The role of CYP17A1 in prostate cancer development: structure, function, mechanism of action, genetic variations and its inhibition

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Abstract. Androgens play an important role during the development of both normal prostate epithelium and prostate cancer and variants of genes involved in androgen metabolism may be related to an increased risk of prostate disease. Cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1) is a key regulatory enzyme in the steroidogenic pathway; it catalyses both 17α-hydroxylase and 17,20-lyase activities and is essential for the production of both androgens and glucocorticoids. In this review, we focus on the structure and enzymatic activity of CYP17A1 and the mechanism of modulation of CYP17A1 activities. We discuss the relationship between common genetic variations in CYP17A1 gene and prostate cancer risk and the main effects of these variations on the prediction of susceptibility and clinical outcomes of prostate cancer patients. The mechanism of action, the efficacy and the clinical potential of CYP17A1 inhibitors in prostate cancer are also summarized.

Key words: CYP17A1 — Steroid 17 alpha-hydroxylase/17,20-lyase — CYP17A1 polymorphisms — CYP17A1 inhibitors — Prostate cancer

Abbreviations: AA, abiraterone acetate; ACTH, adrenocorticotropic hormone; ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; CYP17A1, cytochrome P450 17α-hydroxylase/17,20-lyase; DHEA, dehydroepiandrosterone; GWAS, genome-wide association studies; KLK2, kallikrein-related peptidase 2; KLK3, kallikrein-related peptidase 3; mLTC-1 cells, murine primary Leydig cells; P-450-red, NADPH-cytochrome P450 reductase; PCa, prostate cancer; PSA, prostate-specific antigen; SF-1, steroidogenic factor-1; SLC45A3, prostein; SNPs, single nucleotide polymorphisms; TNM, tumour-node-metastasis stage; UTR, untranslated region.

Introduction

Prostate cancer (PCa) is the second most common cancer-related cause of death in men worldwide and is caused in its aetiology by numerous genetic and environmental factors (Nelson and Lepor 2003). It is estimated that 161,360 new PCa cases will be diagnosed and that 26,730 deaths will occur in the United States in 2017 (Siegel et al. 2017). Epidemiological data demonstrate that the incidence and mortality rate of PCa varies in different countries and regions and, hence, the influence of racial or ethnic differences varies (DeSantis et al. 2016; Torre et al. 2016; Siegel et al. 2017). With early diagnosis, radical prostatectomy and/or radiation therapy are potentially curative. For advanced or metastatic PCa, hormonal therapies, reducing androgen levels by surgical or chemical castration or by inhibiting the androgen receptor protein, are employed (Rove et al. 2012; Zhuang and Johnson 2016). Despite technological advancements, the management of PCa has become progressively more complex and controversial for both early and late-stage disease. The limitations and potential harm associated with the use of prostate-specific antigen (PSA) as a diagnostic marker have stimulated significant investigation of numerous novel biomarkers that demonstrate various capacities to detect PCa...
and that can decrease unnecessary biopsies (Cabarkapa et al. 2016; Sharma et al. 2017).

Genetic alterations in the testosterone metabolism pathway are expected to alter hormonal homeostasis and probably influence PCa development and progression (Henríquez-Hernández et al. 2015). Several genes have been identified as risk factors contributing to PCa. One of them is the gene for cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17A1), a pivotal enzyme for androgen synthesis. CYP17A1 catalysis leads to either steroid precursors of glucocorticoids (e.g. cortisol) that regulate immune response or androgens (e.g. testosterone) that drive the development and maintenance of male characteristics or are converted to oestrogens in females (Auchus and Miller 1999; Pandey and Miller 2005; Yoshimoto and Auchus 2015). Mutations in CYP17A1 gene cause 17α-hydroxylase deficiency, a rare form of congenital adrenal hyperplasia, and sexual infantilism (Costa-Santos et al. 2004). The discovery that the CYP17A1 gene is polymorphic has prompted the investigation of the role of gene variants in the aetiology of diseases and conditions in which oestrogens or androgens play an important role, notably breast cancer, polycystic ovary syndrome, endometrial cancer and PCa (Sharp et al. 2004).

This review aims to summarize the recent gains in our comprehension of the role of CYP17A1 in PCa and of the mechanisms regulating and modifying its activity. We explore the influence of CYP17A1 gene polymorphisms in PCa development and progression and the effects of established CYP17A1 inhibitors, such as ketoconazole, abiraterone acetate, galeterone and VT-464, which are agents currently at various stages of development.

**CYP17A1 structure, function and mechanism of action**

CYP17A1 (EC 1.14.99.9) is a membrane-bound dual-function monooxygenase that possesses 17α-hydroxylase and 17,20-lyase activities. According to the structural model of CYP17A1, it is composed of 508 amino acids, with 4 important structural domains, including a substrate-binding domain, a catalytic activity area, a haem-binding region and a redox-partner binding site (Auchus and Miller 1999; Auchus 2001). It is localized to the endoplasmic reticulum in the adrenal glands, testicular Leydig cells and ovarian thecal cells and lies at the crossroads of sex steroid and glucocorticoid synthesis (Missaghian et al. 2009). Human

![Figure 1. Testosterone synthesis and enzymatic activity of CYP17A1. Inhibitors of CYP17A1 in the pathway are also indicated. Androgen synthesis requires two key cytochrome P450 enzymes (CYP11A1 and CYP17A1) and two hydroxysteroid dehydrogenases (3βHSD and 17βHSD). CYP17A1 catalyzes two essential reactions in androgen biosynthesis. The first one is the conversion of pregnenolone to 17α-hydroxypregnenolone and progesterone to 17α-hydroxyprogesterone through its 17α-hydroxylase activity. The second reaction in androgen biosynthesis is conversion of 17α-hydroxypregnenolone to DHEA and 17α-hydroxyprogesterone to androstenedione through its 17,20-lyase activity. Ketoconazole is a weak and nonspecific CYP17A1 inhibitor. AA inhibits both the 17α-hydroxylase and 17,20-lyase activity of CYP17A1. Orteronel and galeterone have increased specificity for the 17,20-lyase reaction over 17α-hydroxylase. AA, abiraterone acetate; 3βHSD, 3β-hydroxysteroid dehydrogenase; 17βHSD3, 17β-hydroxysteroid dehydrogenase 3; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.](image-url)
CYP17A1 is known to catalyse at least 13 different reactions with endogenous substrate and even some minor activities are physiologically important (Yoshimoto and Auchus 2015). The 17α-hydroxylase activity of CYP17A1 is required for the hydroxylation of pregnenolone and progesterone at the C17 position to generate 17α-hydroxypregnenolone and 17α-hydroxyprogesterone. Its second enzymatic activity follows with the cleavage of the C17-C20 bond of either 17α-hydroxypregnenolone or 17α-hydroxyprogesterone to form dehydroepiandrosterone (DHEA) and androstenedione, respectively (Fig. 1) (Auchus 2001; Pandey and Miller 2005; Yoshimoto and Auchus 2015). In human adrenal steroidogenesis, CYP17A1 is the qualitative regulator that determines the class of steroids synthesized in various cell types: in its absence, mineralocorticoids are produced; if only its 17α-hydroxylase activity is present, glucocorticoids are produced; if both its 17α-hydroxylase and 17,20-lyase activities are present, precursors of sex steroids are produced (Pandey and Miller 2005; Yoshimoto and Auchus 2015).

The reaction mechanism for each activity is thought to involve the formation of distinct iron–oxygen complexes. For the hydroxylase mechanism, the oxo-intermediate, Fe$^5$=O, is considered to be the active catalytic oxygen-bound CYP17A1 complex (Atkinson and Ingold 1993). Possible candidates for the acyl-carbon bond cleavage have been suggested, namely both the iron-peroxo, Fe$^{III}$-OOH, and iron-oxo, Fe$^5$=O species (Lee-Robichaud et al. 1995; Akhtar et al. 2005).

Previous observations have shown that the following factors contribute to the regulation of the ratio of 17,20-lyase activity to 17 α-hydroxylase activity: (a) the input of two electrons from NADPH of NADPH-cytochrome P450 reductase (P-450-red) to CYP17A1 (Auchus and Miller 1999). (b) The presence of cytochrome b$_5$. Two general mechanisms have been proposed to explain the enhanced action of cytochrome b$_5$ in CYP17A1 catalysis. The first mechanism implies that, during the reductive stages of CYP17A1, the second electron for the completion of the catalytic cycle can be derived from cytochrome b$_5$, an alternative redox partner to the conventional P-450-red (Estabrook 1999). A second model suggests that cytochrome b$_5$ serves as an allosteric modulator that can increase 17,20-lyase activity as an allosteric effector on the CYP17A1–P450-red complex, facilitating electron transfer from P450-red to CYP17A1 or promoting the facile breakdown of the CYP17A1-substrate intermediate in the catalytic cycle (Storbeck et al. 2013). (c) Phosphorylation of the serine/threonine residues of the CYP17A1 protein increases 17,20-lyase activity but does not affect 17α-hydroxylase activity (Zhang et al. 1995; Biaison-Lauber et al. 1997; Miller and Tee 2015). The activities of CYP17A1 have been hypothesized to be differentially regulated by protein phosphorylation based on the differential expression of protein kinases and/or phosphatases in various cell types or at various times during in development, thus determining the pattern of steroid hormones produced (Pandey and Miller 2005).

Notably, CYP17A1 has been shown to have additional properties, namely by metabolizing xenobiotics and catalysing the formation of a third class of active steroids, the 16-ene steroids. However, the overall functional effect of the 16-ene steroids in normal physiology is still poorly understood (Vasaitis et al. 2011).

**CYP17A1 gene**

The human CYP17A1 gene is localized to chromosome 10q24.3, spans 6.6 kb and contains eight exons and seven introns (Picado-Leonard and Miller 1987). An identical 2.1 kb mRNA is transcribed from this gene in the both the adrenals and the gonads (Chung et al. 1987; Fan at al. 1992; Auchus 2017). The expression level of CYP17A1 is regulated by adrenocorticotrophic hormone (ACTH) in the adrenals and by gonadotropic hormone in the testes and ovaries (Yanase et al. 1991; Porubek 2013). The expression of CYP17A1 mRNA has been shown to be absolutely dependent on cAMP stimulation. Initial studies with reporter gene constructs to define ACTH-dependent transcription of the human CYP17A1 gene have revealed that both basal and cAMP-responsive elements lie within the first upstream 63 bp of the CYP17A1 promoter and that a second basal element lies between -184 and -206 bp in the CYP17A1 promoter (Rodriguez et al. 1997). Subsequently, Sewer and co-workers have shown that the binding of transcription factor steroidogenic factor-1 (SF-1) to this region and its dephosphorylation play an integral role for ACTH/cAMP-mediated steroidogenic CYP17A1 gene expression (Sewer and Waterman 2002; Sewer et al. 2002).

Several other transcription factors regulate CYP17A1 gene expression, cell differentiation, and tumorigenesis in diverse cell types, including the gonads and adrenals (Lin et al 2001; Gilep et al. 2011). The ability of these factors to increase CYP17A1 mRNA expression requires the formation of higher order coregulatory complexes, many of which contain enzymatic activities that post-translationally modify both the transcription factors and histones (Sewer and Jagarlapudi 2009). One of these is the GATA family of transcription factors. GATA1–3 are primarily involved in haematological development, whereas GATA4 and GATA6 have been implicated in human CYP17A1 expression. GATA6 is highly expressed in the adrenal cortex and the stimulatory actions of GATA6 on CYP17A1 transcription are independent of DNA binding but occur through the interaction of GATA6 with specificity protein 1 (Sp1) (Kiiveri et al. 2004; Sewer and Jagarlapudi 2009).

GATA4 plays a role in the differentiation and/or steroidogenic function of gonadal somatic cells, including fetal and
adult Leydig cells (Viger et al. 1998; Ketola et al. 1999, 2002). The silencing of GATA4 in mLTC-1 cells (murine primary Leydig cells) and primary adult Leydig cells has been shown to lead to the decreased expression of genes in the androgen biosynthetic pathway including CYP17A1. In mLTC-1 cells, this is accompanied by the reduced production of sex steroid precursors (Schrade et al. 2015). Adrenal transcription of the CYP17A1 gene is also controlled by transcription factors Sp1 and Sp3 (binding to the -127/-184 bp site) and nuclear factor NF-1C proteins (binding to the -107/-185 bp or the -178/-152 bp sites) (Lin et al. 2001). Another transcription factor that regulates the expression of the human CYP17A1 gene is SET (also known as TAF-1β, I2PP2A and INHAT). It is an evolutionarily conserved transcription factor that participates in the early ontogenesis of the gonadal system, that regulates CYP17A1 gene transcription in Leydig cells, and that might also activate other genes expressed in immature oocytes, thus playing a role in oocyte development (Xu et al. 2013).

Moreover, epigenetics provides an additional layer of gene regulation through DNA methylation and histone tail modifications. Initial studies of CpG methylation came from studies of bovine and rodent adrenals (Hornsby et al. 1992). Missaghian et al. (2009) have shown that, in rodent adrenals, methylation of the CYP17A1 promoter region is correlated with the silencing of gene expression and the production of corticosterone as the main glucocorticoid. The absence of a CpG island in the human CYP17A1 gene suggests that the direct epigenetic regulation of the CYP17A1 promoter is more essential in rodents and, therefore, that the expression of CYP17A1 in humans is driven by the above-mentioned complex interaction of transcription factors (Martinez-Arguelles and Papadopoulos 2010).

**CYP17A1 gene polymorphisms**

Single nucleotide polymorphisms (SNPs) are the most common form of human genetic polymorphisms that can contribute to an individual’s susceptibility and progression to cancer. Although many factors can contribute to the underlying biology and clinical course of PCa, genetic variation in androgen biosynthesis is thought most likely to influence the eventual outcome of the disease (Sissung et al. 2014). genetic variation in CYP17A1 has been studied extensively in relation to PCa. Most of these studies have focused on rs743572 gene polymorphism (denoted T34C or A1/A2), located 34 bp upstream from the initiation of translation and downstream from the transcription start site (Fig. 2). The variant creates a recognition site for the MspA1 restriction enzyme (Sharp et al. 2004). Studies that have reported a relationship between CYP17A1 gene polymorphism and the risk of PCa have been contradictory in terms of which allele is associated with the increased risk for PCa. Some case-control studies have reported an elevated risk for PCa being related to the A1/A2 or A2/A2 genotype (Lunn et al. 1999; Gsur et al. 2000; Haiman et al. 2001; Kittles et al. 2001; Yamada et al. 2001; Sobti et al. 2008; Souiden et al. 2011), whereas other studies indicate an association between PCa and the A1/A1 genotype (Wadellius et al. 1999; Habuchi et al. 2000). Further studies have reported no difference in the distribution of the various alleles among healthy controls and PCa patients (Chang et al. 2001; Latil et al. 2001; Standford et al. 2002; dos Santos et al. 2002; Madigan et al. 2003; Hamada et al. 2007; Sivonova et al. 2012; Cai et al. 2012; Karimpur-Zahmatkesh et al. 2013; Erseceri et al. 2015; Han et al. 2015; Henriquez-Hernández et al. 2015).

Differences also exist in the association between the rs743572 polymorphism and PCa risk in different ethnicities. Meta-analyses have suggested that variants within CYP17A1 play a role in susceptibility to PCa among African-Americans but not in Caucasian or Asian populations (Ntais et al. 2003; Wang et al. 2011; Taioli et al. 2013; Wang et al. 2015). The reasons for the large ethnic differences might be explain by the observation that African-Americans experience earlier puberty, higher serum levels of total testosterone and a higher incidence of PCa (Loukola et al. 2004). Most recently, Brureau et al. (2016) have found that the A2 allele and the A2/A2 genotype are not associated with a significant risk of PCa in two different populations of African ancestry, namely an Afro-Caribbean population from the French West Indies and a native African population from the Democratic Republic of Congo.

The A2 allele is thought to enhance promoter activity (through creating an additional Sp1-binding site – CCACC.

**Figure 2.** Human CYP17A1 gene with designated SNPs. Black blocks mark coding exons (Ex1-8), white blocks mark 5' and 3' UTRs, and connecting lines between blocks are introns.
box) resulting in an increased rate of transcription and, thus, an increased production of androgens and oestrogens that might affect PCa risk (Stanford et al. 2002). A few studies have shown an association of the A2 allele with higher levels of plasma testosterone (Zmuda et al. 2001; Kakinuma et al. 2004) but this observation is again contradictory (Lunn et al. 1999; Allen et al. 2001; Haiman et al. 2001).

Similarly no consistent results have been observed relating age, clinical variables (Gleason pathological grade, tumour-node-metastasis (TNM) stage, serum PSA levels and serum levels of sex hormones) and family history with rs743572. A few epidemiologic studies have determined a positive association between this polymorphism and the Gleason score/clinical stage and serum PSA levels (Sobti et al. 2006, 2008) but many more conclusions are negative (Haiman et al. 2001; Stanford et al. 2002; Madigan et al. 2003; Mononem et al. 2006; Okugi et al. 2006; Hamada et al. 2007; Wright et al. 2010; Risio et al. 2011; Souiden et al. 2011; Sivonova et al. 2012; Yamada et al. 2013; Han et al. 2015; Henriquez-Hernández et al. 2015; Brureau et al. 2016; Song et al. 2016).

Some of the studies suggest that the CYP17A1 gene is a risk factor for PCa in males of advanced age (Souiden et al. 2011; Song et al. 2016). Hamada et al. (2007) have reported that the CYP17A1 polymorphism is a potential prognostic predictor for survival in patients with androgen-independent disease, because patients who carry the CYP17A1 variant A2 allele have a longer survival time than patients who do not carry this variant.

**Other CYP17A1 gene polymorphisms**

To date, several other CYP17A1 gene polymorphisms in various gene locations (in the intron regions, in the promoter region, in the coding regions of the exon and in the S’ untranslated region (UTR) region of the exon) have been studied, mainly together with rs743572 (Fig. 2). A family-based study of Loukola et al. (2004) has found no association between 14 SNPs in CYP17A1 and PCa in a total case-control sample of 1117 brothers from 506 sibships. A family-based study by Douglas et al. (2005) has shown a 2-fold increased risk of PCa in individuals with the common SNP rs619824. Modest but significant positive associations were observed between PCa and two SNPs (rs2486758 and rs6892); this seemed to be stronger among aggressive PCa. Moreover, the variant allele for rs2486758 SNP was found to be associated with a 7% increase in PCa risk (Setiawan et al. 2007). A contemporary study by Lindström et al. (2006) showed that carriers of one allele of the rs2486758 SNP located in the promoter region of CYP17A1 were at a 15% higher risk of developing PCa.

Yamada et al. (2013) observed significant association of the rs6162, rs6163 and rs1004467 CYP17A1 polymorphisms with the risk of progression to castration-resistant PCa (CRPC) after initial hormonal therapy for PCa in the Japanese population. They also assumed that rs6162 and rs6163 exhibited their functions in coordination with rs743572 as a haplotype. An association was also seen between genotypes and haplotype distributions of patients and a control group in the Korean population in the analysis of Han et al. (2015). They found that haplotype-2 of CYP17A1 was significantly associated with PCa susceptibility, whereas rs17115149 and haplotype-4 of CYP17A1 showed a significant association with the histological aggressiveness associated with Gleason scores.

Significant associations have also been seen between the rs6162, rs6163 and rs743572 genotypes and PCa status in African-American men. Interestingly, Sarma et al. (2008) have observed a strongly decreased risk for PCa in heterozygotes for these three CYP17A1 SNPs. Another large study has evaluated the association of eight genetic variants of CYP17A1 in 2,452 samples (886 cases and 1,566 controls) of non-Hispanic Caucasian, Hispanic Caucasian or African-American origin. In African-Americans, the association with PCa risk remained significant for rs104467 and rs17115144 and, in non-Hispanic Caucasians, a significant increase in risk for PCa has been reported for rs10883782 (Beuten et al. 2009).

The relationship was studied between three CYP17A1 SNPs (rs10883783, rs17115100 and rs743572) and PCa-specific survival and progression outcomes. No genetic association with disease progression was identified. However, men with the variant A allele in rs10883783 had a 56% risk reduction in PCa-specific survival (Wright et al. 2010).

**GWAS**

Although the use of genome-wide association studies (GWAS), next-generation sequencing, whole-exome sequencing and RNA sequencing has allowed the comprehensive analysis of PCa genomes, it has also given an indication of the complexity and heterogeneous nature of PCa (Sissung et al. 2014). GWAS have emerged as a new approach for identifying less penetrant cancer susceptibility alleles that might be associated with the initiation and progression of cancer.

GWAS of PCa have identified approximately 100 different SNPs associated with PCa risk in various racial populations (Gudmundsson et al. 2009; Schumacher et al. 2011; Eeles et al. 2013; Al Olama et al. 2014; Dluzniewski et al. 2015; Hoffmann et al. 2015; Panagiotou et al. 2015; Kim et al. 2016; Hofmann et al. 2017). In some of the GWAS, attempts have been made to evaluate the associations between specific PCa risk SNPs, disease aggressiveness and survival (Schumacher et al. 2011; Al Olama et al. 2014; Berndt et al. 2015; Szulkin et al. 2015). The large GWAS of PSA by Hoffman et
al. (2017) in 28,503 Kaiser Permanente whites and 17,428 men from replication cohorts detected 40 independent SNPs associated with PSA levels: seven common independent SNPs at kallikrein-related peptidase-3 and kallikrein-related peptidase 2 (KLK3-KLK2), five SNPs in or near SLC45A3 (prostein) and a novel SNPs associated with PSA levels in genes in pathways involved in cellular signalling, growth and differentiation. Additionally, results from other GWAS and linkage analyses have reported risk loci associated with aggressive disease among familial cases (Gudmundsson et al. 2008; Liu et al. 2011; Nam et al. 2011; Teerlink et al. 2016).

Thus, GWAS are a part of multi-omic approaches (including proteomics, metabolomics and epigenomics) in pursuit of precision medicine and provide opportunities to gain new perspectives regarding the genetic architecture of PCa by identifying new candidate genes and targets.

CYP17A1 inhibitors

More than half century ago, Huggins and Hodges provided clinical evidence that prostate morphogenesis occurs under the control of androgens and is modulated by oestrogens (Huggins et al. 1941). Nowadays, androgen and its androgen receptor (AR) are accepted to be key factors for the development of not only normal prostate, but also PCa (Heinlein and Chang 2004; Fujimoto 2016). This explains the high response rate of PCa patients to androgen deprivation therapy (ADT). However, after an initial response to ADT, most patients experience cancer progression to metastatic CRPC, which is defined by rising PSA and/or clinical progression despite systemic androgen depletion (Damber and Aus 2008; Chang et al. 2014; Attard et al. 2016). CRPC occurs because of the reactivation of the androgen axis either by adaptive intra-tumoral androgen biosynthesis (Locke et al. 2008; Cai et al. 2011) or by changes in the AR (e.g. AR gene amplification and mutation) (Taplin et al. 1999; Shi et al. 2002).

Therapeutic CYP17A1 inhibition for the treatment of PCa and other androgen-dependent diseases has been envisioned for over 50 years (Fig. 3; Arth et al. 1971). Generally, CYP17A1 inhibitors have been structurally categorized as steroidal or non-steroidal. The steroidal inhibitors are similar in structure to the natural substrates of CYP17A1, pregnenolone or progesterone and often involve the modification of the substrate’s D-ring at the C17 position (Vasaitis et al. 2011). An early developed compound, ketoconazole, is an antifungal with weak and nonspecific CYP17A1 inhibitory properties and has been extensively used for the ‘off-label’ treatment of advanced CRPC (Fig. 1; Yap et al. 2008). It has typically been used at high dosage (800–1200 mg/d) for PCa
treatment, lowering not only testosterone levels, but also the levels of adrenal steroids, androstenedione and DHEA (De Coster et al. 1996). However, high doses of ketoconazole have been associated with significant potential side-effects including hepatotoxicity, gastrointestinal toxicity and adrenal insufficiency (Vasaitis et al. 2011). Ketoconazole leads to a decrease in serum PSA by ≥ 50% in 27% of patients, whereas anti-androgen withdrawal causes a PSA response in 11% of patients (Small et al. 2004).

By 2011, the United States Food and Drug Administration (FDA) had approved abiraterone acetate (AA), the first specific inhibitor of CYP17A1 (Fig. 1). AA and its metabolite, abiraterone, are selective inhibitors of 17α-hydroxylase and 17,20-lyase (Vasaitis et al. 2011). Recently, a more active form of AA, namely Δ4 abiraterone, has been shown to block 17β-hydroxysteroid dehydrogenase and steroid 5α reductase, which are required for dihydrotestosterone synthesis, in addition to CYP17A1 enzymes (Li et al. 2015). It induces PSA declines of ≥ 50% in 29–62% of patients, achieves overall survival benefits in both docetaxel refractory and chemotherapy-naive patients, delays and reduces skeletal-related events and palliates pain (Ryan et al. 2013). In the COU-AA-301 and COU-AA-302 registration trials, abiraterone demonstrated overall survival benefits in post-docetaxel and pre-docetaxel settings (Lorente et al. 2015; Fizazi et al. 2016). The suppression of 17α-hydroxylase leads to reduced cortisol synthesis and compensatory overproduction of mineralocorticoids. Increased mineralocorticoid levels result in some adverse events, such as hypokalaemia, fluid retention, hypertension and cardiac disorders; however, these toxicities are largely abrogated by the co-administration of low-dose glucocorticoids (Attrard et al. 2009). Abiraterone is currently approved in combination with prednisone for the treatment of metastatic CRPC in men both prior to and after treatment with docetaxel (de Bono et al. 2011; Ryan et al. 2013). Although abiraterone represents a significant therapeutic advance, tumours ultimately become resistant and progress. Furthermore, abiraterone-resistant tumours are also frequently resistant to subsequent treatment with enzalutamide, a recently developed AR antagonist that otherwise confers a survival benefit that is similar to that of abiraterone for CRPC (Brasso et al. 2015).

One additional drug with abiraterone-like properties is orteronel (TAK-700) (Fig. 1). It is a nonsteroidal selective inhibitor of 17,20-lyase. In preclinical studies, orteronel more potently inhibited 17,20-lyase relative to 17α-hydroxylase, up to 5.4-fold, with minimal effect on other CYP drug-metabolizing enzymes (Yamaoka et al. 2012). Preliminary results from phase I/II studies found a 63% PSA response rate at 12 weeks with patients given 300 mg twice daily (Zhu and Garcia 2013). More selective specificity of orteronel inhibition leads to less inhibition of 17α-hydroxylase with a reduction in the risk of overproduction of mineralocorticoids. Thus, orteronel is potentially an attractive drug for longer duration therapy or when prolonged corticosteroid is not ideal. However, in a clinical setting, many trials have included prednisone coadministration (Zhu and Garcia 2013; Alex et al. 2016).

Galeterone (VN/124-1, TOK-001) is a CYP17A1 inhibitor with multiple mechanisms of action, including CYP17A1 inhibition, AR antagonism and a decrease in intratumoral AR levels (Fig. 1 and 3; Alex 2016). Additionally, galeterone has a unique mechanism of action by disrupting AR signaling via a proteosomal-dependent pathway, leading to AR degradation (Kwegyir-Afful et al. 2015). In a phase I study of chemonaive men with CRPC, 22% demonstrated a decrease in PSA of more than 50%, whereas an additional 26% had a PSA decline of 30–50% after 12 weeks. No evidence of adrenal mineralocorticoid excess was noted (Montgomery et al. 2016).

Finally, an additional drug, namely seviteronel (VT-464, Viamet Pharmaceuticals), is in early stages of development (Fig. 1). It is a novel nonsteroidal CYP17A1 inhibitor and AR antagonist. It preferentially inhibits 17,20-lyase over 17α-hydroxylase, thus offering an advantage over AA from the perspective of not requiring concomitant therapy with prednisone, because of to its minimal effects on upstream steroid levels (Suzman and Antonarakis 2014).

Conclusions

This review summarises the role of CYP17A1 in the synthesis of androgens and the influence of CYP17A1 SNPs on the susceptibility to the risk of PCa. We also discuss potential new therapeutic strategies that may lead to improvements in the oncological outcomes of this disease. In the future, advances in new technologies with clinical information will offer the possibility of the earlier detection of PCa pathology and will lead to different or specific treatments that will prolong patient survival, delay symptom progression and maintain, if not improve, quality of life.

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