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Review

Androgen receptor variation affects prostate cancer progression and drug resistance

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ABSTRACT

Significant therapeutic progress has been made in treating prostate cancer in recent years. Drugs such as enzalutamide, abiraterone, and cabazitaxel have expanded the treatment armamentarium, although it is not completely clear which of these drugs are the most-effective option for individual patients. Moreover, such advances have been tempered by the development of therapeutic resistance. The purpose of this review is to summarize the current literature pertaining to the biochemical effects of AR variants and their consequences on prostate cancer therapies at both the molecular level and in clinical treatment. We address how these AR splice variants and mutations affect tumor progression and therapeutic resistance and discuss potential novel therapeutic strategies under development. It is hoped that these therapies can be administered with increasing precision as tumor genotyping methods become more sophisticated, thereby lending clinicians a better understanding of the underlying biology of prostate tumors in individual patients.

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1. Introduction

Prostate cancer is the second leading cause of death from cancer and the most prevalent cancer in men; currently, 14% of the men in America are diagnosed with prostate cancer over their lifetime [1]. The androgen receptor (AR) is quintessential to prostate carcinogenesis, progression, and treatment. Metastatic prostate cancer is therefore treated with androgen deprivation therapy (ADT), which includes surgical or chemical castration that deprives tumor cells of testicular androgens thereby slowing growth. Typically, ADT initially proves to be effective, but in most cases the patient progresses to castration resistant prostate cancer (CRPC). Treatment for CRPC may include continuing ADT concurrent with immunotherapy, radiotherapy, cytotoxic chemotherapy, and/or other hormone manipulations.

Therapeutic development has recently improved upon two classes of anti-androgens. AR ligands (e.g., bicalutamide) inhibit AR signaling by binding to the AR itself and preventing the transcription of AR effectors. More recently, more potent inhibitors have been developed that simultaneously inhibit both AR ligand binding and the DNA-binding capacity of the AR (e.g., enzalutamide). Androgen synthesis inhibitors (e.g., ketoconazole) block the synthesis of androgens from their many precursors. Newer androgen synthesis inhibitors more-specifically inhibit these enzymes at lower concentrations (e.g., abiraterone). While such innovations have greatly improved prostate cancer treatment, patients inevitably acquire resistance toward newer therapies as well. The purpose of this review is to summarize current knowledge about how AR splice variants and mutations affect tumor progression and therapeutic resistance, address precision treatment options for patients harboring such AR variants, and discuss emerging therapies to target these variants.

2. Androgen receptor signaling

2.1. AR signaling in the normal prostate

The AR is encoded by the *AR* gene (located at chromosome Xq12), and the full-length transcription product has a molecular weight of 100 kDa. In normal cells, the *AR* consists of four domains: a transactivation domain (encoded by exon 1), a DNA-binding domain (exons 2–3), a hinge region (encoded by the 5' portion of exon 4), and a ligand-binding domain (exons 4–8), as shown in Fig. 1 [2].

Cytosolic AR is sequestered by heat shock proteins (HSPs) until it binds to androgens [3,4]. Ligand binding is a function of the conformation of the ligand-binding pocket, which prefers dihydrotestosterone (DHT) and testosterone (to a lesser extent) while excluding weaker androgens and non-androgens [3,4]. Following ligand binding, the AR undergoes a conformational change in which helix 12 covers the hormone-binding pocket, causing the AR to adopt the active conformation [5]. The AR then forms a homodimer that is transported to the nucleus where it binds to DNA and activates gene transcription (Fig. 2) [6].

The full-length AR contains a bipartite nuclear localization sequence that runs from the C-terminal end of the DNA-binding domain to the N-terminal end of the hinge region (Fig. 1), which is necessary for regulation of nuclear transport by alpha and beta importin [7]. In addition to the regulation by alpha and beta importins, the full-length AR also relies upon cytoskeletal nuclear transport to translocate to the nucleus [8,9]. In this modified version of nuclear transport, a portion the nuclear localization signal binds to dynein, which moves along microtubules toward the nucleus and enhances nuclear transport by alpha and beta importin [9]. DNA binding results in the subsequent transactivation of various genes that contain AR elements in their promoter regions [10]. Such genes are responsible for a range of functions, including cell growth and proliferation (Fig. 2) [11].

2.2. AR signaling in metastatic prostate cancer progression and CRPC

Therapeutic resistance typically develops through several mechanisms that confer a selective advantage to tumor cells in a low-androgen environment: reliance on non-AR signaling pathways, intratumoral androgen biosynthesis, androgen scavenging, AR overexpression, AR splicing variation, and/or AR mutation [12]. Whereas ADT resistance was thought to be a function of increased AR copy number in most cases, it has recently been proven that clinically relevant AR splice variants also contribute to progression on ADT [13,14]. Mutations that uncouple AR signaling from ligand binding are very-often involved in resistance to other classes of antiandrogens [13,14]. Taxanes also affect the AR pathway, which may be responsible for certain taxane-resistant tumors [13,14]. As these therapy-resistant cells grow, they become the dominant cell population that eventually progress in spite of treatment [13,14]. There are several biochemical mechanisms by which CRPC and/or therapeutic resistance arise; those that are caused by genomic alterations to the AR are summarized below.

3. Biochemical effects of androgen receptor variants

3.1. AR mutations

AR mutations, particularly those affecting the ligand-binding domain, contribute to prostate cancer progression and resistance to anti-androgens. Marcelli et al. indicated that while none of the study patients with early stage prostate cancer had mutations in their AR coding sequence, 21% of patients with advanced disease did [13]. In general, somatic mutations that substitute an amino acid with a large size difference from the amino acid encoded by the germline in the ligand-binding pocket allow the AR to be more easily activated by alternative ligands [15]. The AR is normally activated when DHT binds the ligand-binding pocket and helix 12 then moves into the active position [5]. In the mutated state, amino acids that have a stronger affinity for helix 12 than the original amino acid can pull helix 12 closer to the active position and make the AR less reliant on ligand binding for activation [15]. Alternatively, smaller amino acid substitutions in the ligand-binding domain result in a larger ligand-binding pocket that can accommodate more ligands. Although over 70 different AR missense mutations have been identified, H874Y, F876L, T877A, and W741L/C (Fig. 3) are known to cause drug resistance and disease progression [16,17].