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Review

Resistance to Abiraterone in Castration-resistant Prostate Cancer: A Review of the Literature

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Abstract. *Persistent androgen signaling is functionally significant in castration-resistant prostate cancer (CRPC) and it is actually considered a validated therapeutic target. Residual intra-tumoral androgens compensate for the effects of androgen ablation, activating the androgen receptor (AR), AR-mediated gene expression and driving CRPC. The intra-tumoral biosynthesis of androgens takes place in different ways and cytochrome P450 17A1 (CYP17A1) has a crucial role in this context. Abiraterone, a CYP17A1 inhibitor, has shown impressive results in pre- and post-chemotherapy settings, prolonging the survival of patients with CRPC. However, not all patients respond to the treatment and most responders develop resistance, with a widely variable duration of response. Although many hypotheses are emerging, the mechanisms of resistance to abiraterone treatment have not yet been elucidated. The aim of the present review is to describe the main data currently available on resistance to abiraterone.*

Persistent androgen signaling is functionally significant in castration-resistant prostate cancer (CRPC) and it is actually considered a validated therapeutic target. The intra-cellular levels of testosterone and dihydrotestosterone (DHT) also do not decrease in CRPC (1). Residual intra-tumoral androgens compensate for the effects of androgen ablation activating the androgen receptor (AR), AR-mediated gene expression and driving castration-resistant tumors (2). The synthesis of testosterone in the testes (canonical pathway) (Figure 1) starts from cholesterol as the initial substrate and ends with the conversion of Δ4-androstendione by 17β-hydroxysteroid dehydrogenase-3 to testosterone. Finally, testosterone is converted to DHT by the steroid-5α-reductase-2 in prostate cells. The intra-tumoral or intracrine biosynthesis of androgens takes place in two ways: conversion of adrenal androgens, *i.e.* dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (3), and potentially *via de novo* steroidogenesis (4). The intracrine androgen synthesis from adrenal precursors (5α-androstenedione pathway) differs from the canonical pathway because it bypasses testosterone as an intermediate metabolite (5). The *de novo* 'backdoor' pathway is an alternative and more complex route for androgen synthesis in CRPC cells which does not requires andrenal precursors but requires more than eight enzymatic steps.

In the human male, the cytochrome *P450* 17A1 enzyme is expressed in adrenal glands, testes and CRPC and is crucial for adrenal and tumor-derived extragonadal androgen synthesis (2). Abiraterone is principally a CYP17A1 inhibitor. It was recently reported that it is also able to inhibit 3β-hydroxysteroid dehydrogenase (which is responsible for the conversion of dehydroepiandrosterone to androstenedione and androstenediol to testosterone) (6) and *AR* mRNA/protein expression (7). Abiraterone has shown impressive results in terms of progression free survival (PFS) compared with placebo in patients with metastatic CRPC, both in pre and post docetaxel therapy settings (8, 9). However, not all patients respond to the treatment and most responders develop resistance, with a widely variable duration of response. Although many hypotheses are emerging, the mechanisms of resistance to abiraterone treatment have not yet been elucidated. The aim of this review is to describe the main data currently available on resistance to abiraterone.

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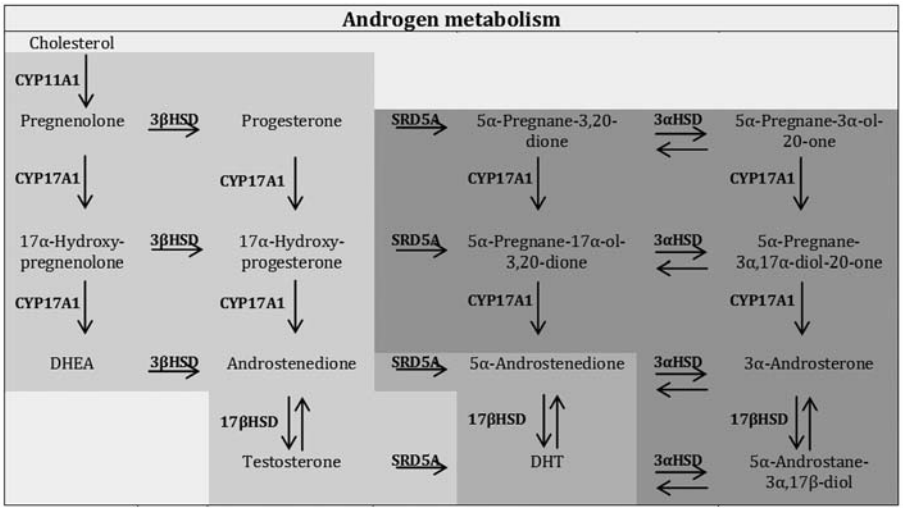

Figure 1. *Pathway of androgen metabolism. CYP11A1, cytochrome P450, family 11, subfamily A, polypeptide 1; CYP17A1, cytochrome P450, family 17, subfamily A, polypeptide 1; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; 3βHSD, 3β-hydroxysteroid dehydrogenase; SRD5A, 5α-reductase; 17βHSD, 17β-hydroxysteroid dehydrogenase; 3αHSD, 3α-hydroxysteroid dehydrogenase. The canonical pathway is shown in light grey, the 5α-androstenedione pathway in grey, and the 'backdoor' pathway in dark grey.*

Hypotheses on Mechanisms of Resistance to Abiraterone

AR splice variants, up-regulation of CYP17A1 and other consideration on AR signaling axis. The truncated AR variants are alternative splicing products of *AR* gene transcription. Many of these *AR* mutant forms show a strong ligand-independent activity, being able to promote proliferation and expression of AR target genes in the absence of the ligand. Mostaghel *et al*. showed in CRPC xenografts that abiraterone may be able to reduce cancer growth through intra-tumoral androgen suppression (10). They also observed that treatment with abiraterone was associated with an increased expression of full-length *AR*, truncated *AR* variants and CYP17A1. Therefore, they hypothesized that mechanisms concurring with abiraterone resistance may be the up-regulation of *CYP17A1* or the induction of constitutively active AR and *AR* splice variants (10, 11). Efstathiou *et al*. showed in patients with metastatic CRPC that pretreatment intense nuclear AR expression, coupled with ≥10% cytoplasmatic CYP17 lyase expression were linked to a longer time to abiraterone treatment discontinuation (>4 months) (12). More recently, a constitutively active AR receptor splice variant has been proposed as one of the possible mechanism of resistance to abiraterone and enzalutamide. Antonarakis and colleagues showed that AR-V7 is an *AR* splice variant expressed at approximately 20-fold higher levels in patients with CRPC than in those without, and its detection in circulating tumor cells from men with metastatic CRPC is associated with resistance to enzalutamide and abiraterone. They proposed AR-V7 status as a putative biomarker to predict resistance to AR-targeting agents, facilitate treatment selection and enable the development of new-generation AR inhibitors (13). Based on these observations, it is also reasonable to hypothesize that patients with metastatic CRPC which maintain an active AR signaling axis are more likely to benefit from therapy with androgen biosynthesis inhibitors.

AR activation by noncanonical ligands. Other potential mechanisms of resistance include activation of mutant AR by noncanonical ligands. Data also suggest the possibility of AR activation by exogenous corticosteroids or steroid precursors upstream of CYP17A.

Exogenous corticosteroids: Pre-clinical models showed that hormones upstream of CYP17, which are increased as a result of high adrenocorticotropic hormone (ACTH) levels in patient receiving AA, activated a promiscuous AR (14). In a phase I study, addition of dexamethasone suppressed ACTH and steroids upstream of CYP17, and reversed resistance to AA (15). However, the exogenous glucocorticoids or mineralocorticoid antagonists used to reduce the side-effects of abiraterone may themselves activate mutant AR. Zhao *et al*. showedthat glucocorticoids could activate mutated AR and promote androgen-independent growth of the MDA PCa 2b prostatic cancer cell line, which expresses low-affinity mutant AR with lower responsiveness to DHT, (16).

Steroid precursors upstream of CYP17A: In patients receiving abiraterone, hormones upstream of CYP17A1 are

increased as a result of the compensatory high levels of ACTH. CYP17A1 inhibition with abiraterone is associated with increased substrates of the 'backdoor' pathway of DHT synthesis (17). Preclinical data suggest that this hormone activates a promiscuous AR (7, 18, 19). Grigoryev *et al*. suggested that sometimes in patients with prostate cancer, hormone independence may arise as a result of stimulation by pregnenolone *via* mutated AR. They showed that pregnenolone sustained its proliferative activity *in vivo* and stimulated the growth of LNCaP tumor xenografts in intact male severe combined immunodeficiency mice, as well as in castrated animals, through binding to the cellular mutated AR (14). Interestingly, pregnenolone is upstream of the abiraterone target, CYP17A, in the androgen metabolism pathway.

Preventing DHT loss and the glucuronidation pathway. DHT is the ligand with the highest binding affinity for AR. It is reversibly converted by 3α-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase to a very low binding affinity steroids (back conversion). Back conversion is the chief mechanism of negative regulation of the level of DHT in CRPC. The interruption or reversal of DHT loss mechanisms could provide an alternative explanation for elevated DHT concentrations in CRPC (20). Testosterone, DHT and the two metabolites 5α-androstane-3α,17β-diol and 3α-androsterone are substrates of the enzyme UDP-glucuronosyltransferase, responsible for their glucuronidation resulting in modulation of their activity and protection of the androgen-sensitive tissues from harmful high concentrations of DHT, androsterone and 5α-androstane-3α,17β-diol (21). Conversely, the main precursors of testosterone and DHT in the alternative 5α-androstenedione pathway (*i.e*. androstenedione and 5α-androstenedione) are not substrates of this enzyme (5). Therefore, the prevalence of this alternative pathway of androgen synthesis in CRPC could lead to a net increase of DHT.

MicroRNA (miRNA). A suggestive hypothesis on the androgen sensitivity of prostate cancer with possible implication in resistance to anti-androgen therapy concerns miRNAs. miRNA is a small non-coding RNA, which may have both oncogenic and tumor-suppressing roles, which regulates many cellular processes (*e.g*. invasion, progression, metastasis, apoptosis, epithelial–mesenchymal transition of cells, regulation of cancer stem cells and chemoresistance) at a post-transcriptional level (22). Of particular interest is their interaction with the AR pathway. Many studies suggest that miRNAs are modulators of AR signaling, regulating *AR* gene expression and its targets (23). Conversely, evidence suggests that miRNAs may be regulated by androgens (24). Ribas and colleagues measured levels of miRNA-21 in prostate cancer and benign tissue, reporting that the up-regulated expression of this molecule, as observed in malignant tissue, may promote cancer cell growth in a ligand-dependent or ligand-independent way (25). miR-21 and miR-616 may be also overexpressed in CRPC. Conversely, several tumor-suppressive miRNAs may be down-regulated in CRPC, including miR-146a (26), miR-let-7c (27), miR-124 (28), miR-34a and miR-34c (29, 24), miR-148a (30), miR-31 (31), miR-200b-3p (32), miR-185 (33) and miR-205 (34), leading to cancer progression and resistance to androgen deprivation therapy. These molecules involved in prostate cancer cell growth by the regulation of AR signaling and other crucial cellular processes in an androgen-independent way, may also have a role in promoting resistance to new-generation anti-androgens, such as abiraterone, which interferes with mechanisms upstream of those regulated by miRNAs.

Role of other pathways. The phosphatidylinositol-3-kinase (PI3K)/tyrosine kinase A (AKT)/mammalian target of rapamicin (mTOR) pathway constitutes an important pathway regulating multiple biological processes. Phosphatidyl-inositol,3,4,5-triphosphate (PIP3) is the product of PI3K activity. PIP3 recruits AKT to the cell membrane where it is activated by other kinases also dependent on PIP3. AKT regulates several cellular processes, including protein synthesis, cell survival, proliferation, and metabolism. The activity of the PI3K–AKT signaling pathway is negatively-regulated by the protein phosphatase and tensin homolog deleted on chromosome ten, whose main substrate is PIP3. Alterations of this pathway have been described as causal forces in prostate cancer (35, 36). The PI3K/AKT/mTOR pathway also contributes to prostate cancer development and progression through interaction with other critical pathways. Carver *et al*. showed in pre-clinical models that the AR and PI3K signaling pathways cross-regulate each other by reciprocal feedback. Therefore, inhibition of the AR pathway may lead to an increase in PI3K pathway activity and may enable the development of resistance to therapy with AR pathway inhibitor (37). These observations highlight a possible mechanism of resistance to therapy with AR pathway inhibitor and also suggest alternative therapeutic strategies, currently under evaluation (38). Combining different therapies may further increase their clinical activity or reverse resistance.

Conclusion

AR and AR signaling have key roles in prostate oncogenesis, including disease development, progression, response to initial hormonal therapy, and subsequent resistance to it. Several genetic and epigenetic mechanisms have been described whereby prostate cancer may progress to the lethal castration-resistant form. Generally, they include a number of mechanisms such as *AR* amplification/overexpression, alternative sources of androgens, mutated or promiscuous AR,

overexpression of AR co-regulators, which keep the androgen-responsive program active (39, 40). Both clinical and pre-clinical data suggest that resistance to novel drugs such as abiraterone is also associated with the reactivation of AR signaling, due to different causes. The mechanisms that may contribute to the development of resistance to abiraterone are to be found among the more general mechanisms that lead to CRPC. In this review, we attempted to select which of these mechanisms could continue to have a role in the development of resistance to treatments for CRPC. As these are only hypotheses, their real role should be investigated in patients under treatment with abiraterone. Such knowledge, in our opinion, might help future studies on the tailored therapy of prostate cancer move towards the identification of predictive biomarkers of response to CYP17A1 inhibitors.

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