INTRODUCTION

Benign prostatic hyperplasia (BPH) is characterized by proliferation, smooth muscle changes, and fibrosis of the prostate. The single greatest risk factor for BPH is age, with nearly 100% of men in their eighties affected. Many men with BPH develop lower urinary tract symptoms (LUTS), which significantly reduce their quality of life as disease severity progresses. Given the multifactorial nature of the disease, current treatment options fail to provide long-term relief for the majority of BPH/LUTS patients. While the physiological link between BPH and aging is clear, the molecular mechanisms have yet to be fully elucidated. Recently, it has been demonstrated that an aged mouse model recapitulated the lower urinary tract dysfunction of BPH/LUTS. Additionally, the aging process is characterized by multiple molecular changes including cellular senescence, mitochondrial dysfunction, deregulated nutrient-sensing, and loss of proteostasis. This study aims to identify the role of mitochondrial dysfunction in the prostate of aged mice and determine how it contributes to fibrosis and disease progression.

HYPOTHESIS

We hypothesize that mitochondrial dysfunction is occurring due to a poorly functioning complex I of the electron transport chain, and that this dysfunction is contributing to fibrosis in BPH/LUTS.

METHODS

- C57Bl/6j mice were obtained from Jackson Laboratory (2 months) and the NIA (24 months). Mice were euthanized and the prostate harvested; tissues were formalin-fixed and paraffin-embedded.
- Tissue sections were stained using multispectral quantitative immunofluorescence via the OPAL kit for NDUFS3 and PINK1. Using InForm® software, we spectrally unmixed each fluorophore and quantified optical density.
- BPHPrS1 cells were cultured and 24 hours post-plating, cells were treated with DMSO vehicle, 25 μM rotenone, or 25 μM idebenone in combination with 1 μM idebenone.

RESULTS

- Mitochondrial dysfunction contributes to fibrosis in aging-associated benign prostatic hyperplasia (BPH)

CONCLUSIONS

- NDUFS3 is decreased in old mice, suggesting mitochondrial function associated with complex I of the electron transport chain is diminished in the aged prostate.
- PINK1 is decreased in old mice, suggesting Parkin-dependent mitophagy of dysfunctional mitochondria is decreased in prostate.
- Rotenone treatment of BPHPrS1 cells results in an increase in markers associated with mitochondrial dysfunction, fibrosis, and increases in genes associated with collagen. 
- Collagen gene expression induction can be bypassed with a synthetic CoQ10 analog.

FUTURE DIRECTIONS

- Treat an aging mouse model of BPH with idebenone or other bypass agents to determine if mitochondrial dysfunction and fibrosis can be ameliorated in vivo.
- Characterize mitochondrial bioenergetics and overall dysfunction.

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