Prostate Immune Remodeling in Steroid Hormone Imbalance

Petra Popovics, PhD1,2; Kegan O Skalitzky1,2; Elise Schroeder1,2; Chad M Vezina1,2,3; William A Ricke1,2

1Department of Urology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA; 2George M. O'Brien Center of Research Excellence, University of Wisconsin, School of Medicine and Public Health, Madison, WI, USA; 3Department of Comparative Biosciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, USA

Chronic inflammation in the prostate is associated with lower urinary tract symptoms in the aging men, but the molecular mechanism and its connection to steroid hormone imbalance are unknown. Previous studies investigating the effects of testosterone and estradiol did not evaluate initial changes in the immune environment that may drive chronic inflammation contributing to the pathogenesis of urinary dysfunction. Thus, our study aims to characterize immunological changes specifically driven by steroid hormone imbalance.

Hormonal imbalance was generated by the surgical implantation of pellets containing 25 mg testosterone (T) and 2.5 mg estradiol (E2) to male C57BL/6J (WT) or Spp1tm1Blh/J (OPN-KO) mice for two or six weeks. Nanostring analysis was performed on ventral prostates. OPN, CD45 and Vimentin protein expression was investigated using immunohistochemistry. Fluorescent in situ hybridization was used to identify T-cells (Cd3e), macrophages (Cd68) and B-cells (Cd19). H&E, toluidine blue and lipid staining was also utilized.

Nanostring analysis identified the upregulation of several pathways related to the changing immune environment. It also identified OPN as an important T+E2-inducible gene. Steroid hormone treatment significantly increased immune cell-infiltration, specifically that of the macrophages, which effect was diminished in OPN-KO mice. Osteopontin levels were highly increased in luminal macrophages, which were predominantly identified as foam cells in T+E2 mice.

Our study associated tissue macrophages, luminal foam cells and osteopontin with the early stages of prostate steroid hormone imbalance and as potential drivers of urinary dysfunction.