STERIOD HORMONE IMBALANCE STIMULATES OSTEOPTONIN EXPRESSION AND INFLAMMATION IN THE MOUSE PROSTATE

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Background

Inflammatory processes in the prostate are linked to the development of lower urinary tract symptoms (LUTS) in men. Steroid hormone imbalance is a major age-associated factor driving LUTS, but its relationship to inflammation is not fully understood. Our previous studies identified that osteopontin (OPN), a pro-inflammatory cytokine, is abundant in the prostate of men with LUTS and its secretion is stimulated by inflammation.

This study investigates whether an increase in estradiol-testosterone ratio drives inflammation in the prostate and whether OPN is involved in this process.

Methods and Materials

Male C57BL/6J (WT) or C57BL/6J (OPN-KO) mice were surgically implanted with slow-releasing subcutaneous pellets containing 25 mg testosterone (T) and 2.5 mg estradiol (E2) (T+E). Mice were euthanized two or six weeks later.

The protein expression of OPN, and inflammatory markers, cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NFκB), was detected by immunohistochemistry. Nuclear and cytoplasmic optical density was detected and quantified by the ImageJ software package.

Results

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Inflammation

Dorsal epithelium

Estradiol

Testosterone

OPN

NFκB

Conclusions

We identified that testosterone and estradiol treatment specifically stimulates osteopontin expression in epithelial cells in the ventral prostate. Elevated OPN secretion will potentially trigger NFκB expression and its translocation to the nucleus. NFκB is known to promote the expression of various cytokines and chemokines which will attract immune cells to the prostate causing inflammation.

Future Goals:

➢ Investigate the expression of cytokines and chemokines in WT and OPN-KO mouse prostates
➢ Determine whether OPN and NFκB expression are increased in the prostatic urethra where pathological changes can be associated with urinary function

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Figure 1: OPN expression is elevated in the ventral prostate two weeks after T+E2 pellet implantation. Optical density of OPN staining shows an increase in the epithelium of the ventral (VP) A and C, but not that of the dorsal prostate (DP B). OPN expression was not significantly increased six weeks after pellet implantation. Significance was assessed with the Mann-Whitney test **: p<0.001.

Figure 2: NFκB optical density, but not COX2, is upregulated in response to T+E2 treatment in prostate epithelial cells. Cytoplasmic COX2 in the DP (A) or in the VP (B) was not significantly affected by steroid hormone treatment. Nuclear NFκB expression was significantly upregulated by T+E2 treatment in the VP (C) but not in the VP (B). Significance was assessed with the Kruskal-Wallis test *: p<0.05; **: p<0.01.

Figure 3: Stromal NFκB is increased in response to steroid hormone treatment in the VP which effect is abolished in OPN-KO mice. Stromal nuclear NFκB expression was unaffected by T+E2 treatment in the DP (A) but was significantly increased in the VP in OPN-KO mice (B) 2 weeks after pellet implantation. No significant change in nuclear NFκB was observed after 6 weeks in the DP (C) or the VP (D). Significance was assessed with the Kruskal-Wallis test*: p<0.05.