EXPRESSION AND HORMONAL REGULATION OF A PROSTATIC SECRETORY PROTEIN OF 94 AMINO ACIDS (PSP94) IN RAT AND HUMAN PROSTATE GLANDS

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Introduction

The prostatic secretory protein of 94 amino acids (PSP94) was first purified from the human seminal plasma. It was then found to be one of the 3 most abundant secretory proteins of the human prostate gland, in addition to prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA)[1]. Human PSP94 is a non-glycosylated and cysteine-rich protein with a molecular size of 10.7 kDa[2,3]. It is secreted in a mature form of 94 amino acids after removal of a 20-amino-acid signal peptide. This protein has been described previously by different authors under different names such as inhibin-like peptide or β-inhibin, β-microseminoprotein and PSP94[4]. The exact biological function of PSP94 in reproduction still remains obscure ever since its first isolation in 1984. It was first suggested to possess some inhibin-like activity but was proved to be untrue subsequently. It was also reported to be a sperm-binding protein[5]. Recently, it is also suggested to be an immunoglobulin-binding factor and may function as an immunosuppressive factor[6] in the female reproductive tract. Because of its abundance in the seminal fluid and also a prostate specific protein, the potential use of PSP94 as a diagnostic and prognostic marker for prostate cancer has been investigated. However, its usefulness, as compared to PSA which is an established marker for prostate cacner, is still remained to be established. It has been shown that its serum level is increased in benign prostatic hyperplasia and prostate cancer patients[7]. Its immunoreactivity pattern is said to correlate with some clinical parameters such as Gleason score[8]. On the other hand, there are reports showing that its expression is reduced in prostate cancers[4]. However, as development and use of new antibodies which can distinguish the free and bound forms of PSP94, it is shown that the serum levels of the bound forms may be useful as a prognostic marker for patients receiving radiotherapy for nonmetastatic prostate cancer[9]. In addition to human, cDNA and genes of PSP94 have been cloned in other mammals. These include monkey, pig and baboon. Recently, PSP94 has also been cloned in rat[10] and mouse prostates[11].

Methods and Materials

In this paper, we review mostly our recently published results on the gene expression of PSP94 in human and rat prostate glands as shown by RT-PCR, in-situ hybridization, Northern and western blottings, and immunohistochemistry[4,12]. In order to study the hormonal regulation of PSP94, we also examined and compared the effects of testosterone, glucocorticoid, progestin, and zinc on the gene expression of 3 major secretory proteins, the PSP94, probasin and seminal vesicle secretion II (SVSII), in the long-term castrated lateral prostate in Noble rat[13]. Finally, we also examined the gene expression of PSP94 in three rat models of prostate cancer: the hormone-induced Noble rat model, an androgen-independent Noble rat prostatic tumor (AIT) and Dunning rat prostatic tumors.

Results and Discussion

In the normal human pubertal and adult prostates, the PSP94 mRNA and its protein were localized to the secretory epithelium. No hybridization signals and immunoreactivity of PSP94 were detected in fetal prostates at 6-7 month of gestation, whereas some glandular cells were stained positive for both PSA and PAP at these stages. The delayed expression of PSP94, as compared to PSA and PAP, in the fetal prostates appears to correlate with the development of the prostate gland. In the adult prostate, the PSP94 expression was intense in the acini in the peripheral zone, less intense in the transition zone, and variable in the central zone. Such a differential zonal expression pattern is more distinct in the pubertal prostates. On the other hand, such a zonal pattern was not seen in the immunohistochemistry of PSA and PAP in the pubertal and adult prostates. We also observed that the hybridization signals and immunoreactivity of PSP94 became reduced or lost in the premalignant prostatic intraepithelial neoplastic (PIN) lesions and different grades of prostatic carcinomas. This down-regulation of PSP94 was also confirmed in three rat models of prostate cancer. Its expression was reduced in the different forms of PINs induced in the Noble rat lateral prostate and also in both Dunning R3327H tumor and an androgen-independent Noble rat prostatic tumor (AIT).

In the rat prostate, PSP94 was found to be highly expressed and synthesized in the lateral lobe, moderate in the dorsal lobe, weak in the coagulating gland, but negative in the ventral lobe and seminal vesicle, as shown by RT-PCR, in-situ hybridization and Western blotting. The gene expression of PSP94 was not detected in all tested non-prostatic tissues. Similar prostate specific expression of PSP94 was also observed in the mouse prostate gland.

We also examined and compared the *in vivo* hormonal regulation of PSP94, probasin and SVSII in log-term castrated lateral prostates by in-situ hybridization and semi-quantitative RT-PCR. We found that the hybridization signals of probasin and PSP94 disappeared only in the 60-day postcastrated lateral prostates, whereas the signals of SVSII dropped sharply in the 14-day postcastrated prostates. The results indicate that the 3 secretory proteins are all under androgen regulation in the rat lateral

prostate. We also observed that the mRNA transcripts of both PSP94 and probasin were increased after treatments with dihydrotestosterone, dexamethasone, and medroxyprogesterone acetate, suggesting that these two proteins could also be regulated by glucocorticoid and progestin, in addition to androgen. In contrast with probasin, PSP94 and SVSII were not induced by $ZnSO_4$ treatment. On the other hand, SVSII expression was only increased significantly by dihydrotestosterone and moderately by medroxyprogesterone, but not by dexamethasone, suggesting that SVSII is under a strict control by androgen.

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