PROSTATE-SPECIFIC ANTIGEN AND HISTORY OF ITS DISCOVERY

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ŠPECIFICKÝ ANTIGÉN PROSTATY A HISTÓRIA JEHO OBJAVU

In contradistinction to prostatic acid phosphatase (PAcP), prostate-specific antigen (PSA) is currently the most reliable and most frequently used marker for identification of normal and pathologically altered prostatic tissues both in the male and female. In clinical practice, it has become an appreciated serum marker in the assessment and management of prostate carcinoma in the male, although it is far from being a perfect "tumor" marker. Our knowledge on female PSA is expected to be broadened by the introduction of novel highly sensitive serological methods (IMMULITE^R — immunochemiluminiscent third-generation PSA assay and others), which in some females have already demonstrated surprisingly high values. Biochemically, PSA in seminal fluid in its free form has a molecular weight of about 30 000 daltons, while in serum, where it occurs in the complex form with alpha$_1$-chymotrypsin, its molecular weight is approximately 100 000 daltons being comparable to that of PAcP. On immunohistochemical examination, PSA is expressed in the highly specialized apically-superficial layer of male and female secretory (luminal) cells of the prostatic glands, as well as at other sites of the urogenital tract, frequently coinciding with glucosamine glucans, glycoproteins and numerous enzyme proteins. With regard to the increasing interest in PSA evidenced in urology, gynecological urology, in the orthology and pathology of male and female prostates, the interest in the history of discovery of this exceptional prostatic marker appears to be justified. PSA was discovered by Richard Ablin and co-workers in the USA, who published their pioneer work in the Journal of Reproduction and Fertility and in the Journal of Immunology as early as in 1970. Thus their results had been available nine years before the publication of Wang et al. appeared in Investigative Urology (1979), on the basis of which the latter are frequently incorrectly considered and cited as the authors of PSA discovery. *(Ref. 46.)*

Key words: prostate-specific antigen, male prostate, female prostate (Skene's gland), orthology, pathology, history.

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Na rozdiel od prostatickej kyslej fosfatázy (PAcP) je špecifický antigén prostaty (PSA) zatiaľ najspoľahlivejším a v súčasnosti najčastejšie používaným markerom na identifikáciu normálneho a patologicky zmeneného prostatického tkaniva u muža a ženy. V klinike sa stal vyhľadávaným sérovým markerom hodnotenia a managementu karcinómu prostaty u muža, aj keď zďaleka asi nejde o dokonalý "nádorový" marker. Rozšírenie našich znalostí o ženskom PSA sa očakáva od nových vysoko citlivých metód sérologického dôkazu (IMMULITE^R imunochemiluminiscent tretej generácie PSA assay a ďalšie), ktoré už demonštrujú u niektorých žien prekvapujúco vysoké hodnoty. Biochemicky má PSA vo svojej voľnej forme v seminálnej tekutine molekulovú hmotnosť približne 30 000 daltonov, v sére, kde existuje v komplexnej forme s alfa$_1$-chymotrypsínom je molekulová hmotnosť približne 100 000 daltonov, takmer ako u PAcP. Pri imunohistochemickom vyšetrení je PSA exprimovaný vo vysokošpecializovanej apikálne povrchovej vrstve mužských a ženských sekrečných (luminálnych) buniek prostatických žliaz a na iných miestach urogenitálneho traktu, často v koincidencii s ďalšími glykozaminoglykánmi, glykoproteínmi a početnými enzýmovými proteínmi. Vzhľadom na stále vzrastajúci záujem o PSA v urológii, gynekologickej urológii v ortológii a patológii mužskej a ženskej prostaty je odôvodnený aj záujem o históriu objavu tohto výnimočného prostatického markeru. Objaviteľmi PSA sú Richard Ablin so spolupracovníkmi z USA, ktorí svoje objaviteľské práce publikovali už roku 1970 v Journal of Reproduction and Fertility a v Journal of Immunology. Tak boli ich výsledky k dispozícii už o 9 rokov skôr ako publikácia Wanga a spolupracovníkov v Investigative Urology (1979), na základe ktorej ich mnohí považujú nesprávne za autorov objavu PSA a takto nesprávne sú v mnohých prácach aj citovaní. *(Lit. 46.)*

Kľúčové slová: špecifický antigén prostaty, mužská prostata, ženská prostata (Skeneove žľazy), ortológia, patológia, história.

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Immunohistochemical evidence of prostate-specific antigen (PSA), at present the most reliable prostatic marker, plays a crucial role in the identification of normal and pathologically altered prostatic tissue in the male (Nadji, 1981; Svanholm, 1986; Jöbsis, 1990), yet it is of equal importance also in the identification of normal (Pollen and Dreilinger, 1984; Tepper et al., 1984; Zaviačič

et al., 1994) and of pathologically changed prostatic tissue in the female (Svanholm et al., 1987; Wernert, 1991; Zaviačič et al., 1993; Sloboda et al., 1997).

The introductory sentence maintains its validity despite some indications of caution that appeared in the recent overview on PSA as published by Ablin last year (1996). I quote: "Some of the zealousness for PSA may be tempered by the recent demonstration of PSA in female breast cancer, primary ovarian carcinoma and milk of lactating women. In particular, this apparently more than coincidental non-prostatic expression of PSA has implications on future immunoassays for PSA, notably its heretofore thought of cell-type specificity, as well as its physiological function (s). In consideration of the molecular basis of the apparent anomalous expression of PSA, a possible caveat is the existence in women of the male counterpart of the prostate (also known as the paraurethral or Skene's glands) shown to have PSA. Given observations of the association of PSA in breast cancer with steroid hormone-receptor positive tumors, one may envision the existence of a complex regulatory gene network controlling the expression of PSA. As such, a given tissue may, depending on the state of cellular differentiation, express previously repressed genes after neoplastic transformation. Also, and not mutually exclusive, somatic mutations may lead to specific changes in PSA genes in cancer cell clones (Ablin, 1996).

Up to the early 80s, positivity of another prostatic marker, i.e. prostate-specific acid phosphatase (PSAcP), used also to be highly evaluated. Its exclusive specificity for prostatic tissue has however been decisively disproved so that nowadays it is designated P(S)AcP, or the letter S (specific) is completely omitted and the acronyms PAcP or PAP are used. The latter is however no good choice as in immunohistochemistry it overlaps with the designation for peroxidase-anti-peroxidase technique (PAP). The given acid hydrolase cross-reacts not only with male and female prostatic tissue but also with several other tissues, such as pancreatic islet cells, gastric parietal cells, hepatocytes, renal tubular epithelium, epithelial cells of seminal vesicules, breast cancer cells, carcinoids of the rectum, and adenocarcinomas of the urinary bladder (Jöbsis et al., 1981; Epstein et al., 1986; Sobin et al., 1986; Svanholm, 1986). Thus the results obtained on immunohistochemical examination of PSA and PAcP can be by no means considered to be of equal value and with regard to prostatic tissue of both genders great preference is to be given to PSA. In the identification of cases with carcinoma of the male prostate spreading extracapsularly, PAcP examination in serum has however retained a certain clinical value (Cooner, 1993).

In clinical practice, PSA has proved to be a great aid in the assessment and management of patients with carcinoma of the prostate and it has gradually become a favored serum marker of this most frequently occurring carcinoma in elderly men. Its serological parameters are indicative of carcinoma of the prostate when considerably elevated levels are established and of the absence of carcinoma when no elevation is recorded. Moreover, critical assessment of the obtained values can suggest grading and staging of the tumor, its size as well as prognosis. Its further advantages are the good reproducibility of the test, patient tolerance, and the relatively low cost of the examination, as stated by Cooner (1993).

To date clinical experience with PSA in female patients with carcinoma of the prostate has been scarce. The low occurrence rate of female compared to male prostate carcinoma may account for this fact. Sloboda et al. (1997) listed in their table fifteen cases where immunohistochemical examination of PSA crucially contributed to the diagnosis of female prostate cancer. It can not be excluded that novel more sensitive serological methods introduced into clinical practice will enhance our knowledge on further parameters characterizing female PSA. Randell et al. (1996) and Ferguson et al. (1996) reported their experience with IMMULITE^{R}, immunochemiluminiscent third-generation assay (Diagnostic Products Corp., Los Angeles, CA, USA), assessing it as very promising.

It has to be emphasized that PSA is present in normal and pathologically altered prostatic tissue in both genders, as well as in metastases and in benign myoadenomatous hyperplasia of the male prostate. We can thus speak of organ specificity bound to the tissue of the male and female prostate rather than of PSA specificity for a certain disease of the prostate. Chronobiologically only inconsiderable circadian (diurnal) variations have been observed, yet on the other hand, PSA values keep increasing with the age of men. This is presumably associated with the fact that there is an increasing occurrence rate of pathological changes of prostatic tissue, concerning particularly benign prostatic hyperplasia and carcinoma of the prostate. From the practical andrological point of view, responsible assessment of serological parameters of PSA has to consider elevations of PSA values after massage of the prostate, after cystoscopy, biopsy of the prostate, transurethral resection, and even after physical activity (Myrtle et al., 1986; Stamey et al., 1987; Braweret al., 1988; Deijter et al., 1988; Maatman, 1989; Chybowski et al., 1992; Yuan et al., 1992; Crawford et al., 1993).

It PSA value were found to be increased after massage of the erotogenic zone on the anterior wall of the vagina, known as G-spot (Zaviačič et al., 1984, 1988; Zaviačič and Whipple, 1993), this may provide the missing evidence on the still discussed relationship between the G-spot and the female prostate (Zaviačič, 1987; Whipple and Komisaruk, 1991).

PSA is immunologically and biochemically different from PAcP. In its free form present particularly in seminal fluid, its molecular weight is approximately 30 000 daltons, while in serum, where it occurs in a complex form with alpha$_1$-chymotrypsin, its molecular weight is much greater, amounting to about 100 000 daltons, which is almost as much as the molecular weight of P(S)AcP (Lilja et al., 1991; Stenman et al., 1991; Christensson et al., 1993).

Immunohistochemical examination of PSA by PAP technique and by the method of biotin-streptavidin-alkaline phosphatase yielded concordant expression of the examined marker in the highly specialized apically-superficial layer of male and female secretory (luminal) cells of the prostatic glands and in membranes of secretory and basal cells (Zaviačič et al., 1994, 1997), which is in agreement with PSA expression reported by other authors. In addition to secretory cells, PSA is expressed in membranes and on the surface of the epithelium of the luminal border of the ducts of the female and male prostate, as well as of the whole female urethra and the prostatic part of the male urethra. This unique layer of the described sites of the urogenital tract is distinctly formed and richly equipped with glucosamine glucans, glycoproteins and enzymatic proteins. Besides numerous enzymes (Zaviačič, 1984 a, b, 1985) and the presence of human protein 1 (urinary protein 1),

as demonstrated in our comparative study of the male and female prostate (Zaviačič et al., 1997), it has marked, and for the male and female prostate distinct immunological properties given by the presence of antigen specific for prostate.

Even without discussing pertinent details, this short overview of selected clinical, biochemical and immunohistochemical parameters of PSA clearly points out the exceptional status of PSA among markers of prostatic tissue and its value for urology, gynecological urology, and prostatic pathology. Interest in this marker keeps increasing. Concerning women, the interest has been promoted by new knowledge on the value of PSA for the orthology and pathology of the female prostate. The value of PSA has generally been accepted in medicine and especially in the field of urology and gynecological urology, though further studies defining physiological function(s) of PSA and its role in the pathophysiology of the prostate have yet to be carried out.

Of the extensively increasing number of publications concerned with the PSA marker in a broad range or relationships, the reader may however infer that only a minor part of the authors know the names of the actual discoverers of this prostatic marker, while the majority of the publications supply the reader with incorrect and misleading information.

It has to be noted that the tissue specific antigens of the human prostate, now known as PSA, were first identified by the team of Richard Ablin, at present Director and Scientific Investigator of the company Innapharma in New Jersey. Dr Ablin and his co-workers (W.A. Soanes, P. Bronson and E. Witebsky) have a justified priority claim as they published their results in two renown journals (Journal of Reproduction and Fertility and Journal of Immunology) in 1970. Thus their pioneer publications (Ablin et al., 1970 a, b) appeared nine years before the paper of Wang et al. (1979). Nevertheless, the latter are often incorrectly presented as discoverers of PSA. The first identification of PSA by the team of Dr Richard Ablin has before us been pointed out by Dr William H. Cooner from the Emory University School of Medicine (Cooner, 1993) and by group of Dr Joseph E. Oesterling (Monda, Barry and Oesterling, 1994). Although some authors, incorrectly mentioned as discoverers of PSA, did publish some important partial findings concerning PSA, essentially their work was based on the ground-breaking studies of the Ablin team. Hara et al. (1971) were the first to identify PSA in seminal fluid, in which it was successfully purified by Li and Beling (1973). In serum, PSA was first identified by Papsider and co-workers as late as in 1980.

Biochemical techniques of PSA determination in serum have undergone considerable development and are nowadays far more sensitive than they used to be in the early 80s. Itoh (1997) reported that the new approaches allow to determine PSA in female serum in sometimes surprisingly high values, which in my opinion may actually reflect the given functional state of the prostate (Skene's gland) in these female subjects. These findings should no longer be considered surprising since they are well in line with the non-vestigial concept of the female prostate, a female organ with an already well defined structure, function and pathology comparable to that of the male prostate (Zaviačič, 1987).

Our contribution to the relatively short, almost 30-year-old, history of the discovery of PSA attempts to put the merit of Dr Richard Ablin and his co-workers into the deserved proper light. We are doing so with full respect to the achievements of Dr Ablin, who has cited and thus called attention to some of our studies on the prostate in the female. Our findings (Zaviačič et al., 1993, 1994, 1997) and those of other authors (Pollen and Dreilinger, 1984; Tepper et al., 1984) have broadened and enhanced the biological value of PSA since this prostatic marker has been found relevant not only in studies of the male but equally so of the female prostate. This has been reflected also by Dr Richard Ablin in his long-term correspondence with our team (Ablin, 1985, 1989, 1997).

Concluding it appears safe to state that the situation concerning the priority claim of PSA discovery may best be expressed as follows: "Prostate-specific antigen (PSA) was initially identified by Ablin et al. (1970 a, b) but purified and characterized by Wang et al. (1979)".

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