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Biomarkers for Benign Prostatic Hyperplasia Progression

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Abstract

Despite the fact that almost all men will develop symptoms associated with benign prostatic hyperplasia within their lifetimes, no molecular markers for the disease or its likelihood to progress have been established. A marker of this type could be used to stratify patients into subpopulations as well as to identify individuals whose disease is most likely to progress. Several molecular biomarkers have high potential to fulfill these needs, although none is currently approved for the clinical setting. The future does look promising as research to find novel biologic biomarkers is progressing while existing markers are optimized and validated for clinical use.

Introduction

It is almost a certainty that at some point in every man's life he will develop a urologic condition, the most common being benign prostatic hyperplasia (BPH). The prevalence of BPH is estimated to increase from 5% to 10% in the third decade of life to greater than 90% for men older than age 85 [1]. BPH is a disease that contributes to a significant loss of quality of life in patients and is a major health problem throughout the world. Although they are typically described as BPH, the symptoms associated with the disease represent several conditions that are more accurately termed lower urinary tract symptoms (LUTS). These symptoms include but are not limited to nocturia, incomplete emptying of the bladder, urinary hesitancy, weak stream, frequency, and urgency leading to the development of acute urinary retention, along with an array of sexual dysfunctions [2,3]. Commonly, BPH is initially managed with pharmacologic agents such as α_1-adrenergic antagonists and 5-α-reductase inhibitors [4]. The Medical Therapy of Prostatic Symptoms (MTOPS) Study demonstrated that by using these pharmaceuticals together as combination therapy, a patient's risk of LUTS progression could be reduced by 66% compared with placebo [5]. Despite the success of these pharmacologic treatments for the disease, one in five men with BPH will undergo prostate surgery or have an episode of prostate-related acute urinary retention within 1 year of initiating treatment for the disease [6]. It has been estimated that the total annual cost of BPH management in the United States exceeds 1.1 billion dollars, and it is expected to increase with the rising average age of the population [7].

As described, BPH is a common disease but its cause and biology have not been well elucidated. The development of BPH, as well as the function of the normal prostate, is known to be principally regulated by androgens [8]. Recent data suggest that the action of androgens alone may not explain the hyperplastic development of the prostate gland [9,10]. Other regulatory factors, such as transforming growth factor-β, stromal–epithelial interactions, and α-adrenergic receptors, are thought to contribute to development and progression of BPH [1,11,12].

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Despite the common name and pathologic features, studies have demonstrated that BPH is not a single disease at the cellular and molecular levels [13]. Using microarray analysis, BPH in individuals with moderate to severe symptoms, BPH in individuals with histologic disease, and the normal prostate have all been shown to be genetically distinct. These studies examined samples taken from the same area of the prostate to provide consistency within tissue comparisons. In addition, the lesions studied were predominantly epithelial and the selected areas lacked overt inflammatory infiltrates. Interestingly, BPH in individuals with severe symptoms possesses a gene expression pattern that is closer to the BPH found in the prostates of individuals with prostate cancer, although these patients are asymptomatic [14••]. In addition, symptomatic patients with familial BPH differ clinically from those with sporadic BPH [15]. Patients presenting with familial BPH have earlier onset of disease, larger prostate volumes, and an increased risk that they will need surgical intervention [16–18]. These observations only complicate the possible hypotheses regarding the genetic complexity of BPH.

In recent years, researchers and physicians have brought us much closer to fully understanding the mechanisms of BPH and have made advances in the treatment of the disease and accompanying LUTS, but a reliable early detection method remains elusive. As mentioned previously, the most common indicators of BPH are a patient's symptoms or discovery via digital rectal examination and transrectal ultrasonography. By the time either of these occurs, the patient most likely has a serious and perhaps irreversible situation. Recent studies have shown BPH to be a gradually progressive disease [19]. With this evidence, it has been proposed that if BPH were detected before symptoms arose, treatment with pharmacologic agents including a 5-α-reductase inhibitor could be administered to prevent the progression of the disease [20]. A biomarker that could detect the more aggressive form of the disease (highly symptomatic BPH) might allow for earlier therapeutic approaches that may provide for a more effective clinical response. In addition, differentiation of asymptomatic BPH from symptomatic disease may allow for the application of varying therapeutic approaches based on the different disease types. In addition, and perhaps most importantly, a marker that could determine the progression of the disease would assist in determining the therapeutic success of individualized treatment strategies. In order to make significant therapeutic advances in the treatment of this disease, molecular markers are required that will provide for these clinical insights.

Despite the urgent need for biomarkers of BPH, none is currently being used clinically. Several are undergoing clinical trials or are in development, however. This review outlines some of the potential biomarkers of the disease including the current state of their evaluation and application. In addition, we describe the application of novel technologies to address these important questions.

Prostate-Specific Antigen

The use of serum-based prostate-specific antigen (PSA) has revolutionized the detection of prostate cancer and dramatically changed the course of this disease. This is despite its lack of specificity as it is not a prostate *cancer*–specific antigen and is often found to be elevated in the blood of men with BPH and with prostatitis. Although the frequent increases in PSA levels in men with BPH may be considered to be a weakness in screening men for prostate cancer, this may serve as a possible opportunity to use PSA as a serum biomarker for BPH. A correlation between prostate volume and PSA levels has been determined [21]. With the use of a biopsy to rule out prostate cancer, a patient's PSA level could be used to determine the progression of their BPH, particularly in men with enlarged prostates. Bartsch et al. [22] proposed that PSA could be used as a substitute for prostate volume and as a biomarker for BPH progression. It has also been suggested that men with symptoms and with a PSA of 1.5

ng/mL or greater should be considered a group at increased risk for clinically significant progressive BPH [22]. Although it is true that men with enlarged prostates are more likely to have symptoms, many men with small prostate volumes also present with symptomatic BPH. In these patients, it is likely that PSA levels will be low and therefore will not be sensitive for this population of symptomatic patients.

Other work has concentrated on how to detect the serum PSA isoforms. Froehner et al. [23] observed in a study enrolling 263 men that the amount of total PSA (tPSA) in serum could be used to determine whether an elevated PSA score was the result of prostate cancer or BPH. Jung et al. [24] examined three PSA isoforms: tPSA; free PSA (fPSA), the 10% to 30% of tPSA not bound to proteins; and complexed PSA (cPSA), all complexed PSA except PSA complexed with α_2-macroglobulin. It was observed that an fPSA/cPSA or fPSA/tPSA ratio has the potential to differentiate normal subjects, subjects with BPH, and subjects with prostate cancer [24]. cPSA alone also has potential as a diagnostic tool, but it does not harness the discriminatory power of the isoform ratios [24]. These studies were conducted as an attempt to improve PSA as a prostate cancer biomarker and not as a BPH marker. Therefore, the sensitivities and specificities are much better for prostate cancer than for BPH. Also, the PSA isoforms show little potential for early BPH detection and the monitoring of the progression of BPH as the disease worsens or during treatment. Ultimately, the presence of PSA, in any form, may be the result of prostate cancer or prostatitis. Therefore, patients still need biopsies, which in many cases will rule out prostate cancer but do not indicate what is happening within the prostate, leaving the door open for a more specific BPH molecular marker.

BPH-Associated Prostate-Specific Antigen

Using immunoaffinity chromatography and high-performance hydrophobic interaction chromatography to purify PSA from prostate tissue, Mikolajczyk et al. [25] identified a specific molecular form of clipped fPSA that is elevated in the transitional zone of prostates exhibiting nodular BPH, which was termed BPSA. BPSA is one of the three inactive forms of fPSA and contains clipped polypeptide bonds at amino acid residues Lys145–146 and Lys182–183 [26,27]. Linton et al. [28] developed an immunoassay to determine the concentration of BPSA in the serum of men with BPH. By harnessing a monoclonal antibody, the assay was performed against serum from patients with BPH, patients with prostate cancer, urologic outpatients with no urologic complications, young men (< 30 years), women, and post–radical prostatectomy patients. The median BPSA/total PSA values were significantly different between the cancer and benign cohorts [28]. BPSA was detected only in patients with measurable amounts of PSA. The young men, the women, postprostatectomy patients, and outpatients with no measurable PSA had undetectable levels of BPSA. When evaluating BPSA as a potential BPH molecular biomarker, limitations are evident. Levels of BPSA increase with prostate size and have the potential to also be the result of prostate cancer and not BPH. As noted by Linton et al. [28], the use of BPSA would require another marker to rule out the presence of prostate cancer in patients with elevated BPSA levels. To date, the patients with BPH who have been included in studies examining BPSA levels have not been evaluated in terms of their degree of symptoms. Most patients studied here had increased PSA levels, negative biopsy findings, and confirmed histologic BPH [28]. BPSA does have relevance for detecting BPH, but from what we know today, not for classifying the type of BPH, assisting with treatment assessments, or monitoring the progression of the disease. This is an evolving story, however, and these studies of BPSA are encouraging; further analysis may shed light on the potential of BPSA as a molecular biomarker for BPH and disease progression.

JM-27

As a component of the studies described earlier in which targets were identified that could classify BPH into distinct genetic subtypes, the gene encoding the protein JM-27 was shown to be differentially upregulated in symptomatic BPH [13]. Using microarray analysis with large numbers of tissue types and samples within each group, expression of JM-27 was tissue specific, with expression being limited to the prostate and certain female reproductive tissues [13]. Based on these findings, antibodies were developed against JM-27 and used in immunoassays to discover whether the protein has potential as a diagnostic tool for identifying BPH [13,14••]. Immunohistochemical analysis was performed on samples from normal prostate, asymptomatic BPH, and symptomatic BPH tissues. Results demonstrated that JM-27 is significantly upregulated in symptomatic BPH tissue in comparison with the other groups and that expression of JM-27 was confined to stromal cells with no expression in the epithelium [13]. These immunohistochemical findings were encouraging and strengthened the pursuit to use JM-27 as a molecular biomarker for BPH.

To determine whether JM-27 could be used as more than a tissue marker for the disease, a monoclonal antibody raised against the protein was used to construct an indirect enzyme-linked immunosorbent assay to test serum from the MTOPS trial to explore the novelty of JM-27 as a serum biomarker for BPH [14••]. Among a sample set of patients with asymptomatic BPH, patients with symptomatic BPH, and patients with prostate cancer without symptoms of BPH, the JM-27 levels were able to differentiate patients with symptomatic BPH from the other two populations [14••]. The marker did so with a sensitivity of 90% and a specificity of 77% [14••]. Furthermore, prostate volume does not affect the serum levels of JM-27, unlike other potential BPH molecular biomarkers. Because BPH is not limited to one disease, it is important to find a molecular biomarker that has the potential to classify the disease states. JM-27 appears to accomplish this. By identifying men who express JM-27 before the onset of symptoms, treatments could be administered exclusively to patients who have a high potential of developing symptomatic BPH and accompanying LUTS. Also, JM-27 is homologous to a family of MAGE/GAGE-like proteins, suggesting that overexpression of JM-27 may be involved in the progression of BPH [29]. JM-27 is a very exciting potential BPH molecular biomarker, but further analysis must be conducted. Future studies of JM-27 will include an evaluation of serum JM-27 levels in the complete set of MTOPS samples. These studies will provide further evidence for the potential utility of JM-27 as a molecular biomarker for symptomatic BPH and the progression of the disease.

P25/26

A monoclonal antibody, P25/26, was isolated by immunizing mice with seminal plasma from patients with histologic BPH [30]. The cDNA for the protein associated with P25/26 was isolated and Western blot, immunohistochemical analysis, and reverse transcription polymerase chain reaction analysis confirmed elevated levels of P25/26 in BPH tissues versus prostate cancer and normal tissues [30]. Furthermore, indirect enzyme-linked immunosorbent assay confirmed higher levels of P25/26 in seminal plasma from men with BPH [30]. The gene that encodes the protein appears to have a strong homology with the superimmunoglobulin gene family. This study appears to present a potentially promising marker for BPH. Due to the absence of symptom scores, we cannot conclude at this time, however, that the marker would be a sufficient tool to monitor the progression of BPH or of a patient’s symptoms. Also of concern, the study was conducted 7 years ago, and apparently no subsequent studies have been published. It would be fascinating to see further investigations of P25/26 conducted based on the success of these original findings.

MTOPS Prostatic Samples Analysis Consortium

A group established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in cooperation with the National Institute on Aging (NIA), the MTOPS Prostatic Samples Analysis (MPSA) consortium was developed as a BPH biomarker discovery and validation effort follow-up study to the MTOPS clinical trial. The MPSA consortium is using novel approaches to molecular biomarker discovery in hopes of identifying markers for clinical diagnoses and disease progression. Apparently, the best tool that exists to validate progression markers is the sample set collected as part of the MTOPS trial. These samples provide for the opportunity to ask important questions such as the following: Before therapy can we differentiate individuals who have varying International Prostate Symptom Scores (IPSS)? Can the men who respond to individual therapies or combination therapy be identified before beginning their treatment? Can we predict which men will have progressive disease? Additionally, questions can be asked related to changes in levels of biomarkers over time. Can a biomarker be used to monitor the efficiency of a therapy? Can we determine which ones succeed and which fail in a quantitative fashion? The MPSA consortium was set up as a collaborative effort composed of researchers from Vanderbilt University, the University of Colorado, the University of Michigan, the Brigham and Women's Hospital, the Dana Farber Cancer Institute, the University of Texas Southwestern, Baylor College of Medicine, the University of Pittsburgh, Johns Hopkins University School of Medicine, along with members of the NIDDK and the NIA. Participants include urologists, pathologists, molecular biologists, protein chemists, biostatisticians, and others. The fruits of their labors are beginning to be realized. This first-of-its-kind effort is providing us with new tools and directions in which research efforts in BPH biomarkers can be conducted. In addition, the assembled sample sets will provide an opportunity for investigators to advance the study of BPH progression biomarkers at a rapid pace.

Conclusions

With the increasing prevalence of BPH comes the demand for a molecular biomarker that can confidently identify and monitor disease progression [2]. Currently the IPSS is the most reliable tool for measuring BPH, but even this instrument has subjectivity and may not always accurately reflect the state of the disease. Studies have shown that women can have similar IPSS scores when compared with age-matched men [31,32]. Therefore, the IPSS can reliably identify LUTS but does not assist with diagnosing the cause as BPH or other potential causes of the symptoms, such as structural alteration of an aging detrusor or other urologic complications [31]. A molecular biomarker that could identify symptomatic BPH could lend insight into what a high IPSS may represent for an individual patient. Also, a marker with the ability to detect symptomatic BPH before the onset of LUTS may have the potential to prevent complications of the bladder caused by BPH, which often tend to be irreversible. Furthermore, a marker that could differentiate between symptomatic BPH and asymptomatic BPH would allow physicians to confidently treat patients with different levels of treatment aggression. An analysis of BPH treatments demonstrated that transurethral resection of the prostate is more cost-effective when medical therapy begins in patients younger than 70 years versus medical management (α_1-adrenergic antagonists or 5-α-reductase inhibitors) [7]. With so many of the men to whom pharmaceutical treatments are administered eventually having to undergo transurethral resection or other minimally invasive surgical therapy, a marker that could assist physicians in making treatment decisions would also be economically beneficial. Ultimately, this would require a marker that monitors the progression of BPH and would provide additional benefit by acting as an internal monitor to guide treatment decisions. Currently, there is no biologic marker that can fulfill these necessities with assurance. Many of the markers highlighted in this review are promising, but few are ready for clinical utility.

As new approaches to identifying molecular markers are proposed and older studies are validated, the need will remain strong for a molecular biomarker for BPH and progression of the disease. A disease this prevalent and one that makes such an economic impact requires a better diagnostic tool and means of monitoring than those currently in place. Although the lack of these tools contributes to the complexity and frustration associated with BPH, it is reassuring to see the amount of work going into accomplishing these goals and the potentially exciting biomarkers (ie, JM-27) that are on the horizon.

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