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Personalized Medicine for Management of Benign Prostatic Hyperplasia

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Abstract

Purpose—Benign prostatic hyperplasia (BPH) affects over 50 percent of men by age 60 and is the cause of millions of dollars of healthcare expenditure for treatment of lower urinary tract symptoms (LUTS) and urinary obstruction. Despite the widespread use of medical therapy, there is no universal therapy that treats all men with symptomatic BPH, and at least 30% of patients do not respond to medical management and a subset require surgery. Significant advances have been made in understanding the natural history and development of the prostate, such as elucidating the role of the enzyme 5 α reductase Type 2 (5AR2), and advances in genomics and biomarker discovery offer the potential for a more targeted approach to therapy. We review the current understanding of BPH progression as well as key genes and signaling pathways implicated in the process such as 5 α reductase. We also explore the potential of biomarker screening and gene-specific therapies as tools to risk stratify BPH patients and identify those with symptomatic or medically resistant forms.

Materials and Methods—A PubMed® literature search of current and past peer-reviewed literature on prostate development, lower urinary tract symptoms, BPH pathogenesis, targeted therapy, biomarkers, epigenetics, 5AR2 and personalized medicine was performed. An additional Google Scholar™ search was conducted to broaden the scope of the review. Relevant reviews and original research articles were examined as well as their cited references, and a synopsis of original data was generated with the goal of informing the practicing urologist of these advances and their implications.

Results—BPH is associated with a state of hyperplasia of both the stromal and epithelial compartments, with 5AR2 and androgen signaling playing key roles in development and maintenance of the prostate. Chronic inflammation, multiple growth factor and hormonal signaling pathways, and medical comorbidities play an intricate role in prostate tissue homeostasis as well as its evolution into the clinical state of BPH. Resistance to medical therapy with finasteride may occur through silencing of the 5AR2 gene by DNA methylation, leading to a state in which 30% of adult prostates do not express 5AR2. Novel biomarkers such as single nucleotide polymorphisms may be used to risk stratify patients with symptomatic BPH and identify those at risk of progression or failure of medical therapy. Several inhibitors of the androgen receptor and

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other signaling pathways have recently been identified which appear to attenuate BPH progression and may offer alternative targets for medical therapy.

Conclusions—Progressive worsening of LUTS and bladder outlet obstruction secondary to BPH is the result of multiple pathways including androgen receptor signaling, pro-inflammatory cytokines and growth factor signals. New techniques in genomics, proteomics and epigenetics have led to the discovery of aberrant signaling pathways, novel biomarkers, DNA methylation signatures and potential gene-specific targets. As personalized medicine continues to grow, the ability to risk stratify patients with symptomatic BPH, identify those at higher risk of progression, and seek alternative therapies for those likely to fail conventional options will become the standard of targeted therapy.

Keywords

prostate; benign prostatic hyperplasia; 5-alpha reductase; finasteride; personalized medicine

INTRODUCTION

Personalized medicine is an approach to medical care that tailors therapy to the individual characteristics of each patient. With advances in genomic analysis and the ability to develop biomarker assays and targeted therapeutics using small molecules, personalized medicine can more accurately diagnose disease, prognosticate those at risk of developing more aggressive disease, and identify who will likely respond to a medication to help direct the optimal course of management while minimizing morbidity and potential side effects from ineffective therapies. This approach can also improve efficiency and lessen the financial burden on the current healthcare system.

Lower urinary tract symptoms (LUTS) negatively impact quality of life for millions of patients and cost the US healthcare system over \$4 billion each year.¹ These symptoms include voiding or obstructive symptoms such as weak stream, hesitancy, and sensation of incomplete emptying, and storage or irritative symptoms such as urgency, frequency, and nocturia. The etiology of LUTS includes urological, neurological and comorbid conditions. While the hallmark of symptomatic benign prostatic hypertrophy (BPH) involves bladder outlet obstruction, other causes of LUTS include bladder cancer, prostate cancer, urinary tract infection, overactive bladder, urethral stricture, cerebrovascular accident or other neurologic injury, Parkinson's disease, diabetes mellitus, congestive heart failure, and obesity.² For personalized medicine to succeed in the treatment of LUTS, it should identify the specific disease which is the cause of the LUTS. Our goal in this review is to focus on the application of personalized medicine for management of bladder outlet obstruction secondary to BPH, which as mentioned above, is one of many causes of LUTS.

BPH appears to be associated with a state of hyperplasia of both the stromal and epithelial compartments, with the enzyme 5 α reductase Type 2 (5AR2) playing a key role in driving organ growth. The mainstays of medical therapy include 5 α reductase inhibitors (5ARIs) and alpha-adrenergic blockers. However, at least 25–30% of patients do not respond to this therapy.³ Understanding specific mechanisms and differential gene expression amongst individuals will allow for a better targeted approach to medical therapy. The purpose of this

review is to briefly summarize the pathogenesis of BPH and explore the current evidence about variably expressed genes and signaling pathways such as 5AR2. Recent advances in molecular biology and genomics offer the possibility of identifying and targeting specific pathways and developing new strategies for BPH surveillance and treatment. We discuss the potential of biomarker screening and genetic-based prescriptions as powerful tools to risk stratify patients with BPH and offer effective targeted therapy in the management of symptomatic BPH.

Pathogenesis of BPH

Since the first description of prostatic enlargement resulting in symptomatic bladder outlet obstruction in 1649,⁴ much effort has been directed towards studying the development of the prostate gland. Understanding the pathophysiology of BPH can lead to the discovery of new biomarkers for personalized medicine. The prostate is the only male internal organ that continues to grow throughout adulthood, and it grows at different rates in each individual (Figure 1).⁵ Some have suggested that BPH may be caused by reactivation of a dormant embryonic growth process in the adult stroma.⁶ Stromal-epithelial interactions, under the influence of the androgen receptor and dihydrotestosterone (DHT), are crucial to promote tissue expansion and form the hyperplastic benign nodules characteristic of the disease.⁷

Many cellular alterations including changes in proliferation, differentiation, quiescence and apoptosis have been implicated in the pathogenesis of BPH. Multiple families of growth factors act through paracrine signaling to stimulate proliferation; these include fibroblast growth factor (FGF), epithelial growth factor, insulin-like growth factor (IGF), keratinocyte growth factor (KGF), hepatocyte growth factor, and vascular endothelial growth factor (VEGF).^{8–10} DHT serves to modulate or augment these growth factor effects.

In addition to growth factor signaling, other proposed mechanisms for BPH progression include changes in androgen and estrogen levels with age,^{11–13} loss of cell cycle regulators,⁸ and increased oxidative stress.¹⁴ Chronic inflammation has been implicated as a primary stimulus for both prostate cancer and symptomatic BPH development, and factors such as IL-8, hypoxia-inducible factor 1 α (HIF-1 α) and vitamin D analogues have been identified as potential therapeutic targets.^{10, 15, 16} Finally, comorbid disease states such as diabetes, hypercholesterolemia, obesity and the metabolic syndrome have been identified as risk factors for BPH.^{8, 16–18}

Despite the growing number of targets implicated in disease progression, the main driver of prostatic growth to date remains serum androgen which exerts its effect through the androgen receptor. Over 90% of serum testosterone is converted into the more potent hormone DHT in the prostatic tissues by 5AR2. The clinical significance of this pathway is demonstrated by medically castrated BPH patients, who showed a significant decrease in prostate size and improvement in LUTS within several months.¹⁹ Inhibitors of 5AR such as finasteride have been shown to reduce DHT levels and prostate volume and are a mainstay of current medical therapy. However, this pathway is not the sole regulator of prostate growth as evidenced by the fact that over 25% of patients do not respond to 5ARIs. In addition, in situ hybridization and immunohistochemical studies have shown that 5AR2

expression in the BPH prostate is variable, further supporting the presence of additional pathways of BPH pathogenesis.²⁰

Medical Management of BPH and Mechanisms of Resistance

To date, medical therapy for LUTS due to symptomatic BPH consists of alpha-adrenergic blockers (*e.g.* alfuzosin, doxazosin, terazosin, tamsulosin) and 5ARIs (*e.g.* dutasteride, finasteride). Alpha blockers target the adrenergic alpha-1 receptors on smooth muscle cells within the prostate stroma and bladder neck to inhibit their contraction, which leads to a 10–20% improvement in patients' urinary symptoms. However, alpha blocker therapy does not reduce prostate volume or the risk of disease progression.³

By contrast, 5AR inhibitors block androgen receptor signaling by reducing serum DHT levels, thereby decreasing prostate volume.³ Chronic use of finasteride, a selective 5AR Type 2 inhibitor, decreases total prostate gland size by 20% and improves urinary flow rate and patient urinary symptom scores.^{21, 22} The inhibitors cause a progressive decrease in epithelial cell size (atrophy) and an increased rate of apoptosis. Several large clinical trials have shown that the greatest long term improvements result from combination therapy with an alpha blocker and a 5ARI, suggesting complementary medical effects acting through multiple pathways.^{23, 24} In addition, patients with larger prostates over 40cc have been shown to benefit the most from 5ARIs over the long term.²⁵ Therefore, prostate volume may be used as a guide for personalized therapy in prescribing 5ARIs.

Although 5ARIs have been shown to reduce the volume of BPH in many patients, approximately 25–30% of patients do not show any improvement in their urinary symptoms and another 5–7% develop worsening symptoms and may ultimately require surgery.³ Recent studies have evaluated the transition zone from adult human prostate specimens and found that the 5AR2 protein is variably expressed (Figure 2). Importantly, 5AR2 protein is absent in 30% of histologically benign-appearing samples (Figure 2A), raising the question of whether silencing of the 5AR2 gene in adulthood may play a role in patients who are resistant to finasteride.²⁰

Epigenetics is defined as the study of heritable changes in gene expression that are not caused by alterations in DNA sequence. Two mechanisms, DNA methylation and chromatin remodeling, are crucial for the successful growth and development of benign organs—and also tumors—by stabilizing the underlying histone and chromatin machinery. DNA methylation adds a methyl group at the carbon-5 position of cytosine residues in CpG dinucleotides (Figure 3A). Over 60% of gene promoters have CpG-rich regions called CpG islands. In the unmethylated state, chromatin is accessible and enables binding of transcription factors and subsequent gene transcription. DNA methylation at promoters within CpG islands alters the chromatin structure, recruits methylated DNA-binding proteins and prevents transcription factor binding, leading to gene silencing (Figure 3B–D). The 5AR2 gene contains a CpG island in its promoter region, and recent work has shown that DNA methylation of this promoter region is correlated with a lack of 5AR2 protein expression in prostatic tissues.²⁰ Interestingly, patients from whom the prostates were obtained did not show phenotypic evidence of hereditary 5AR2 deficiency such as lack of

virilization during development, suggesting that methylation events take place during adulthood and more likely represent a somatic epigenetic event rather than an inherited one. New evidence is emerging to support the concept that DNA methylation in the adult is a dynamic process.²⁶ Finally, a longitudinal population study found that prostate size in 30% of men did not grow over a 10-year period.⁵ Taken together, this evidence has led to the hypothesis that methylation of the 5AR2 promoter in some adult prostates is associated with reduced gene expression which may translate into a slower growth rate of the prostate gland during adulthood (Figure 3).²⁰ Absence of 5AR2 in benign prostatic tissue could also explain why some men are resistant to the intended clinical effects of 5AR2 inhibitors such as finasteride. Alternatively, these men may be experiencing LUTS due to an etiology other than BPH, which would require a different medical therapy.

As a new treatment alternative, phosphodiesterase-5 inhibitors (PDE5-Is) have recently been demonstrated to have an effect on improving LUTS due to symptomatic BPH. A recent meta-analysis of 12 studies and over 3400 patients compared the effects of PDE5-Is and PDE5-Is plus alpha blockers against alpha blockers alone and placebo. Although the studies were of small sample size and short duration (12 weeks), the analysis found that PDE5-Is used alone or in combination with alpha blockers significantly improved both erectile function (International Index of Erectile Function [IIEF] scores) and LUTS (International Prostate Symptom Score [IPSS] scores), suggesting a potential new treatment option for patients with symptomatic BPH.²⁷ Moreover, a recent large multi-institutional randomized, double-blinded, placebo controlled trial showed tadalafil significantly improved IPSS and quality of life scores regardless of erectile dysfunction status.²⁸ The ability to determine which men would derive greater benefit from 5ARI versus PDE5-I therapy would be a powerful application of personalized medicine with important implications for cost savings and reduced morbidity to patients. While prostate volume can be used to predict response to 5ARI, at present there is no genetic biomarker to address this question.

Biomarkers in BPH: Opportunities for Personalized Medicine

Despite the increasing prevalence of BPH with the aging population, its symptomatic burden on patients, and its costs to healthcare, no universal therapy exists to treat all men with BPH. Combination therapy with an alpha blocker and 5ARI has significantly reduced the risk of clinical progression more than monotherapy or placebo. However, one in four men does not experience improvement in his urinary symptoms as measured by IPSS scores and 7% of men worsen, requiring surgical intervention. Lack of response to medical therapy and progression of disease are suggestive of the heterogeneity of the underlying pathophysiology among men presenting with LUTS. Another potential explanation for present therapy failures may be due to the contribution of comorbidities to BPH. Obesity and the metabolic syndrome have been shown to markedly increase the risk of symptomatic BPH.¹⁸ In addition, a subanalysis of the Prostate Cancer Prevention Trial (PCPT) found that obesity attenuates the therapeutic effect of 5ARIs on BPH.²⁹ It is not yet clear through what mechanisms these conditions influence the prostatic microenvironment, but the identification of comorbidities could be used to better stratify and treat patients in the future, and even be used in preventative therapy and lifestyle modification.

When focusing on BPH as a cause of LUTS, prostate growth rates are highly variable in the aging male population.⁵ Distinct forms of BPH likely exist, ranging from more aggressive, fast-growing states to more indolent, slow-growing states. Differentiating individuals in these groups would enable better risk stratification and identification of men who would become symptomatic from BPH and, furthermore, which among them would be resistant to medical therapy and ultimately require surgery. Indeed, studies have demonstrated that BPH is not a homogeneous disease at the molecular level.³⁰ Microarray analysis compared gene expression in five groups of prostate samples: normal prostate tissues from men aged less than 20 years, aged 30 to 50 years, men with symptomatic BPH and LUTS (clinical BPH), men with asymptomatic BPH diagnosed on histology only (histological BPH), and men with asymptomatic BPH and concomitant prostate cancer. The gene expression profile in men with clinical BPH is similar to that of asymptomatic men with prostate cancer but distinct from histological BPH.³⁰ In addition, there is a correlation between inflammatory genes and clinical BPH, demonstrating a spectrum of disease with differing pathways that may require unique targeted therapies.

Recognizing the importance of targeted therapies for management of BPH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the MTOPS Prostatic Samples Analysis (MPSA) Consortium in 2002 to “identify and validate molecular markers that may better define BPH-related pathologies, identify risk of progression of LUTS, and predict response to drug therapy.”³¹ Since its establishment, the group has developed a variety of methodologies for acquiring and processing tissue, extracting genetic information, and analyzing potential biomarkers and therapeutic targets. The aforementioned gene expression analysis comparing clinical BPH to histologic BPH identified a novel biomarker JM-27.³⁰ The Johns Hopkins MPSA Consortium site confirmed that clinical BPH has higher JM-27 expression at the level of the gene, mRNA, and protein as compared to histologic BPH. Next, a serum-based ELISA assay was developed using an anti-JM-27 monoclonal antibody which could measure serum levels of JM-27 and distinguish between symptomatic and asymptomatic BPH patient sets.^{31, 32} Unlike PSA, serum JM-27 levels are not affected by prostate volume, giving JM-27 potential as a biomarker that could be obtained as a diagnostic blood test to risk stratify patients for symptom and disease progression. However, additional studies are needed to validate these initial results amongst a larger sample size in order to demonstrate the utility of JM-27.

With the rapid advancement of genomic and sequencing technology, another avenue for characterizing BPH is to identify genetic markers linked to the disease. Family history is a major risk factor for early onset of BPH, yet few specific genes have been identified as a cause or marker of BPH.³³ In one case-control study of men who developed symptomatic BPH before the age of 64 years, first degree relatives had a four-fold greater age-specific risk of undergoing surgery for BPH.³⁴ Another study found that genetic factors contribute up to 72% of the risk of high or severe LUTS.³⁵ A recent genome wide association study (GWAS) identified 36 single nucleotide polymorphisms (SNPs) associated with prostate cancer.³⁶ In an additional study of those SNPs in patients with BPH, after adjusting for BPH medication and patient age, 3 were noted to be associated with LUTS severity (based on IPSS scores) and 3 were associated with BPH medication use.³⁷ Interestingly, the presence of one SNP (rs5945572) on chromosome Xp11 was associated with both BPH medication

use and LUTS severity.³⁷ The authors suggest that men with severe LUTS and men requiring pharmacotherapy can be identified by a unique set of SNPs compared to men with asymptomatic BPH. Although the original cohort for the study was healthy men as part of a prostate cancer screening trial and may not represent the population of older men with symptomatic BPH, these findings highlight a role for SNPs as potential biomarkers to differentiate between different BPH presentations and aid in pharmacogenomics or choice of optimal therapy. Despite their promise to better identify men with symptomatic BPH, SNPs do not account for epigenetic and microenvironmental changes that can also affect disease progression and contribute to a changing prognosis of BPH. Further studies will be needed to investigate the SNP locations, their effects (if any) on nearby genes, and potential mechanisms by which they influence LUTS and BPH. In addition, a GWAS focusing on men with severe LUTS instead of prostate cancer would likely yield additional SNPs with a stronger association with symptomatic BPH.

Emerging Targets for BPH Therapy

In the setting of chronic prostatic inflammation, stromal and epithelial androgen receptors play a role in recruiting proinflammatory mediators including lymphocytes and macrophages, resulting in increased stromal cell growth and BPH development and progression.³⁸ Furthermore, macrophages may mediate epithelial-to-mesenchymal transition (EMT), which could further enhance the stromal compartment expansion. ASC-J9, a selective androgen receptor degradation enhancer, suppressed both stromal and epithelial cell growth without lowering serum androgen levels.^{38, 39} In a mouse model of BPH induced by prolactin, ASC-J9 systemic therapy prevented BPH development. Moreover, the utility of ASC-J9, which does not alter serum testosterone or affect fertility,⁴⁰ is being investigated for treatment of prostate cancer, bladder cancer and liver cancer.^{41–43} Clinical trials in these applications will be the next step in investigation of its efficacy.

Another key player in cell growth signaling is gastrin-releasing peptide (GRP), a hormonal peptide that acts in an autocrine fashion to stimulate and regulate cellular differentiation, growth, and apoptosis. It has been shown to promote growth of several types of cancers including lung, colon, breast, and prostate. GRP antagonists have been shown to successfully inhibit growth of numerous cancers and suppress tumor growth pathways including VEGF and FGF.⁴⁴ GRP receptor subtype 1 is expressed in human prostate tissues in normal, hyperplastic, and cancerous specimens.⁴⁵ Recently, Rick *et al.* demonstrated that the potent GRP antagonist RC-3940-II not only inhibits prostate cancer growth but also diminishes prostate size.⁴⁴ Using a model of BPH in which rats were injected with testosterone, addition of RC-3940-II resulted in dose dependent shrinkage of prostate volume by over 15% by 6 weeks as well as decreased levels of androgen receptor and inflammatory markers. Application of this inhibitor to prostate epithelial and stromal cell lines inhibited cell proliferation and led to a decrease in levels of growth factors and proinflammatory mediators involved in BPH progression. The reduction in prostate volume using RC-3940-II in an animal model of BPH was comparable to the size reduction with finasteride based on clinical trials, and the mechanism of action appears to be similar.⁴⁴ RC-3940-II and GRP inhibition may offer a promising new approach to BPH treatment, on

its own or in combination with alpha blockers, as well as an alternative therapeutic pathway for patients who do not respond to 5AR inhibitors.

Future Directions for Personalized Medicine

The US President's Council of Advisors on Science and Technology defines personalized medicine as tailoring of medical treatment to the individual characteristics of each patient; to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment so that preventive or therapeutic interventions can then be focused on those who will benefit, sparing expense and side effects for those who will not.⁴⁶

For symptomatic BPH causing LUTS, the need for personalized medicine is great due to the magnitude of the disease and the lack of a universal treatment. Novel genomic and proteomic technologies now offer the potential to sub-classify the disease based on differences in gene expression (ie, 5AR2) and biomarker presence between aggressive and benign forms. Several candidates such as the above mentioned SNPs show promise in this regard. At present, advances in biomarkers for LUTS due to BPH is in its infancy. Current "markers" such as prostate volume and presence of comorbidities can help drive decision making, but only with more focus and dedication can meaningful biomarkers be found. Rather than focusing on one drug or combination of drugs (such as 5ARIs and alpha blockers) to treat all BPH, we need to evaluate individual patients and tailor their care. Early identification of a patient at risk for developing aggressive BPH resistant to finasteride would be crucial in order to prescribe alternative approaches. In those who are considered to be resistant to medical therapy and at high risk of BPH progression to severe obstructive urinary symptoms, early surgical intervention can spare men many years of failed medical therapies, recurrent office visits with accompanying diagnostic tests, and ultimately reduce the financial burden on the healthcare system.

Conclusions

The discovery and characterization of aberrant signaling pathways in BPH will facilitate further biomarker discoveries with the hope of providing more targeted therapies. Gene microarrays and transcriptional profiling provide information about gene expression and epigenetic alterations, and protein microarrays allow investigation of protein interactions and posttranslational modifications. These techniques have led to our current understanding of BPH progression, the role of androgen receptor signaling, and the importance of pro-inflammatory cytokines and their paracrine effects. This personalized approach to medicine is rapidly becoming mainstream. Over the next ten years, personalized medicine is estimated to grow and account for 5–10% of the entire pharmaceuticals market.⁴⁷ As we become better at identifying patients with early BPH or at high risk of symptomatic prostatic growth, treatment paradigms will shift from reactive to proactive, to an approach that will be predictive, personalized, preemptive, and participatory.

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Key of Standard Abbreviations Used

5AR	5 α reductase
5AR2	5 α reductase Type 2
5ARI	5 α reductase inhibitor
BPH	Benign prostatic hyperplasia
DHT	Dihydrotestosterone
EMT	Epithelial-to-mesenchymal transition
FGF	Fibroblast growth factor
GRP	Gastrin-releasing peptide
GWAS	Genome wide association study
HIF-1α	Hypoxia-inducible factor 1 α
IGF	Insulin-like growth factor
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
KGF	Keratinocyte growth factor
LUTS	Lower urinary tract symptoms
MPSA	MTOPS Prostatic Samples Analysis
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
PCPT	Prostate Cancer Prevention Trial
PDE5-I	Phosphodiesterase-5 inhibitor
SNP	Single nucleotide polymorphism
UG	Urogenital
VEGF	Vascular endothelial growth factor

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Figure 1.

Prostatic growth occurs at variable rates. Depicted in the CT scan are two similarly aged men. The prostate in panel (A) is measured at 40cc (4×5×4cm), while the prostate shown in panel (B) is 195cc (7.5×7.5×7cm).

Figure 2.

Expression of 5 α reductase Type 2 (5AR2) in adult human prostate tissue samples is variable. Paraffin embedded samples of BPH were stained with a polyclonal antibody against 5AR2 (brown) and counterstained with hematoxylin (blue/purple). Prostate specimens have variable expression of 5AR2 within the epithelial (E) and stromal (S) compartments ranging from total lack of expression (A) to expression only in the epithelial compartment (B) to expression in both epithelial and stromal compartments (C) (For complete data see: Niu, Y., et al. *Prostate*, 71: 1317, 2011).

Mechanism of 5 α R2 Suppression

Figure 3.

Mechanism of 5AR2 suppression. (A) DNA methylation adds a methyl group (star) at the carbon-5 position of cytosine residues in CG dinucleotides. (B) In unmethylated DNA (blue CG dinucleotides), chromatin is uncondensed and transcription factors (TF) can bind the gene promoter region, enabling gene expression. (C–D) DNA methylation (red CG dinucleotides with stars) attracts methylated DNA-binding proteins and histone deacetylase complexes (horizontal ovals and diamonds) to form condensed, inactive chromatin that prevents TF binding and silences gene expression. (Adapted from Albany, C. et al. Prostate Cancer, 2011: 580318,2011).