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Review

Recent progress in the development of protein–protein interaction inhibitors targeting androgen receptor–coactivator binding in prostate cancer

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ABSTRACT

The androgen receptor (AR) is a key regulator for the growth, differentiation and survival of prostate cancer cells. Identified as a primary target for the treatment of prostate cancer, many therapeutic strategies have been developed to attenuate AR signaling in prostate cancer cells. While frontline androgen-deprivation therapies targeting either the production or action of androgens usually yield favorable responses in prostate cancer patients, a significant number acquire treatment resistance. Known as the castration-resistant prostate cancer (CRPC), the treatment options are limited for this advanced stage. It has been shown that AR signaling is restored in CRPC due to many aberrant mechanisms such as AR mutations, amplification or expression of constitutively active splice-variants. Coregulator recruitment is a crucial regulatory step in AR signaling and the direct blockade of coactivator binding to AR offers the opportunity to develop therapeutic agents that would remain effective in prostate cancer cells resistant to conventional endocrine therapies. Structural analyses of the AR have identified key surfaces involved in protein–protein interaction with coregulators that have been recently used to design and develop promising AR-coactivator binding inhibitors. In this review we will discuss the design and development of small-molecule inhibitors targeting the AR-coactivator interactions for the treatment of prostate cancer.

Contents

Abbreviations: AB, Sandrogen-binding site; AF, activation function; AR, androgen receptor; ARA, androgen receptor-associated protein; ARE, androgen-responsive elements; BF3, binding function 3; CBI, coactivator binding inhibitor; CBP, CREB-binding protein; CPRC, castration-resistant prostate cancer; CYP, cytochrome P450; DBD, DNA-binding domain; DHT, 5α-dihydrotestosterone;; ER, estrogen receptor; FP, fluorescence polarization; GRIP1, glutamate receptor interacting protein 1; LBD, ligand-binding domain; NLS, nuclear localization signal; NR, nuclear receptor; NTD, N-terminal domain; PC, aprostate cancer; PELP1, proline- glutamic acid- and leucine rich protein 1; PPI, protein–protein interaction; PSA, prostate specific antigen; SAR, structure-activity relationship; SPR, surface plasmon resonance; SRC, steroid receptor coactivator;; TF, transcription factor; TR-FRET, time-resolved fluorescence resonance energy transfer.

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1. Introduction

The androgen receptor (AR) is a member of the nuclear receptor (NR) superfamily of ligand regulated transcription factors that plays an integral role in primary and secondary male sexual development. As a key regulator for the growth, terminal differentiation and function of the prostate gland, excessive stimulation of the AR can result in prostate cancer (PCa) and the related but benign prostatic hyperplasia [1–5]. PCa is the most common solid tumor and the second leading cause of cancer death among men worldwide with ~20% of patients developing metastatic castration-resistant prostate cancer (CRPC) [6]. Playing a critical role in PCa development and progression, the AR has emerged as a primary therapeutic target. Different strategies have been developed to block the production or action of androgens that provide growth and survival signals to prostate cells [7–14]. The currently used AR antagonists, such as flutamide, bicalutamide, nilutamide and enzalutamide (MDV3100), act by binding to the androgen binding site (ABS) of the AR, resulting in conformational changes that prevent its activation [7,11,14]. Although initial responses to AR antagonists are usually favorable and suppression of prostate tumor growth is observed, with time, the diseases transforms and progresses to metastatic CRPC where patients develop resistance to antiandrogen drugs [8,15–19]. The therapeutic options are very limited for this disease stage and include the addition of cytotoxic agents such as taxanes, the selective CYP17 inhibitor abiraterone acetate, radium-223 (for men with bone metastases) or the vaccine sipuleucel-T to the androgen deprivation therapy [17,20–22]. Many studies on CRPC have shown that functional AR signaling is inappropriately restored in castrate or androgen-depleted environment [23,24]. A wide variety of cellular modifications have been proposed for the emergence of resistance in CRPC including AR mutation (*e.g.* in the ABS), overexpression of the AR and/or its coactivators, constitutively active splice variants, intracrine androgen production and alternative AR activation [25–35]. Taken together, these mechanisms underscore the addiction of CRPC to AR signaling [17,24]. As a result, new chemical approaches with innovative mode of action are urgently needed to overcome resistance to antiandrogens and successfully inhibit AR signaling in advanced PCa. In this review we will discuss the recent progress in the design and development of promising small-molecule inhibitors targeting AR-coactivator protein–protein interactions for the treatment of prostate cancer.

2. The androgen receptor

In the absence of ligands, the AR predominantly resides in the cytoplasm where it is associated with heat shock proteins in a transcriptionally inactive form until it is activated by testosterone or the more potent metabolite, 5α-dihydrotestosterone (DHT) [36,37]. Upon ligand binding, the AR undergoes a substantial conformational change leading to dissociation from repressor proteins, dimerization, translocation to the nucleus and association to androgen-responsive elements (ARE) in the regulatory regions of target genes [38]. Through this pathway, the AR regulates the expression of more than a thousand genes including the prostate specific antigen (PSA), an important biomarker for PCa. The DNA-bound receptor can then exert a positive or negative

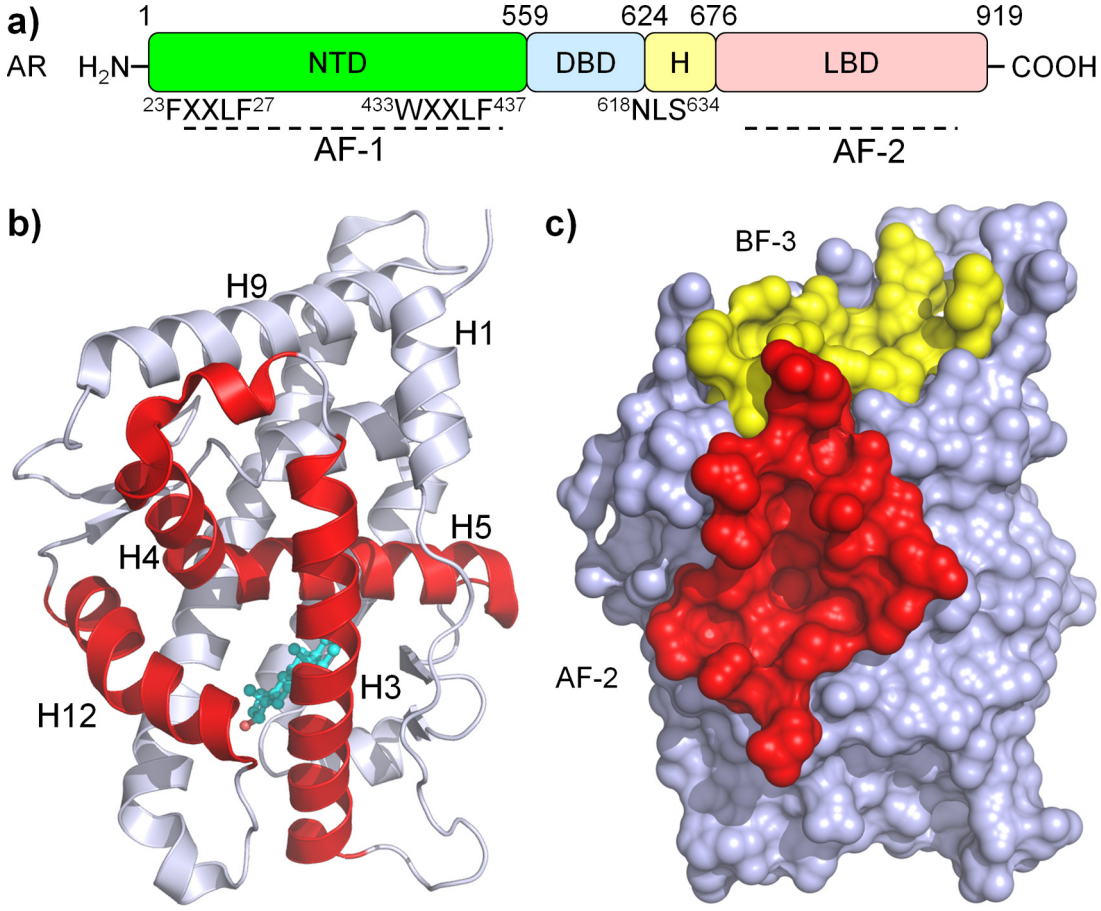

Fig. 1. Structure of the AR and its LBD. (a) Functional domains of the AR. (b) Crystal structure of the AR-LBD bound to testosterone (balls and sticks; cyan, carbon; red, oxygen) with key helices 3, 4, 5 and 12 (red ribbon) forming the coactivator binding site (PDB: 2Q7I) [63]. (c) Space-filling model of the AR-LBD showing the BF-3 (yellow) and AF-2 (red) sites. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)