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INTERLEUKIN 18 MAY INDUCE CHANGES IN THE PROSTATIC STROMAL COMPONENTS VIA THROMBOSPONDIN 1 PRODUCTION IN A NEWLY DEVELOPED RAT BENIGN PROSTATIC HYPERPLASIA MODEL.

Hypothesis / aims of study

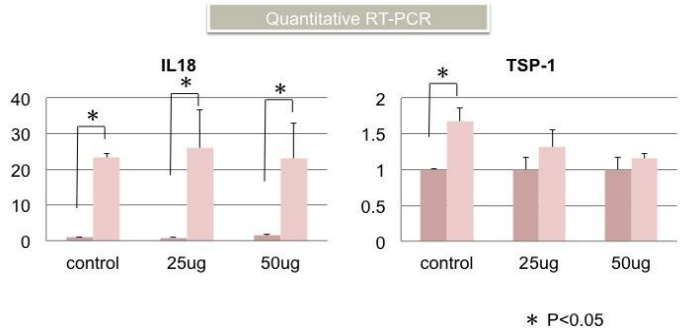
Inflammation plays an important role in the development of benign prostatic hyperplasia (BPH), but little is known about the exact pathogenetic mechanism of the relationship. To elucidate the relationship between the inflammatory reaction and development of BPH, we used a stromal hyperplasia rat model and analyzed its genomic profile by using a cDNA microarray. We focused on the most strongly expressed proinflammatory cytokine, interleukin 18 (IL-18), in several cytokine genes related to the inflammatory response. Previously, we reported in an in vitro study that IL-18 might lead to prostatic stromal hyperplasia via the production of thrombospondin -1 (TSP-1), which is known as an activator of transforming growth factor beta 1 (TGF-beta-1) (1). The aim of the present study was to elucidate the relationship between the development of BPH and the roles of IL-18 and TSP-1 by performing an in vivo study.

Study design, materials and methods

We produced an experimental BPH rat model with pathologically stromal component-dominant hyperplasia (2). The fetal urogenital sinuses (UGSs) of 20-day-old rats were dissected and transplanted into the right ventral prostate of 7-week-old Sprague-Dawley rats. After 21 days, the host rats were killed and the transplanted tissues were harvested as BPH tissues. The left ventral prostates of the host rats were dissected and used as controls. To clarify the role of IL-18 in the development of BPH, we administered 25 or 50 µg/mL of the IL-18-binding protein (IL-18BP), an inhibitor of IL-18, or saline as the vehicle in the peritoneum of the model rats on days 1, 4, and 7. To assess the expression levels of IL-18 and TSP-1, which were identified in the analysis, qRT-PCR was performed by using BPH and control tissues in the respective groups. Furthermore, to analyze the function of these proteins, we performed Masson trichrome staining by using rat BPH tissues.

Results

No significant differences in body and transplanted tissue weights were observed between the groups. The mRNA expression level of IL-18 significantly increased in the BPH tissues in both groups. The administration of IL-18BP affected the dose-dependent decreases in TSP-1 mRNA expression levels. The Masson trichrome stain showed that the BPH and control tissues had fibrils of collagen and smooth muscle in the stromal components. Moreover, the expression levels of the collagen fibrils were likely decreased by the administration of IL-18BP in the BPH tissues.



Interpretation of results

Previously, we reported that IL-18 expression induces TSP-1 production in prostatic smooth muscle cells and that TSP-1 is involved in the proliferation of prostatic stromal cells in vitro. Thus, we considered that IL-18 and TSP-1 have important roles in the development of BPH. In this study, administration of IL-18BP, which inhibits IL-18 activities, decreased the mRNA expression level of TSP-1 and the ratio of collagen fibrils to the stromal components. Although the decrease in TSP-1 expression level did not contribute to the transplanted tissue weight, this might have led to histological changes in the prostatic stromal components. We speculate that TSP-1 expression may exert an indirect effect on the development of BPH via the activation of TGF-beta-1 and may be directly involved in the proliferation of prostatic stromal components.

Concluding message

IL-18 may act in the pathogenesis of BPH by inducing TSP-1 production in the prostatic stromal components. We consider that inflammation contributes to BPH development and that IL-18 and TSP-1 play an integral part in this process.

References

1. Hamakawa et al. Prostate. 74:590-601, 2014
2. Mori et al. J Urol. 181:890-898, 2008

Disclosures
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