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Strategies for targeting the androgen receptor axis in prostate cancer

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Androgen receptor (AR) signaling plays a critical role in prostate cancer cell proliferation, survival, and differentiation. Therapeutic strategies targeting the androgen receptor have been developed for the treatment of metastatic hormone-naïve prostate cancer; however, despite effective targeting recent studies have demonstrated that during progression to a castrate-resistant phenotype there is restoration of AR target gene expression. On the basis of this observation, second-generation therapeutics have been developed to target AR in the castrate-resistant setting resulting in a survival benefit. In this review we will discuss the mechanisms promoting AR signaling and the development of second-generation therapeutics targeting AR in castrate-resistant prostate cancer.

Introduction

The androgen receptor (AR) gene, located on chromosome Xq11–12, encodes for a 110 kDa nuclear receptor protein that activates or represses the transcription of target genes. These androgen-regulated genes modulate cell growth, differentiation and homeostasis of androgen-dependent cells. AR signaling is crucial for the development and maintenance of male reproductive organs including the prostate gland. The dependence of prostate cancer cells on androgen signaling was first demonstrated by Huggins and Hodges who observed that bilateral orchiectomy resulted in regression of disease in patients with metastatic prostate cancer [1]. Since that time, androgen-deprivation therapy has been the treatment of choice for metastatic and locally advanced prostate cancer. However, despite androgen-deprivation therapy, the majority of metastatic prostate cancers progress to a castrate-resistant phenotype [2,3]. Although a minority of castrate-resistant prostate cancers bypass the requirement for AR signaling (neuroendocrine and small-cell differentiation lacking AR expression), the vast majority remain dependent on the androgen pathway. In this review we will discuss the molecular mechanisms of AR signaling in castrate-resistant disease and therapies directed at further inhibiting AR function in the castrate-resistant setting.

Castrate-resistant prostate cancer maintains a functional AR axis

Progression of metastatic prostate cancer following androgen deprivation (castrate-resistant disease) was previously referred to as hormone refractory prostate cancer. However, it has long been observed clinically that this disease state is in fact still dependent on androgen signaling. Prostate-specific antigen (PSA), an AR-regulated gene and marker for prostate cancer disease activity as measured by serum levels, declines following androgen-deprivation therapy and a subsequent rise in serum PSA levels is often the hallmark for the emergence of castrate-resistant disease. This increase in serum PSA levels clearly indicates reactivation of AR target gene activity. Additionally, after the development of castrate-resistant disease, the administration of first-generation AR antagonists, such as flutamide or bicalutamide, has been demonstrated to elicit a therapeutic response associated with reduction in serum PSA levels [4,5]. Thus, directly inhibiting AR in the setting of castrate-resistant disease is associated with serum PSA responses in the majority of patients. Lastly, patients demonstrating progression of castrate-resistant disease following treatment with flutamide or bicalutamide, once again defined by increases in serum PSA levels, were observed to have declining serum PSA levels following antiandrogen withdrawal, indicating that the antiandrogens began working as agonists toward AR [6,7]. Collectively, these clinical observations led to the appreciation that castrate-resistant disease is still dependent on AR signaling.

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Molecular alterations of AR in castrate-resistant prostate cancer

Several molecular mechanisms have been implicated to promote reactivation of AR in the castrate environment. Initial studies focused directly on molecular analyses of AR in the castrate-resistant setting. Investigators sequencing AR in cell lines and metastatic prostate cancer specimens have identified several mutations that allow other steroids, such as corticosteroids, and antiandrogens to act as agonists. These mutations are detected in approximately 10% of castrate-resistant prostate cancers, frequently observed following antiandrogen therapy, although the actual incidence could be higher [8,9]. The majority of mutations occurs in the ligand-binding domain of the AR, resulting in structural changes in the AR protein altering the specificity of ligand binding. Thus, the mutated AR can be activated by other steroid hormones such as progesterone or convert known AR antagonists, such as flutamide, to agonist activity.

Other mechanisms resulting in activation of AR include amplification of AR, upregulation of AR expression, expression of AR transcript variants lacking the ligand-binding domain, modulation of AR co-factors and activation of kinase pathways promoting AR function. Figure 1 summarizes the potential mechanisms of AR activation in castrate-resistant disease and rationale for the development of therapeutics targeting these mechanisms.

Amplification and overexpression of AR in castrate-resistant prostate cancer

Overexpression of AR is a frequent event in prostate cancer. Q3 Compared to hormone-naive organ-confined prostate cancer, castrate-resistant prostate cancer is enriched for AR amplification and increased AR gene expression. Although AR amplification has not been observed in primary prostate cancer, approximately 20% of castrate-resistant metastases will demonstrate AR amplification [10–12]. Furthermore, mRNA upregulation is observed in approximately 60% of castrate-resistant prostate cancers [12,13]. Studies have demonstrated that exogenous overexpression of AR is sufficient to induce castrate-resistant disease in preclinical models [14]. Intriguingly, overexpression of AR also resulted in reduced efficacy of the antiandrogen bicalutamide, converting this AR antagonist to a weak agonist in cell lines and xenograft models [14]. In conjunction with the overexpression of AR, it has been observed that there is an associated increase in the expression of transcript variants of AR lacking the ligand-binding domain while maintaining functional activity even in the absence of androgens.

Androgen production in castrate-resistant prostate cancer

Androgen deprivation therapy does not completely eliminate circulating serum androgens. Serum testosterone levels are reduced to a mean of 15 ng/ml from a normal range of greater than 200 ng/ml, whereas serum levels of adrenal androgens such as androsteindione and dehydroepiandrosterone (DHEA) are unaffected following androgen-deprivation therapy [15]. Studies have demonstrated that adrenal androgens and downstream metabolites are capable of binding to and activating the AR in a castrate setting [16,17]. Although serum testosterone levels significantly decrease following androgen-deprivation therapy, the intraprostatic concentration of androgens is reduced much less dramatically [18]. Although this level of reduction is sufficient to induce cellular response in hormone-naive prostate cancer, molecular alterations evolve that result in an increased sensitivity of AR to low levels of ligands in the castrate-resistant setting.

In addition to low-level production of testosterone by the testes following androgen-deprivation therapy, the adrenal glands also serve as a source of circulating androgens promoting castrate-resistant disease. Recent data are also emerging to support the fact that intratumoral production of androgens could also play an important part. Expression profiling studies comparing castrate-resistant prostate cancer with primary tumors found that enzymes involved in androgen synthesis, such as cytochrome P450 (CYP)17, are upregulated in castrate-resistant disease [13,19,20]. These enzymes play a crucial part in the conversion of cholesterol and pregnenolone to androgens (DHEA). Furthermore, using mass spectrometry to measure intratumoral androgens directly, it has been shown that castrate-resistant metastatic prostate cancers have higher levels of testosterone compared with primary tumors in hormone-naive patients [21]. These data suggest that adrenal and intratumoral production of androgens might allow prostate cancers to progress despite low serum testosterone levels associated with androgen-deprivation therapy. This is especially realized in the setting of AR mutation or overexpression, where the AR is sensitive to low levels of ligand.

Targeting the AR in castrate-resistant prostate cancer

On the basis of the knowledge that castrate-resistant prostate cancer is still dependent on AR and the identification of molecular alterations leading to AR activity despite low levels of androgen, several novel therapies have been developed for patients with castrate-resistant disease. At the initial progression to castrate-resistant prostate cancer, an antiandrogen such as flutamide or bicalutamide is typically combined with continued androgen-deprivation therapy and, in some cases, this can result in stabilization of disease [4,5]. However, in the majority of patients, the time to disease progression is usually short. These antiandrogens bind directly to the ligand-binding domain and out-compete low levels of androgens for binding. However, because bicalutamide and flutamide allow AR nuclear translocation and DNA binding, these antiandrogens have been observed to convert to AR agonists as demonstrated by a clinical rise Q4 in serum PSA levels followed by a paradoxical decline upon antiandrogen withdrawal [6,7]. Several second-generation AR antagonists are currently in various stages of early clinical development.

MDV-3100 (enzalutamide), a novel second-generation antiandrogen, was rationally designed using the crystal structure of the AR and cell-based screening [14]. Because biclutamide is converted to an agonist in LNCaP cells that overexpress AR, candidate compounds were screened for their ability to inhibit cell growth and PSA production. MDV-3100 binds directly to AR in the ligand-binding domain, inhibiting the ability of AR to translocate efficiently to the nucleus and bind to DNA [14]. These properties lessen the probability of agonist conversion for MDV-3100 that has previously been observed with earlier antiandrogens [14,22]. Furthermore, in preclinical studies MDV-3100 has demonstrated efficacy in the setting of AR overexpression and known mutations. A Phase III trial of MDV-3100 in patients with castrate-resistant metastatic prostate cancer who have progressed following chemotherapy has demonstrated a significant improvement in

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