Androgenic to estrogenic switch due to epigenetic silencing of steroid 5-α reductase 2

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BACKGROUND: The steroid 5-α reductase type 2 (SRD5A2) is critical for prostatic development and growth. Hormonal regulations, including strategies to block SRD5A2 using 5-alpha reductase inhibitors (5ARI), are a mainstay in the treatment of prostatic diseases. However, contrary to common belief, we have found that expression of SRD5A2 is not static but epigenetic modulations by DNA methyltransferase and pro-inflammatory cytokines play important roles in silencing of SRD5A2. Here we demonstrate that silencing of SRD5A2 leads to a switch from an androgenic to an estrogenic phenotype in human adult prostates.

METHODS: Prostatic samples were obtained from patients with symptomatic BPH undergoing transurethral resection of prostate (TURP) surgery. Methylation of SRD5A2 promoter was assessed using Methylated CpG Island Recovery Assay (MIRA). RNA was extracted for whole-transcriptome profiling analysis by Illumina Human BeadChip Arrays. Prostatic protein expression of SRD5A2, androgen receptor (AR), estrogen receptor (ER) subunits, and aromatase were determined in a panel of six BPH patients by Western blot, immunohistochemistry (IHC), and ELISA assays. Prostatic levels of testosterone (T), dihydrotestosterone (DHT), estradiol (E) were measured by HPLC-MS. In in vitro study, primary prostatic stromal cells and epithelium cell line BPH-1 were cultured and treated with TNF-α and IL-6, mRNA levels of different moleculars were determined by qPCR.

RESULTS: In prostate specimens that were methylated at the SRD5A2 promoter locus, estrogen response genes were identified as one of the most significantly upregulated gene family members. SRD5A2 methylation and lack of protein expression was associated with significantly upregulated levels of T, E and aromatase, while DHT was significantly decreased. Phosphorylated ERα (pERα) was significantly upregulated, but the levels of ERα, ERβ and pERβ were not significantly affected in the absence of SRD5A2. In primary prostatic stromal cells, pro-inflammatory mediators, TNF-α but not IL-6, suppressed the level of SRD5A2 and upregulated aromatase activity and ERα. The level of SRD5A1 and ERβ did not change significantly.

CONCLUSIONS: Our study demonstrates, for the first time, that estrogen response genes are a key distinguishing feature in prostatic specimen lacking SRD5A2 expression. Our findings of elevated aromatase and ERα levels suggest an androgenic to estrogenic switch in prostate tissues with silenced SRD5A2, which may potentially modulate the prostate growth and therapeutic responses. Targeting the aromatase-estrogen-ER axis in patients who lack SRD5A2 expression may serve as an effective treatment strategy in patients suffering from prostatic diseases.

Conflict of Interest: None

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