Targeting the Mechanisms of Progression in Castration-resistant Prostate Cancer

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Until recently, few treatment options were available for metastatic castration-resistant prostate cancer (mCRPC). However, in recent years, there has been a rapid increase in the number of therapeutic options in addition to docetaxel. Novel therapies include the androgen synthesis inhibitor abiraterone, the antiandrogen enzalutamide, the taxane cabazitaxel, immunotherapeutic sipuleucel-T, and bone-targeting radium 223.

Although these new therapies have shown an improvement in overall survival for patients with mCRPC, and although clinical trials optimising their sequence with one another may further increase survival values, death from mCRPC is invariably due to resistance to contemporary treatment modalities. Understanding the biology behind mCRPC is of crucial importance if we are to develop new and better treatment regimens for this patient group.

In this month’s issue of European Urology, Karantanos et al provide an updated and in-depth review of issues pertaining to mechanisms behind development of resistance in mCRPC [1]. While the molecular basis implicated in the development of CRPC is complex and varied, it is clear that androgen receptor (AR) signalling remains an important driver of mCRPC despite systemic androgen deprivation and the new therapeutic options available today. Schweizer et al recently showed that docetaxel has only limited antitumor activity in CRPC patients previously treated with abiraterone [2], and this cross-resistance is likely due to interference of taxanes with the AR pathway [3]. Likewise, it has been reported that there is cross-resistance between abiraterone and enzalutamide therapy, although a proportion of patients benefit from sequential treatment therapy [4]. Such resistance may be associated with selective pressure and upregulation of AR splice variants, as ligand-independent AR splice variants have been described as being associated with resistance to both docetaxel and enzalutamide monotherapy and upregulated in mCRPC [5]. Recent studies further suggest that AR splice variants not only can transactivate target genes independent of full-length AR but also can activate the normally ligand-dependent full-length receptor and facilitate its nuclear localisation and transcription of target genes.

Karantanos and colleagues outline several additional important and alternative pathways that are aberrantly activated or upregulated in CRPC, such as de novo intratumoural androgen production and/or AR gene amplifications and mutations leading to persistent AR activation [1]. Furthermore, activation of AR by growth factors and cytokines or the involvement of aberrant signalling pathways may occur. In the majority of metastatic prostate cancer (PCa) cases, for example, there is a loss of PTEN and/or activation of PI3K signalling, potentially leading to Akt-mediated AR phosphorylation and interaction with the p300 cofactor involved in both androgen-dependent and -independent transactivation of AR.

The review [1] highlights an important mechanism whereby CRPC cells may become resistant: differential epigenetic transcriptional repression or activation of AR target genes in CRPC cells as compared to hormone naive PCa cells. This may result in activation of genes normally repressed by androgens [6]. It has been shown, for example, that the embryonic stem cell regulator Sox2 is expressed by basal cells but not luminal cells in the normal prostate and that Sox2 is repressed by AR binding to its promoter in normal prostate epithelial cells and cancer cell lines;
however, when cells become resistant to enzalutamide, Sox2 expression is unpressed and markedly upregulated [7]. Likewise, increased expression of AR and normally AR-repressed genes may activate various cell cycles or oncogenes and contribute to cellular survival, proliferation, and resistance.

In a similar manner, it has been shown that related cell lines derived from the same relapsed tumour have significantly different gene expression profiles in response to androgens; one gene may be elevated in response to androgens in one of the cell lines but repressed in the other. This suggests that clones with different AR transcriptional programs within the same tumour may have different selective advantages during CRPC therapy and serve as a basis for heterogeneity and resistance in PCa [8].

Emerging evidence also indicates that androgen deprivation causes epithelial–mesenchymal transition (EMT), leading to changes in cellular morphology, increased invasiveness, and induction of stem cell characteristics. EMT is required for normal embryonic development and has been implicated as a driver of metastasis and therapy resistance. This transition involves a range of transcription factors, including Twist. Recently, a preclinical study that combined enzalutamide and a vaccine against Twist in a TRAMP mouse model showed more than doubled overall survival in the combination treatment group when compared with the monotherapy groups, suggesting that treatment strategies based on EMT targeting may be clinically relevant and may improve survival [9].

Directly targeting PCa stem cells (cancer stem cells [CSCs]) may perhaps prove to be more successful because CSCs are hypothesised to be responsible for metastatic spread and to cause tumour resistance and relapse. Unfortunately, progress has been slow when it comes to identifying the prostate CSC, but emerging evidence suggests that the prostate may have luminal in addition to basal progenitor cells [10], opening up for the possibility of a stem-like luminal cell of origin in PCa carcinogenesis and progression. Advances in basic research may soon provide evidence of whether CSC-based strategies will be able to tackle mechanisms related to resistance and progression in mCRPC.

In conclusion, despite recent survival improvements for men with mCRPC, this stage of disease remains incurable. At a molecular level, progression to CRPC is characterised by an increase in intratumoral androgen biosynthesis, aberrant AR expression, crosstalk with other oncogenic pathways, reactivation of EMT processes, and upregulation of genes that regulate stemness and self-renewal. It can be anticipated that more novel strategies directed at the androgen pathway are yet to come. Enzalutamide and current antiandrogens depend on the presence of the ligand-binding domain of the AR, and this domain is often mutated or completely missing in mCRPC. New agents that target the AR for destruction or for its transcriptional activity may prove to block the AR pathway more effectively in relapsed tumours. Finally, other novel agents may target alternative oncogenic signalling, EMT, or CSCs. Molecules associated with such phenomena may further serve as predictive biomarkers in patients to guide therapeutic decisions.

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**References**


