Expression of Heat Shock Protein 27 in Benign Prostatic Hyperplasia with Chronic Inflammation

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Background: Heat shock protein 27 (HSP 27) is known as a mediator in immune response and has been recently found to be expressed in prostate cancer. This study aimed to investigate the role of HSP27 in inflammatory BPH.

Material/Methods: Hospitalized BPH patients who received TURP were divided into 4 groups by the presence and degrees of chronic inflammation: non-inflammatory BPH (NI BPH), mild-inflammatory BPH (MI BPH), moderate-inflammatory BPH (MOI BPH), and severe-inflammatory BPH (SI BPH). Expressions of HSP 27, TNF-α, IL-6, and CD3 in prostate tissues and serum of patients were detected by immunohistochemistry and ELISA.

Results: Expression of HSP27 in BPH with histological inflammation was significantly higher than in non-inflammatory BPH. In inflammatory BPH groups, HSP27 expression gradually increased along with increasing inflammation. There was a significant correlation between the expression of TNF-α, IL-6, CD3 and HSP27 among different inflammatory BPH groups.

Conclusions: HSP27 expression level is associated with the degree of chronic inflammation in BPH and may participate in the pathological process in inflammatory BPH.

MeSH Keywords: Cytokines • HSP27 Heat-Shock Proteins • Inflammation • Prostatic Hyperplasia

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Benign prostatic hyperplasia (BPH) is the most common urological disease among aged men, with incidence over 50% at age 60 years [1] and over 90% at age 80 years. It is estimated that BPH will affect 20% of men worldwide. The development and progression of BPH is a long-term process. In recent years accumulating evidence strongly suggests the role of prostatic inflammation in the pathogenesis and progression of BPH [2,3]. Recent studies suggest that inflammation and abnormal immunoregulation may contribute to cytokine production by inflammatory cells driving local growth factor production and angiogenesis in the prostatic tissue, and that this proinflammatory microenvironment is closely related to BPH stromal hyperplication and tissue remodeling [4].

Heat shock proteins (HSPs) are a family of proteins that are produced by cells in response to exposure to stressful conditions. HSPs are crucial for the maintenance of cell integrity during both normal cell growth and pathophysiological conditions [5–7]. By controlling binding and release, HSPs function mainly as molecular chaperones, which participate in the folding and assembly of nascent and unfolding proteins and facilitate protein transport to subcellular compartments. HSPs are classified into 4 major families according to their biological activities: HSP90, HSP70, HSP60, and small HSPs. HSP27 is a widely expressed 27 kDa protein as a member of the small HSP family. It has been implicated in different diseases, playing both protective and counter-protective roles, such as renal injury and fibrosis [8], cancer [9], and neuro-degenerative and cardiovascular diseases [10], highlighting its role as a potential biomarker and therapeutic target. Recently, it has been reported that HSP27 presents in the prostate cancer cell line and its expression is related to the prostate cancer malignancy level [11]. Accumulating evidence now suggests that BPH and prostate cancer share important anatomic, pathologic, and genetic links in addition to the well-established epidemiologic association. Recent publications support the hypothesis that BPH and prostate cancer are part of the metabolic syndrome, and inflammation as a major contributor to the development of both BPH and prostate cancer [12]. However, the expression of HSP27 in BPH and its correlation with inflammation level are unclear.

In this study, to investigate the role of HSP27 in inflammatory BPH, we evaluated HSP27 expression and its relation to conditions of prostatic inflammation associated with BPH, correlating it with the levels of inflammatory factors such as tumor TNF-α, IL-6, and CD3.

**Material and Methods**

**Ethics statement**

This study was approved by the ethics committee of the Third Affiliated Hospital of Hebei Medical University. Written informed consent was obtained from all subjects.

**Subjects**

We recruited 60 BPH patients who received transurethral electro-resection of prostate (TURP) because of urinary retention or lower urinary tract symptoms (LUTS) at the Third Affiliated Hospital of Hebei Medical University between April 2013 and October 2013 into this cross-sectional study. Finasteride and α receptor blockers were the main drugs taken by participants for the treatment of BPH before the surgery.

Before the surgery, all the patients received tests for blood routine, urine routine, liver and renal function, chest radiograph, electrocardiogram, abdominal and urethral system ultrasonography, prostate-specific antigen (PSA), and C reactive protein (CRP). International prostate symptom score (IPSS) and quality of life (QOL) were also evaluated for each patient. The patients whose prostate volume detected by ultrasonography was over 30 ml were included. Patients with the following conditions were excluded: history of acute prostatitis or chronic bacteriogenic prostatitis, urinary tract infection, a history of chronic pelvic pain, incidentally discovered prostate cancer (IDPC) or endometrial hyperplasia of prostate, cerebrovascular disease or spinal cord disease, and oral antibiotics a week before the surgery.

**Groups**

Prostate tissues were obtained from the surgery and pathological sections were made. Prostate tissues were serially cryo-sectioned at a thickness of 4 μm after 10% neutral formalin fixing for 24 h and paraffin embedding. Sections were dewaxed in xylene and rehydrated through graded ethanol to water followed by hematoxylin and eosin staining. All the sections were evaluated by 2 experienced pathologist for hyperplasia of prostate and histological inflammation. All 60 patients were diagnosed as having BPH.

Histological inflammation was certified when inflammatory cell infiltration and accumulation were found in the prostate gland. Among the 60 BPH patients, there were 15 cases of non-inflammatory BPH (NI) and 45 cases of inflammatory BPH. The inflammatory BPH group was further divided into 3 different degrees by the number of inflammatory cells, the extent of the damage to prostate gland, and the emergence of lymph nodules: mild-inflammatory BPH (MI, n=12) with sporadic...
inflammatory cell infiltration and no damage to the glandular epithelium; moderate-inflammatory BPH (MOI, \(n=25\)) with inflammatory cell accumulation but no damage to the glandular epithelium basement, or lymph nodules; and severe-inflammatory BPH (SI, \(n=8\)) with inflammatory cell accumulation, damage to the glandular epithelium basement, or emergence of lymph nodules.

**Demographic and clinical data**

Basic demographic information and clinical data were collected, including age, height, weight, the history of urinary retention, complications, International Prostate Symptom Score (IPSS), quality of life (QOL), prostate volume, residual urine volume (RUV), maximum flow rate (Qmax), prostate specific antigen (PSA), C-reactive protein (CRP), leucocyte counts in blood test and urine test, and body mass index (BMI). PSA in the blood was measured with a Roche Cobas e601 (Roche, Germany). Blood of the patients was collected on the next morning after hospital admission. Blood of patients with urine retention was collected a week after catheter setting. CRP in the blood was measured with latex particle-enhanced immuno-turbidimetric assay using a Hitachi 7170A biochemistry analyzer (Hitachi, Japan). Blood of the patients was collected on the next morning after hospital admission. Urodynamic tests were performed for each patient, and patients with urine retention were tested a week after catheter setting. The indexes observed included postvoid residual urine, maximum flow rate, detrusor pressure, and bladder capacity.

**Immunohistochemistry**

Formalin-fixed, paraffin-embedded sections (4 μm) of prostate tissues were immunostained for HSP27 (rabbit polyclonal antibody BS1177, BioWorld Technology, USA), TNF-α (rabbit polyclonal antibody BS6000, BioWorld Technology, USA), IL-6 (rabbit polyclonal antibody BS6419, Bioworld Technology, USA) and CD3 (rabbit polyclonal antibody BS6280, Bioworld Technology, USA) as follows. After being dewaxed and rehydrated, endogenous peroxidase activity was blocked using 3% hydrogen peroxide in methanol. Sections underwent antigen retrieval by incubation with streptavidin-horseradish peroxidase (SA-HRP) conjugate for 15 min at 37°C. Then sections were again washed in PBS and the antibdy-HRP complex was visualized by incubation with diaminobenzidine (DAB) for 5 min. Slides were briefly counterstained in hematoxylin, dehydrated, and mounted.

Mean optical density (MOD) of each section was analyzed with an Image-Pro Plus 6.0 (Media Cybernetics, CA, USA). Preference settings were: select positive color under HIS mode, H (chromaticity)=30, I (grayscale)=230, S (saturability)=255. Measuring items include: Area, Mean Density and Integrated Optical Density (IOD); for Area measurement, positive color ratio <50% were excluded. Batch processing was applied by macroprocessor Pathology 6 (MediaCybemetics) and MOD values were obtained for each visual field. For each section, 5 visual fields were selected and the mean MOD was calculated.

**Enzyme-linked immuno sorbent assay**

Concentrations of HSP27, TNF-α and IL-6 in sera were measured using commercially available enzyme-linked immunoassay (ELISA) kits (Uscllife, Shanghai, China) according to the manufacturer’s instructions. The minimum and maximum detectable values were 0.312 ng/ml and 20 ng/ml. All samples were assayed in duplicate.

**Statistical analysis**

All data are presented as mean ±SD. Results were analyzed by t test or 1-way ANOVA. \(P<0.05\) was considered significant. Correlation between HSP27 and TNF-α and IL-6 expression was analyzed using the Spearman rank correlation test. Data were analyzed using SAS 16.0 (SAS Institute Inc., Cary, NC, USA).

**Results**

A total of 60 BPH patients who received TURP were enrolled in this study. Hyperplasia of prostate and tissue inflammation were evaluated via hematoxylin-eosin staining by 2 experienced pathologists. Microscopic observation showed papillary or cluster hyperplasia of gland epithelial cells in prostate tissues. Glandular epithelial cells were larger and columnar with inconspicuous nucleoli; interstitial tissues mainly consisted of myofibroblasts, which had pink cytoplasm and short spindle nuclei without clear cell boundaries, arranged around the blood vessels in bundles or whorls to form thick-walled vessels. All 60 patients were diagnosed as having BPH.

Histological inflammation was certified when inflammatory cell infiltration and accumulation were found in the prostate gland. Mild-inflammatory BPH was judged as diffused distribution of lymphocytes around the gland; moderate-inflammatory BPH was judged as increase and aggregation of lymphocyte, glandular atrophy, and saccular enlargement of the glandular lumens; and severe-inflammatory BPH was judged as accumulation and infiltration of inflammatory cells, damage of glandular epithelium basement or emergence of lymph nodules (Figure 1). Among the 60 BPH cases, there were 15...
non-inflammatory BPH (NI), 12 mild-inflammatory BPH (MI), 25 moderate-inflammatory BPH (MOI), and 8 severe-inflammatory BPH (SI).

General data of BPH patients in different groups are listed in Table 1. We found that, compared with BPH groups, patients in inflammatory BPH groups had higher IPSS, more RUV, bigger prostates, and higher expression of PSA and CRP. The value of IPSS, RUV, prostate volume, PSA, and CRP were also significantly different (P<0.05) between different inflammatory BPH groups. The value of QOL and Qmax showed no significant difference between the groups.

Table 1. General data of BPH patients with different degrees of inflammation (\( \bar{x} \pm s \)).

| Group  | IPSS  | QOL   | RUV (ml) | Qmax (ml/s) | Prostate volume (ml) | PSA (ng/L) | CRP (mg/L) |
|--------|-------|-------|----------|-------------|-----------------------|------------|------------|
| NI BPH | 23.7±4.5 | 4.2±1.3 | 157.5±21.1 | 7.8±2.1 | 54.4±18.7 | 3.1±1.2 | 0.2±1.3    |
| MI BPH | 24.7±5.5 | 4.0±0.6 | 178.5±31.1 | 6.6±1.2 | 58.4±15.7 | 3.6±0.9 | 2.4±1.1    |
| MOI BPH| 27.6±4.1 | 4.5±1.0 | 218.5±12.1 | 5.1±0.3 | 67.8±11.3 | 5.4±0.7 | 4.1±1.8    |
| SI BPH | 30.6±5.2 | 5.4±0.6 | 289.6±16.1 | 4.6±1.4 | 76.8±16.3 | 6.2±1.3 | 6.8±1.3    |

IPSS – International Prostate Symptom Score; QOL – quality of life; RUV – residual urine volume; Qmax – maximum flow rate; PSA – prostate specific antigen; CRP – C-reactive protein.

Figure 1. Pathological observation via HE staining of each group. (A) Non-inflammatory BPH group; (B) mild-inflammatory BPH group; (C) moderate-inflammatory BPH group; (D) severe-inflammatory BPH group.
Expression HSP27, TNF-α, IL-6 and CD3 in prostate tissue

The expression of HSP27 and inflammatory cytokines TNF-α, IL-6, CD3 were detected by immunohistochemistry. Results showed that HSP27 was mainly expressed in glandular epithelium and were hardly expressed in mesenchymal cells (Figure 2). HSP27 expression was higher in inflammatory BPH groups than in the non-inflammatory BPH group and increased along with the degree of inflammation. MOD values of HSP27 expression in each group were: NI BPH, 0.0427±0.0062; MI BPH, 0.0371±0.012; MOI BPH, 0.0485±0.014; SI BPH, 0.0565±0.009 (Figure 3). The differences of HSP27 expression between 2 groups were all statistically significant (P<0.01).

There were similar expression patterns of TNF-α, IL-6, CD3 among the 4 groups. Expressions of TNF-α, IL-6 and CD3 were significantly increased in inflammatory BPH groups and were much higher in the SI BPH group (Figures 4–6). Results from MOD showed the same tendency.

Correlation between HSP27 and TNF-α, IL-6, CD3 expression in the NI BPH group and inflammatory BPH group was also analyzed in this study (Table 2). In the NI BPH group Spearman correlation coefficients between the MOD value of HSP27 and TNF-α, IL-6, CD3 were 0.556, 0.651, and 0.571 (P <0.01), respectively. In inflammatory BPH groups, Spearman correlation coefficients between the MOD value of HSP27 and TNF-α, IL-6, CD3 were 0.673, 0.582, and 0.632 (P <0.01), respectively. The results suggested a significant correlation between the expression of HSP27 and TNF-α, IL-6, and CD3.

Expression of HSP27, TNF-α and IL-6 in serum

Serum levels of HSP27, TNF-α, and IL-6 were also detected by ELISA. Expressions of HSP27, TNF-α, and IL-6 in serum were significantly higher in inflammatory BPH groups compared with the NI BPH group (P<0.05) and increased along with the degree of inflammation (Figure 7).
Certain differences exist in the detection rate of histological inflammation in BPH patients reported by Chinese studies and international reports, which are mainly because of the different diagnostic standards. According to the National Institutes of Health Classification System for Prostatitis [13], histological prostatic inflammation is classified as type IV prostatitis. A standardized histopathological classification system for chronic prostatitis was established by the North American Chronic Prostatitis Collaborative Research Network and the International Prostatitis Collaborative Network [14], which provided a common standard for the basic and clinical research on prostatic inflammation associated with BPH. But in China, the...
diagnostic criteria of histopathological prostatic inflammation associated with BPH is not only the presence of inflammatory cells around the glands, but also the infiltration of inflammatory cells into the glandular epithelium and lumen, and destruction of the basement membrane, which is equivalent to Grade 3 (severe) inflammation according to the international standard. In this study, prostate samples from 60 BPH patients were assessed and classified according to the international standard. Among all the 60 BPH cases, 75% of patients presented chronic inflammation with 20% mild-inflammatory BPH (MI, n=12), 41.7% moderate-inflammatory BPH (MOI, n=25), and 13.3% severe-inflammatory BPH (SI, n=8), which further suggested the role of chronic prostatic inflammation in the pathogenesis and progression of BPH.

Heat shock proteins (HSPs) are a group of evolutionarily highly conserved proteins, which can be divided into several major families according to their molecular weight, such as HSP110, HSP90, HSP70, HSP60, HSP27, and ubiquitin. HSPs play an important role in cellular homeostasis via protein-protein interactions. HSP27 (HSPB1), a member of the small HSP family, is a key player in many signaling pathways contributing to tumorigenicity, treatment resistance, apoptosis inhibition, and inflammation. It has long been known that HSP27 is a component of the p38 mitogen-activated protein kinase (MAPK) signaling pathway [15], which is important in the inflammatory response and other important functions in integrating physiological and pathological stimuli [16]. Alford et al. further demonstrated the role of HSP27 in pro-inflammatory cell signaling and the expression of pro-inflammatory genes by using siRNAs to suppress HSP27 expression in HeLa cells and fibroblasts [17]. They found that HSP27 was needed for the activation of TAK1 and downstream signaling by p38 MAPK, JNK, and their activators. HSP27 was also required for IL-1-induced expression of the pro-inflammatory mediators IL-6 and IL-8. In this work we also detected the expression of IL-6 and found that, along with the high expression level of HSP27 in severe-inflammatory BPH patients, the expression of IL-6 relevantly increased, suggesting the activated pro-inflammatory cell signaling by HSP27, which might be mediated by the p38 MAPK signaling pathway, but further verification is needed.

Figure 5. Immunohistochemistry staining of IL-6 in the 4 groups. (A) Basal-inflammatory BPH group; (B) mild-inflammatory BPH group; (C) moderate-inflammatory BPH group; (D) severe-inflammatory BPH group.
Overexpression of HSP27 has also been linked to the development of some cancers, such as pancreatic cancer [18], non-small cell lung cancer [19], colorectal cancer [20,21] and prostate cancer [22], which led to its use as a prognostic marker for these cancers [23]. Liu et al. studied the expression of HSP27 in prostate hyperplasia, prostatic intraepithelial neoplasia, and adenocarcinoma of the prostate by immunohistochemistry, showing that there was a significant increase in HSP27 expression between BPH tissues and cancerous tissues. The positive rate of HSP27 was 6.67% in prostatic hyperplasia, 26.67% in prostatic intraepithelial neoplasia, and 60.00% in adenocarcinoma of the prostate. They also found the expression of HSP27 in poorly differentiated group was higher than that of the well-moderately differentiated group, and HSP27 expression was higher in the bony metastasis group than in the no bony metastasis group, which suggested a potential prognostic role of HSP27 in the occurrence and development of prostate cancer. Our preliminary results also suggested the use of HSP27 as a potential prognostic biomarker for inflammatory BPH.

Epidemiological, histopathological, and molecular pathological studies have been providing emerging evidence implicating

Table 2. Nonparametric correlation between HSP27 expression and TNF-α, IL-6, CD3 in non-inflammatory BPH group and inflammatory BPH group based on the results from immunohistochemistry.

| Group                  | TNF-α | IL-6   | CD3    |
|------------------------|-------|--------|--------|
| Non-inflammatory BPH   | 0.556 | 0.651  | 0.571  |
| Inflammatory BPH       | 0.673 | 0.582  | 0.632  |
| P value                | 0.00143* | 0.00346* | 0.00562* |

Figure 6. Immunohistochemistry staining of CD3 in the 4 groups. (A) Non-inflammatory BPH group; (B) mild-inflammatory BPH group; (C) moderate-inflammatory BPH group; (D) severe-inflammatory BPH group.
inflammation in the pathogenesis of both BPH and prostate cancer [24–26]. De Marzo proposed that exposure to environmental factors such as infectious agents and dietary carcinogens, as well as hormonal imbalances, could lead to injury of the prostate and to the development of chronic inflammation and proliferative inflammatory atrophy (PIA), which might finally make the transition to adenocarcinoma. Based on the potential role of histological inflammation in prostatic hyperplasia and prostate cancer, and the role of HSPs in inflammation, HSP27 might be important in prevention and as a treatment target for inflammatory BPH and prostate cancer. More studies are needed to elucidate the detailed mechanisms underlying the relevance of HSP27 to development and pathological process of BPH with chronic inflammation.

Conclusions

In this study, the expression of HSP27 was detected in the cytoplasm of prostate epithelial cells, without presence in mesenchymal cells, which is consistent with its reported role in EMT in prostate cancer. With more inflammation, the expression of HSP27 increased, suggesting that elevated inflammatory stimulation induces HSP27 expression and promotes progression of clinical symptoms of prostate hyperplasia, resulting in urinary retention or severe urinary tract symptoms in patients. In this study we also found that CD3 expression was positively correlated with HSP27 expression and proinflammatory cytokines TNF alpha and IL-6 expression, which suggests that inflammatory stimuli activates the immune system and stress response, which at the same time participates jointly in the development of prostatic inflammation associated with BPH. Our work suggests the potential role of HSP27 as a prognostic biomarker and therapeutic target for inflammatory BPH.

Statement

There is no conflict of interest in this work.

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