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Mol Cell Pharmacol. Author manuscript; available in PMC 2010 April 22.

Published in final edited form as:
Mol Cell Pharmacol. 2010 January 1; 2(1): 1–5.

Targeting the Androgen Receptor by Taxol in Castration-Resistant Prostate Cancer

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Abstract

Both cell culture and clinical studies show that the androgen receptor (AR) plays a key role in the growth and survival of castration-resistant prostate cancer (CRPC), a lethal form of the disease in the clinic, suggesting that AR remains to be a major target for the treatment of CRPC. Taxol chemotherapy is one of the few therapeutic options for patients with CRPC albeit the underlying mechanism is not fully understood. We have demonstrated recently that Taxol (paclitaxel and its semisynthetic analogue docetaxel) treatment of 22Rv1, a CRPC cell line that expresses the tumor suppressor gene PTEN, inhibits AR transcriptional activity. In contrast, paclitaxel failed to inhibit AR activity in the PTEN-deficient C4-2 CRPC cells. Docetaxel treatment of 22Rv1 xenografts in mice induced mitotic arrest and a decrease in expression of the AR target gene prostate-specific antigen (PSA) mainly in tumor cells adjacent to vascular vessels. Further studies demonstrated that Taxol inhibition of the AR is mediated, at least in part, by Taxol-induced nuclear accumulation of FOXO1, a key downstream effector protein of PTEN and increased association of FOXO1 with the AR. These studies suggest that the status of the functional PTEN/FOXO pathway and the drug bioavailability may be the two key determinants for Taxol chemoresistance of CRPC in the clinic.

Keywords

Androgen receptor; Prostate cancer; Taxol; Chemotherapy; PTEN; FOXO1

Prostate cancer is the most frequently diagnosed and the second-leading cause of cancer death in men in the United States. Due to the androgen-dependent nature of prostate cancer cells, androgen deprivation therapy (e.g. surgical or medical castration) is currently a standard treatment for metastatic/disseminated prostate cancer. However, in virtually all patients the tumor ultimately becomes CRPC approximately 2–3 years after castration. Patients with CRPC have a progressive disease with a median survival of 10–12 months (1,2).

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Conflicts of Interest

No potential conflicts of interest to disclose.

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The receptor for androgens belongs to the nuclear receptor superfamily. It primarily functions as a transcription factor that transcriptionally regulates gene expression (2). Increasing evidence suggests that the AR not only plays a pivotal role in the development of androgen-dependent prostate cancer, but it is also important for growth and survival of CRPC. Expression of PSA, a clinical marker for prostate cancer, is directly regulated by the AR. A decline in serum PSA levels is often associated with tumor regression after androgen deprivation therapy. However, PSA failure or insurgency invariably occurs during the progression of CRPC, indicating that the AR is aberrantly active at this stage of the disease. A number of mechanisms have been proposed for the promiscuous activation of the AR in CRPC (Figure 1), which includes mutations and amplification of the AR gene, activation of the AR by nonandrogenic factors such as interleukin-6 (IL-6) and insulin-like growth factor 1 (IGF-1), and alternations in the expression of transcription coregulators such as overexpression of coactivators and downregulation of corepressors (3). Moreover, recent findings add another layer of complexity of AR activation in CRPC. Although serum testosterone levels significantly decrease following androgen deprivation therapy, intraprostatic androgens, especially the dihydrotestosterone (DHT) which is the most active androgen, are not only detected at concentrations sufficient to activate the AR (4), but they are also locally synthesized in the CRPC cells (5). The castration levels of intraprostatic androgens are believed to provide necessary “fuel” for CRPC cells to continue to grow and survive, stressing that the AR remains to be a promising target for the treatment of CRPC.

Development of effective therapeutics for patients with CRPC is one of the major challenges for the management of this disease today. Chemotherapy with Taxol (paclitaxel and its semisynthetic analogue docetaxel) is one of the few therapeutic options for the treatment of CRPC. A series of clinical trials have demonstrated that treatment of CRPC patients with paclitaxel/docetaxel results in at least 50% decline in PSA in 50% of the patients (6–8). Docetaxel is now approved by the U.S. FDA for treatment of patients with CRPC. However, the exact mechanisms underlying the Taxol-induced decline of serum PSA are not entirely clear.

Multiple mechanisms have been revealed for Taxol chemotherapy of human malignancies. A well-known action of Taxol is to inhibit the depolymerization of microtubules and thereby block the exit from mitosis and ultimately promote apoptotic cell death (9). It has also been shown that Taxol kills cancerous cells by inducing phosphorylation and inhibition of the antiapoptotic protein Bcl-2 (10). Several recent studies suggest that Taxol induces apoptosis in breast and ovarian cancer cells by inducing nuclear localization of forkhead box O (FOXO) transcription factors and expression of their downstream effector gene Bim (11–13).

We and others demonstrated previously that the forkhead protein FOXO1 interacts with and inhibits the transcriptional activity of the AR (14–17). We further demonstrated that treatment of the CRPC cell line 22Rv1 with both paclitaxel and docetaxel at very low doses (1 ~ 2.5 nM) results in a decrease in expression of AR transactivated genes PSA and Nkx3.1 and an increase in AR repression gene maspin (18), suggesting that Taxol inhibits AR function. This was further supported by the finding that paclitaxel treatment also inhibits the transcriptional activity of the AR as demonstrated by luciferase reporter gene assays (18). In line with these observations, treatment of 22Rv1 xenografts in mice with docetaxel induces mitotic arrest and a decrease in PSA expression in tumor cells adjacent to vascular vessels (18). Further investigation demonstrated that paclitaxel treatment of 22Rv1 cells induces nuclear accumulation of FOXO1 and increases the association of FOXO1 with AR proteins in the nucleus. Moreover, increased levels of FOXO1 proteins were detected in the promoter of the PSA gene in cells treated with paclitaxel. Furthermore, FOXO1 knockdown with small interfering RNA attenuates the inhibitory effect of paclitaxel on AR transcriptional

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activity, expression of PSA and Nkx3.1, and cell survival. Thus, our study reveals a previously uncharacterized, FOXO1-mediated, AR-inhibitory effect of Taxol in CRPC cells that may play an important role in Taxol-mediated inhibition of CRPC growth (18).

It is well established that loss of the PTEN tumor suppressor gene or activation of Akt promotes phosphorylation and nuclear exclusion of FOXO1 (19). Indeed, we demonstrated previously that FOXO1-mediated inhibition of the AR requires the nuclear localization of FOXO1 (16), suggesting that loss of PTEN promotes promiscuous activation of the AR (Figure 1). In agreement with this hypothesis, we demonstrated in a recent study (18) that paclitaxel failed to inhibit expression of AR target genes in LNCaP cells, which do not express a functional PTEN (20). In addition to the nuclear/cytoplasmic translocation, activation of Akt also promotes Skp2 E3 ligase-mediated proteasome degradation of FOXO1 (21). Indeed, expression of FOXO1 protein is much lower in PTEN-null cells (e.g. LNCaP) relative to PTEN-positive cells (e.g. 22Rv1) (16). Because (i) the PTEN tumor suppressor gene is frequently mutated/deleted (22), (ii) the E3 ligase Skp2 is often upregulated in prostate cancer and associated with increased levels of PSA (23), and (iii) the FOXO1 gene is deleted at the genomic level in a sub-set of human prostate cancers (14), our findings (16,18,21) suggest that deregulation of the PTEN/AKT/SKP2/FOXO1 pathways may provide one of the mechanisms that promotes promiscuous activation of the AR (Figure 1) and that the functional PTEN/FOXO pathway is an important factor in determining the anti-AR efficacy of Taxol in prostate cancer.

A decrease in the AR protein level was detected in 22Rv1 cells when cells were treated with very low doses (1 ~ 2.5 nM) of paclitaxel, but for a longer time (more than 48 h) (18). Decreased AR protein levels were also observed in tumor cells adjacent to blood vessels in 22RV1 xenografts in animals (18). Taxol-induced decrease in AR levels and PSA expression was also observed in PCa cells treated with high doses of docetaxel (5 ~ 1000 nM) in an independent study led by Drs. N. H. Bander and K. Kuroda (24). Hence, it is likely that Taxol-induced decreases in AR protein levels and AR activity are common events. However, it is currently unclear as to which signaling pathways are responsible for Taxol-induced decrease in AR protein in prostate cancer cells.

Androgens and the AR are known to be required for prostate development and maintenance of normal prostate function. Paradoxically, they are also the key promoters of prostate cancer (2). The dilemma could be reconciled, at least in part, by the recent discovery of the recurrent gene fusions involving the androgen-regulated gene TMPRSS2 and the members of the ETS proto-oncogene family (25). Importantly, TMPRSS2-ETS fusions are frequently detected in human prostate cancers (26). Further studies demonstrate that these fusion oncogenes play an important role in promoting prostate tumor progression in mice (27,28). Given that chromosomal proximity and the TMPRSS2-ETS gene fusion can be induced by androgens (29,30), it would be of interest to determine whether treatment of prostate cancer cells with Taxol decreases expression of the AR target gene TMPRSS2 and TMPRSS2-ETS fusion genes and whether tumors with TMPRSS2-ETS fusion genes are sensitive to Taxol chemotherapy.

It is worth noting that clinical trials demonstrate more than 50% PSA decline in approximately 50% of patients treated with docetaxel whereas only up to 17% of patients exhibit the measurable disease responses. Taxol-induced inhibition of PSA expression suggests that PSA inhibition may be more sensitive to Taxol than disease response. In addition, our studies with 22Rv1 xenografts showed that docetaxel-induced mitotic arrest was only detected in cancer cells surrounding the vascular vessels (18). Thus, the drug bioavailability may be a critical factor that needs to be considered for better therapeutic effect of Taxol *in vivo*.

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In summary, the findings that Taxol inhibits the AR activity in CRPC cells in culture and in animals suggest that the therapeutic effects of Taxol may be mediated, at least in part, by inhibition of the AR function. Since the AR-inhibitory effect of Taxol requires the nuclear accumulation of FOXO1 proteins and increased interaction between FOXO1 and the AR, frequent loss of the tumor suppressor gene PTEN, an event that leads to nuclear exclusion of FOXO1, may contribute to the development of Taxol resistance in prostate cancer.

Acknowledgments

This work was supported in part by funds from the National Institutes of Health (R01CA134514), the Department of Defense (W81XWH-07-1-0137 and W81XWH-09-1-622) and the Brainstorm Award from University of Minnesota Masonic Cancer Center (to H.H.).

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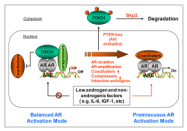


Figure 1. Possible molecular mechanisms underlying the shifting of the AR activation from the balanced mode in the normal prostate to the promiscuous mode in prostate cancer, especially the castration-resistant disease

These mechanisms include (1) mutations in the AR gene; (2) AR amplification; (3) overexperssion of AR coactivators; (4) downregulation of AR corepressors; (5) local synthesis of androgens in the prostatic epithelial cells through the so-called intracrine mechanism; (6) dissociation of the nuclear factor FOXO1 from the AR transactivation complex caused by its phosphorylation mediated by Akt activation due to loss of the PTEN tumor suppressor gene or aberrant activation of Akt; (7) dedradation of FOXO1 due to Akt phosphorylation and overexpression of the E3 ligase Skp2.

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