology 122: 552–562.
10. Osman, I., Drobnjak, M., Fazzari, M., Ferrara, J., Scher, H.I., and Cordon-Cardo, C. 1999. Inactivation of the p53 pathway in prostate tumors growing: Impact on tumor progression. Clin. Cancer Res. 5: 2082–2088.
11. Sweat, S.D., Pacelli, A., Bergstralh, E.J., Slezak, J.M., and Bostwick, D.G. 1999. Androgen receptor expression in prostatic intraepithelial neoplasia and cancer. J. Urol. 161: 1229– 1232.
12. Takahashi, S., Shan, A.L., Ritland, S.R., Delacey, K.A., Bostwick, D.G., Lieber, M.M., Thibodeau, S.N., and Jenkins, R.B. 1995. Frequent loss of heterozygosity at 7q31.1 in primary prostate tumors growing is associated with tumor aggressiveness and progression. Cancer Res. 55: 4114–4119.

5/30/2014