

INHIBITORY EFFECTS OF TADALAFIL ON PROSTATE CELL GROWTH; A STUDY USING A NOVEL HUMAN BENIGN PROSTATIC HYPERPLASIA XENOGRAPHS IN SUPER-SCID MICE

Hypothesis / aims of study

Benign prostatic hyperplasia (BPH) is characterized by a pathologic proliferation of the prostate glandular and stromal tissues, and subsequent induction of lower urinary tract symptoms. Emerging evidences suggest that phosphodiesterase-5 (PDE-5) inhibitors improve urinary symptoms in patients with BPH. However, the underlying mechanisms are not well understood. This is partly because there is no established human BPH xenograft model. Therefore, the objective of this study is to establish a novel human BPH xenograft model, and to evaluate the effect of Tadalafil, the PDE-5 inhibitor, on BPH tissues using our BPH xenograft model.

Study design, materials and methods

Human BPH tissue was obtained from a single patient who had undertaken retropubic prostatectomy for the treatment of BPH and was transplanted under the skin of super-SCID mice; SCID mice with macrophage dysfunction. BPH tissues were collected 2, 6 and 12 months after transplantation with sustained release of testosterone pellet. Tissues of 2 months treatment with Tadalafil orally or nothing (control) were also collected. Immunohistochemical study was performed to examine the histology and expression of cell type-specific markers in xenografts, including PSA, androgen receptor (AR), p63 (basal cell marker), cytokeratin 8(K8, luminal cell marker) and human-specific CD31 (human vessel marker). We next assess the effect of Tadalafil on the prostate cell proliferation by Ki67 and apoptosis by cleaved caspase-3. Endothelial NOS (eNOS), cGMP-dependent kinase G, and COX-2 expression were also examined.

Results

The implanted tissue contained normal prostatic components; the gland showed two layers of epithelial cells. Inner layer expressed K8, AR and PSA, and outer layer was positive for p63 (Fig.1). A considerable amount of the human originated vessels was apparent. After 2 months of Tadalafil treatment, a proliferation index (percentage of Ki-positive cells) was significantly reduced, compared with control in epithelial cells (1.4% vs. 3.9%, $p<0.05$) as well as in stromal tissues (51.7 vs.14.1 cells/mm², $p<0.05$) (Fig. 2). Cleaved caspase-3 positive cells were significantly increased by Tadalafil. In addition, Tadalafil induced up-regulation of eNOS expression and down-regulation of COX-2 expression.

Interpretation of results

Our novel xenograft model has maintained appropriate histology and protein expression after 12 months transplantation, and may serve as a useful human BPH model. Our study also indicates that Tadalafil attenuates the cell growth and induce apoptosis in benign prostate cells through NO signalling.

Concluding message

This study provides a therapeutic potential of Tadalafil for reducing prostate volume in patients with BPH.

Fig. 1 Protein expression of transplanted BPH tissue in super-SCID mice

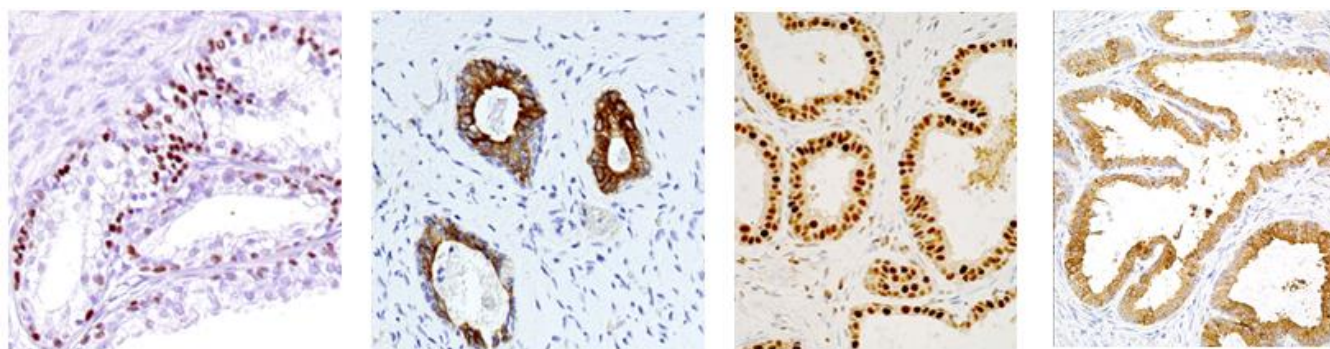
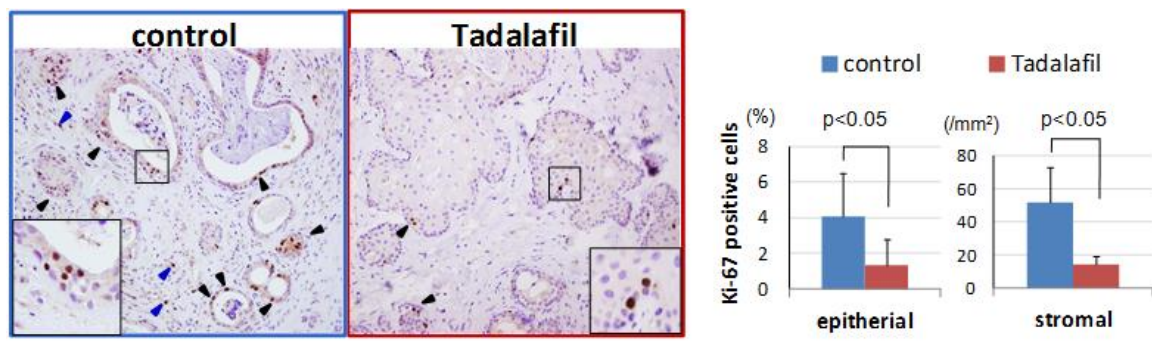


Fig.2 Quantitative assessment of proliferation by Ki-67 expression in xenografts.



References

1. Nomura T, et al., Cancer Res. 1997

Disclosures

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