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INVITED EDITORIAL

Prostate Cancer

Global developments in prostate cancer research and clinical practice

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The prostate cancer foundation (PCF) is committed to the facilitation of global knowledge exchange as a mechanism for more rapidly discovering and developing new medicines and treatments for prostate cancer (PCa) patients worldwide. For the past 3 years, PCF has partnered with the Chinese Prostate Cancer Consortium and Shanghai Changhai Hospital to host a conference in China that brings together basic, translational, and clinical researchers from China and abroad to form new partnerships and exchange findings, insights, perspectives, and ideas toward improving the treatment of PCa. The seventh forum of prostate disease held in Shanghai, China, on July 26–28, 2013, focused on current and emerging developments and approaches in PCa diagnosis, prognosis, and treatment, and the discovery and targeting of disease mechanisms that drive metastasis and lethal subtypes of castrate-resistant PCa (CRPC). This special edition of the *Asian Journal of Andrology* highlights some of the most pressing topics that were presented and discussed at the forum.

The first Review article, by Lipianskaya *et al.*[1] describes the prevalence and molecular and clinical features of neuroendocrine cells in the benign prostate, and premalignant through recurrent forms of PCa, with a focus on an aggressive, untreatable form of PCa: small cell neuroendocrine cancer (SCNC). Epithelial cells with neuroendocrine morphology and function that lack expression of and dependence on the androgen receptor (AR) have been observed in PCa at all stages. Of significant clinical concern are neuroendocrine PCa subtypes including SCNC, which arise in response to treatments with androgen deprivation therapies (ADT) and are becoming more prevalent with the second generation ADT medications enzalutamide and abiraterone acetate. Lipianskaya *et al.*[1] further review studies identifying molecular pathways that may drive SCNC, the difficulty of clinically diagnosing heterogeneous neuroendocrine tumor subtypes, and clinical trials, which indicate that certain chemotherapy regimens may be a viable treatment option for this lethal, ADT-resistant disease state.

The article by Le *et al.*[2] reviews new technologies that enable lesion-targeted prostate biopsies in an attempt to improve PCa diagnosis. Conventional transrectal ultrasound-guided (TRUS) biopsies essentially "blindly" sample the prostate, and many men with negative TRUS biopsies are later discovered to have tumors on follow-up biopsies. With the advent of multi-parametric magnetic resonance imaging (mp-MRI), the location of suspicious lesions can be radiologically assessed prior to biopsy. This enables targeted biopsies, which increase detection of clinically relevant prostate tumors, reduces identification of indolent tumors, and decreases morbidities associated with additional biopsies, delayed treatments, and overtreatment of indolent tumors. This article provides a thorough review of these and other MRI-guided, targeted biopsy technologies and methodologies, their successes and failures, and associated morbidities.

The review article by Nelson[3] addresses the significant clinical questions: how to define and identify which PCa patients need to be treated, and how to treat clinically relevant cancers to gain the most benefit with the least treatment-induced morbidity. The vast majority of men diagnosed with PCa will die from other causes, making it imperative to properly assess PCa mortality risks to reduce unnecessary treatments. Extremely low recurrence and mortality rates observed in studies of patients with a Gleason grade of 6 or less who underwent radical prostatectomy, argues that these patients should not be universally subjected to definitive local therapy. A true determination of tumor grade is inherently difficult by biopsy alone, thus mortality rates increased in patients who abstained from radical prostatectomies in favor of active surveillance and selective delayed intervention. These issues, and the benefits and challenges of choosing focal therapy, as a less morbid treatment approach compared with radical prostatectomy are discussed.

Parikh *et al.*[4] present the hypothesis that an alternate method of intermittent ADT (IADT) – administration of 5 alpha-reductase inhibitors during IADT off-cycles – may reduce ADT-associated morbidities while prolonging life. Continuous ADT with luteinizing hormone releasing hormone agonists is the mainstay therapy for treatment of hormone-naïve recurrent or metastatic PCa. Clinical trials demonstrated less morbidity from IADT compared with continuous ADT, but similar or inconclusive differences in mortality benefits. IADT may act in a mechanism different from continuous ADT: intermittent restoration of androgen levels during the IADT off-cycle may allow PCa cells to differentiate, resensitizing them to apoptosis. Testosterone and DHT have different effects during the initial prostate tumor regrowth phase following castration: both induce differentiation while only DHT induces proliferation. Thus, inhibiting the conversion of testosterone to DHT with 5 alpha-reductase inhibitors during fixed or

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short term IADT off-cycles, might allow testosterone-driven differentiation and apoptosis sensitization without inducing proliferation. Studies supporting the testing of this hypothesis in clinical trials are reviewed.

Epithelial to mesenchymal transition (EMT) is a mechanism by which tumor cells gain migratory ability for metastatic spread. In the research highlight by Morley *et al*.,[5] the discovery of an alternate migratory tumor cell type, "amoeboid" cells, is described. This paper details differences between amoeboid and EMT cells including morphology – rounded instead of spindle-like – and mechanisms regulating their activity and formation. Amoeboid cells have been observed to shed "large oncosomes:" microvesicles that act as vehicles for horizontal transfer of nucleic acids, proteins, and other molecules between cells. Emerging understandings on the role of amoeboid cells and oncosomes in tumor pathogenesis and as diagnostic or prognostic tools is discussed.

With the gradual introduction of PSA screening in China, the rates of PCa incidence have increased 7-fold since 1988. PSA elevation is not PCa-specific, and unnecessary biopsies and treatments of indolent tumors cause excessive morbidities, an obvious medical challenge, particularly in countries such as China with developing medical resources and large populations. Xu[6] reviews biomarkers that when added to PSA screening, improve PCa risk stratification. He has developed several charts, presented in the Review, depicting PCa diagnosis rates at various PSA levels alone, versus with the addition of single nucleotide polymorphism-derived PCa genetic risk scores, as determined from Caucasian and Chinese population studies. This chart is intended as a clinician-patient communication tool to discuss diagnostic plan decisions including undergoing biopsies or additional biomarker tests.

Defining the genes that drive PCa metastasis is critical for developing new therapies to treat this lethal disease state. The research highlight by Chiang *et al*.[7] describes results from a study in which metastatic and non-metastatic tumor lines derived from tissues from the same patient, were grown in a subrenal capsule transplantation xenograft mouse model. Gene expression analyses identified novel metastasis associated genes, TIMELESS and DLX1, that were also elevated in a secondary PCa patient cohort. Future studies will determine the role of these genes in metastatic processes. *In vitro* assays are not sufficient to study a gene's contribution to multi-factorial metastatic events that involve numerous cell types and tissues. Clinically relevant *in vivo* models should continue to be developed and employed.

Qu *et al*.[8] review diagnostic biomarkers that have the potential to increase the specificity of PSA testing alone, in stratifying indolent from aggressive cancers to reduce overtreatment. The discussion includes alternate PSA readouts as well as detection of PCa-associated genes (via protein, DNA, or RNA) and circulating-tumor cells, from tissue, serum, urine, and semen. Of note are United States Food and Drug Administration-cleared prostate health index tests, which calculate a score based on levels and ratios of PSA isoforms, and urinary tests that measure RNA expression levels of TMPRSS2-ERG and PCA3, which markedly improve sensitivity and specificity of risk assessment over PSA testing alone.

Wadia and Petrylak[9] review disease mechanisms and treatment of CRPC. ADT is the primary treatment for metastatic PCa, but ADT-resistant CRPC inevitably develops within 24 months. Despite being "androgen-resistant," CRPC cells often remain dependent on AR-driven biology through two major escape mechanisms: AR mutations that allow for alternate activation, and upregulation of intracrine androgen production. These mechanisms can be targeted with the second-generation anti-androgens, abiraterone acetate and enzalutamide. Mechanisms of ADT-resistance and treatment strategies for CRPC treatment are discussed.

In the review by Balk,[10] the normal and PCa-associated functions of AR are detailed. In normal prostate cells, AR promotes differentiation rather than proliferation, and suppresses expression of itself and other genes involved in androgen synthesis and proliferation. In PCa cells, AR acquires new functions enabling it to drive tumorigenesis. ERG is an important coregulator in this scheme, by unveiling normally restricted AR-binding sites in genes including SOX9, a critical mediator of the ERG-promoted growth and tumorigenic properties of PCa cells. Alternate AR activities in PCa cells may also be mediated via epigenetic mechanisms, including interactions with the EZH2 methyltransferase, and differential transcriptional activity of AR splice variants.

Lapuk *et al*.[11] review the regulation and role of alternative splicing of genes involved in PCa. A number of genes including BCL-X and cyclin D1 have alternatively spliced isoforms which are expressed in and have oncogenic roles in PCa. Alternative isoforms of AR that lack the ligand binding domain (LBD) and are constitutively active have been associated with enzalutamide resistance, CRPC, and poor clinical outcome. AR-variants may arise from aberrant alternative splicing mechanisms, and/or genomic deletions or inversions of the exons encoding the LBD. Aberrations in trans-splicing factors may play a larger role than mutations in genomic cis-elements in the expression of PCa-associated alternatively spliced genes. In addition, changes in alternative splicing may participate in the emergence of neuroendocrine PCa following treatment with second generation anti-androgen therapies.

This special issue of *Asian Journal of Andrology* is a valuable resource as part of the PCF global knowledge exchange that will contribute ultimately to the development of improved therapies and clinical diagnostics for PCa patients worldwide.

REFERENCES

1 Lipianskaya J, Cohen A, Chen CJ, Hsia E, Squires J, *et al*. Androgen-deprivation therapy-induced aggressive prostate cancer with neuroendocrine differentiation. *Asian J Androl* 2014; 16: 541–4.
2 Le JD, Huang J, Marks LS. Targeted prostate biopsy: value of multiparametric magnetic resonance imaging in detection of localized cancer. *Asian J Androl* 2014; 16: 522–9.
3 Nelson JB. Perspectives on the clinical management of localized prostate cancer. *Asian J Androl* 2014; 16: 511–4.
4 Parikh RA, Pascal LE, Davies BJ, Wang Z. Improving intermittent androgen deprivation therapy: lessons learned from basic and translational research. *Asian J Androl* 2014; 16: 505–10.
5 Morley S, Hager MH, Pollan SG, Knudsen B, Di Vizio D, *et al*. Trading in your spindles for blebs: the amoeboid tumor cell phenotype in prostate cancer. *Asian J Androl* 2014; 16: 530–5.
6 Xu J. The Xu's chart for prostate biopsy: a visual presentation of the added value of biomarkers to prostate-specific antigen for estimating detection rates of prostate cancer. *Asian J Androl* 2014; 16: 536–40.
7 Chiang YT, Gout PW, Collins CC, Wang Y. Prostate cancer metastasis-driving genes: hurdles and potential approaches in their identification. *Asian J Androl* 2014; 16: 545–8.
8 Qu M, Ren SC, Sun YH. Current early diagnostic biomarkers of prostate cancer. *Asian J Androl*. 2013; 16: 549–54.
9 Wadia R, Petrylak DP. New developments in the treatment of castration resistant prostate cancer. *Asian J Androl* 2014; 16: 555–60.
10 Balk SP. Androgen receptor functions in prostate cancer development and progression. *Asian J Androl* 2014; 16: 561–4.
11 Lapuk AV, Volik SV, Wang Y, Collins CC. The role of mRNA splicing in prostate cancer. *Asian J Androl* 2014; 16: 515–21.

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