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GENE EXPRESSION PROFILING AND FUNCTIONAL NETWORK ANALYSIS OF BENIGN PROSTATIC HYPERPLASIA MODEL RAT

Hypothesis / aims of study
Benign prostatic hyperplasia (BPH) is a progressive disease that is histologically defined as overgrowth of the epithelial and stromal cells of the transition zone. Recently, various growth factors have been described in the pathophysiology of BPH, but the cellular and molecular processes underlying the pathogenesis and development of BPH remain poorly understood.
In this study, in order to characterize the molecular features of BPH, we performed genome-wide gene expression profiling analysis using experimental BPH rat model, which was recently established as an experimental rat BPH model resembling clinical BPH pathology by implanting fetal urogenital sinus (UGS) into the pubertal male rat ventral prostate.[1]

Study design, materials and methods
BPH model:
Fetal UGS isolated from male 20-day rat embryo was implanted into the pubertal male rat ventral prostate. Implanted UGS, initially weighing approximately 1mg, grew time-dependently, being more than 100mg at 21 days after implantation. Pathological findings show epithelial hyperplasia as well as stromal hyperplasia, which closely resembles human BPH.
The whole-genome oligonucleotide microarray:
The whole-genome oligonucleotide microarray utilizing approximately 30,000 oligonucleotide probes was performed using prostate specimens during the growth process of the prostate (21 days after implantation).

Results
Microarray analyses revealed 209 up-regulated genes (>2 fold change, $p<0.01$) and 85 down-regulated genes (<0.5 fold change, $p<0.01$) in BPH compared with normal prostate (Figure 1).
Gene Ontology Analyses:
Gene ontology analyses of up-regulated genes revealed genetic themes predominantly involved in immune system process (99 genes, $p=1.72 \times 10^{-33}$) developmental process (53 genes, $p=3.54 \times 10^{-6}$), response to stimulus (160 genes, $p=2.21 \times 10^{-16}$), growth (biological regulation; $p=1.64 \times 10^{-6}$, regulation of growth; 6.86×10^{-6}) (Figure 2).
Functional Network Analysis:
Functional network analyses showed that some of the differentially expressed genes belonged to the pathways such as apoptosis, androgen receptor and TGF-beta signaling pathways, as reported previously. We also identified other differentially expressed genes that have been correlated with cell adhesion molecules (GDI-beta, leupaxin, PTPN18 etc), inflammation response pathway (IL-15, CSF-1, IL-18, IL2R etc), and cholesterol biosynthesis (Hmgcs1, Mvk, Mvd, etc).

Interpretation of results
It is thought that BPH involves reactivation of physiologic growth and differentiation pathway that act in embryonic and fetal development. Therefore, this BPH model that emblyonic UGS is implanted into the prostate of adult rat, corresponds to the circumstances of human BPH. We found that this BPH model resembled not only histology but also up-regulated genes or activated pathways of human BPH. We also identified many differentially expressed genes related to the extracellular matrix (ECM) or inflammation of prostate tissue. Such ECM involves passive elastic properties that cannot be relaxed urethral resistance with alpha 1 adrenoceptor antagonists. In addition, it has been reported that inflammation in BPH is associated with focal up-regulation of cytokines and lower urinary tract symptoms. Thus, the investigation that regulates ECM or stroma using this BPH model may develop into new BPH treatment.

Concluding message
This BPH model is more suitable to examine the molecular mechanism of BPH progression compared with other BPH models. Our microarray analysis of BPH model rat contribute to understand the molecular mechanism of BPH progression and to identify molecular targets for BPH treatment.
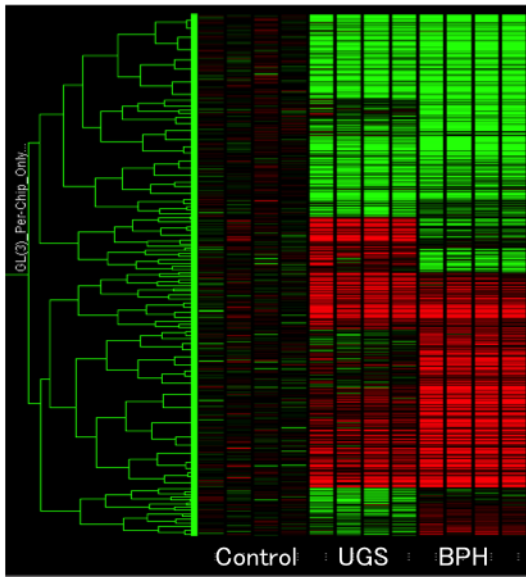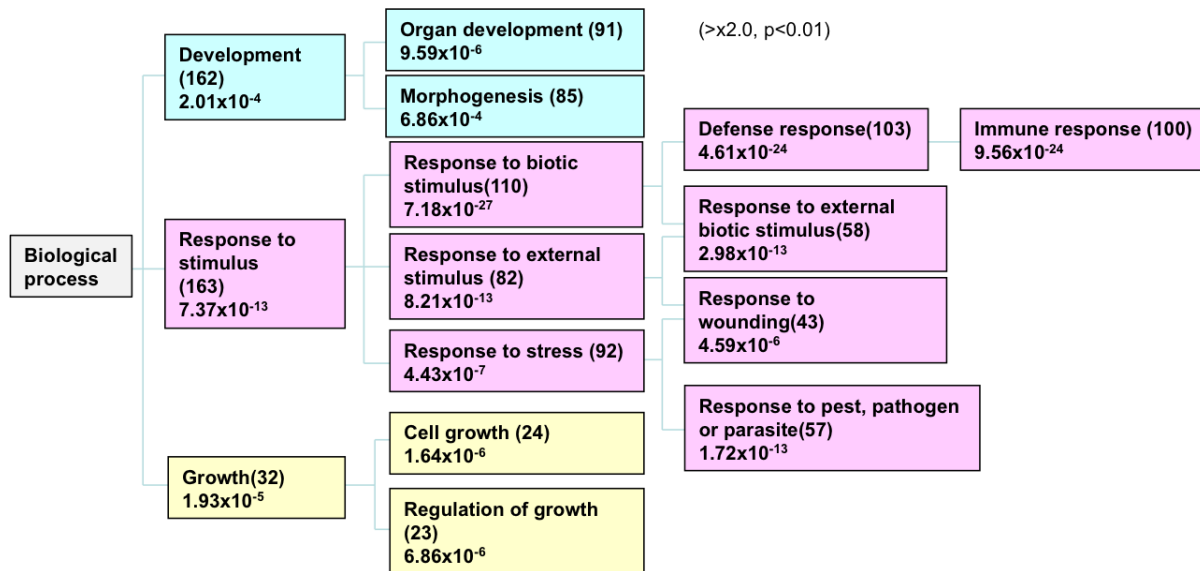
Figure 1: Microarray Analyses

Figure 2: Gene Ontology Analyses

Biological process

Development (162) 2.01×10^{-4}
- Organ development (91) 9.59×10^{-6}
- Morphogenesis (85) 6.86×10^{-4}

(>x2.0, p<0.01)

Response to stimulus (163) 7.37×10^{-13}
- Response to biotic stimulus (110) 7.18×10^{-27}
  - Defense response (103) 4.61×10^{-24} → Immune response (100) 9.56×10^{-24}
  - Response to external biotic stimulus (58) 2.98×10^{-13}
- Response to external stimulus (82) 8.21×10^{-13}
  - Response to wounding (43) 4.59×10^{-6}
- Response to stress (92) 4.43×10^{-7}
  - Response to pest, pathogen or parasite (57) 1.72×10^{-13}

Growth (32) 1.93×10^{-5}
- Cell growth (24) 1.64×10^{-6}
- Regulation of growth (23) 6.86×10^{-6}

References
1. Mori F, Oda N, Sakuragi M, Sakakibara F, Kiniwa M, Miyoshi K. New histopathological experimental model for benign prostatic hyperplasia: stromal hyperplasia in rats. J. Urol., 181, 890–898 (2009).