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PSA-ACT Complex

This new marker for prostate cancer exhibits what serum assays for PSA lack: the ability to differentiate prostate cancer from benign prostatic hyperplasia.

Assays for PSA-α_1-Antichymotrypsin Complex May Soon Stand Alone in the Diagnosis of Prostate Cancer

PSA-ACT

PSA assays fail to differentiate prostate cancer from benign prostatic hyperplasia

Since 1981, the number of reported prostate cancer cases in the US has increased by 50%, and the number of related deaths by 40%. Approximately 130,000 cases are reported each year, resulting in over 30,000 annual deaths.[1] As the population ages and average life-span lengthens, these numbers are expected to increase. As such, early diagnosis and effective treatment of prostate cancer are increasingly important.

To date, Prostate Specific Antigen (PSA) is the most effective marker for prostate cancer. Serum assays for PSA are used for early detection of prostate cancer, monitoring disease progress, evaluation of therapy, and detecting early recurrence of disease after radical prostatectomy.[2,3]

The goal of PSA serum assays is to detect prostate cancer prior to metastasis, that is, while still in the organ-confined state. Detecting prostate cancer localized to the prostate gland is paramount for reliable surgical excision. PSA's ability to do this has recently come into question. An excellent review of serum assays for PSA is presented by JT Wu, PhD[3]; in it, PSA's short-comings are discussed and solutions proposed.

What has distinguished PSA from other cancer markers is its tissue-specificity; PSA is produced only in the prostate epithelium, making it arguably the best serum marker available today for any type of cancer.[3] Although PSA is tissue-specific, it is not, however, cancer-specific. Serum levels of PSA are elevated in both prostate cancer and benign prostatic hyperplasia (BPH).[4,5] And frequently, only extreme elevations of PSA (>50µg/L) are specific for prostate cancer.[6] As a result, difficulty arises when distinguishing prostate cancer from BPH in patients with serum PSA levels in the 4-20µg/L range. PSA's lack of specificity for prostate cancer can cause the BPH patient unnecessary anxiety and even unnecessary surgery.

One of the solutions to PSA's low specificity for prostate cancer, as presented by Dr. Wu[3], is a relatively new discovery. Recent studies suggest the existence of a potentially better serum marker for prostate cancer, PSA-α_1-Antichymotrypsin Complex (PSA-ACT). In a report published in November 1993, measuring serum levels of PSA-ACT improved the ability of PSA measurements to differentiate prostate cancer from BPH. Assay specificity increased from 55% to 73%, at a sensitivity of 90%. More importantly, specificity in the critical 4-20µg/L range was also significantly increased, with no loss of sensitivity.[7]

PSA is a 33-34 kD glycoprotein with chymotrypsin-like protease activity.[8] Normally, very low concentrations of PSA are released into the bloodstream, approximately 0-4ng/mL. This enzymatically active form of PSA complexes with the serum protease inhibitor α_1-antichymotrypsin (ACT) and represents the predominant form of PSA in serum.[6,9] PSA also forms a complex with the enzyme inhibitor α_2-macroglobulin (A_2M) in serum, but to a much lesser degree.

In addition, a significant percentage of PSA is present unbound to any inhibitor in serum. This form of PSA possesses no enzymatic activity and, thus, does not interact with serum protease inhibitors like ACT and A_2M. Recently, the different complexes of PSA with various serum protease inhibitors have been identified and characterized.[9,10,11] Although the reported percentage of each PSA-complex varies from study to study, a table presented by EP Diamandis, MD PhD[12] nicely summarizes the various forms of PSA (see Table 1).

These studies led to the discovery that the ratio of PSA-ACT to total PSA increases in the serum of prostate cancer patients and that the percentage of free, unbound PSA decreases in prostate cancer. That these ratios remain normal in the serum of BPH patients is of particular clinical importance. In a study by Stenman, *et al*[10], prostate cancer patients had a significantly higher proportion of PSA-ACT than those patients with BPH. In a related experiment, Christensson, *et al*[6] measured the proportion of free PSA to total PSA and found the ratio to be 36% lower in prostate cancer than in BPH. Although the mechanism is not yet understood, both studies indicate that prostate malignancies release more enzymatically active PSA than other conditions. This leads to a higher percentage of PSA-ACT in the serum of prostate cancer patients.

At present, commercially available PSA assays do not consistently recognize PSA-ACT, nor do they give compatible PSA results from the same patient sample. Two excellent reviews summarize these issues, which will not be discussed in this review.[3,13]

Two interesting reports were published in 1993 describing newly developed assays for PSA-ACT. One of the studies details a monoclonal-polyclonal antibody immunofluorometric assay that equally recognizes both free PSA and PSA-ACT.[14] This mono:poly assay has a very low detection limit of 0.002µg/L; this should prove useful in the detection of residual disease after radical prostatectomy.

The second report also describes a mono:poly immunofluorometric assay.[15] What makes this assay unusual, however, is that it concurrently measures free PSA and PSA-ACT, providing separate serum levels for each analyte. This greatly simplifies the determination of the percentage of PSA-ACT to total PSA in the serum of prostate cancer patients. In fact, the authors found this assay to reduce the frequency of false-positive results due to BPH by 38%.

An issue that remains to be resolved is the calibration of the PSA-ACT assay. An assay standard containing the appropriate ratio of PSA-ACT to free PSA is inherently complex. One must take into account the normal serum ratio of PSA-ACT to free PSA, as well as any interference presented by other PSA-inhibitors like A_2M. Zhou, *et al*[13] describe yet another sensitive mono/poly immunoassay for PSA-ACT that employs calibrators prepared by adding purified PSA to female serum that had been treated with immobilized antibody to A_2M. Using such a calibrator, they reported a recovery of >98% of PSA values throughout the standard curve. In addition, the authors cite a December 1992 international standardization conference where it was recommended that PSA standards should include serum protease inhibitors so that patient sera is more accurately reproduced.

Given the evidence presented above, it seems undeniable that the determination of serum levels of PSA-ACT is invaluable in the differential diagnosis of prostate cancer from BPH. Most importantly, PSA-ACT determinations have significantly greater specificity for prostate cancer than serum PSA evaluations alone. Optimistically, further study will show that PSA-ACT immunoassays, coupled with other diagnostic procedures, like digital rectal exam and transrectal ultrasonography, will considerably reduce the morbidity and mortality of prostate cancer.

Table 1. Molecular Forms of PSA in Human Serum[12]

Molecular Form	Approximate Mol. Weight	% of Total	Comments
Free PSA	30 kD	10-40	Percentage of free PSA decreases in the serum of cancer patients as total PSA increases
PSA-ACT	100 kD	60-90	Percentage of PSA-ACT complex increases as total PSA increases
PSA-α_1-proteinase inhibitor	190 & 80 kD	< 1	Present only when PSA exceeds 40 µg/L
PSA-A_2M	800 kD	< 0.1	Not measured by commercial PSA kits
PSA-inter-α-trypsin inhibitor	250 kD	< 0.1	Not measured by commercial PSA kits

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