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REVIEW

The importance of targeting intracrinology in prostate cancer management

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Abstract

Accumulating evidence has shown that intracrinology in prostate cancer (PCa) has a pivotal role in survival of cancer cell. PCa cells are able to produce androgens from different androgen precursors, such as dehydroepiandrosterone, thereby maintaining androgen receptor signaling. Several drugs have been developed that target intracrinology, some of which are now being used as standard treatment for the so-called castrate-resistant prostate cancer (CRPC) patients. Recently, the US FDA approval has changed the indication of drugs targeting intracrinology, e.g., abiraterone and enzalutamide where it evolved from post-chemotherapy CRPC to hormone-naive metastatic PCa cases. This approval raises question whether those drugs can also be used as the first-line treatment in localized stage PCa cases. In addition, development of additional drugs targeting major components of intracrinology is ongoing. Application of these new drugs and administration of combinations of existing drugs will ultimately lead to an increase in the efficacy of such treatments as well as to reduce the toxicity of the therapy and to prevent the risk of resistance.

Keywords Abiraterone · Androgen deprivation therapy · Enzalutamide · Intracrinology · Prostate cancer

Introduction

Prostate cancer (PCa) is one of the most fatal cancers in men worldwide. Furthermore, the incidence of PCa is quite high and it is the second most common cancer in men. The incidence is higher in the more developed countries where it is ranked as the most common cancer in men while it is fifth in the less developed countries [1]. Compared with other continents, Asia has the lowest incidence. However, in the last 10 years, PCa incidence has increased to 4–15% in Asia, whilst in the US and many European countries the incidence of PCa is stable for many years now [2]. In contrast to the lower incidence of PCa cases in less developed countries, the mortality rate is higher compared to more developed countries. One of the most important factors for this fact is the stage at first diagnosis. In more developed countries, most PCa cases are diagnosed at an early stage which results in good prognosis after local treatments, such as radical prostatectomy and radiotherapy. On the other hand, in less developed countries, particularly in Asia, up to 60% of new PCa cases are detected late and tumors often are at an advanced stage [3].

Since introduced in 1941 by Huggins and Hodges, Androgen Deprivation Therapy (ADT) has been used as the first-line treatment for advanced PCa, based on discovery that PCa cells need androgen hormones to survive [4]. However, despite the initial efficacy, the disease will eventually progress within 2–3 years after the initial treatment [5]. At this stage, the PCa is known as castrate-resistant Prostate cancer (CRPC) [6]. Several mechanisms of resistance have been proposed to explain the nature of CRPC, and one of the theories that has gained a lot of attention recently is the acquired intratumoral steroidogenesis or intracrinology.

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Intracrinology in CRPC

Intracrinology is the study of local active steroid hormone synthesis (a.k.a. steroidogenesis) in peripheral target tissues, whereby the action of steroids is exerted in the same cells where synthesis takes place without their release in the extracellular space and systemic circulation [7]. Understanding of this process is important because intratumoral steroidogenesis, at least in part, is responsible for the growth and progression of PCa under castrate conditions. In normal circumstances (i.e, non-pathological conditions), the androgen precursor dehydroepiandrosterone (DHEA) is converted into testosterone (T) in organs such as the adrenal glands and the testis. Testosterone will be released in the circulation and it will be absorbed by the luminal and basal prostate cells and then reduced to dihydrotestosterone (DHT) by 5-alpha-reductase enzymes (Fig. 1a). Both T and DHT are high affinity ligands for the androgen receptor (AR) which, upon ligand binding, becomes activated and will trigger growth, proliferation and differentiation of the prostate cells [8, 9]. Circulating levels of DHEA and its sulfated form, DHEAS, while both are an important precursors of DHT and T, are unaffected by ADT [5]. CRPC cells that thrive in low androgen (castrate) conditions are able to absorb DHEA and convert it into T and DHT (Fig. 1b), thereby maintaining the androgen-mediated tumor cell survival and tumor cell proliferation. The conversion of androgen precursors inside the tumor cell is known as intracrinology.

In CRPC cells all steroidogenesis pathways, including the classical and the "backdoor" pathway (Fig. 2), are activated to maintain high intratumoral T and DHT levels. The classical pathway is done by converting androstenedione

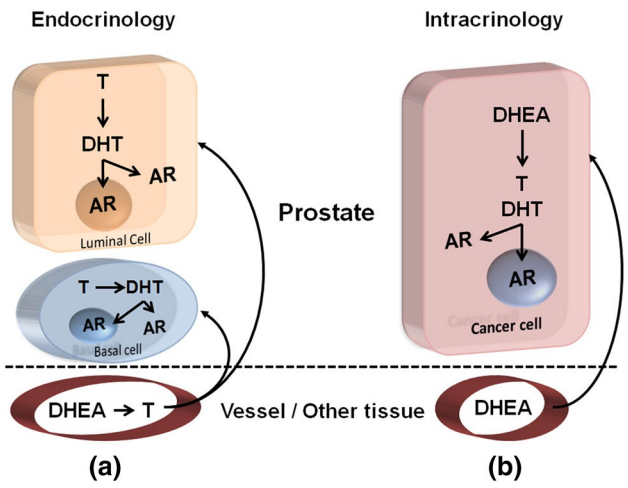

Fig. 1 **a** Endocrinology in normal prostate and primary prostate cancer cells, and **b** intracrinology in castration-resistant prostate cancer cells

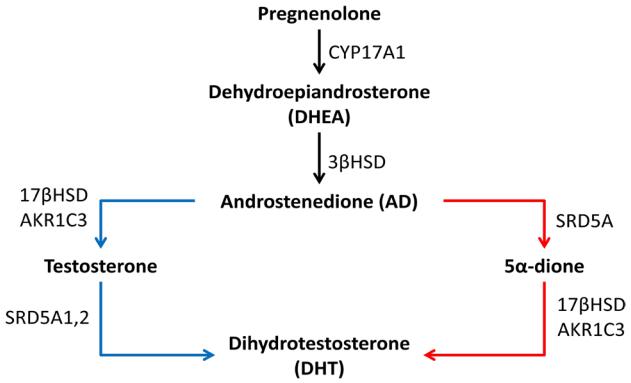

Fig. 2 The classical (blue arrow) and "backdoor" (red arrow) pathway of steroidogenesis

(AD) to testosterone as the intermediary using AKR1C3 and 17βHSD enzyme where it can be reduced to produce DHT (Fig. 2, blue arrow). On the other hand, the "backdoor" pathway (Fig. 2, red arrow) mainly uses the reduced form of AD. In this pathway, AD is reduced to 5α-androstanedione (5α-dione) which then can be converted directly to DHT by using AKR1C3 and 17βHSD enzyme, bypassing testosterone completely [5, 10]. This backdoor pathway is actually a normal process which occurs in male sex organogenesis in fetus and will be less active in the adult male [11]. However, this pathway seems to be reactivated in CRPC cells. It is proven by the high conversion rate of AD into DHT in CRPC cell lines and the tissues obtained from CRPC patients [12].

Targeting intracrinology in CRPC management

It has been mentioned above that lowering the intratumoral levels of androgens holds a key point in treating PCa patients. ADT only reduces serum T and DHT level, and it does not influence or target the intratumoral steroidogenesis process in CRPC cells. Therefore, the main goal of CRPC management is to target intratumoral steroidogenesis in the tumor tissue by understanding the pathway of DHT and T production.

One of the novel strategies in PCa management is targeting the CYP17A1 enzyme using inhibitors such as abiraterone acetate. As seen in Fig. 2 above, CYP17A1 holds a crucial role to convert pregnenolone to DHEA. Inhibiting this enzyme will be able to reduce the androgen production from DHEA in the peripheral organs, including the prostate. Abiraterone is 10–30 times more potent than ketoconazole, which is a non-specific inhibitor of p450 enzymes. However, abiraterone also blocks glucocorticoid biosyntesis, in which therefore the administration of abiraterone should also be accompanied with a glucocorticoid such as prednisone to

limit adverse effects [13]. In a phase III trial (COU-AA-301), it has demonstrated that the use of abiraterone (with prednisone) gives a 4.6-month survival benefit over placebo/prednisone in patients who had been resistant to docetaxel therapy [14].

Enzalutamide is a novel anti-androgen drug that has a far greater affinity for the AR receptor than flutamide or bicalutamide, both in primary PCa and in CRPC cells. Furthermore, it can also prevent AR nuclear translocation and impairs AR dimerization [15]. Enzalutamide monotherapy is also able to inhibit the proliferation of CRPC cells [16]. The phase III AFFIRM trial has demonstrated a 4.8-month survival benefit of enzalutamide-treated over placebo-treated CRPC patients who had failed on docetaxel therapy [5].

Development in PCa management

There has been an evolution in the treatment of advanced PCa or metastatic CRPC. For a long time, metastatic CRPC patients were treated with docetaxel as standard care. The use of abiraterone or enzalutamide has always been considered as a second-line treatment after docetaxel therapy [17]. Recently, the US Food and Drug Administration has approved abiraterone on 2012 and enzalutamide on 2014 for the treatment of chemotherapy-naive mCRPC patients [18, 19]. The clinical efficacy of abiraterone and enzalutamide treatment in mCRPC raises the question whether those drugs also can and should be used as a first-line therapy in hormone treatment-naive PCa patients.

Recent studies have suggested that abiraterone can be beneficial as well to treat the hormone-sensitive metastatic PCa cases. The LATITUDE trial has shown that there was a lower relative risk of death (38%) and lower radiographic progression (53%) in patients with metastatic, castration-sensitive PCa treated with abiraterone–prednisone plus ADT than in those treated with ADT alone [20]. In addition, at a median follow-up of 40 months, the STAMPEDE trial has shown that the combination of abiraterone with ADT had a 71% relative improvement in the time to treatment failure compared to ADT treatment alone, which translated into a 37% difference in overall survival [21] (Table 1).

In 2014, a phase II trial published by Tombal et al. [25] showed that enzalutamide monotherapy of hormone and

Table 1 Clinical studies for the treatment of prostate cancer

Indication and study (participants)	Comparison	Median overall survival	References
Post chemotherapy mCRPC			
COU-AA-301 (1195 mCRPC)	Abiraterone acetate (1000 mg, once daily) plus prednisone (5 mg, orally twice daily)	15.8 mo (95% CI 14.8–17.0)	Lancet Oncol 2012 [14]
	Placebo plus prednisone	11.2 mo (95% CI 10.4–13.1)	
AFFIRM (1199 mCRPC)	Enzalutamide 160 mg per day	18.4 mo (95% CI 17.3 to not yet reached)	NEJM 2012 [22]
	Placebo	13.6 mo (95% CI 11.3–15.8)	
Pre chemotherapy mCRPC			
COU-AA-302 (1088 chemotherapy-naive mCRPC)	Abiraterone acetate (1000 mg, once daily) plus prednisone (5 mg, orally twice daily)	34.7 mo (95% CI 32.7–36.8)	Lancet Oncol 2012 [23]
	Placebo plus prednisone	30.3 mo (95% CI 28.7–33.3)	
PREVAIL (1717 chemotherapy-naive mCRPC)	Enzalutamide 160 mg per day	32.4 mo	NEJM 2015 [24]
	Placebo	30.2 mo	
Hormone naive metastatic PCa			
LATITUDE (1199 patients)	ADT plus abiraterone acetate (1000 mg once daily as four 250-mg tablets)	Not reached	NEJM 2017 [20]
	ADT plus prednisone (5 mg daily)	34.7 mo Hazard ratio for death: 0.62 (95% CI 0.51–0.76; $p < 0.001$)	
STAMPEDE (1917 patients)	ADT plus abiraterone acetate (1000 mg daily) and prednisone (5 mg daily)	83% 3-year survival	NEJM 2017 [21]
	ADT alone	76% 3-year survival Hazard ratio for death: 0.63 (95% CI 0.52–0.76; $p < 0.001$)	

mo month

chemotherapy-naive PCa patients was able to suppress the disease, as shown by the reduction in serum PSA level. This finding is interesting because it might lead to a change in the indication of enzalutamide for patients with hormone-naive metastatic PCa. Furthermore, a phase III trial of enzalutamide being used for patients with hormone-sensitive metastatic PCa is now ongoing: ARCHES (ClinicalTrials.gov number, NCT02677896). Based on their efficacies and low toxicity profiles, these drugs have the potential to become first-line therapy even for a localized hormone-naive PCa and to replace the conventional ADT in the future (Fig. 3).

New potential drugs for intracrinology-targeted therapy

New compounds that target intracrinology may have therapeutic potential in PCa and CRPC. However, it should also be noted that, even though abiraterone and enzalutamide offer great efficacy, some resistances may occur. A study conducted by Liu et al. [26] showed that there is a possibility of resistancy to abiraterone and enzalutamide. The possible reason of this occurring is that abiraterone and enzalutamide may activate an enzyme called AKR1C3. As mentioned above (Fig. 2), AKR1C3 is an enzyme that catalyzes several reactions involved in the conversion of DHEA into T and DHT, both in classical and backdoor pathways. Inhibition of AKR1C3 may be able to delay disease progression. It should also be noted that there are other isoforms of AKR1C, that is AKR1C1 and AKR1C2. However, in contrast to AKR1C3, these isoforms are able to inactivate DHT. Therefore, finding a substance that selectively inhibits AKR1C3 is important. Indomethacin is an NSAID that can inhibit AKR1C enzymes and shows selectivity to AKR1C3 over AKR1C1/AKR1C2. Recent study found that by inhibiting AKR1C3, it can resensitize PCa cells that have developed resistance to abiraterone and enzalutamide [26, 27]. Therefore, using indomethacin in combination with abiraterone or enzalutamide is a logical consideration. However, such combinations have not yet been established. A phase I/II clinical trial is now ongoing to assess the efficacy and the toxicity profile of the combination of indomethacin and enzalutamide (ClinicalTrials.gov number, NCT02935205). Recently, analogs of indomethacin have also been discovered and studies testing their specificity for AKR1C3 inhibition are ongoing [13].

Another strategy that has been explored is to decrease the cellular uptake of the androgen precursor DHEAS, by interfering with the transportation process of this hormone. Organic anion-transporting polypeptides (OATPs) are a family of transport proteins that are responsible for the influx of a number of substrates, including androgens and other steroids. OATPs are ubiquitously expressed in normal tissues and have been found to be upregulated in PCa. The OATP transporters may be able to maintain intratumoral androgen (precursor) concentrations and sustain AR signaling [28]. Among all OATPs transporters identified, there is one OATP that is called SLCO2B1. This OATP is crucial in transporting the sulfated form of DHEA (DHEAS) into the prostate cells. It must also be noted that high expression of this particular OATP is associated with more aggressive pathological feature of PCa and worse disease-free survival after radical prostatectomy in PCa. The possible cause of this finding is that high expression of SLCO2B1 gene is associated with higher expression of the epithelial mesenchymal transition-related genes, which promote the recurrence of PCa [29].

Harshman et al. [29, 30] have shown that DHEAS is not the only substrate for SLCO2B1. Another substrate for this OATP is statin, which has been known to have an anticancer behavior in various types of cancers. The study assessed whether statins can act as a competitor so that the transporter will take statin instead of DHEAS. In the end, they found

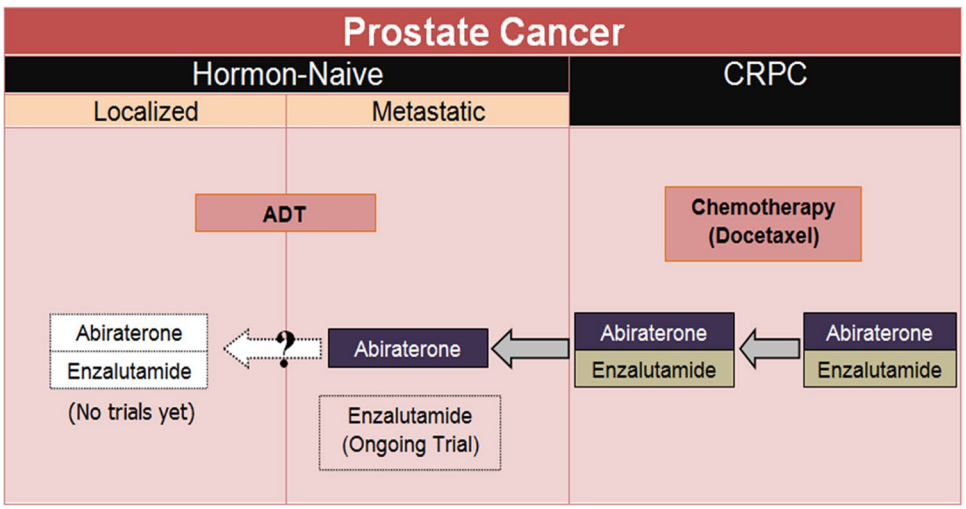

Fig. 3 The potential changes in indication of abiraterone and enzalutamide for prostate cancer management

that statins can indeed reduce DHEAS uptake by competitively binding to SLCO2B1 and, therefore, decreasing the available intratumoral androgen pool (Fig. 4). However, as promising as they can be, combination treatment is preferred. Another study conducted by Sekine et al. [31] shows that the combination of simvastatin and one of the AKR1C3 inhibitors, meclofenamic acid, further inhibited cancer cell proliferation and migration in PC-3 cell model than simvastatin alone. Moreover, it is also shown that statin in combination with ADT can prolong the time of progression in PCa cases [30]. All these findings lead to an interesting possibility of inhibiting the OATPs to treat PCa. However, more studies are required since there is still limitation on dataset available to further determine the application of this approach [29].

Targeting the AR has also been a crucial part in treating PCa from intracrinological aspect. While there are many ways to target the AR, resistancy may occur. Therefore, finding novel strategy to target the intracrinology can be challenging. Study found that the AR protein level is regulated by many co-activators, and one of the new co-activators that has been found to positively stabilize and enhance the AR functions is the deubiquitinating enzyme USP12. Lately, it is found that this enzyme is found to be promising as a target in PCa management [32]. McClurg et al. [33] showed that apart from USP12, there was also another deubiquitinating enzyme that has a functional overlap with USP12 called USP46, which is also found to help in upregulating the AR activity. The study also demonstrated that it is actually possible to inhibit these enzymes and thus inhibit the progression of PCa. They found a novel small anti-androgen molecule; galeterone is able to selectively bind with both USP12 and USP46 (Fig. 4), thus inhibiting their activity to stabilize the AR, hence delaying the progression of the PCa disease [33]. This finding is interesting because the study showed that galeterone is able to effectively inhibit the cancer cell proliferation in almost all cancer cell models, including the castrate-resistant and AR-negative models. In addition, galeterone also plays a role in inhibiting the CYP17 enzyme activity as well as directly binding to the AR. However, the study also found that galeterone seems to be less effective in the AR variant (AR V) models, especially AR V7. The possible reason to this finding is that the shorter AR variants lacked the C-terminal ligand binding domain and were not ubiquitinated, so that USP12 and USP46 as the deubiquitinating enzymes had little role in regulating the AR; thus, inhibiting those enzymes will have little or no effect on decreasing the AR activity. Nevertheless, there were studies found that galeterone is able to cause substantial reduction in AR V level. Therefore, more studies are needed to determine the effects of galeterone in patients with PCa expressing AR variants [33].

There is also a possibility of targeting the AR signaling pathway through directly degrading the AR. One of the compounds that has been found to have this ability is ASC-J9®. In animal study, this compound can inhibit the AR activity and selectively degrade the AR but has little effect on other steroid receptors such as glucocorticoid receptor and

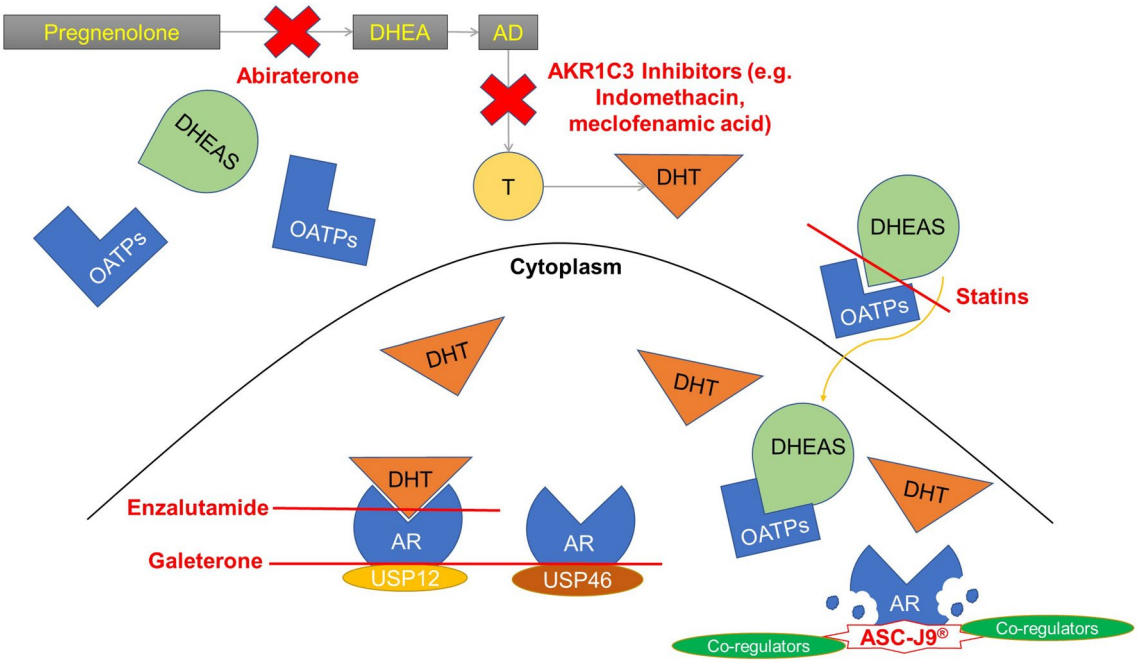

Fig. 4 Various mechanisms of targeting intracrinology in PCa

estrogen receptor α [34]. It must also be noted that this compound mechanism of action is quite different than the usual drugs targeting the AR. It helps to promote the degradation of the AR through disrupting the interaction of the AR with AR co-regulators (Fig. 4), and has been shown to be effective against the AR variants lacking in ligand binding domain (LBD), which is the primary target site for antiandrogen such as enzalutamide. This is important because as mentioned above, it is quite challenging to treat the PCa with AR variants that lack the LBD [34].

Combination therapy

Since there are many ways tumor cells may adapt to ADT (and other cancer treatments), targeting only one of the resistance mechanisms will not be sufficient to combat this disease effectively. Furthermore, there are many studies revealing resistance to the current secondary hormonal monotherapy [35]. Therefore, combination therapy is recommended in treating PCa patients. Several possible effective combinations have been suggested in many studies. For example, it has been shown that the combination of enzalutamide and dutasteride synergistically inhibits the proliferation of PCa cells. However, both drugs have not yet been tested together in CRPC patients. The combination of abiraterone with prednisolone or prednisone and enzalutamide is currently being evaluated in a single-arm phase 1b clinical trial for metastatic CRPC, where the preliminary data show no increased toxicity. In addition, there are also several other studies conducted to measure different outcomes for this combination such as a phase III trial comparing this combination and enzalutamide alone is also now ongoing with overall survival as its primary outcome (ClinicalTrials.gov number, NCT01949337) and a phase IV study comparing this combination with abiraterone, prednisone and placebo with radiologic progression-free survival as its primary outcome (ClinicalTrials.gov number, NCT01995513) [36]. Moreover, it is also interesting to see the possibility of combination therapy between the current hormonal therapy such as enzalutamide and abiraterone with the potential novel drugs mentioned above to overcome any resistance mechanisms that may occur in the future.

Conclusion

Intracrinology in PCa cells plays a key role in survival of tumor cells and in the development of CRPC. New drugs targeting intracrinology have recently been implemented in PCa and CRPC management. Development of additional drugs targeting the major components of intracrinology is ongoing. Application of these new drugs and administration of combinations of existing drugs will ultimately lead to an increase in the efficacy of such treatments, as well as to reduce the toxicity of the therapy and to prevent the risk of resistance.

Compliance with ethical standards

Conflict of interest None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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