Mitochondrial dysfunction in benign prostatic hyperplasia

Don DeFranco, PhD

α-adrenergic blockers treat the symptoms of BPH/LUTS
5α-reductase (5AR) inhibitors decrease prostate size
TURP may need to be performed if drug treatments fail

Increased Cox-2 expression in inflammatory vs non-inflammatory BPH
Combination therapies: 5ARi + NSAIDs (mixed results, beneficial effects not long lasting) – Why?

Focal areas of Cox-2 overexpression in BPH (Damber Lab, 2004)
Reciprocal Regulation of Cox-1 and Cox-2

BPH-1 Cells

COX-1 vs COX-2 in MΦ: Differential gene expression
(Li X et al., (2018) J. Lipid Res.)

Genomic and lipidomic analyses differentiate the compensatory roles of two COX isoforms during systemic inflammation in mice

Xinzi Li,* Lindmila L. Mazalenskaya,† Laurel L. Ballantyne,† Hu Meng,‡ Garret A. FitzGerald,* and Colin D. Funk*
COX-1 IHC in Human Prostate

Statistically significant increase in COX-1 expression in BPH compared to normal adjacent tissue.

Physiologic or Pathophysiologic Regulators of COX-1?
Age-dependent gradual mitochondrial dysfunction: Is this relevant to BPH progression?

Focus on ETC Complex I: Dysfunction associated with human diseases
**Rotenone:** an inhibitor of complex I of the mitochondrial respiratory chain

- Leading to a blockade of oxidative phosphorylation with limited ATP production;
- Incomplete electron transfer to oxygen could cause the formation of ROS.

Rotenone exposure has been shown to correlate with the occurrence of several Parkinson’s disease (PD)-like symptoms in humans. Chronic administration of rotenone has been used to create experimental animal models of PD.
Hypothesis: Age-dependent decline in mitochondrial ETC Complex I activity contributes to BPH pathogenesis

Repression of NDUFS3 in prostates of rotenone-treated rats

Rotenone induction of COX-1 & COX-2 in RWPE-1 Cells (K. He)

Normal BPH

TOM 20 IIF (D. Stolz) in BPH tissue

Compensatory increase in mito mass?

Confidential
ROTENONE DISRUPTS AUTOPHAGIC FLUX (MITOPHAGY?) IN PrECs

Rot E F

MITOPHAGY ASSESSMENT
Proximity Ligation Assay
Tom20 & p62 Colocalization
RWPE-1 Cells (K. He & R. Di Maio)

Diversion of p62 to damage mito?
Rotenone Effects on Cell Junction Proteins In RWPE-1 Cells

Kai He

**Permeability Assay**

**In Vivo** Rat Study (Neuroniol Dis 2018): Rotenone treatment induced intestinal hyperpermeability and disrupted expression of ZO-1, Occludin, Claudin-1

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Does mitochondrial dysfunction contribute to prostatic fibrosis?

Idiopathic Pulmonary Fibrosis: Aging, Mitochondrial Dysfunction, and Cellular Bioenergetics
**FUTURE DIRECTIONS**

Is mitochondrial (ETC Complex I) dysfunction (or altered mitophagy) associated with the BPH progression?

*Complex-I Alteration and Enhanced Mitochondrial Fusion Are Associated With Prostate Cancer Progression.*

“Respiratory Complex I-mtDNA mutations (in the NADH ubiquinone oxidoreductase chain 4 gene), MFN2, and IMMT proteins were detected in the circulating exosomes in serum of men with benign prostate hyperplasia (BPH) and progressive PCa!

Can drugs that “restore” mitochondrial function reverse various phenotypes observed with in vitro and in vivo models of prostatic epithelial cell dysfunction, inflammation, or LUTS?
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