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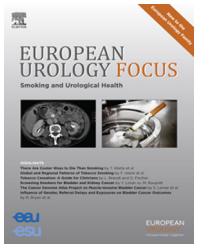

Review – Prostate Cancer

Understanding Mechanisms of Resistance in Metastatic Castration-resistant Prostate Cancer: The Role of the Androgen Receptor

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Article info

Article history:
Accepted November 23, 2016

Associate Editor:
James Catto

Keywords:
Androgen receptor
Metastasis
Castration-resistant prostate cancer
Mechanisms
Review

Abstract

Context: After initiation of androgen deprivation therapy (ADT), most patients progress to castration-resistant prostate cancer (CRPC) within 2 or 3 yr. In the USA, approximately 67 000 men are estimated to have metastatic CRPC.
Objective: To provide an overview of different mechanisms driving resistance to therapy in metastatic CRPC, with a focus on androgen receptor (AR)–dependent pathways.
Evidence acquisition: A Medline search via PubMed was performed using the keywords *metastatic castration resistant prostate cancer (mCRPC)*, *castration-resistant*, *CRPC*, *prostate cancer*, *androgen resistance*, *hormone-refractory*, *hormone-independent*, *androgen receptor*, *and androgen receptor axis*. Only articles in the English language were included. Abstracts and full-text articles were reviewed and assessed for relevant content. The majority of the articles selected were published between 1993 and 2016. Older studies were included selectively if relevant.
Evidence synthesis: Numerous resistance mechanisms characterize the development of CRPC. The review focuses on AR-dependent pathways, including mechanisms of resistance to new agents. These include reactivation of AR (via AR amplification, mutations, or splice variants), stress-activated pathways, and aberrant activation of AR.
Conclusions: Mechanisms of resistance in CRPC are manifold and require multiple combinations of therapeutic approaches to be overcome. An understanding of the mechanisms by which resistance to ADT develops is the basis for identifying future therapeutic targets.
Patient summary: Castration-resistant prostate cancer is characterized by multiple resistance mechanisms to androgen deprivation treatment and remains an incurable disease. An understanding of the mechanisms underlying this resistance is necessary to identify future therapeutic targets.

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http://dx.doi.org/10.1016/j.euf.2016.11.013
2405-4569/

1. Introduction

Prostate cancer remains one of the leading causes of cancer death worldwide [1]. In the era of prostate-specific antigen (PSA) screening, the majority of cancers detected are localized and can be cured. In locally advanced and metastatic prostate cancer, treatment consists of androgen deprivation therapy (ADT), which has been the standard of care since Huggins and Hodges first introduced the concept that prostate cancer is an androgen-dependent disease [2]. However, ultimately all patients will progress to castration-resistant prostate cancer (CRPC), which usually occurs within a few months to 2–3 yr of initiation of ADT. The mechanisms driving the emergence of the CRPC state have been elusive; however, within the last decade it has become clear that androgens and the androgen receptor (AR) are crucial drivers of CRPC. Several resistance mechanisms including reactivation of AR (via AR amplification, mutations, or variants), activation of AR via aberrant pathways, and intratumoral or alternative androgen production have been described. New agents approved for treatment of CRPC such as enzalutamide and abiraterone acetate target a subset of these resistance mechanisms. However, mechanisms of resistance evolve over time against these new agents as well.

The aim of this review is to provide an overview of different mechanisms of treatment resistance in metastatic CRPC (mCRPC) with a focus on AR-dependent pathways.

2. Evidence acquisition

A literature review was performed by searching the electronic PubMed/Medline databases. The search was performed using combinations of the following terms: *metastatic castration resistant prostate cancer (mCRPC)*, *castration-resistant*, *CRPC*, *prostate cancer*, *androgen resistance*, *hormone-refractory*, *hormone-independent*, *androgen receptor*, and *androgen receptor axis*. Articles (only English) were selected based on the title, abstract, study format, and content by consensus among the authors. In addition, guidelines from the European Association of Urology (EAU) and American Urological Association were studied to identify relevant studies and recommendations. References from selected studies were reviewed manually. The majority of the articles selected were published between 1993 and 2016. Older studies were included selectively if historically relevant.

3. Evidence synthesis

3.1. AR

The AR is a ligand-inducible transcription factor of the nuclear receptor superfamily [3]. It consists of a polymorphic N-terminal domain (NTD), a DNA-binding domain (DBD), a small hinge region, and a C-terminal ligand-binding domain (LBD; Fig. 1) [3,4] AR exon 1 encodes the entire NTD, which comprises the bulk of the AR and is the least conserved of the four domains [5]. The *AR* gene is located on the X chromosome at Xq11-12 and is therefore single-copy in males, which allows for phenotypic manifestation of mutations without the influence of a wild-type codominant allele [6]. The unliganded AR associates with a heat shock protein 90 (HSP90) chaperone complex in the cytoplasm and undergoes proteasome-mediated degradation in the absence of ligand [7].

Binding of androgens (testosterone or dihydrotestosterone) to AR results in dissociation of the AR-HSP complex, nuclear translocation, and dimerization. The AR dimer binds to androgen response elements (AREs) in the promoter regions of target genes, and recruits cofactors for regulation of the expression of androgen-regulated genes [6]. The AR is subject to multiple post-translational modifications in response to agonist binding, which include phosphorylation, methylation, acetylation, ubiquitylation, and sumoylation [7].

3.2. ADT and castration resistance

ADT is a mainstay in the treatment of metastatic prostate cancer. Testosterone is the main source of circulating androgens in males. The goal of ADT is to reduce serum testosterone to castrate levels, thus inducing regression of the tumor [8]. This approach was based on the important insight by Huggins and Hodges in 1941 that prostate cancer is androgen-dependent [2].

The upper limit of castration concentrations of serum testosterone has been considered to be 50 ng/dl (1.7 nmol/l), although lower concentrations (20 ng/dl; 1 nmol/l) may be more desirable for optimal therapy [9]. In the current EAU guidelines, the castration level is defined as a testosterone concentration of $<$20 ng/dl, and new methods demonstrated a testosterone level of 15ng/dl after surgical castration [1].

ADT can be achieved via either medical or surgical castration [1]. Luteinizing hormone–releasing hormone (LHRH) agonists and antagonists suppress the production of LH via negative feedback or competitive inhibition, and thus suppress testicular testosterone production [10]. Antiandrogens are competitive inhibitors of AR and block the androgen effect. Two different types of antiandrogen exist, nonsteroidal antiandrogens and steroidal antiandrogens, which are derivatives of hydroxyprogesterone.

Sun et al [11] retrospectively evaluated 3295 men who received ADT via orchiectomy or LHRH agonists. The authors noted a lower risk of any fractures in the surgical castration compared to the medical castration group. At 1 yr after prostate cancer diagnosis, there was no significant difference in median total expenditure between surgical castration ($9726.98) and LHRH agonists ($8478.46). They concluded that surgical castration is underutilized and should be considered more frequently in the routine care of patients with metastatic disease [11].

Data from a Southwest Oncology Group (SWOG) trial identified the PSA response after 7 mo of ADT as an independent predictor of survival. The median survival was 13 mo for patients with PSA $>$4 ng/ml, 44 mo for patients with PSA of 0.2–4 ng/ml, and 75 mo for patients with PSA $<$0.2 ng/ml [12].

Please cite this article in press as: Tilki D, et al. Understanding Mechanisms of Resistance in Metastatic Castration-resistant Prostate Cancer: The Role of the Androgen Receptor. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.11.013