

Prostate cancer resistance to second generation hormonal agents

Prostate cancer is a hormone-dependent disease that is treated with a variety of hormonal therapies targeting the androgen receptor (AR) pathway. AR is a transcription factor that has a relevant contribution to the etiology and progression of prostate cancer. The AR protein has distinct functional domains that include the COOH-terminal ligand binding domain (LBD), a DNA-binding domain (DBD), and an amino-terminal domain (NTD) [1]. Androgen deprivation therapy (ADT) with luteinizing hormone releasing hormone agonists or antagonists is the standard first line systemic therapy for metastatic prostate cancer [2]. ADT initially induces tumour regression in most patients, however disease progression inevitably occurs resulting in castration-resistant prostate cancer (CRPC). CRPC, at least initially, still remains AR-driven, through various mechanisms: 1) AR protein over-expression, 2) mutations in the NH₂-terminal domain, or LBD that render the receptor more sensitive to androgen activation, 3) autocrine androgen synthesis by prostate cancer cells, 4) cross talk with other oncogenic pathways [3, 4].

Mechanisms of resistance to abiraterone and enzalutamide

Recently, two therapeutic agents for prostate cancer have been approved that directly or indirectly target the AR: enzalutamide and abiraterone. Other endocrine therapies are under development. Both enzalutamide and abiraterone have significantly increased survival of CRPC patients [5-8]. Unfortunately, prostate cancers escape these second generation agents leading to three phenotypes/genotypes: neuroendocrine prostate cancer (NEPC), persistent AR-dependent prostate cancer, and AR-pathway independent prostate cancer [9]. Clinically 2 distinct groups of patients are seen: 1) gradually progressive disease in bone and lymph nodes with raising PSA serum levels; 2) rapidly progressive disease with visceral metastases and low or non-raising PSA. The majority of patients with disease progression to abiraterone and enzalutamide maintains an AR dependency, as a matter of fact PSA, that is an AR regulated enzyme, often increases in these patients. The mechanisms of resistance to abiraterone are similar but not superimposable to those of enzalutamide, this is the reason why a minority of patients with disease progression to abiraterone may respond to enzalutamide therapy and vice versa [10-13]. Prostate cancer resistance to abiraterone may occur as a consequence of amplification and/or overexpression of AR and upregulation of CYP-17 [14]. In addition,

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abiraterone therapy results in progesterone elevation that may induce AR T878A, a progesterone activated mutation [15]. Mechanisms of resistance of prostate cancer to enzalutamide involve activating mutations in LBD of AR that induce inappropriate agonist responses to the drug [16]. In the majority of cases, enzalutamide and abiraterone share the same mechanisms of resistance such as glucocorticoid receptor (GR) mediated transcriptional activation [17], activation of PI3K/AKT signaling [18] and AR splice variants (AR-*Vs*) [19]. AR-*Vs* occur as a consequence of altered AR mRNA splicing leading to synthesis of COOH-terminally truncated proteins lacking the AR LBD [20, 21]. As a consequence, these proteins do not bind with either the natural ligand or AR antagonists, but remain constitutively active as transcription factors. One of them, the AR-V7, was recently studied as circulating marker of resistance to second generation hormonal agents. A recent study showed that CRPC patients with AR-V7 positivity on circulating tumor cells failed to respond to both abiraterone and enzalutamide [20-22]. Finally, ligand-independent AR activity is modulated by post-translational modifications, including phosphorylation, sumoylation, methylation, ubiquitination, and acetylation. Each of these protein modifications can functionally interact with each other in a signaling pathway that may converge on the AR to support persistent activity [23]. A subset of patients with advanced castration-resistant prostate cancer may eventually evolve into an AR-independent phenotype, with a clinical picture associated with the development of rapidly progressive disease involving visceral sites and hormone refractoriness, often in association with low rising serum prostate-specific antigen levels. With the introduction of new generation hormonal agents, aggressive variants of prostate cancer are increasingly recognized. Preclinical data and clinical experience suggest that transformation to AR-independent prostate cancer likely occurs as a potential mechanism of adaptive resistance to AR-targeting therapies. Prostate cancer cells exposed to ADT and drugs targeting the AR can trans-differentiate to NEPC. Several mechanisms have been identified such as stimulation of the transcription factor hASH-1 (human homologue-1 of *achaete-scute gene*) [24] or down regulation of REST [25]. But the most important molecular changes leading to aggressive neuroendocrine phenotype are Rb-1 loss and p53 mutation [26]. Patients developing aggressive NEPC have a poor prognosis with a median survival perspective of 7 months, as recently reviewed [27].

Conclusions

Although AR still remains a relevant therapeutic target for prostate cancer, the selection pressure induced by androgen deprivation therapies and in particular the new endocrine hormonal therapies favour the onset of heterogeneous tumor populations with different aggressiveness. In this scenario it will be important to identify patient subsets for whom specific therapies are most appropriate or contraindicated. Re-biopsy with re-assessment of tumor characterization is destined to be crucial to understand when, in the course of prostate cancer progression, specific therapies should be applied.

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