PERSPECTIVE

History of the discovery and clinical translation of prostate-specific antigen

William J. Catalona

Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Received 1 August 2014; received in revised form 28 August 2014; accepted 6 September 2014
Available online 13 September 2014

1. Introduction

In recent years, there has been considerable controversy concerning the discovery and translation into clinical practice of the prostate-specific antigen (PSA) [1–4]. In this brief review, I offer the relevant historical facts as I believe them to be true.

Before the development of the PSA blood test, prostatic acid phosphatase was the most important blood test for prostate cancer, but it was of no value for the early detection of prostate cancer, because serum acid phosphatase levels became elevated mainly in men who already had bone metastases [5].

2. Early discovery of prostate-specific antigen

In the 1960s and 1970s, many researchers were searching for tumor-specific antigens that might be useful as biomarkers or targets for immunotherapy of cancer. Typical experiments involved injecting an extract of a human tissue or body fluid, such as a prostate tissue or seminal fluid, into rabbits and testing the rabbit serum for antibodies against the antigens present in the extract or fluid.

The earliest report on the properties of antigens in the prostate was by the American urologist, Rubin Flocks, in 1960 [6,7]. In 1966, Mitsuwo Hara, a Japanese forensic scientist, reported on and partially characterized a protein, which he called “gamma-semnoprotein”. He suggested its possible value as forensic evidence in rape cases [8]. In 1970, Tien Shun Li and Carl Beling [9,10], conducting research on male infertility, reported on antigens in human semen, one of which was later shown to have the same amino acid sequence of PSA. That same year, Richard Ablin and coworkers reported finding two antigens that were specific to the human prostate, one of which was distinct from acid phosphatase [11–13]. Ablin then moved on to pursue clinical studies attempting to induce an anti-tumor immune response through cryoablation of the prostate gland. In 1978, forensic scientist George Sensabaugh also identified a protein in semen that was similar to one of Li’s antigens and was later shown to have the same amino acid sequence as PSA [14,15].

3. Purification, characterization, and development of PSA as a biomarker blood test for prostate cancer

In my opinion, the real credit for the discovery of PSA as a clinically useful biomarker for prostate cancer and for translating it into clinical use belongs to T. Ming Chu and his research group, most notably Ming C. Wang, who conducted a remarkable series of studies over several years at the Roswell Park Memorial Institute [1,2]. In a landmark study in 1979, Wang and coworkers purified and characterized PSA and suggested potential clinical applications as a biomarker for prostate cancer [16]. This set the stage for the development of a PSA blood test, which was subsequently achieved in steps by Lawrence D. Papsidero [17] and Manabu Kuriyama [18], Wang and their coworkers in Chu’s research group. They developed a sensitive ELISA
immunoassay that could be used for blood testing, and performed early studies exploring the potential clinical uses of PSA as a biomarker in prostatic diseases. Ultimately, T. Ming Chu and Roswell Park Memorial Institute received the patent for the discovery of "purified human prostate antigen" in 1984, and Chu has been honored on many occasions as the discoverer of PSA [19].

What emerged from the early clinical studies by Chu’s group, and was further validated by Thomas A. Stamey [20] and others, was that PSA was clinically useful for monitoring the course of patients already known to have prostate cancer. However, because there was overlap of serum PSA levels between patients with prostate cancer, benign prostatic hyperplasia, and prostatitis, and PSA levels were sometimes "normal" or low in patients with prostate cancer, it was not believed that PSA could be used as a first-line screening test for prostate cancer. Rather, physicians and researchers were focused on finding a marker that functioned like a pregnancy test, i.e., always positive when cancer was present and always negative when cancer was absent. Therefore, until the 1990s, PSA was largely used for monitoring the response of prostate cancer patients to treatment.

In the early 1990s, it was first demonstrated that the PSA blood test could be used as a first-line screening test for prostate cancer [21], which led to the approval of the PSA test by the United States Food and Drug Administration (FDA) as an aid to the early detection of prostate cancer [22]. PSA derivatives, such as PSA velocity [23], PSA density [24,25], and the free-to-total PSA ratio [26] (also FDA approved) served to improve the accuracy of PSA testing. More recently, other PSA isofoms, such as the [-2]proPSA, have been found to be a more cancer-specific biomarker for prostate cancer, which has led to FDA approval of the Prostate Health Index (PHI) in 2013 [27].

4. PSA testing reduces prostate cancer-specific mortality

During the "PSA era" in the United States, the proportion of patients having advanced disease at diagnosis has decreased by 80%, and the age-adjusted prostate cancer mortality rate has decreased by more than 42% [28]. Statistical modeling studies have estimated that 45%–70% of this mortality decrease is attributed directly to PSA screening [29,30]. Similar trends have been observed in countries that have adopted widespread PSA screening but not in those that have not adopted PSA screening [31]. Two large prospective, randomized clinical trials in Europe have demonstrated a 21% and 44%, respectively, decrease in prostate cancer-specific mortality associated with PSA screening [32,33].

5. Concerns about overdiagnosis and overtreatment

Although in recent years, population-based PSA screening has been called into question because of concerns that the benefits of screening may not justify the risks of overdiagnosis and overtreatment of possibly harmless prostate cancers [34], I believe that PSA-based testing (including PHI) is the best cancer blood test in all branches of medicine, and certainly the best test currently available for early prostate cancer detection. Although PSA-based testing has limited specificity, I am convinced that the intelligent use of PSA-based testing, careful selection of patients for screening and treatment, combined with high quality, effective treatment, could reduce the overall prostate cancer death rate by more than half.

Conflicts of interest

The author declares no conflict of interest.

References

[1] Catalona WJ. The ‘true’ history of the discovery of prostate-specific antigen. ASCO Post December 15, 2012;3(18). http://www.ascopost.com/issues/december-15-2012/the-%E2%80%99true%E2%80%99-history-of-the-discovery-of-prostate-specific-antigen.aspx [accessed 06.02.14].

[2] Chu TM. Prostate Specific Antigen (PSA): the historical perspective. [http://www.medicine.mcgill.ca/mjm/v02n02/psa.html] [accessed 06.02.14].

[3] Rao AR, Motiwala HG, Karim OMA. The discovery of prostate-specific antigen. BJU Int 2008;101:5–10.

[4] De Angelis D, Rittenhouse HG, Mikolaiczak SD, Blair Shamel L, Semjonow A. Twenty years of PSA: from prostate antigen to tumor marker. Rev Urol 2007;9:113–23.

[5] Gutman AB, Gutman EB. An “acid” phosphatase occurring in the serum of patients with metastasizing carcinoma of prostate gland. J Clin Invest 1938;17:473–8.

[6] Flocks RH, Ulrich VC, Patel CA, Opitz JM. Studies on the antigenic properties of prostatic tissue. I. J Urol 1960;84:134–43.

[7] Flocks RH, Bandhaur K, Patel C, Begley BJ. Studies on spermagglutinating antibodies in anhuman prostate sera. J Urol 1962;8:475–8.

[8] Hara M, Inoue T, Koyanagi Y. Preparation and immunoelectrophoretic assessment of antisera to human seminal plasma. Nippon Hoigaku Zasshi 1966;20:356.

[9] Li TS, Behrman SJ. The sperm- and seminal plasma-specific antigens of human semen. Fertil Steril 1970;21:565–73.

[10] Li TS, Beling CG. Isolation and characterization of two specific antigens of human seminal plasma. Fertil Steril 1973;24:134–44.

[11] Ablin RJ, Soanes WA, Bronson P, Witebsky E. Precipitating antigens of the normal human prostate. Reprod Fertil 1970;22:573–4.

[12] Ablin RJ, Bronson P, Soanes WA, Witebsky E. Tissue- and species-specific antigens of normal human prostatic tissue. J Immunol 1970;104:1329–39.

[13] Ablin RJ. Immunologic studies of normal, benign, and malignant human prostatic tissue. Cancer 1972;29:1570–4.

[14] Sensabaugh GF. Isolation and characterization of a semen-specific protein from human seminal plasma: a potential new marker for semen identification. J Forensic Sci 1978;23:106–15.

[15] Sensabaugh GF, Blake ET. Seminal plasma protein p30. Simplified purification and evidence for identity with prostate specific antigen. J Urol 1990;144:1523–6.

[16] Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. Invest Urol 1979;17:159–63.
[17] Papsidero LD, Wang MC, Valenzuela LA, Murphy GP, Chu TM. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980;40:2428–32.

[18] Kuriyama M, Wang MC, Papsidero LD, Killian CS, Shimano T, Valenzuela L, et al. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. Cancer Res 1980;40:4658–62.

[19] US patent number 4446122. Available from: http://patft.uspto.gov/nethtml/PTO/search-bool.html. [accessed 05.07].

[20] Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909–16.

[21] Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156–61.

[22] Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283–90.

[23] Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. J Am Med Assoc 1992;267:2215–20.

[24] Veneziano S, Pavlica P, Querzé R, Nanni G, Lalanne MG, Vecchi F. Correlation between prostate-specific antigen and prostate volume, evaluated by transrectal ultrasonography: usefulness in diagnosis of prostate cancer. Eur Urol 1990;18:112–6.

[25] Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992;147:815–6.

[26] Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. J Am Med Assoc 1998;279:1542–7.

[27] Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/mL prostate specific antigen range. J Urol 2011;185:1650–9.

[28] http://seer.cancer.gov/faststats/selections.php?#Output. [accessed 06.03.14].

[29] Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008;19:175–81.

[30] Etzioni R, Gulati R, Tsodikov A, Wever EM, Penson DF, Heijnsdijk EA, et al. The prostate cancer conundrum revisited: treatment changes and prostate cancer mortality declines. Cancer 2012;118:5955–63.

[31] Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981–90.

[32] Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomized population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725–32.

[33] Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. J Urol 2013;190:419–26.