Asian Journal of Andrology (2019) 21, 213–214
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INVITED EDITORIAL

Prostate Cancer

Prostate cancer: molecular and cellular mechanisms and their implications in therapy resistance and disease progression

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Asian Journal of Andrology (2019) **21**, 213–214; doi: 10.4103/aja.aja_31_19; published online: 9 April 2019

Prostate cancer is among the most common malignancies in Western countries, and its incidence is rapidly rising in Asia where it was traditionally considered an uncommon tumor. Our understanding of the disease and management strategies continue to evolve. The first revolution of its treatment was in the 1940s when hormonal therapy was used to treat patients. The discovery of prostate-specific antigen (PSA) and the subsequent adoption of widespread PSA screening have made it possible to diagnose the disease early, but it was not until recently that the field realized that we had been overdiagnosing and overtreating a large number of men with indolent diseases that will not impact their quality of life or life expectancy. Distinguishing indolent tumors from aggressive ones remains a challenge, although recent advances in multiparametric MRI have given clinicians more confidence in choosing men for active surveillance. However, more need to be done to fundamentally understand the molecular and cellular bases that determine the biologic behavior of each of the tumors.

We have also made strides in treating men whose tumors will likely progress if left untreated. Low-grade, organ-confined tumors can be cured by radical prostatectomy, and advances in surgical technologies such as laparoscopic surgery and robot-assisted surgery have contributed to better outcomes. Multiple studies have demonstrated that radiation therapy is equally effective. Unfortunately, a large number of men still experience disease progression that requires hormonal therapy which shuts down androgen production and/or inhibits androgen receptor (AR). Although this treatment is initially effective, the disease will eventually progress to castration-resistant prostate cancer (CRPC). For decades, CRPC was essentially untreatable except with the highly toxic chemotherapy. The recent introduction of abiraterone and enzalutamide has given us new tools that extend patients' lives. They treat CRPC by the inhibition of intratumoral androgen synthesis and better inhibition of AR, respectively. Unfortunately, therapy resistance and disease progression still occur despite near-maximal inhibition of AR activity. Apparently, inhibition of AR alone is unlikely to fundamentally change the treatment landscape. Therefore, further understanding of human prostate cancer holds the key for novel treatment strategies.

This special issue contains several review articles dealing with some of the most important aspects of prostate cancer. Gritsina *et al.*[1] review the transcriptional repression function of AR and its potential roles in the progression of PCa to CRPC and small-cell neuroendocrine carcinoma. Liu *et al.*[2] summarize the role of B-lymphoma Moloney murine leukemia virus insertion region 1 (BMI1) as an oncogenic and epigenetic regulator in tumor initiation, progression, and relapse of prostate cancer. Lin *et al.*[3] discuss the role of cancer stem cell (CSC) phenotypes as a possible underlying mechanism for CRPC. Blee and Huang discuss how tumor cells' lineage reprogramming in response to hormone therapy may be a key mechanism of therapy resistance.[4] Bai *et al.*[5] discuss how docetaxel and cabazitaxel, two taxanes that have been used for patients with metastatic CRPC, impact androgen receptor signaling in prostate cancer. Zhao and Li discuss how beta-adrenergic signaling affects neuroendocrine differentiation, angiogenesis, and metastasis during prostate cancer progression.[6] Chris Lau *et al.*[7] discuss the contrasting roles of testis-specific protein Y-encoded (TSPY) and TSPX in human oncogenesis. Xu and Qiu discuss how combination therapy for castration-resistant prostate cancer may work and the underlying mechanisms.[8] Liao and Xu discuss epigenetic regulation in the carcinogenesis and treatment of prostate cancer.[9] Huang *et al.*[10] discuss how neuroendocrine differentiation may contribute to therapy resistance and disease progression.

Therefore, we have put together a number of different articles dealing with many different molecular and cellular aspects of prostate cancer, and we promise this to be a highly informative and stimulating issue for readers who are interested in prostate cancer and cancer in general. It is our belief that novel, innovative treatment strategies will only result from better understanding the disease biology and pathology, and future success will likely come from molecular approaches beyond directly targeting androgen receptor alone.

COMPETING INTERESTS

Both authors declare no competing interests.

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Received: 21 March 2019; Accepted: 22 March 2019

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