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INVITED EDITORIAL

Prostate Cancer

Translation of genomics and epigenomics in prostate cancer: progress and promising directions

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During the last several years, exciting discoveries have been made in prostate cancer (PCa) as a result of significant advances in genomic technology and information. For example, using genome-wide association studies, more than 100 inherited genetic variants associated with PCa risk have been identified. Similarly, with the use of next-generation sequencing, various types of recurrent somatic DNA alterations in prostate tumors have been revealed. Some of these discoveries have potential clinical application to supplement existing tools for better decision-making regarding the need for screening, biopsy, and treatment of PCa. However, because of the complexity of these genomic findings and incomplete understanding of the genetics of this multifactorial disease, this potential has not yet been fully realized.

In this *Asian Journal of Andrology* special issue, we aim to summarize genomic findings related to risk, progression, and response to treatment of PCa, to synthesize available evidence for their clinical validities, to outline areas in which additional evidence is needed, and to propose genomic translational studies and trials to evaluate their efficacies. This special issue is intended to target urologists, oncologists, primary care physicians, and genomic translational researchers, as well as policy makers and payers. The goal is to promote genomic translational medicine to benefit patients by reducing PCa mortality, improving the quality of life, and decreasing the cost to individuals, families, and society.

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HIGHLIGHTS

This special issue includes 11 review articles describing most, if not all, genomic discoveries and clinical implications in PCa, two original manuscripts presenting new findings on genetic risk score (GRS) and one perspective paper painting a picture from screening to treatment for personalized PCa care. In this introduction, we highlight major points from each paper for the audience to capture the entire field quickly and to reach specific area of interest for more comprehensive reading. We start with the inherited genetic variants and their potential for clinical utility; continue on acquired genomic alterations, epigenetic modifications, their clinical validities and translational utilities; and conclude with perspectives of utilizing these genetic and epigenetic variations in personalized cancer care.

Recent evidence from studies on inherited genetic variants has consistently supported the validity and utility of a Genetic Risk Score based on PCa risk-associated single nucleotide polymorphisms (SNPs) for risk stratification of men in the general population as reviewed by Helfand *et al*.[1] Multiple methods for generating GRSs are commonly used, which are compared by Conran *et al*.[2] Between simple risk allele count, weighted risk allele count, and population-standardized methods, the performances of the weighted risk allele count and population-standardized methods are superior to the simple allele count. However, the population-standardized method is deemed best for clinical use of GRS as its values are the most stable and easily interpreted. All three GRS methods perform better than family history (FH), which is currently the most widely used predictor of PCa risk. Helfand reviews current evidence to assess the performance of GRS and its ability to supplement FH as an independent predictor of PCa risk.[3] Although GRS is a promising method for PCa risk assessment, it should be noted that questions about SNP race-specificity have been raised as a potential barrier to the widespread clinical implementation of GRS. Na *et al*. conduct analyses to address this issue and find that, indeed, race-specific GRSs more accurately predict PCa than nonrace-specific.[4] While more evidence is needed to be able to offer GRS to men of all races, current evidence supports the clinical use of GRS for PCa risk assessment. Men who are aware of their heightened risk status based on FH and/or GRS should undergo PCa screening, and GRS information can be particularly useful in biopsy decision-making. Studies on heritable mutations in high-penetrance genes, including *HOXB13*, *BRCA1/2*, and *ATM*, are summarized by Pilie *et al*.[5] Evidence suggests that mutations in these DNA repair genes confer a more aggressive PCa phenotype.

Reviewing the major, somatically acquired genomic characteristics of various subtypes of PCa and key findings on the relationships between genomic alterations and clinical parameters, Liu shows that the landscape of somatic aberrations is highlighted by DNA copy number alterations (CNAs) and *TMPRSS2-ERG* fusion derived from complex rearrangements, numerous single nucleotide variations or mutations, tremendous heterogeneity, and continuously punctuated evolution.[6] Genome-wide CNAs, *PTEN* loss, *MYC* gain in primary tumors, and *TP53* loss/mutation and *AR* amplification/mutation in advanced metastatic PCa have consistently been associated with worse cancer prognosis. Clinical variability and molecular heterogeneity in primary, metastatic PCa, and between foci have been reviewed by Shoag and Barbieri.[7] The temporal and spatial genomic heterogeneity

as they described apparently defines distinct molecular subclasses and contributes to various pathological phenotypes of PCa and has clinical implications for cancer diagnosis, predicting outcomes, and developing novel therapeutics. Yegnasubramanian describes the concept of epigenetic programming as "writers," "erasers," "readers," and "preservers" in establishing, altering, and maintaining cell identity and cell function with an emphasis on the findings of recurrent DNA hyper- and hypo-methylations, histone modifications, and epigenetic machinery including DNA/RNA protein interaction.[8] He discusses the potentials and methods of epigenetic markers in cancer screening and diagnosis, monitoring disease burden and treatment response, as well as the potential for targeting epigenetic processes for cancer therapy. MicroRNAs (miRNAs), which are noncoding, well-conserved and broadly regulate gene expression, their biogenesis and function in various pathways during PCa initiation, progression and treatment are recapped by Kumar and Lupold.[9] The most common miRNAs that the authors outline in cancer tissues and body fluids, including blood and urine, may hold potential as future diagnostic or prognostic markers, as well as therapeutic targets. Malik and Feng review long noncoding RNAs (lncRNAs), their functional roles, and their molecular mechanisms in PCa progression.[10] They describe a number of important lncRNAs associated with PCa and highlight their potentials as noninvasive biomarkers for diagnosis, prognosis, or predicting response to specific therapies, and as therapeutic targets.

To capture the potential for translating these inherited and somatically acquired genetic alterations and epigenetic modifications described above into personalized cancer care, Na *et al*. compare the utilities of three clinically available RNA profiling tests, including Oncotype Dx, Prolaris and Decipher, for PCa. The authors recap that the evidence demonstrating these tests may offer dependable approaches for predicting cancer progression in active surveillance patients or early recurrence after radical treatments.[11] Luo describes the development of an androgen receptor splice variant (AR-V7) test for metastatic castration-resistant PCa (mCRPC).[12] Harboring functional AR splice variants represents potential resistance to newer AR-directed drugs treating mCRPC. Therefore, the studies and methods to detect AR-V7 in both tissue and circulating tumor cells support its clinical utility as a putative biomarker for treatment selection. Reviewing genomic predictors for the treatment of late-stage PCa, Shevrin highlights genomic alterations in several pathways, including AR, PTEN, and ETS gene fusion, as well as the growing importance of PARP inhibition.[13] He also summarizes evidence on the development of neuroendocrine tumors and the evolutionary history of lethal PCa via polyclonal seeding and interclonal cooperation in response to treatment, and he outlines a path to genomics-driven therapies.

To fully utilize the recent genomic discoveries mentioned above, and to overcome the passive approach focusing primarily on late-stage disease, Conran *et al*. propose a "Pyramid Model" of personalized PCa care for four stages of disease chronology.[14] While specific novel tests for each stage are recommended based on their perspective analysis, the authors also present implementation challenges and stress a four-step method for clinical implementation of the Model, including evidence-based evaluation, robust/cost-effective tests, pilot clinical trials, and ethical/legal/social soundness to address the changes. This proactive and comprehensive model will reduce PCa mortality, improve the quality of life, and decrease healthcare costs if used properly.

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