603

Hata J[1], Matsuoka K[1], Koguchi T[1], Satoh Y[1], Akaihata H[1], Ogawa S[1], Kataoka M[1], Haga N[1], Ishibashi K[1], Aikawa K[1], Kojima Y[1]

1. *Fukushima Medical University*

COMPLEMENT ACTIVATION MECHANISM ACTIVATED BY AUTOANTIGEN RECOGNITION DURING GROWTH OF BENIGN PROSTATIC HYPERPLASIA

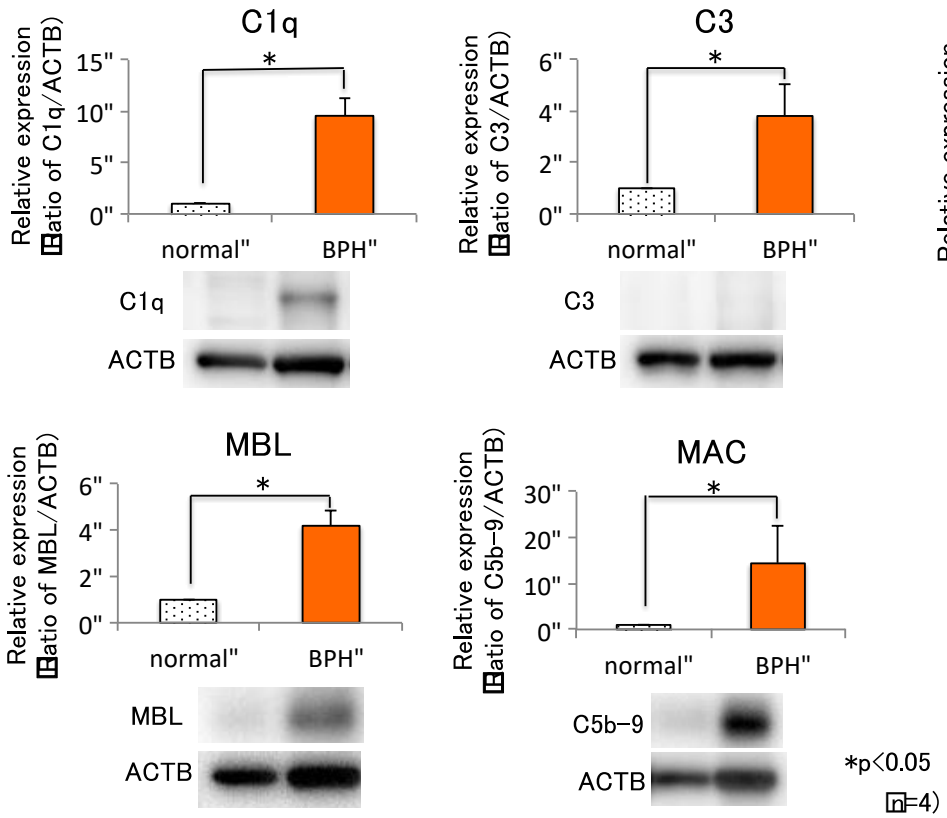
Hypothesis / aims of study

The association between the pathogenesis of benign prostatic hyperplasia (BPH) and inflammation has recently received attention. We previously showed that both the inflammation response pathway and the classical complement pathway are activated in BPH tissue from model rats with stroma-dominant BPH[1)]. The classical complement pathway is activated by autoantigens that recognize immunocomplexes and is responsible for various diseases via a mechanism that amplifies inflammation. We postulated that immunocomplexes amplify inflammation through complement activation, which leads to prostatic proliferation. Therefore, we expressed complement factors, analyzed their functions, and identified autoantigens to understand the pathogenic mechanism of BPH.

Study design, materials and methods

Fetal urogenital sinus (UGS) isolated from male 20-day-old rat embryos was implanted into the ventral prostate of pubertal male rats to create rat models of BPH. Complement factors were expressed and functionally analyzed in BPH tissues, and then serum concentrations of IgG and the expression of complement factors in BPH tissues were assessed. We immunoprecipitated BPH protein using an anti-IgG antibody to identify antigens, and analyzed the protein by mass spectrometry after SDS-PAGE separation. The expression of complement factors in human BPH tissue was also analyzed.

Fig 1. Expression of complement factors in BPH



Results

Expression of complement factors C1q, C3, MBL, Factor B and MAC was significantly up-regulated in tissues from BPH rats when compared with those from normal rats (Fig 1. $p<0.01$). The classical complement pathway was initially activated, followed by an alternative complement pathway activated in BPH. These complement factors were also up-regulated mostly in stromal areas of human BPH. Serum IgG concentration was significantly increased (398.1 ng/mL, $p<0.01$) in rat BPH and IgG was deposited in

stromal areas of the BPH. Mass spectrometry of IgG binding protein identified Annexin, Hsp90, α-SMA and β-actin as antigens of immunocomplexes.

Interpretation of results

Annexin, Hsp90 and β-actin are known to present in various cells. It has also been reported that these molecules are exposed as antigens on the cell surface due to cytotoxicity by stimulation such as ischemia. On the other hand, α-SMA is reported to be a marker of myofibroblasts in BPH and is thought to be involved in the BPH growth process. In the present study, antigen-antibody reactions recognizing these molecules as autoantigens occur in the BPH growth process. Subsequently, immunocomplexes activate the classical complement pathway through binding to C1q, and then the lectin pathway is activated. Complement system activation was thought to be responsible for the proliferation process of BPH by various inflammatory cell proliferation and tissue remodeling. In other words, the autoimmune reaction may be involved in the growth process of BPH.

Concluding message

We clarified that the immune system is responsible for the development of BPH. Complement pathway activation by immunocomplexes recognizing Annexin, Hsp90, α-SMA and β-actin as autoantigens might be responsible for the pathogenesis of BPH.

References

1. Hata J, Akaihata H, Kojima Y, et al. Molecular classification of benign prostatic hyperplasia: A gene expression profiling study in a rat model. Int J Urol. 2016 Jul;23(7):599-612.

Disclosures

Funding: NONE **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** the Animal Care Committee of Fukushima Medical University