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Review

Adaptive pathways and emerging strategies overcoming treatment resistance in castration resistant prostate cancer

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Abstract The therapies available for prostate cancer patients whom progress from hormone-sensitive to castration resistant prostate cancer include both systemic drugs, including docetaxel and cabazitaxel, and drugs that inhibit androgen signaling such as enzalutamide and abiraterone. Unfortunately, it is estimated that up to 30% of patients have primary resistance to these treatments and over time even those who initially respond to therapy will eventually develop resistance and their disease will continue to progress regardless of the presence of the drug. Determining the mechanisms involved in the development of resistance to these therapies has been the area of intense study and several adaptive pathways have been uncovered. Androgen receptor (AR) mutations, expression of AR-V7 (or other constitutively active androgen receptor variants), intracrine androgen production and overexpression of androgen synthesis enzymes such as Aldo-Keto Reductase Family 1, Member C3 (AKR1C3) are among the many mechanisms associated with resistance to anti-androgens. In regards to the taxanes, one of the key contributors to drug resistance is increased drug efflux through ATP Binding Cassette Subfamily B Member 1 (ABCB1). Targeting these resistance mechanisms using different strategies has led to various levels of success in overcoming resistance to current therapies. For instance, targeting AR-V7 with niclosamide or AKR1C3 with indomethacin can improve enzalutamide and abiraterone treatment. ABCB1 transport activity can be inhibited by the dietary constituent apigenin and antiandrogens such as bicalutamide which in turn improves response to docetaxel. A more thorough understanding of how drug resistance develops will lead to improved treatment strategies. This review will cover the current knowledge of resistance mechanisms to castration resistant prostate cancer therapies and methods that have been identified which may improve treatment response.

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1. Introduction

Prostate cancer is the second leading cause of cancer related deaths and the most commonly diagnosed cancer in men with an estimated 220,800 new cases yearly in the United States [1,2]. First line treatments for prostate cancer aim to reduce circulating androgen levels through the use of androgen deprivation therapies (ADT). This is accomplished using one of two methods: surgical bilateral orchiectomy which inhibits androgen synthesis by the testes or through the use of castration inducing drugs to reduce androgen levels and androgen receptor (AR) activation. While ADT is initially effective at reducing prostate cancer growth, after 2–3 years of treatment the majority of patients will progress to castration resistant prostate cancer (CRPC) and tumor growth will proceed even in the presence of castrate levels of androgen. At this point of disease progression, the number of therapeutic options is currently limited but is the focus of intense research to improve the outcome for patients [3].

Clinically, CRPC is defined as progression of prostate cancer in the presence of castrate levels of circulating testosterone [4,5]. Often times, the AR is either overexpressed, hyper-activated, or both leading to the transcription of downstream target genes which ultimately promotes tumor progression despite the patient having negligible levels of androgen present. The mechanisms which lead to the development of CRPC from hormone-sensitive prostate cancer are widely studied. The identified mechanisms, including AR amplification and mutation, AR co-activator and co-repressor modifications, aberrant activation and/or post-translational modification, AR splice variants, and altered steroidogenesis, each results in an increase in AR activation and signaling. This can be due to an increased amount of androgen, enhanced response to existing androgen, and activation of the AR by non-classical ligands or no ligand at all among other methods [6–10].

Treatment of CRPC is currently achieved with the administration of taxanes, such as docetaxel and cabazitaxel, which interrupt the growth of fast-dividing cells through disruption of microtubule function, or with anti-androgen therapies including enzalutamide and abiraterone. The primary mechanism of anti-androgens is to inhibit AR activation either directly, by antagonizing the receptor, or indirectly by blocking androgen synthesis. Unfortunately, it is estimated that one third of patients given abiraterone and one fourth of patients given enzalutamide will fail to respond to initial treatment with these drugs [11,12]. Furthermore, within 24 months of initiating treatment, even those who initially respond to the drugs will develop resistance.

New methods by which treatment resistance develops in prostate cancer are constantly being identified. Due to the numerous dysregulated pathways that are implicated in prostate cancer drug resistance, elucidating ways to reverse this resistance becomes both increasingly complicated and important. This review will outline the current understanding of the major compensatory mechanisms that prostate cancer cells use to overcome the presence of the drugs (Fig. 1). In addition, successful experimental strategies that have been observed to improve treatment response will be discussed (Fig. 2).

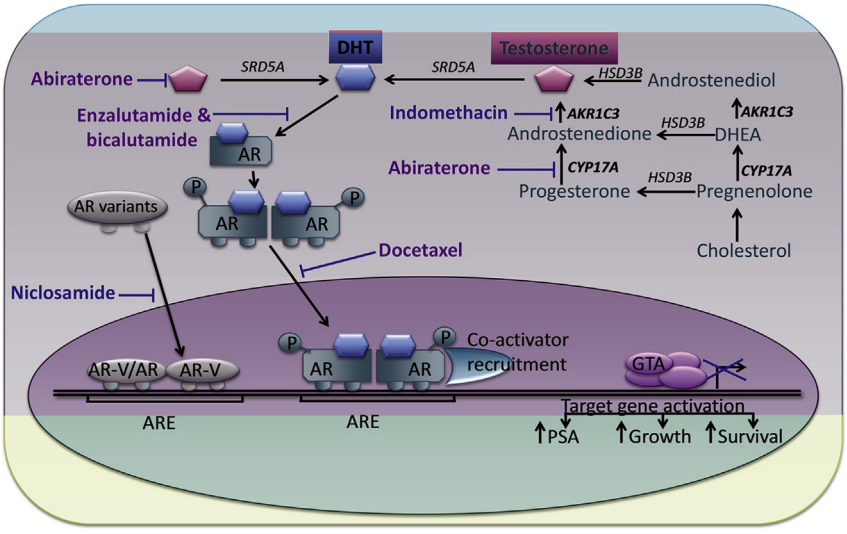

Figure 1 Approved (orange) and experimental (red) therapies for CRPC and their targets. AR, androgen receptor; ARE, androgen-response element; AR-V, androgen receptor variants; CRPC, castration resistant prostate cancer; DHT, dihydrotestosterone; PSA, prostate specific antigen.

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