Perspective

Emerging mutations and functional changes of androgen receptor associated with treatment resistance in prostate cancer

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Abstract: Androgen receptor (AR) signaling is deeply involved in prostate cancer (PCa) development and growth, and castration-resistant prostate cancer (CRPC) transformation. Currently, the use of anti-androgen drugs, such as abiraterone and enzalutamide, has temporary effects on CPRC patients due to several patient-related resistance mechanisms, such as the development of *AR* mutations. Extensive research is being conducted on *AR* mutations in both tissues and cell free DNA (cfDNA), in order to identify those mutations responsible for treatment resistance. A recent study identified *AR* mutations in cfDNA samples from CRPC patients treated with different anti-androgen drugs. In particular, these mutations occurred in exon 8, which codes for ligand binding domain (LBD), causing functional protein changes *in vitro*, leading to anti-androgen drugs resistance. Moreover, a novel drug tested on PCa cell line, VPC-13566, has been proposed as a potentially alternative therapeutic approach in presence of AR-LBD mutations. This evidence underlines the importance of monitoring *AR* mutations in cfDNA in order to obtain information about the most efficacious treatment and timely therapy switch.

Keywords: Androgen receptor (AR); prostate cancer (PCa); mutations; anti-androgen treatment; castration-resistant prostate cancer (CRPC); cell free DNA (cfDNA)

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Introduction

Androgen receptor (AR) signaling axis seems deeply involved in prostate cancer (PCa) development and growth making androgen-deprivation the first therapeutic approach. However, PCa can temporarily benefit from androgen-deprivation, progressing to a castration-resistant prostate cancer (CRPC) status after some months of treatment (1). Despite resistance to hormonal drugs, AR axis remains the favorite target for the next generation hormonal therapies, such as abiraterone and enzalutamide (2,3). Abiraterone inhibits cytochrome P450 17 α-hydrolase (CYP17A1) reducing androgen production in the adrenal glands, testicles and tumor microenvironment (4). Enzalutamide has a great affinity for AR, inhibiting its interactions with dihydrotestosterone (DHT) (5). The use of these drugs has led to an increase in the overall survival of CRPC patients: their maintained efficacy after resistance to older anti-androgen drugs such as bicalutamide and hydroxyflutamide encouraged further testing of novel anti-androgen drugs (6-10).

AR aberrations such as *AR* copy number variations (CNVs), alternative splice variants and *AR* point mutations are among the main causes of resistance to anti-androgen treatment (3,11-13). *AR* mutations are directly related to protein changes, which could lead to an enhanced affinity for ligands, cofactors and DNA, resulting in increased activity (5). Mutations affecting the *AR* ligand binding domain (LBD) are

likely to be responsible for resistance to anti-androgen drugs which impair the interaction between the AR protein and its natural ligands such as DHT (14). Such mutations produce promiscuous AR mutants able to evade anti-androgen action converting AR-antagonists into AR-agonists (15), and allowing AR to bind with alternative ligands (16).

In the past years, many studies investigated primary, bioptic and autoptic tissues from CRPC patients in order to identify *AR* mutations causing treatment-resistance (17,18). The analysis of serum/plasma cell free DNA (cfDNA) can overcome the limitations of tissue-based approaches, giving a real time picture of disease evolution and treatment efficacy (11-13).

A study investigated CNVs of PCa-related genes (including *AR*) and mutational status of *AR* exon 8 in plasma from CRPC patients who had progressed on enzalutamide, abiraterone or other treatments (19). They identified *AR* amplification and three novel *AR* mutations (D879E, L881I and E893K) not as yet described in literature. They confirmed other well-known *AR* mutations, in particular H875Y, F877L, T878A.

Unfortunately, data about *AR* mutational status were not available for some samples as *AR* sequencing was impossible to perform due to low DNA yield. Such data have been updated by Lallous *et al*. in their recent study featuring an improved sequencing pipeline with a whole-genome pre-amplification step of cfDNA and characterized *AR* mutational status of all patients recruited in previous case series. Deep sequencing was performed for *AR* exon 8, which codes for AR-LBD, detecting four additional novel *AR* mutations (H875Q, D891H, E898G, T919S). In addition, the authors performed *in vitro* AR functional studies evaluating the effects on AR-LBD of the mutations detected in CRCP patients and of other mutations already described in literature.

AR mutations and treatment resistance

The majority of documented *AR* mutations falls in the LBD or cofactor binding regions (20). Alterations in the LBD can interfere with the action of AR-antagonists, turning them into AR-agonists and leading to treatment resistance, as it often happens with first-generation AR-antagonists such as hydroxyflutamide and bicalutamide (21). Such mutations are also able to alter AR specificity for ligands leading to a great affinity for other hormones, such as progesterone, with a pivotal role in the development of resistance against CYP17A1 inhibitors (16). Lallous *et al*. sequenced *AR* exon 8 in order to identify mutations which alter the AR-LBD and that could be responsible for anti-androgen treatment resistance.

AR mutations in codon 878 (T878A and T878S) are among the most investigated mutations in PCa patients (22-26). Functional studies have shown that in presence of T878A and T878S mutations hydroxyflutamide acts as an AR-agonist (27-29). According to Lallous *et al*. also bicalutamide and high concentration enzalutamide and ARN509 exhibit an AR-agonist behavior in presence of these two mutations, with an important role also in new-generation AR-antagonist treatments. In addition, T878A and T878S could be activated by estrogens (2). T878A is frequent in abiraterone-treated CRPC patients producing a progesterone-activated AR mutant protein leading to abiraterone-resistance (16). Similarly, H875Y is associated with elevated AR promiscuity, in particular with increased AR affinity for progesterone (30,31) and also estradiol and hydroxyflutamide (32). Lallous *et al*.'s findings are concordant with these previous studies. They found *in vitro* that T878A/S and H875Y mutants convert AR-antagonists into AR-agonists, and obtain higher affinity for progesterone and estradiol binding. In fact, the authors frequently found these three mutations in cfDNA from both abiraterone- and enzalutamide-resistant patients.

L702H mutation was reported in abiraterone- and enzalutamide-resistant patients receiving glucocorticoid treatment (11,18). This agrees with Lallous *et al*. functional studies, showing that L702H is the only single mutant activated by hydrocortisone. The authors did not found the mutation in cfDNA, probably because none of the patients had undergone glucocorticoid-based treatment.

Another critical mutation is F877L: several studies reported its capacity of inducing resistance against new-generation antiandrogens, converting both enzalutamide and ARN-509 into AR-agonists (33-36). Lallous *et al*. reported a partial agonist effect of these drugs on AR-F877L *in vitro*, while F877L/T878A haplotype was far more sensitive to enzalutamide and ARN-509 agonist action. This finding agrees with a recent work reporting only a mild AR-F877L affinity for enzalutamide and a strong agonist activity of enzalutamide against the F877L/T878A haplotype (37). Interestingly, only one patient carried the F877L/T878A haplotype after enzalutamide treatment, which was absent after bicalutamide, suggesting that it could be related to the enzalutamide resistance mechanism. On the other hand, bicalutamide showed no agonistic activity on F877L or F877L/T878A *in vitro*.

Novel treatment strategies

Nowadays, direct anti-AR drugs target AR-LBD, which often acquires genetic variations as mechanism of resistance. In order to overcome treatment resistance, Lallous *et al*. highlighted the importance of developing novel therapeutic strategies with an impact on other AR domains than the LBD. The strategy proposed by the authors is to target the AR binding function-3 (BF3) pocket, i.e., a site distant from the LBD essential for AR transcriptional activity and for recruiting AR co-regulators such as FKBP52 and Bag-1 L (38,39).

VPC-13566 is a quinolone derivate with different pharmacodynamics from classical anti-androgen drugs, targeting BF3 functionality (40). According to Lallous *et al*., VPC-13566 proved effective also in presence of mutations which confer resistance to enzalutamide and ARN-509. The authors proposed it as a promising option against AR-mutants, either alone or in combination with LBD-targeting agents.

VPC-13566 is not the only novel drug targeting a region outside the LBD. Comparison of VPC-13566 activity with other drugs under investigation would be advisable: EPI-001 and its trans isomer EPI-002 are able to bind covalently the AR N-terminus by blocking it from activating downstream signaling pathways (41,42). EPI-001 has proven effective in CRPC xenograft models, and an analogue of the EPI compounds is currently being evaluated in phase I/II trials (NCT02606123) (41). The goal of these compounds is to inhibit both ligand-dependent and -independent activation of AR (41,42). EPI-002 significantly reduced tumor growth even in presence of AR splice variants in a xenograft model (43). Unfortunately, no studies regarding EPI compounds effects and AR-mutants are available. However, thanks to the ability of EPI compounds to inhibit AR in a ligand-independent way, they are likely to maintain their effects also in presence of mutations in the LBD.

Another novel drug under trial is galeterone, a next generation CYP17 inhibitor similar to abiraterone with an additional inhibitory action against AR. It is able to compete with DHT in binding to AR LBD (42), to impair AR binding to DNA (44) and to mediate AR degradation (1). Interestingly, galeterone showed a degrading effect also against the T878A mutant (42). Thanks to its multiple actions galeterone can potentially overcome constitutively-active AR splice variants: this is currently under investigation in a phase III clinical trial (ARMOR3-SV) (6).

The next-generation AR-antagonist ARN-509 is structurally and mechanistically similar to enzalutamide (7); in fact, according to Lallous *et al*., it suffers the negative effects of certain AR-mutations as well as enzalutamide does. Other promising novel anti-androgens, such as the CYP17 inhibitor VT-464 and the AR-antagonist ODM-201, have different biochemical structures than, respectively, abiraterone and enzalutamide (8-10). Therefore it would be interesting to investigate if AR-LBD mutations impair their activity just as it happens with abiraterone and enzalutamide.

Conclusions

Based on the work of Lallous *et al*., several *AR* mutations in exon 8 showed a strong effect on AR protein promiscuity, causing resistance to anti-androgen drugs.

In particular, the authors highlighted that H875Y and T878A/S mutations are involved in resistance to AR-antagonists (hydroxyflutamide, bicalutamide, enzalutamide and ARN-509) and abiraterone *in vitro*. These data suggested that the detection of these mutations in cfDNA could lead to alternative therapeutic strategies, which target another AR domain.

In addition, F877L mutation also caused resistance to enzalutamide and ARN-509 *in vitro*, maintaining its sensitivity to bicalutamide. The authors hypothesized that switching back to a bicalutamide-based treatment could be an option for a carrier of this mutation.

Due to the effect of the mutations analyzed on AR-LBD, the authors also proposed the use of VPC-13566 drug, with proven efficacy also against the AR-mutants investigated *in vitro*. Further studies could compare the effects of VPC-13566 with those of other novel anti-androgen drugs in clinical trials.

However, in CRPC, mechanisms of resistance may be also associated with deregulation of other pathways as PTEN/PI3K/AKT or with the activation of AR-independent pathways as neuroendocrine differentiation, suggesting the importance of targeting both AR and other pathways (45-49).

The cfDNA from CRPC patients was characterized for predictive information about different treatments such as abiraterone and enzalutamide. As Lallous and coworkers collected plasma samples at abiraterone and other treatments progression, but not at enzalutamide progression for all patients, no data are available on the *AR* mutational status subsequent to enzalutamide treatment. However, the few data available on the samples of three patients collected during enzalutamide treatment showed interesting mutation

status: two of them carried additional mutations, absent during previous treatments, suggesting that they could have developed after the administration of enzalutamide.

In addition to other well-known *AR* mutations, Lallous *et al*. found four new AR-LBD mutations (H875Q, D891H, E898G, T919S) in cfDNA of CRPC patients, potentially important for predicting treatment efficacy. Further studies are needed to better understand how these mutations are involved in disease evolution.

In conclusion, a biological characterization of CRPC is pivotal to better select tumor treatments, in addition to clinical poor prognostic factors, such as presence of visceral metastases, early PSA progression, early metabolic progression, or increase of inflammatory biomarkers (50-56).

On the basis of Lallous *et al*.'s research, the monitoring of *AR* mutations in cfDNA could provide additional information about timely treatment change, aiming to improve patient survival.

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