Lessons Learned About Prostatic Transformation from the Age-Related Methylation of 5α-Reductase Type 2 Gene

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A nearly universal plight among aging males throughout the world is the hyperplastic growth of the transition zone within the prostate, known as benign prostatic hyperplasia (BPH).<sup>1</sup> With approximately 50% of males throughout the world developing BPH, it is the most common neoplasia in humans. Although the etiology of BPH is not fully resolved, it is known that its maintenance requires a continuous supply of androgen. This is documented by the observation that testicular suppression via luteinizing hormone releasing hormone superagonist reversibly reduces prostatic size and clinical BPH symptoms.<sup>2</sup> Likewise, the normal prostate is dependent on adequate chronic androgenic stimulation for both its fetal development and adult maintenance.<sup>3</sup>

Treatment with 5α-Reductase Inhibitors in BPH

In both BPH and normal prostate, androgen stimulation requires irreversible conversion within the prostate of circulating testosterone into the more potent androgen, dihydrotestosterone, via enzymatic activity of 5α-steroid reductase (SRD5A). There are at least three SRD5A genetic isoforms expressed within the prostate<sup>4,5</sup>, however, only germline inheritance of loss-of-function mutations in the SRD5A2 gene is known to retard normal prostate development, thus preventing BPH.<sup>3</sup> On the basis of these observations, orally active drugs (eg, finasteride and dutasteride), which reversibly inhibit SRD5A1 and irreversibly inhibit SRD5A2 enzyme,<sup>6</sup> have been clinically developed for the treatment of BPH. Chronic daily treatment with these 5α-reductase inhibitors results in a decrease in prostate size by approximately 25% within 4 to 6 months and is further associated with improvement in clinical symptoms.<sup>7,8</sup> Interestingly, approximately 30% of patients do not respond to such chronic 5α-reductase inhibitor treatment.<sup>7,8</sup>

This overall response rate is intriguing because Niu et al<sup>9</sup> reported that prostatic expression of the SRD5A2 gene is variable and similarly absent in one third of aging men with BPH and that this down-regulation is associated with hypermethylation of CpG islands in the promoter of SRD5A2 gene detected using methylation-specific pull-down PCR. In the current issue of *The American Journal of Pathology*, this group proposes an inflammation-driven process involving DNA methyltransferase 1-dependent tumor necrosis factor-α/NF-κB/IL-6 signaling pathway as a mechanism for such epigenetic silencing of the SRD5A2 gene in BPH.<sup>10</sup> In this study, transurethral resected BPH tissue from patients without 5α-reductase inhibitor treatment was analyzed. Therefore, the study limits assessing whether the hypermethylation of SRD5A2 gene may identify patients who will lack clinical response to inhibition of 5α-reductase. To address this important clinical issue, needle biopsy tissue could be analyzed from BPH patients who are administered 5α-reductase inhibitors to test prospectively if SRD5A2 gene hypermethylation may predict clinical response.

What Does Hypermethylation of the SRD5A2 Gene Inform About Prostatic Neoplasia?

The determination of whether hypermethylation of SRD5A2 gene may predict clinical response to treatment with

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What Drives Chronic Inflammation in the Prostate?

In addition to the findings of Olumi et al.10 other studies also support the hypothesis that chronic inflammation induces epigenetic reprogramming, resulting in a growth advantage in both BPH and prostate cancer during aging. With regard to the development of BPH, there is an increase in the ratio of prostate stromal/epithelial area, going from a 3:1 ratio in nonhyperplastic normal prostates of young men to a ratio of 5:1 in BPH tissue of older men.16 This change is associated with an increase in cellular turnover in both the stromal and epithelial compartments of BPH versus normal prostate tissue.17 Two thirds of this stromal compartment in BPH tissue is composed of smooth muscle (SM),18 and BPH is associated with subtle epigenetic reprogramming in the phenotype of these SM cells, as demonstrated by their down-regulation in SM myosin heavy chain19 and up-regulation of \( \alpha_2 \) macroglobulin mRNA expression.20 The mechanism for such changes is not fully resolved, but it is known that SM cells switch phenotype from contractive to proliferative in response to extrinsic and/or intrinsic stimuli, a process termed SM phenotype modulation.21

There are data supporting the concept that such SM phenotype modulation occurs in BPH due to a chronic immune inflammatory process.22 This idea is based on the fact that nearly all BPH specimens contain inflammatory infiltrates, but no bacterial or foreign antigens have been identified.14,22 The infiltrate consists predominantly of chronically activated CD4+ T lymphocytes, which are permanently recruited to prostate tissue via elevated expression of IL-15 and interferon \( \gamma \), proinflammatory cytokines produced by prostate SM and infiltrating T cells, respectively.22,23 Dysregulation of the immune response in BPH is further compounded by elevated expression of the proinflammatory IL-17 by T cells stimulating enhanced production of IL-6 and IL-8, which themselves stimulate stromal growth, further increasing IL-15 levels.22,23 These combinational events thus initiate a chronic inflammatory process. Such a chronic inflammatory process amplifies disruption of the barrier function of the epithelial tight junctions, allowing more autoantigens (eg, prostate-specific antigen and human glandular kallikrien-2) to leak into the prostate stromal compartment, inducing a vicious cycle of chronic inflammation within the prostate.24,25

In conclusion, such chronic inflammation provides both a driving force for induction of epigenetic changes and a selective microenvironment for the outgrowth of neoplastic cells in the prostate of men as they age. Thus, inhibiting such chronic inflammation within the prostate of aging males is a promising approach for chemoprevention for both BPH and prostate cancer.24,25

References

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