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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).

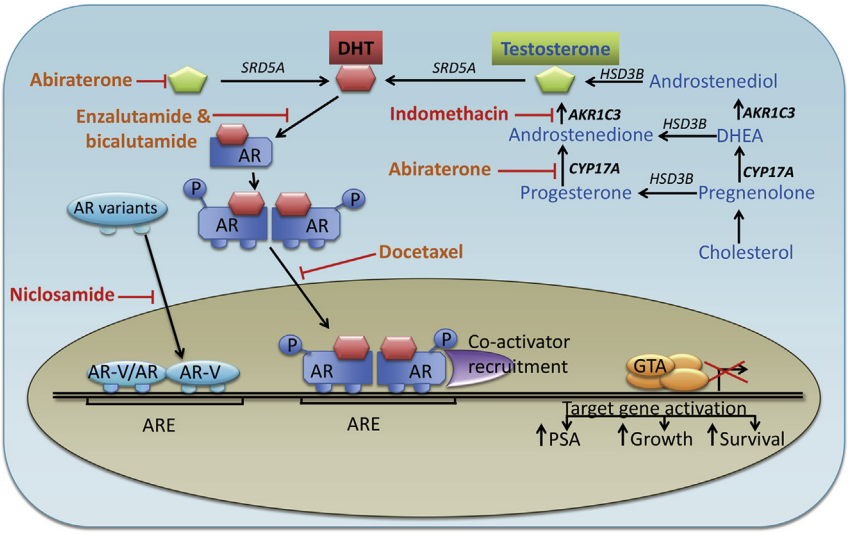

Figure 1 Approved (orange) and experimental (red) therapies for CRPC and their targets. AR, androgen receptor; ARE, androgen-response element; AR-V, androgen receptor variants; CRPC, castration resistant prostate cancer; DHT, dihydrotestosterone; PSA, prostate specific antigen.

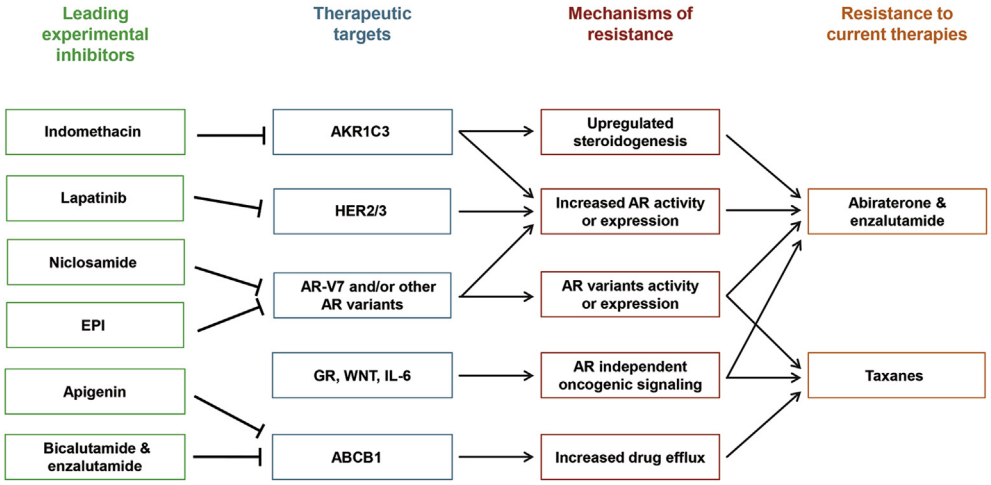

Figure 2 An overview of CRPC drug resistance and promising experimental inhibitors that target resistance mechanisms. ABCB1, ATP Binding Cassette Subfamily B Member 1; AKR1C3, Aldo-Keto Reductase Family 1, Member C3; AR, androgen receptor; CRPC, castration resistant prostate cancer; GR, glucocorticoid receptor.

2. Current CRPC therapies

2.1. Anti-androgens

Anti-androgens seek to slow cancer cell growth by blocking activation of the AR. Despite the ability CRPC cells gain to bypass testosterone using the 5α-dione pathway to produce the more biologically active dihydrotestosterone (DHT), these cells still heavily rely on adrenal androgens which are converted to androstenedione by 3βHSD in the prostate or adrenal gland. DHT is then synthesized from androstenedione. Abiraterone acetate functions by reducing circulating androgens by inhibiting CYP17A1 and blocking the conversion of pregnenolone to DHT. The net result is a loss of androgen synthesis in peripheral tissues as well as a reduction in the precursors required for intratumoral androgen production. In addition to inhibition of CYP17A1, studies have observed that abiraterone can be converted into the more active Δ^4-abiraterone (D4A) and this form of the anti-androgen has also been shown to inhibit 3βHSD and SRD5A, two other enzymes involved in androgen synthesis. Furthermore, D4A has increased inhibition of prostate cancer xenograft growth compared to the parental abiraterone [13].

In regards to its efficacy, the COU-AA-302 trial showed a 4.4-month survival benefit with abiraterone in chemotherapy-naive CRPC patients and in patients who had progressed after docetaxel therapy, the phase III trial COU-AA-301 demonstrated a 3.9-month survival benefit of abiraterone/prednisone over placebo/prednisone [11,14,15]. Despite these promising improvements in patient longevity, nearly a third of patients have primary resistance to abiraterone and even those who initially benefit from treatment will progress in their disease by 15 months of therapy [11].

As with abiraterone, enzalutamide also functions to reduce AR signaling. Instead of blocking production of its ligand, however, enzalutamide binds directly to the AR to inhibit its activation by androgens. Furthermore, enzalutamide inhibits AR translocation to the nucleus, co-activator recruitment, and binding of the AR to DNA, all of which reduce the activation of downstream AR target genes [16]. Despite the fact that enzalutamide has been demonstrated to provide nearly 5 months improved survival compared to placebo treated individuals in CRPC patients who failed docetaxel treatment and is also effective in pre-chemotherapy hormone-naïve prostate cancer patients, as many as one fourth of patients have primary resistance to enzalutamide and all patients had progressed by 24 months of initiating treatment [17,18].

2.2. Taxanes

Docetaxel and cabazitaxel both belong to a class of chemotherapeutics called taxanes. Docetaxel has traditionally been the first-line therapy for patients with CRPC. The introduction of enzalutamide and abiraterone, however, has led to a decrease docetaxel use as the primary treatment for CRPC. In addition to its use in CRPC, docetaxel has also proven to be effective in conjunction with ADT in hormone-naïve prostate cancer patients with high volume or visceral metastases, providing a 17-month survival advantage over ADT alone [19]. Docetaxel functions by binding free tubulin in cells which causes the formation of stable microtubules and prevents depolymerization, resulting in inhibition of mitosis and consequent induction of apoptosis [20–22]. Interestingly, docetaxel has also been demonstrated to reduce AR expression in CRPC cells which could further slow the growth of prostate cancer cells [23].

Cabazitaxel, on the other hand, is primarily used in patients who have failed docetaxel therapy. The TROPIC trial observed a 2.4-month survival benefit over mitoxantrone in patients with metastatic CRPC whose disease had progressed on docetaxel [24]. While both of these drugs are anti-mitotic and inhibit the division of proliferating cells through binding tubulin, unique mechanisms of action have been identified [25].

3. Mechanisms of resistance

While the drugs used for the treatment of CRPC have distinct methods of action and each has individual

mechanisms of resistance, there is a surprising degree of cross-over in the pathways CRPC cells use to overcome drug treatment, particularly in the case of the anti-androgens. The resistance mechanisms can be broken up into several broad categories (Fig. 1), a number of which will be discussed below.

3.1. Androgen receptor splice variants

AR splice variants can be formed by genome rearrangement and alternative splicing involving splicing factors such as hnRNPAs [26,27]. Most commonly, AR variants lack the C-terminal ligand-binding domain and these truncated versions of AR are often ligand-independent and result in constitutive activation and uncontrolled downstream AR signaling [28–32]. While AR variant expression is associated with poorer prognosis and the development of CRPC, the functional implications of AR variants are not yet fully understood, due in part to the lack of reliable variant specific antibodies [33]. Analysis of *in vitro* prostate cancer cell lines has determined that nearly all CRPC lines display some level of AR variant expression and in fact, CWR22Rv1 cells have nearly equal expression of full length AR and AR variants. Furthermore, prostate cancer bone metastases have been found to have high AR variant expression [33].

Expression of these AR variants is strongly associated with resistance to both abiraterone and enzalutamide, and though not as well studied, to docetaxel resistance as well. The most widely studied of these variants, AR-V7, appears to be of particular importance. It has been shown that AR-V7 expression in patients treated with enzalutamide or abiraterone correlates to a significantly lower prostate specific antigen (PSA) response, shorter progression-free and overall survival compared to men who do not express AR-V7 [34].

Targeting AR variant expression is one way in which restoring sensitivity to anti-androgens can be achieved and a number of clinical trials are currently under way investigating various therapies to reduce AR variant expression and improve patient treatment response. Niclosamide, the anti-helminthic drug, has been demonstrated to preferably reduce expression of AR-V7 over full length AR, in enzalutamide resistant cells with comparatively high endogenous AR-V7 expression. Liu et al. [35,36] determined that niclosamide could induce AR-V7 protein degradation and reduce recruitment of AR-V7 to promoter regions of target genes resulting in reduced transcriptional activity and resensitize resistant cells to enzalutamide and abiraterone treatment. Furthermore, niclosamide had significant anti-tumor activity in a number of AR variant expressing CRPC cell lines such as enzalutamide resistant C4-2B cells (C4-2B MDVR) and CWR22Rv1 cells, as well as in an enzalutamide and abiraterone resistant CWR22Rv1 xenograft model. The combination of niclosamide with either enzalutamide or abiraterone produced maximal tumor inhibition in a CWR22Rv1 xenograft model. Based on these encouraging preclinical data, a phase II study with a lead—in safety phase of abiraterone in combination with niclosamide in a CRPC clinical trial was launched in 2016 at the University of California, Davis (NCT02807805). In this trial, recurrent or metastatic CRPC patients will receive abiraterone 1000 mg daily with prednisone 5 mg twice daily plus escalating doses of oral niclosamide/PDMX1001 (400 mg twice daily, 800 mg twice daily). Exploratory analysis of AR-V7 will also be conducted in this trial.

Other studies have also found that inhibiting AR variant expression can improve the response to enzalutamide; Nadiminty et al. [26] determined that downregulation of the splice factor hnRNPA1 reduced AR-V7 expression and consequently sensitized cells to treatment. Inhibition of HSP90 with onalespib was also observed to alter AR splicing and lower the expression of AR-V7 [37]. Furthermore, Yamashita et al. [38] were able to reduce CWR22Rv1 xenograft tumor growth by the addition of ASC-J9, a drug that degrades AR-V3 and full length AR.

Promising progress has also been made in developing drugs that target the N-terminus. This includes EPI and its derivatives. EPI covalently binds the N-terminal domain of both AR and its variants and inhibits transcriptional activity to inhibit prostate cancer cell growth in *in vivo* xenograft models [39,40]. *In vitro* and *in vivo* studies have further demonstrated that EPI can inhibit the proliferation of enzalutamide resistant cells [41]. Currently, a phase 1/2 clinical trial is underway (NCT02606123) investigating the use of EPI in men with metastatic CRPC who have progressed on enzalutamide or abiraterone [42]. This study will determine the safety and tolerability of orally administered EPI and PSA response rate as the primary outcomes. Another class of drugs targeting the N-terminus of the AR, niphatenones, while able to inhibit transactivation of AR and its variants, also promoted the formation of glutathione adducts and therefore may not be as viable for prostate cancer therapy [43].

In regards to the taxanes, studies have demonstrated that AR-V7 can promote docetaxel resistance: Thadani-Mulero et al. [44] found that the AR variant ARV-567 was sensitive to microtubule stabilization induced by taxanes whereas AR-V7 was unaffected. In addition they showed that tumor xenografts expressing AR-V7 were resistant to docetaxel therapy while those with ARV-567 expression were highly sensitive to docetaxel. To compliment this fact, Zhang et al. [45] found that docetaxel resistant cell lines express higher levels of AR-V7 and that transfection of AR-V7 into LNCaP cells protected them against docetaxel treatment. Interestingly, this group also saw an induction of docetaxel resistance when they transfected AR-V567 into the cells which contradicts what Thadani-Muleroand colleagues observed [44]. To further complicate the taxane and AR variant connection, another study which measured AR-V7 expression in circulating tumor cells (CTC) of metastatic CRPC patients found that detection of AR-V7 in these cells was not correlated with primary resistance to taxanes [46]. Furthermore, another study in CTC found that patients with nuclear CTC AR-V7 expression had increased survival benefit on taxanes compared to therapies directed AR signaling [47]. The varying results from these studies suggest that the impact of AR-V7 on taxane resistance may be model-specific and more study in this area is needed.

3.2. Increased AR activation

Increased activation of the full length AR is also a well-documented mechanism for promoting drug resistance,

primarily to the anti-androgens. The observed increase in AR signaling that occurs when cells develop resistance can be due to a variety of methods including altered steroidogenesis or overexpression of the receptor itself.

Prolonged exposure to both enzalutamide and abiraterone incurs alterations in steroidogenesis. The resultant increase in androgen due to up-regulation of and mutations to enzymes involved in this complicated pathway promotes activation of the AR and is a likely contributor to both CRPC progression and anti-androgen resistance. Enzalutamide resistant prostate cancer cells had upregulated expression of androgen and its precursors including cholesterol, DHEA and progesterone. Additionally, genes involved in steroid biosynthesis are significantly over-expressed in enzalutamide resistant compared to enzalutamide-sensitive parental cells [48]. Mostaghel et al. [49] detected up to a 4.5-fold increase in enzymes involved in steroidogenesis in abiraterone treated prostate cancer cells *in vitro*, including CYP17A1, AKR1C3, HSD17B3, and SDR5A2. Additionally, the hyperactive 1245C mutation of HSD3B1 has been observed in abiraterone-resistant xenograft models [50]. Of the enzymes contributing to steroidogenesis, AKR1C3 is of particular import. Its activation contributes to both abiraterone and enzalutamide drug resistance in CRPC patients and it has been proposed as a biomarker for assessing prostate cancer progression [48,51]. Liu et al. [48] found that indomethacin, a nonsteroidal anti-inflammatory drug, was capable of inhibiting AKR1C3 enzymatic activity and restored enzalutamide sensitivity in resistant prostate cancer cells. This suggests that targeting intracrine androgens improves enzalutamide therapy. Based on these promising preclinical studies, a single-arm phase II trial with a lead—in safety phase to determine the efficacy and toxicity of an indomethacin and enzalutamide combination in the treatment of CRPC will be launched at the University of California, Davis.

Upregulated AR activation can also be the result of mutations to the *AR* gene. It is estimated that 10%—30% of CRPC patients have *AR* mutations and these mutations can result in increased coactivator recruitment, and alter ligand specificity and affinity [52]. The most commonly identified AR mutation, T878A, occurs most commonly in response to drugs targeting androgen synthesis, like abiraterone [53]. This mutation, and others, are correlated to decreased ligand specificity of the AR allowing the receptor to activate in response to a broader range of molecules, including estrogen and glucocorticoids, that the wildtype AR is not responsive to [10,54,55]. This could be of importance to patients receiving abiraterone since prednisone, a glucocorticoid, is co-administered with the anti-androgen to counterbalance some of its side effects. Also with abiraterone treatment, androgen precursors, including pregnenolone and progesterone, have been demonstrated to accumulate and some of these have also been identified to bind mutated AR and instigate downstream AR signaling [55—57]. Furthermore, the F877L mutation of the AR is associated with changing ligand binding specificity of the AR to switch from agonist to antagonist activation, causing enzalutamide to activate the AR instead of inactivate it [58,59]. The F877L mutation has also been identified in circulating cell-free DNA samples from patients whose disease had progressed while receiving enzalutamide or ARN-509, another anti-androgen structurally similar to enzalutamide [60]. Interestingly, Korpal et al. [59] demonstrated that while the F877L mutation confers resistance to enzalutamide *in vitro*, cells expressing this mutation remain responsive to bicalutamide.

3.3. Increased AR expression

In addition to an upregulation in androgen synthesis pathways and AR mutation, increased AR activation can be attained through modulation of wildtype AR expression. In CRPC, the AR is commonly overexpressed however the method that drives this overexpression is not completely understood. One mechanism which has recently been determined is through upregulation of retinoic acid receptor-related orphan receptor γ (ROR-γ). ROR-γ was found to be upregulated in CRPC and could drive AR expression. ROR-γ recruited the AR co-activators SRC-1 and SRC-3 which in turn promoted *AR* transcription. Furthermore, treatment with ROR-γ antagonists suppressed prostate cancer xenograft growth and improved the response to enzalutamide [61]. Also affecting AR expression, Gao et al. [62] observed that abiraterone treated patients had higher ErbB2 activity and this correlated with increased AR expression in the nucleus, suggesting a potential increase in AR signaling. They further went on to demonstrate that abiraterone resistant xenograft models had increased ErbB2 activity and in turn this led to stabilization of AR protein through PI3K/AKT signaling. By blocking ErbB2 using lapatinib in combination with abiraterone they were able to enhance treatment response in xenograft models. Mellinghoff et al. [63] determined that HER2 and HER3 signaling can increase AR signaling; knockdown of HER2 was found to inhibit transcription of the AR and both HER2 and HER3 stabilized the AR and promoted binding to androgen-response elements (ARE). Another group, Shiota et al. [64], found that enzalutamide resistant tumors and cells have increased HER2 expression and that enzalutamide treatment induced HER2 expression in LNCaP cells. Furthermore, they determined that enzalutamide response could be enhanced by lapatinib through inhibition of the HER2 signaling axis.

The AR also plays a role in the response to taxanes. In fact, part of the mechanism of action attributed to taxanes is through modulation of the AR. Taxanes have been demonstrated to reduce AR expression, nuclear translocation, and transcriptional activity [23,65,66]. These effects can be induced by docetaxel, but not cabazitaxel, treatment [65,67]. Komura et al. [68] found that expression of lysine-specific demethylase 5D (KDM5D) is decreased in CRPC and low expression levels are associated with a poor patient prognosis. They further determined that knocking down KDM5D, which regulates AR transcriptional activity, induced docetaxel resistance in LNCaP cells, which are normally highly susceptible to docetaxel treatment, supporting a link between the AR and docetaxel sensitivity.

3.4. Androgen receptor co-regulators

A number of molecules have been identified that function as co-activators or co-repressors for the AR [69]. These co-

regulators help modulate AR transcriptional activity by acting on other molecules in the transcription complex through methylation, phosphorylation, ubiquitylation or acetylation, and can also act as molecular chaperones and help with recruitment of transcriptional machinery [70–72]. The AR co-activator FKBP51 has been observed to be upregulated in relapsed LAPC-4 tumor xenografts in castrated mice resulting in increased activation of the AR in response to ligand [73]. The p300/CBP and the steroid receptor co-activators (SRC) class of co-activators, which includes SRC-1, Tif-2, and SRC-3, are also associated with prostate cancer disease progression and SRC-1 and p300/CBP have been linked to IL-6 induced androgen-independent AR activation [74,75].

AR co-activators can also mediate AR activation of truncated, ligand-independent AR splice variants. In particular, McGrath et al. [76] demonstrated that the co-activator FHL2 (four and a half LIM protein 2) interacts with AR-V7. They determined that AR-V7 activation, as determined by ARE-luciferase reporter and in the absence of androgen, was enhanced by FHL2 expression and this response could not be abrogated by enzalutamide.

3.5. AR independent anti-androgen resistance

While most of the identified mechanisms inducing resistance to the anti-androgens are associated in one way or the other with increasing androgen signaling, there are also compensatory pathways that become activated that are independent of the AR and androgen synthesis. Downstream signaling of the glucocorticoid receptor (GR), another nuclear receptor like the AR, is increased by treatment with anti-androgens and treatment response to enzalutamide in prostate cancer patients is inversely correlated to GR expression. Furthermore, GR mRNA and protein expressions were found to be upregulated in anti-androgen resistant tumors and knockdown of the GR in resistant cells resensitized them to enzalutamide treatment *in vitro* [77]. These effects are hypothesized to be a result of the commonality between the GR and AR allowing the GR to compensate for the reduced AR activity induced by anti-androgens.

IL-6 has also been proposed to play a role in the response to enzalutamide; Handle et al. [78] found that enzalutamide (as well as bicalutamide, another anti-androgen) up-regulates suppressor of cytokine 4 signaling 3 (SOCS3) mRNA which in turn modulates IL-6/Stat3 signaling. When they knocked down SOCS3, they were able to reverse an IL-6/enzalutamide induced reduction in AR target genes. Further implicating IL-6/Stat3 in enzalutamide resistance, Liu et al. [79] found that overexpression of constitutively active Stat3 induced resistance to enzalutamide treatment whereas downregulation of Stat3 improved enzalutamide response and increased apoptosis. In another study, Liu et al. [80] also determined that the drug niclosamide can also down-regulate Stat3 target gene expression and resensitize enzalutamide resistant cells to treatment. Wnt/β-catenin signaling is another proliferative pathway that is upregulated in enzalutamide resistance and inhibition of this pathway has also been observed to increase enzalutamide sensitivity [81].

3.6. Altered drug efflux

A method primarily associated with docetaxel resistance involves overactivation or overexpression of multidrug resistance proteins (MDRP). These proteins, including ABCB1, serve as pumps on the cell membrane to excrete exogenous compounds, such as docetaxel, out of the cell. This results in a lower intracellular drug concentration and a loss of drug efficacy. Multiple studies have shown that docetaxel resistant cells express significantly increased levels of ABCB1 compared to docetaxel sensitive parental cells lines [82,83]. Hour et al. [84] determined that the increase in ABCB1 observed in docetaxel resistant cells is likely due in part to the increased epidermal growth factor receptor (EGFR) expression also found in these cells. Others have observed that an increase in expression and phosphorylation of breast cancer resistance protein, another transporter protein, promotes docetaxel resistance as well [85].

Regulating these drug efflux pathways has been an area of intense study for resensitizing prostate cancer cells to docetaxel treatment. A number of phase I and II clinical trials have investigated the possibility of using MDRP inhibiting drugs, such as elacridar, in combination with chemotherapy. Despite phase I trials showing promise, only minimal clinical activity was observed in phase II trials [86,87]. *In vitro* and *in vivo* studies have found that ABCB1 activity and/or expression can be reduced by a variety of dietary flavonoids including apigenin, naringenin, and genistein [83,88]. Treatment of docetaxel resistant C4-2B cells with apigenin was observed to overcome ABCB1 mediated docetaxel resistance and resensitize cells to drug treatment by reducing ABCB1 expression [83]. In a separate study, Zhu et al. [89] also determined that anti-androgens could reduce ABCB1 activity as assayed by Rhodamine 123 efflux. Furthermore, co-treatment in both AR-positive and AR-negative docetaxel resistant mouse xenograft models with bicalutamide and docetaxel was observed to significantly reduce tumor growth, indicating that this effect by bicalutamide is independent of AR status.

3.7. β-tubulin dysregulation

Also specific to taxane resistance, the presence of β-tubulin isoforms promotes both docetaxel and cabazitaxel resistance in prostate cancer. Specifically, taxanes have reduced efficiency for binding to the class III β-tubulin isoform [90,91]. Studies have also found increased expression of class IV β-tubulin and mutations to class 1 β-tubulin which results in impaired polymerization in docetaxel resistant cells [92,93]. Galletti et al. [94] found that ETS-related gene (ERG) overexpression in prostate cells leads to cabazitaxel resistance both *in vitro* and *in vivo* by interacting with β-tubulin and tubulin dimers. They further determined that cytoplasmic interruption of this interaction restores cabazitaxel sensitivity. Additionally, suppressed expression of β-tubulin isoform IVa by the synthetic estrogen diethylstilbestrol has been demonstrated to enhance tumor growth inhibition in combination with docetaxel in prostate cancer xenograft models [95]. Others have demonstrated that the N-terminal domain of the AR

interacts with tubulin and targeting this domain with the small-molecule inhibitor EPI improved docetaxel effectiveness and reduced the number of cells displaying the epithelial-mesenchymal-transition (EMT) phenotype [96,97].

3.8. Cell survival/growth pathways and cytokines

Most prostate cancer cells that display resistance to one drug therapy or another have aberrant regulation of molecules involved in cell survival and death. Specifically, docetaxel resistance is associated with overexpression of signal transducers and activator of transcription (Stat) 1, Stat3, clusterin, heat shock proteins (HSP), GATA2, and nuclear factor kappa B (NF-κB) [82,98—103]. Reduced activity and expression of wildtype p53 has also been linked to docetaxel insensitivity [104]. Furthermore, expression of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8 chemokine ligand 2 (CCL2), transforming growth factor-β1 (TGF-β1) and macrophage inhibitory cytokine-1 (MIC-1) have been shown to promote docetaxel resistance [105—109].

In many cases, correcting the aberrant expression of these molecules has been demonstrated to reintroduce sensitivity to docetaxel treatment. For instance, inhibition of IGF1R expression, a molecule downstream of GATA2 signaling, was observed to improve both docetaxel and cabazitaxel sensitivity in resistant cell lines [103]. Modulating cytokine expression has also proven effective *in vitro*; reducing IL-6 and TNFα and inhibiting NF-κB expression using either synthetic or naturally occurring compounds results in an increased response to docetaxel in prostate cancer cells [82,110].

4. Conclusion

Resistance to the current therapies available for CRPC is inevitable. The variety of adaptive mechanisms by which this resistance occurs makes overcoming treatment resistance a challenging dilemma. Fortunately, numerous studies have identified several of these aberrantly functioning pathways and have put forth treatment strategies for how to best re-introduce sensitivity. With a more thorough understanding for how drug resistance occurs, novel therapies can be developed and tested for likely therapeutic benefits.

Conflicts of interest

The authors declare no conflict of interest.

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