Obesity-associated inflammation induces androgenic to estrogenic switch in the prostate gland

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BACKGROUND

- The steroid 5-α reductase type 2 (SRD5A2) is critical for prostatic development and growth. Strategies to block SRD5A2 using 5-α reductase inhibitors (5ARIs) remain a mainstay in the treatment of benign prostatic hyperplasia (BPH).
- However, one-third of men are resistant to 5ARIs therapies. We previously showed that body mass index (BMI) correlates with increased SRD5A2 gene promoter methylation and decreased protein expression in men with symptomatic BPH. We have demonstrated that there is an **"androgenic to estrogenic switch" when SRD5A2 is absent in the prostate gland.**
- Here we wished to identify whether obesity-associated inflammation contributes to androgenic to estrogenic switch in human prostate tissue.

METHODS

- Human prostatic stromal cells were from patients undergoing prostate reduction therapy for BPH.
- Macrophages THP-1 were differentiated, followed by treatment of myristic acid (MA) to induce inflammation. Conditioned media were collected for culturing stromal cells.
- Mice prostatic tissues were collected from C57BL6 mice fed with regular fat diet (RFD) or high fat diet (HFD) for 6 weeks.
- RNA was extracted from stromal cells and mice prostate tissues, and transcriptional expressions of SRD5A2, aromatase, androgen receptor (AR) and estrogen receptor α (ESR1) were determined by qPCR.
- Prostatic specimens were from 35 patients who underwent transurethral resection of the prostate for symptomatic BPH at Massachusetts General Hospital.
- Prostatic levels of testosterone, dihydrotestosterone (DHT) and estradiol were measured by HPLC-MS.

RESULTS

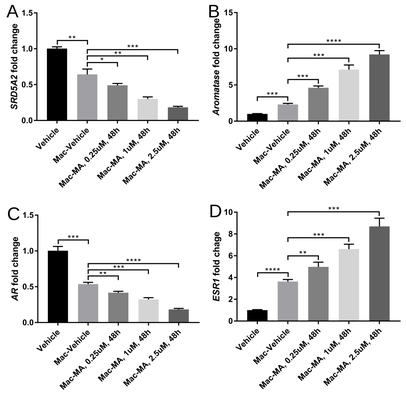


Fig. 1. The levels of SRD5A2 (A) were reduced, aromatase (B) were increased, androgen receptor (C) were reduced and ESR1 (D) were increased in primary cultured prostatic stromal cells when they were treated with macrophage conditioned media. Macrophages were pre-treated with myristic acid (MA) or vehicle, followed by collecting the conditioned media.* P<0.05; **P<0.01; ***P<0.001.

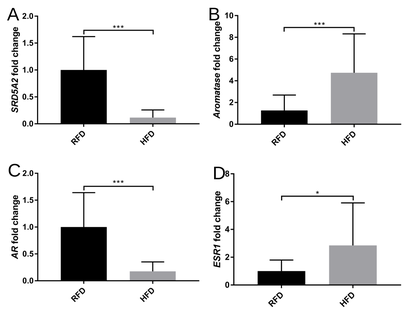


Fig. 2. The levels of SRD5A2 (A) were reduced, aromatase (B) were increased, androgen receptor (C) were reduced and ESR1 (D) were increased in HFD groups, compared with RFD groups. RFD: regular fat diet, n=4; HFD: high fat diet, n=4. * P<0.05; **P<0.01; ***P<0.001.

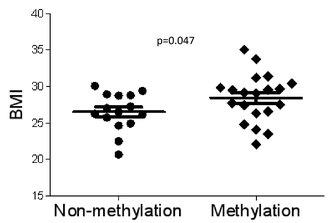


Fig. 3. Increased BMI was significantly correlated with promoter methylation of *SRD5A2* in human prostatic tissues. Non-Methylation group: n=15; Methylation group: n=20. BMI: body mass index.

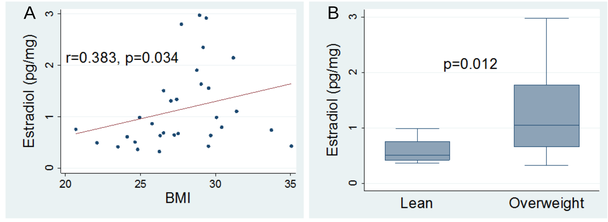
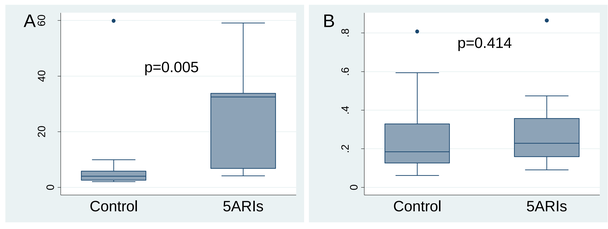


Fig. 4. (A) The level of prostatic estradiol was correlated with BMI. (B) The level of prostatic estradiol in overweight group was significantly higher than in lean group. Lean group: n=8; Overweight group: n=27.



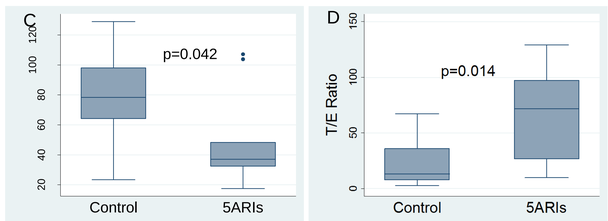


Fig. 5. The prostatic hormonal milieu was changed with 5ARIs therapy. Treatment with 5ARIs dramatically increased the level of testosterone (A), decreased the level of DHT (C), and increased the ratio of testosterone/estradiol (T/E) in the prostate specimens (D). Treatment with 5ARIs did not significantly affect the level of estradiol (B). Control group: n=19; 5ARIs group: n=16.

CONCLUSIONS

- We demonstrated that there is an "androgenic to estrogenic switch" when SRD5A2 is absent in the prostate gland.
- Obesity- associated inflammation further induces androgenic to estrogenic switch, at least partly via *SRD5A2* promoter methylation, silencing of SRD5A2 expression, and increased expression of aromatase.
- Targeting the estrogenic signaling may serve as an effective treatment strategy in BPH patients who do not express SRD5A2.

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