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REVIEW ARTICLE

Impact of Candidate Genetic Polymorphisms in Prostate Cancer: An Overview

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Abstract In the last few years, the presence of single nucleotide polymorphisms (SNPs) has been investigated in many tumors as predictor of disease aggressiveness and clinical outcome. We searched for relevant articles from 1998 to 2015 about the impact of SNPs in prostate cancer. Particularly, in this article, we review the pathogenetic, prognostic and predictive significance of gene polymorphisms in prostate tumor, providing a brief overview of studies in which the possible role of genetic variants was investigated in clinical settings. Because conflicting results often emerge about the impact of gene polymorphisms in prostate cancer, further larger studies are warranted in order to introduce gene polymorphism into clinical practice as biomarkers.

Key Points

SNPs could impact on gene and protein expression; their role as predictor of clinical outcome and/or treatment toxicity could be relevant.

SNPs in principal genes involved in androgen direct (*AR*, *CYP17A1*, *SRD5A*) or indirect pathways (*PI3K/Akt/mTOR*, *EGFR*, *VEGF*) were studied in association with prostate cancer.

Literature data showed the involvement of SNPs in prostate cancer risk and tumor progression, whereas their correlation with mechanisms of treatment resistance remains to be better defined.

1 Introduction

Prostate cancer (PCa) is the most frequent cancer in men, accounting for about one quarter of new tumor diagnoses, and represents the second cause of all cancer deaths [1]. Gonadal androgen depletion by surgical or medical castration remains the mainstay of treatment in patients with advanced-stage disease. Androgen deprivation therapy (ADT) leads to a decrease in prostate-specific antigen (PSA) levels, promoting a longer survival in these patients. However, some cases of PCa are able to continue the androgens biosynthesis through CYP17 and 5α-reductase enzymes converting circulating adrenal androgens or de novo from cholesterol in intratumoral space [2, 3], resulting in castration-resistant prostate cancer (CRPC) patients. Even so, the enduring activation of androgen

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receptor (AR) axis is modulated by alternative pathways such as PI3K/AKT/mTOR, SRC kinases, c-Met and angiogenesis genes [4]. In the last few years, several studies evaluated specific drugs, such as abiraterone and enzalutamide, which target AR-dependent or -independent pathways, resulting in an increasing survival of patients [5, 6]. The significant clinical benefit of abiraterone and enzalutamide therapies in CRPC has been already studied [7, 8], but other pathway inhibitors used as single agents or in combination therapy could help the evolving treatment landscape of CRPC [5]. Even now, it is necessary to focus on the identification of biomarkers able to predict the response or resistance to hormonal therapies. The cause of resistance could involve genomic alterations, such as single nucleotide polymorphisms (SNPs). SNPs within the exons could impact on messenger RNA changes or translation efficiency, resulting in protein alterations. Other SNPs are located outside of the genes and could be implicated in genome organization or in some other levels of gene regulation (alternative splicing, gene expression, etc.).

Focusing on SNPs could pave the way to characterize the tumor heterogeneity and the drug efficacy or resistance. Correlation between SNPs and response to treatment has been showed in several tumors [9–11]. The role of SNPs in prostate cancer has been studied rather extensively, in particular in association with risk prediction, progression and aggressiveness of PCa [12, 13], but how they could have an impact on the efficacy of novel therapeutics is currently a topic of debate.

This review would be an overview of SNPs of principal genes targeting the AR axis. We chose to focus our attention on the *AR*, *CYP17A1*, *SRD5A* genes (androgen direct pathway), and some androgen indirect pathways involved in AR activation (*PI3K/Akt/mTOR*, *EGFR*, *VEGF*) (Fig. 1). Modulation of *AR* in a direct or indirect way could be the core of drug efficacy in prostate cancer. For this reason we reviewed literature data to find the relationship between SNPs and prostate cancer, in particular focusing on their implication on the efficacy of new hormonal therapies (abiraterone and enzalutamide).

2 Methods

Eligible studies were selected via a search of PubMed® archive (from October 1998 to February 2015). The studies focused on the impact of SNPs on prostate cancer

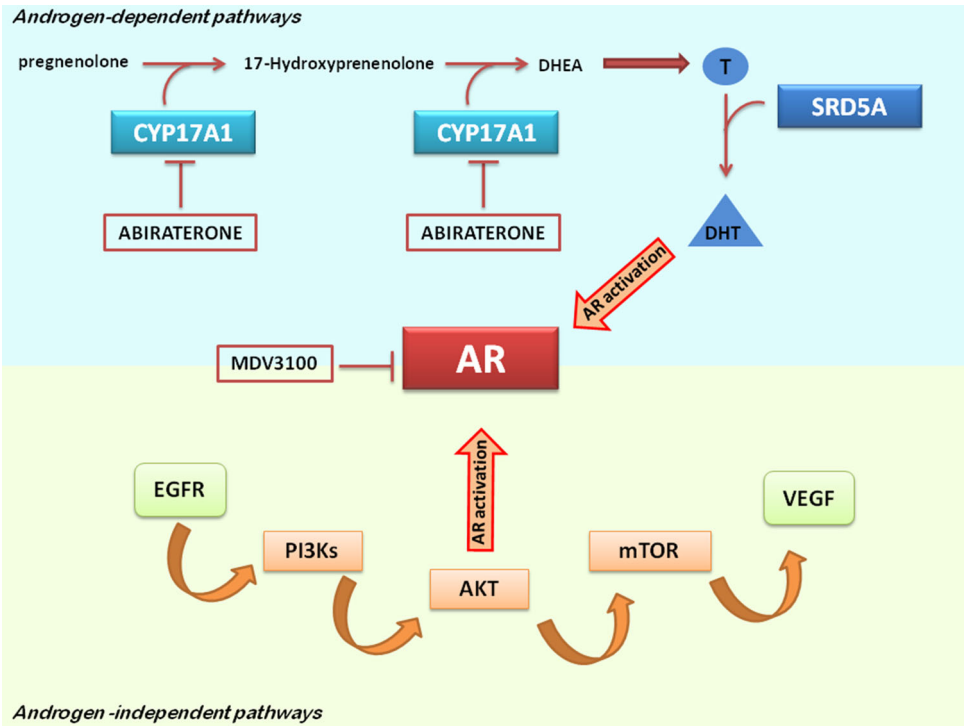

Fig. 1 AR activation by androgen-dependent or -independent pathways. CYP17A1 and SRD5A enzymes are involved in the testosterone biosynthesis, increasing the amount of DHT which binds with high affinity to AR thus activating its pathway. Androgen-independent PI3K/mTOR/Akt and angiongenetic pathways are connected: PI3K activation causes the phosphorylation of Akt, which leads AR and mTOR activation. PI3K could be also activated by an increased expression of epidermal growth factor receptor (EGFR), leading to AR activation and an increase in VEGF secretion (angiogenetic pathway). *Akt* protein kinase B, *AR* androgen receptor, *CYP17A1* cytochrome P450 17A1, *EGFR* epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *PI3K* phosphatidylinositol 3-kinase, *PCa* prostate cancer, *PFS* progression free survival, *SRD5A* 5-α reductase, *VEGF* vascular endothelial growth factor

highlighting the pathogenetic, prognostic, and predictive significance of gene polymorphisms. Studies were extracted using the following keywords: prostate cancer, SNPs, *AR*, *CYP17A1*, *SRD5A*, *PI3K/Akt/mTOR*, *EGFR*, *VEGF* genes, hormonal therapies, abiraterone and enzalutamide. All data were extracted independently by two reviewers (xxx and xxx). Articles were selected based on the description of prostate cancer patients; the statistical power; and the biological and clinical relevance.

3 Androgen-Dependent Pathways

3.1 Androgen Biosynthesis

Cytochrome P450 17A1 (CYP17A1) enzyme is expressed from a gene localized on chromosome 10 whose protein is present in the testes, adrenal glands, ovaries, placenta and tumor environments. CYP17A1 has a catalytic activity because it includes a heme prosthetic group with an iron-oxygen species so it is involved in two important reactions in the synthesis of sex steroid: its 17α-hydroxylase activity converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, which will then be converted to the testosterone precursors (dehydroepiandrosterone and androstenedione, respectively) by 17, 20-lyase activity [14]. *CYP17A1* polymorphisms may be associated with an increased risk of PCa and they have a potential role in heredo-familial prostate cancer patients [15].

The rs743572, located in 5′-UTR region, is the most studied polymorphism in association with risk of prostate cancer. However, in Wang et al. meta-analysis on different ethnic groups, the rs743572 increased the prostate cancer risk only in the Black population [16]. In the study by Hamada et al. the Caucasian androgen independent prostate cancer patients with the A2 allele genotype (−34T>C) had a significantly longer overall survival in respect to those patients with the common A1 allele. The presence of A2 allele reduced the risk of overall mortality of 26 % [17]. However, in another study still on Caucasian men, rs743572 did not seem to be correlated with survival of patients [18]. In the same study, Wright et al. showed the impact of another polymorphism. They observed a 56 % risk reduction in prostate cancer-specific mortality in subjects with the A allele in rs10883783, that is a 110 base-pair located in the intron-exon boundary [18]. However, Lindström et al. found no correlation between rs10883783 and prostate cancer-specific mortality of Caucasian patients [19]. The rs10883783 has been also analyzed in correlation with response to androgen deprivation therapy, but no correlation was found [20]. PCa risk, especially for aggressive prostate cancer, was found in correlation with rs6892 and rs2486758 [21]. The correlation between PCa risk and rs2486758 was confirmed by the meta-analysis of Wang et al. where also rs619824 was found in correlation [16]. In a recent study conducted by Lévesque et al, the rs2486758 and other 3 SNPs in *CYP17A1* (rs1004467, rs6162 and rs743572) were associated prostate cancer progression in patients who underwent prostatectomy. In particular, the rs6162 G allele was present at a high frequency, approximately 50 %, and associated with significant changes in plasma steroid levels [22].

All polymorphisms and their biological and clinical relevance are summarized in the Table 1.

3.2 5α-Reductase

Another important enzyme is SRD5A, which is the target of finasteride and dutasteride [23, 24]. SRD5A has a 5α-reductase activity and converts the testosterone to 5α-dihydrotestosterone (DHT), which is a potent AR ligand. 5α-reductase is an enzyme characterized by two isoenzymes, type I and II, but a higher expression of SRD5A2 than SRD5A1 is present in the prostate [25]. Both isoenzymes convert testosterone to DHT, its active form which stimulates the transcription of several genes with androgen-responsive elements [26].

SRD5A1 is located on chromosome 5p, and its expression is higher in castration-resistant prostate cancer [27, 28]. Moreover, the silencing of SRD5A1 inhibits the conversion of androstanedione to 5α-dione and the synthesis of DHT in CRPC [29]. *SRD5A1* polymorphisms were studied especially in correlation with PCa risk and with the functional activity of enzyme. In particular, the presence of AG or GG in respect to AA in rs1691053 polymorphism is linked to an increased risk of PCa [30]. Audet-Walsh et al. found an association between rs166050 with minor allele C and higher levels of dehydroepiandrosterone (DHEA) and androsterone (ADT). This SNP is also involved in higher risk of biochemical recurrence [31].

SRD5A2 is a gene located on chromosome 2p and involved in normal growth of prostate. Two single nucleotide polymorphisms in *SRD5A2* are correlated to prostate cancer: rs928285 (A49T) is an alanine to threonine substitution at codon 49 [32, 33] that results in a raise in 5α-reductase activity [34], whereas rs523349 (V89L) is a valine to leucine substitution at codon 89 that is associated with prostate cancer risk [35] and with decreased 5α-reductase activity in vitro and in vivo [36]. In Caucasian population, the substitution A49T is found to be correlated with reduced rates of biochemical disease-free survival [33]. Makridakis et al. identified an association between *SRD5A2* 49T and prostate cancer risk in Hispanic and African-American patients; African-American carriers

Table 1 Biological and clinical relevance of genes of interest polymorphisms in androgen-dependent pathways

Polymorphisms	Biological relevance	Clinical relevance	References
CYP17A1			
rs743572	Additional promoter site and higher protein expression	Association with PCa risk in Black population, progression and poor survival	[16, 17, 22, 23]
rs10883783	Splicing alteration	Risk reduction in PCa-specific mortality	[18]
rs2486758	Located in the promoter region. Unknown functional relevance	PCa risk and progression	[16, 22]
rs619824	Located in 3′-UTR. Transcriptional regulation	Higher risk of PCa	[16]
rs1004467	Relevance unknown	PCa progression	[22]
rs6162	Higher protein expression	PCa progression	[22]
rs6892	Located in 3′-UTR. Transcriptional upregulation in cell lines	Increased risk of prostate cancer especially for aggressive disease	[21]
SRD5A			
rs1691053	Unknown relevance	PCa risk	[30]
rs166050	Higher levels of DHEA and ADT	Higher biochemical recurrence risk	[31]
rs928285	Alanine to threonine substitution at codon 49. Higher enzyme activity	Association with high stage of PCa. Controversial association with PCa risk	[34, 38–41]
rs523349	Valine to Leucine substitution at codon 89. Decreased enzyme activity. Controversial PSA levels variation	Risk of PCa, metastases at diagnosis, biochemical recurrence	[31, 35–38, 42–44]
rs676033	Higher DHT, ADT and androstane-3β-17β-diol levels	Higher biochemical recurrence risk	[31, 47]
rs2208532	Lower circulating 3α-androstanediol-glucuronide	Higher biochemical recurrence risk	[31, 45]
rs4952197	Unknown relevance	Higher biochemical recurrence risk	[31]
rs12470143	Lower levels of 3a-diol-3-glucuronide	Lower biochemical recurrence risk	[31, 46]
rs10529926	Unknown relevance	PCa risk	[41]
AR			
rs4045402 $(CAG)_n$ repeats			
<21	Higher AR transcriptional activity	Higher risk of PCa in Caucasian, African and American patients and disease recurrence	[53–55]
>22	Lower AR transcriptional activity	Higher risk and association with PCa-specific mortality	[57, 58]
rs3138869 $(GGN)_n$ repeats	Higher AR activity levels in cell lines	Higher risk of PCa	[55, 59]
rs6152	Not direct effect on protein expression, structure, function	Higher risk of PCa in African-American subjects; lower risk of developing metastases in Caucasians	[62, 65]

AR androgen receptor, *CYP17A1* cytochrome P450 17A1, *PCa* prostate cancer, *SRD5A* 5-α reductase

have a 7.2-fold risk for clinically advanced disease and there is a 3.6-fold risk in Hispanic men [37]. However, Cicek et al. did not confirm an association between 49T allele and an increased risk of prostate cancer in African-American and also in Caucasian men [38]. In a recent meta-analysis, the 49T allele was found to be associated with risk in mixed populations and also in Caucasians [39]. Moreover, Ross et al. identified an association of 10 % between the 49T allele and all advanced prostate cancers in African-American and Latino men [40]; these data were in agreement with the meta-analysis of Li et al. that showed the correlation between 49T allele and the high stage of PCa [41].

Regarding the *SRD5A2* 89L allele, an increased risk of prostate cancer was observed in heterozygous patients with more aggressive disease or younger ages, in agreement with previous studies [35, 38, 42, 43]. In addition, Söderström et al. identified an association between V89L polymorphism in *SDR5A2* and metastases at the time of diagnosis [42]; Shibata et al. reported a correlation between rs523349 and a four-to sixfold risk of PSA increasing levels after surgery, but these results are in contrast with those found in the study by Nam et al. [35, 44]. The

rs523349 and others *SRD5A2* SNPs (rs2208532, rs4952197, rs676033) are associated with higher risk of biochemical recurrence, whereas *SRD5A2* rs12470143 is linked to lower risk of biochemical recurrence in Caucasians and Asians [31]. Moreover, rs2208532 and rs12470143 caused a change in 3α-androstanediol-glucuronide and 3a-diol-3-glucuronide levels, respectively [45, 46]. Patients carrying alleles AA in rs676033 polymorphism, which is in close genetic linkage with rs523349, have higher levels of DHT, androsterone and androstane-3β-17β-diol [47].

Lastly, the meta-analysis by Li et al. showed the correlation between PCa and rs10529926, that is a dinucleotide repeat on 3′-UTR region in *SRD5A2* gene [41].

3.3 Androgen Receptor

AR is the principle player in carcinogenesis, proliferation, differentiation and progression of prostate cancer, through its binding with circulating androgens, especially testosterone and DHT.

AR has a cytoplasmatic localization in the absence of ligand stimulation; the complex AR/ligand causes a protein conformational change and the nuclear translocation, which allows the transcriptional activity of its target genes [48–50]. *AR* gene is located on chromosome Xq11.2-q12 and is composed of an N-terminal domain (NTD) with transcriptional activation function, a central DNA binding domain (DBD) with two zinc-finger motifs, a short hinge region with the nuclear localization signal and a C-terminal domain (CTD) with ligand binding for testosterone and DHT and further transcriptional activation function [51, 52]. NTD contains two highly polymorphic trinucleotide repeat segments: $(CAG)_n$, rs4045402, and $(GGN)_n$, rs3138869. Even if these repeats are not single nucleotide polymorphisms, their involvement in prostate cancer is noteworthy. A meta-analysis revealed a 1.19-fold risk of prostate cancer in Caucasian, African and American men with shorter than 21 $(CAG)_n$ repeats [53]; indeed, shorter CAG repeats are identified in malignant prostate cells but not in adjacent normal tissue [54]. Additionally, Robins showed that shorter CAG repeats causes a higher AR transcriptional activity influencing prostate cancer recurrence; this suggested the involvement of shorter CAG repeats in response to drug targeting androgen biosynthesis such as abiraterone [55]. In reverse, some studies showed important data regarding longer CAG repeats: CAG longer than 22 repeats were associated with higher risk [56]; CAG repeats longer than 23 repeats and *AKR1C3* gene rs12529 polymorphism were associated with prostate cancer-specific mortality after ADT [57]. Lastly, Lindström et al. showed a strong association between longer CAG and higher plasma levels of testosterone and estradiol [58].

Regarding GGN repeats, their correlation with prostate cancer risk is controversial: while Chang et al. showed a higher risk in patients with shorter GGN repeats [59], others studies found no correlations [60, 61]. To our knowledge there is no evidence from the literature about the role of GGN repeats as a prognostic or predictive marker.

rs6152 (G1733A) is located between the trinucleotide repeats. The A allele is associated with a lower risk of developing metastases in Caucasian patients [62], whereas in African–American subjects is linked to increased prostate cancer risk [40].

4 Androgen-Independent Pathways

4.1 PI3K/Akt/mTOR

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is involved in tumorigenesis and therapy resistance in several cancers through its numerous functions such as regulation of cellular survival, differentiation, stem cell-like properties, growth and angiogenesis. In PCa, this pathway is principally implicated in disease progression [63, 64]. The activation of PI3K impacts on the Akt phosphorylation at two residues, resulting in Akt recruitment to the plasma membrane in its active form. Akt is a potent phosphatase that targets several proteins, such as FOXO transcription factors and serine threonine kinase mTOR. In prostate cancer, PI3K signaling represses the AR transcriptional activity and it is inhibited by PTEN, which is frequently lost [65]. Regarding the therapy resistance, the PI3K pathway seems to be implicated, in vitro, in resistance to docetaxel [66]. In a recent trial, the combination of PI3K and AR signaling inhibitors caused near-complete PCa response in human PCa xenografts, indicating that both pathways coordinately support survival [65]. Thus, according to this rationale, new studies combining AR and PI3K pathways inhibitors have been recently started [67]. Also mTOR inhibitors, such as temsirolimus and everolimus have been used in prostate cancer, but they showed a minimal activity as single agents [68, 69].

In a large study of 89 SNPs in *PI3K* genes (*PIK3C2B*, *PIK3AP1*, *PIK3C2A*, *PIK3CD*, and *PIK3R3*), the authors showed a significant association among rs7556371 G allele in *PIK3C2B*, prostate cancer risk, diagnosis of disease before 65 years and a family history in mixed population [70].

In Chinese population, Chen et al. showed significant associations between PCa risk and two SNPs, rs2295080 in *mTOR* and rs7254617 in *AKT2*. Moreover, the genotype combination of the rare alleles of these SNPs was strongly

Table 2 Biological and clinical relevance of genes of interest polymorphisms in androgen-independent pathways

Polymorphisms	Biological relevance	Clinical relevance	References
PI3K			
rs7556371	Protein expression alteration	Association with PCa risk, diagnosis of disease before 65 years and family history	[70]
mTOR			
rs2295080	Lower gene expression	Uncertain association with risk in Chinese population	[71, 72]
rs2536	Transcriptional alteration	PCa risk	[72]
rs1034528	Unknown relevance	PCa risk	[72]
Akt			
rs7254617	Unknown relevance	PCa risk	[67]
rs2125230	Unknown relevance	PCa aggressiveness	[69]
EGFR			
rs6964705	Unknown relevance	PCa aggressiveness in interaction with rs1401862 G/A in MMP16	[77]
rs11238349	Unknown relevance	PCa development	[78]
rs17172438	Unknown relevance	PCa development	[78]
rs984654	Unknown relevance	PCa development	[78]
rs11773818	Unknown relevance	PCa development	[78]
rs17172432	Unknown relevance	PCa development	[78]
VEGF			
rs1570360	Lower VEGF-A levels (AG/GG)	Shorter PFS, reduced PCa risk, risk of higher tumor grade for A allele	[80, 81]
rs201096	Higher VEGF levels	PCa risk, highest histological grade for allele C	[81]

Akt protein kinase B, *EGFR* epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *PI3K* phosphatidylinositol 3-kinase, *PCa* prostate cancer, *PFS* progression free survival, *VEGF* vascular endothelial growth factor

associated with advanced stage of PCa [71]. On the contrary, Li et al. found that the rare allele of *mTOR* rs2295080 is associated with a decreased risk. However, they also found *mTOR* rs2536 CT/CC and rs1034528 CG/CC genotypes associated with PCa risk [72].

In a study by Lavender et al, 172 SNPs in apoptotic genes were analyzed for a correlation with PCa risk and aggressiveness. They detected a modest synergic interaction between rs2125230 in *AKT3* and rs571715 in *PRKCQ* (pro-apoptotic gene) with PCa aggressiveness [73], but no other associations were found.

All polymorphisms and their biological and clinical relevance are summarized in the Table 2.

4.2 Epidermal Growth Factor Receptor (EGFR)

Activation of the EGFR is involved in tumor growth, proliferation, angiogenesis and inhibition of apoptosis. An inhibition strategy targeting EGFR includes a monoclonal antibody that blocks the ligand binding domain and the intracellular tyrosine kinase domain. Gefinitinib and enrotinib inhibit the phosphorylation of EGFR tyrosine kinase that blocks tumor angiogenesis and stimulates apoptosis [74]. SNPs in genes involved in the angiogenesis process may alter gene expression, regulating the efficacy and inhibiting tumor growth in animal models [75, 76].

Lin and coworkers analyzed 1151 prostate cancer patients and 2651 SNPs in genes implicated in angiogenesis: they found a SNP-SNP interaction in three gene pairs (*MMP16*+*ROBO1*, *MMP16*+*CSF1* and *MMP16*+*EGFR*) in association with prostate cancer aggressiveness. They hypothesized a network with EGFR at the core of SNP interactions, especially for the SNP–SNP rs1401862 G/A+rs6964705 C/A in *MMP16*+*EGFR*, but no evidence was found for gene expression alteration due to these polymorphisms [77].

Another study showed that four genes (*EGFR*, *ERBB2*, *PTK2* and *RAF1*) characterized by five SNPs (rs11238349 A/G, rs17172438, rs984654, rs11773818, and rs17172432) might be pivotal factors in the development of PCa [78].

4.3 Vascular Endothelial Growth Factor (VEGF)

VEGF is involved in the regulation of angiogenesis, development, and metastasis of different cancers. In a meta-analysis, Chen et al. analyzed three polymorphisms in VEGF (rs833061; rs3025039; rs2010963) in 5200 prostate cancer cases and the same number of controls but they

found no association with risk of prostate cancer [79]. Interestingly, downregulated VEGF transcription has been associated with the rs1570360 AA haplotype, suggesting that tumors with AG/GG genetic background may produce higher VEGF-A levels after standard chemotherapy administration [80]. The rs1570360 AA haplotype is negatively associated with PCa risk, but the A allele appeared to be associated with an increased risk of higher tumor grade. In the same study, a significant increased risk of prostate cancer was associated with the rs201096 GC+CC combined haplotypes and the C allele was associated with the highest histological grade [81].

4.4 Other Metabolic Pathways

Estrogen as well as androgen may play an important role in the carcinogenesis of prostate cells. The estrogens mediate their action through estrogen receptor α (ESR1) and β (ESR2) with both carcinogenic and anti-carcinogenic effects on the prostate, contributing to cellular proliferation, inflammation, and malignant carcinogenesis [82]. Genetic association studies examining estrogen pathway genes in relation to prostate cancer risk showed that common genetic polymorphisms in *ESR1* (estradiol-binding domain of the estrogen receptor gene) were associated with prostate cancer susceptibility [83, 84] and, recently, also to the response to novel hormonal therapy [85]. Agarwal et al. studied 785 SNPs from the Illumina OmniExpress genotyping platform within the boundaries of 60 genes reported to be involved in the metabolic pathways [85]. They investigated the association between these SNPs and time to treatment failure (TTF) in 49 Caucasian men with mCRPC undergoing treatment with abiraterone. Five SNPs in *ESR1*, and five SNPs in *PRMT8* (protein arginine methyl transferase 8 gene), an active enzyme involved into different metabolic pathways, were related to TTF on treatment with abiraterone ($p < 0.005$).

Recently, two meta-analyses [86, 87] confirmed the association between *ESR1* genetic variation and cancer risk and identified *XbaI* (A>G) polymorphism as a potential prognostic factor for prostate cancer.

Currently, metabolic alterations, such as hyperinsulinemia, increased levels of insulin growth factor-1 (IGF-1), and insulin resistance are considered to be on the basis of development and progression of many tumors, including prostate cancer [88]. Some authors displayed the role of the IGF signaling pathway in prostate cancer survival also with the evaluation of 530 SNPs in 26 *IGF* pathway-related genes and the correlation with prostate cancer mortality. IGF2-AS and SSTR2 were showed to be the main contributors of outcome of prostate cancer patients [89].

In addition, the polymorphisms in the vitamin D and E metabolism genes, especially vitamin D receptor gene *FokI* and *BsmI* polymorphisms and rs964184 near budding-site selection protein 13, zinc finger protein 259, and apolipoprotein A5 on 11q23.3, have been hypothesized to alter the risk of prostate cancer; however, results are very conflicting [90, 91].

5 Alternative Pathways Involved in the Resistance Mechanisms to Treatment

Currently, the identification of SNPs as biomarkers able to predict sensitivity and/or resistance to therapy becomes an interesting field of translational research for CRPC. However, researchers must always keep in mind that gene polymorphisms should be interpreted with caution in prostate cancer because there is no clear biological mechanism through which different polymorphisms could interact with each other regulating androgen axis and inducing different resistance mechanisms. The development of CRPC represents a complex network of different activated pathways, involving mainly AR axis alterations, such as *AR* amplifications, mutations, AR splicing variants and others genes related to this pathway, but also androgen-independent mechanisms. Among these alternative pathways related to treatment resistance in CRPC patients, the onset of neuroendocrine differentiation (NED) is relatively frequent in various stages of PCa, particularly in CRPC [92]. It is usually secondary to androgen deprivation therapy (ADT) and associated with a more aggressive PCa clinical behavior and an unfavorable prognosis. In recent times, with the introduction of novel hormonal drugs, such as abiraterone and enzalutamide, the identification of NED is very important. Many studies were focusing attention on the development of NED in association with epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs), responsible for a complex interaction among ADT, hormone independence, tumor progression, response to novel hormonal drugs, such as abiraterone and enzalutamide [93–95]. Chromogranin A (CgA), an acidic glycoprotein expressed by neuroendocrine cells, represents the most sensitive marker and is most frequently used for detecting NED either at the tissue level or in the general circulation. A study showed men with the GG genotype CgA for Glu264Asp polymorphism were at 2.05 times higher risk for prostate cancer than men with the CC genotype. Consequently, not only the expression of CgA, but also the presence of SNP *CgA* may have a clinical significance in prostate cancer [96].

Accumulating evidence indicates that there is a complex interaction among EMT [97, 98], presence of CSCs [99, 100] and NED that could lead to the development of prostate cancer and progression to CRPC. So the identification of gene polymorphism also involving these aspects

of CRPC pathogenesis could be useful for better understanding the biology of prostate cancer. In fact, the Kallikrein-related peptidase, KLK4, a protein involved in EMT [101], has been shown to be significantly overexpressed in prostate tumors through its role in prostate cancer progression and metastases to bone. Genetic variation in the *KLK4* locus could play a role in prostate cancer predisposition. Indeed, assessment of 61 SNPs in the *KLK4* locus in about 1300 prostate cancer cases and 1300 male controls for associations with prostate cancer risk and/or prostate tumor aggressiveness (Gleason score <7 versus ≥ 7) revealed seven SNPs to be associated with a decreased risk of prostate cancer [102]. Moreover, a recent study showed the association between rs2735839 in *KLK3* gene and PCa aggressiveness (Gleason score ≥ 8) [103].

In addition, emerging evidence suggests that −160C/A polymorphism of E-cadherin gene, a transmembrane adhesion glycoprotein, may confer a risk to prostate cancer [104].

Other proteins involved in epithelial cell-cell adhesion are Wnt and axis inhibition protein 2 (Axin2). The results of a recent study revealed a higher incidence of PCa in the subjects with the homozygous GG genotype and a reduced cancer incidence in the patients with the GA genotype of the rs2240308 SNP (G/A) in the *Axin2* gene [105].

The inflammation represents one aspect of NED which, lately, has also been related to the incidence and clinical outcome in prostate cancer patients. Some studies revealed the association of SNPs involved in immune response, including IL10 and other cytokines, production and detoxification of reactive oxygen species, and repair of oxidative DNA damage with risk of recurrence, independently from pathologic prognostic factors. These studies supported the evidence that genetic variation in immune response could influence prostate cancer recurrence risk and SNPs belonging to these pathways may provide additional prognostic information [106, 107].

6 Conclusions

Prostate cancer is a deadly disease often with poor prognosis, especially in castration-resistant status. However, comprehensive understanding about its pathogenesis remains insufficient. In this review, we aimed to find potential novel markers for the treatment of prostate cancer and explore some of the regulatory pathways underlying prostate cancer progression and therapeutic resistance.

Recent genome-wide association studies (GWAS) have identified several genetic variants as being associated with prostate cancer. Genetic alterations in the androgen metabolism pathway are expected to alter hormonal homeostasis and likely influence PCa development and progression. Other genetic variations involving androgen-independent and other alternative pathways could also act as pathogenetic, prognostic or predictive factors in prostate cancer patients. However, the association between SNPs and prostate cancer is still controversial. Although it has been suggested that some polymorphisms are associated with prostate cancer risk and survival, it is not clear how SNPs affect clinical variables of prostate tumor such as tumor size, prostate-specific antigen (PSA) levels, or Gleason score. In any case, many SNPs involve therapeutic targets, such as CYP17A1 that is also considered an important factor for prostate cancer progression.

In addition, the 5α-reductase, enzyme encoded by the *SRD5A1* and *SRD5A2* genes, has been shown a positive association with prostate cancer outcome in terms of biochemical recurrence. The specific blockade of SRD5A1/A2 with dutasteride or finasteride reduced the incidence of clinically localized prostate cancer and so the identification of SNPs polymorphism in these genes should be extremely interesting also with an important impact on the management of early stages of prostate tumor.

Consequently, the interest of translational research in genetic variations in all tumors, such as prostate cancer, is growing enormously, particularly because several SNPs represent genetic variations of important therapeutic targets and so could provide possible future development of biomarkers. Advances in knowledge of biomarkers in prostate tumor and biomarker-driven therapy may permit to tailor therapeutic algorithm, especially in equivocal scenarios. This could increase treatment benefit, minimize the incidence of adverse events and reduce costs of inadequate therapies.

In prostate cancer, SNPs could become circulating non-invasive biomarkers with an additional prognostic and predictive value that likely may influence the classic factors of prostate disease, especially those with heterogeneous clinical behavior.

In conclusion, the identification of many gene polymorphisms in different pathways associated with prostate cancer could improve early detection, allow for selective chemoprevention and provide further insights into prostate tumor mechanisms. Literature data showed that SNPs could impact on gene and protein expression and on prostate cancer risk, aggressiveness and chemo-response. However, further validation is still to be performed also for other novel hormonal and non-hormonal drugs that are changing management of these patients in recent years. The complexity of biological pathways involved in prostate carcinogenesis and progression reinforces the necessity for larger cohort studies using more and more innovative techniques to develop a suitable therapeutic strategy for CRPC patients.

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Compliance with Ethical Standards

Conflict of interest SS, VC, GG, DC, VC, UD have no conflict of interest to report.

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