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Mini-review

Molecular mechanisms and genetic alterations in prostate cancer: From diagnosis to targeted therapy

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ABSTRACT

Prostate cancer remains one of the most lethal malignancies among men worldwide. Although the primary tumor can be successfully managed by surgery and radiotherapy, advanced metastatic carcinoma requires better therapeutic approaches. In this context, a deeper understanding of the molecular mechanisms that underlie the initiation and progression of this disease is urgently needed, leading to the identification of new diagnostic/prognostic markers and the development of more effective treatments. Herein, the current state of knowledge of prostate cancer genetic alterations is discussed, with a focus on their potential in tumor detection and staging as well as in the screening of novel therapeutics.

1. Introduction

At diagnosis, most PCas are localized and amenable to surgical or radiation treatment [1]. However, almost 40% of patients experience disease progression; at this point, where tumor growth depends on testosterone and dihydrotestosterone (DHT), hormonal therapy directed against androgen signaling represents the treatment of choice. This approach involves the use of GnRH agonists/antagonists, generally given in combination with anti-androgens [1,2]. However, after optimal initial results, recurrence is observed in most patients within about three years, and the tumor reaches a condition of castration resistance (CRPC) [1,2]. The therapeutic options for CRPC patients are still limited, since novel strategies with abiraterone acetate, enzalutamide and chemotherapy provide a short progression-free survival [1]. In this setting, many efforts have been made to understand the molecular mechanisms underlying tumor initiation and progression, in order to identify new diagnostic/prognostic markers as well as promising targets for cancer treatment. This review aims at providing an overview of the molecular and genetic changes associated with PCa and at discussing their role in facilitating the search for novel drugs.

2. Molecular mechanisms and genetic alterations in prostate cancer: diagnostic and prognostic value

The histological evaluation of PCa is crucial to assess tumor staging and provide a prognostic projection. Interestingly, several gene mutations have been shown to correlate with PCa onset and evolution, offering fundamental information about tumor aggressiveness and therapy response. In particular, these alterations are known to affect androgen signaling, DNA repair systems, oncogenes and oncosuppressors, prostate-specific antigens and transcription factors (Fig. 1).

2.1. Androgen receptor

Numerous studies have pointed out that PCa initiation and progression are mediated by the androgen receptor (AR) [3]. This protein is encoded by the corresponding sequence at Xq11-12 and is composed of a N-terminal regulatory domain, a DNA-binding domain (DBD), a ligand-binding domain (LBD) and a C-terminal domain. When androgenic hormones are absent, it is assembled with chaperone proteins in the cytoplasm of the cell. After binding to its ligands, it translocates into the nucleus, where it homodimerizes through the interplays of specific motifs present in the DBD and LBD. In the nucleus, the activated receptor identifies cognate DNA response elements in regulatory regions of androgen target genes. Then, it engages distinct cofactors (*i.e.* FOXA1 and GATA proteins) and coregulators (*e.g.* the p160 coactivator family, comprising SRC1, SRC2, and SRC3) to produce a transcriptionally active complex which promotes the expression of downstream targets [3]. Gene down-regulation after interplay with corepressors has also been observed but still needs to be elucidated [4].

As mentioned above, PCa often progresses towards an androgen-independent stage [2]. One of the main events responsible for this change is represented by the upregulation of AR in cancer cells. In par-

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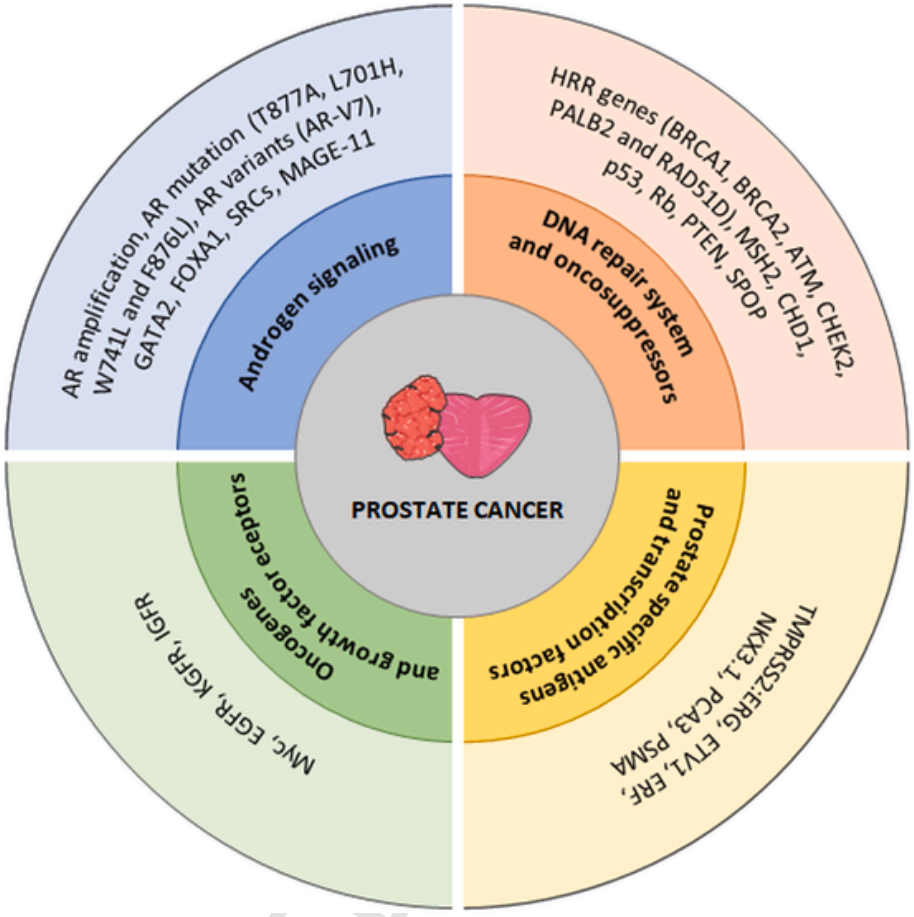

Fig. 1. Molecular mechanisms and genetic alterations in prostate cancer (PCa). The main gene mutations observed in PCa involve: androgen signaling; DNA repair system and oncosuppressors; prostate-specific antigens and transcription factors; oncogenes and growth factor receptors.

ticular, it has been reported that 28% of tumors unresponsive to hormonal therapy are characterized by AR overexpression due to gene amplification [3]. These findings have been further validated in a more recent study, evidencing that AR is upregulated in more than 60% of metastatic PCas [5]. Intriguingly, the concomitant amplification of an enhancer region of the AR has been frequently observed in CRPCs [5,6].

Another mechanism underlying the emergence of castration resistance is ligand promiscuity, caused by *AR* gene mutations that result into amino acid substitutions in the LBD, eventually culminating in reduced specificity/selectivity for ligands: the most frequent of them are *T877A*, *L701H*, *W741L* and *F876L*. These mutant proteins bind to other steroid hormones, such as glucocorticoids, estrogens and progesterone, that activate the hormone cascade and favor PCa progression [3]. *AR* point mutations are observed in 15–30% of CRPCs, where they promote resistance to both first- and second-generation anti-androgens [3]. Remarkably, they can be detected not only by the analysis of tumor specimens but also of circulating DNA (ctDNA) [7]. Indeed, 22% of *AR* mutants and 30% of *AR* gene amplifications have been recently found in 514 CRPC patients through liquid biopsies [8].

AR activation through ligand-independent signaling is the third process that leads to androgen independence [9]. It has been demonstrated that ligands for tyrosine kinase receptors, including epidermal growth factor (EGF), keratinocyte growth factor (KGF) and insulin-like growth-factor-1 (IGF-1), can trigger the AR via the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. The AR can also be activated via interactions with other pathways, including the Src and ERK cascades [9]. In addition, AR activation can be induced by binding to long non-coding RNAs (lncRNAs), such as PRNCR1 and PCGEM1 [10].

More than 20 AR variants lacking the LBD have been recently discovered: the AR NTD is constitutively active in the absence of the LBD and can stimulate castration-resistant growth [3]. *AR-V1* and *AR-V7* are truncated at the end of exon 3 and are composed of 19 amino acids from cryptic exon 1 and of 16 amino acids from cryptic exon 3, respectively; *AR-V9* is also composed of 16 amino acids from cryptic exon 3 but is truncated at the end of exon 5; *AR-V657* has exons 5–7 spliced out and contains only a small LBD portion [11]. Among these variants, AR-V7 is the most widely studied, with a 20-fold higher expression in CRPC compared to hormone-naïve PCa. In particular, it correlates with an increased risk of tumor recurrence and reduced overall survival [11,12]. As in the case of *AR* mutations, recent evidence has highlighted the clinical utility of AR-V7 detection in ct-DNA as a biomarker for CRPC treatment [13]. Similarly, analysis of AR-V7 mRNA levels in circulating tumor cells (CTCs) may represent a useful tool for the choice of the proper therapeutic strategy [14].

As mentioned above, AR transcriptional activity requires the recruitment and cooperation of transcription factors. Interestingly, it has been demonstrated that GATA2 plays a key role in driving both castration and chemotherapy resistance, modulating the molecular pathways associated not only to the wild type receptor but also to its variants [15]. Moreover, it regulates a core subset of clinically relevant genes in an AR-independent manner; among them, IGF-2 appears to be crucially involved in the development of limited responsiveness to docetaxel [15]. Similarly, FOXA1 has been reported to drive PCa aggressiveness, shaping AR signaling and promoting epithelial-to-mesenchymal transition (EMT) without interacting with the receptor [16]. In PCa, mutations converge onto the coding sequence and *cis*-regulatory elements (CREs) of FOXA1, resulting in functional alterations; parallelly, FOXA1

activity can be modulated post-translationally, for instance through LSD1-mediated protein demethylation [16].

The coregulator family of SRCs mediate the complexation of AR enhancer sequences and the promoter region of androgen target genes, thus promoting AR transcriptional activity. SRC levels are positively associated with PCa progression and relapse [3]. In particular, SRC2 seems to interact with AR to enhance tumor sensitivity to androgens and to facilitate the ligand-independent transcription of AR target genes [3]. Likewise, the AR coactivator melanoma antigen gene protein-A11 (MAGE-11) is hypomethylated and thus upregulated in CRPC, contributing to the improved AR signaling observed at this stage [3].

2.2. Homologous recombination repair

Failures in repairing DNA damage and fixing DNA replication stress via homologous recombination repair (HRR) are followed by genomic instability and contribute to tumor onset. Germline and somatic mutations in several HRR genes, such as *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2* and *RAD51D*, have been found to correlate with PCa recurrence and therapy resistance [17]. In particular, *BRCA2* mutations are present in 2–12% of PCas and confer an 8.6–32-fold increased risk of tumor development at younger age (<65 years) [18,19]. *BRCA1* also correlates with higher risk (3.5-fold) of sporadic PCa, although germline mutations in this gene have been found in less than 1% of patients [20]. *ATM* mutations/deletions characterize 8% of tumors [19]. Remarkably, inherited HRR gene mutations have been observed in almost 12% of patients with metastatic carcinoma: 53% *BRCA2*, 1.9% *CHEK2*, 1.6% *ATM*, 0.9% *BRCA1*, 0.4% *PALB2* and *RAD51D* [17]. It should be noted that the global incidence of genetic alterations in DNA repair is significantly higher in invasive (11.8%) than in primary (4.6%) PCas [17].

Twelve percent of advanced PCas have been recently reported to be characterized by mismatch repair gene mutations and microsatellite instability [21]. In particular, this subset of tumors exhibits *MSH2* structural rearrangements [21]. Loss of this gene has also been found in 1.2% of localized PCas; however, it appears to be more frequent in carcinomas with a Gleason score equal to 5 (8% vs 0.4%) [22]. Intriguingly, *MSH2* loss-bearing cancers show a higher density of infiltrating $CD8^+$ lymphocytes [22]. Likewise, PCas with mismatch repair mutational signatures overexpress different immune transcripts, such as CD200R1, BTLA, PD-L1, PD-L2, ADORA2A, PIK3CG and TIGIT [23]. In terms of drug susceptibility, a recent retrospective study has highlighted that patients displaying mismatch repair mutations better respond to initial androgen restriction therapy (67-month progression-free survival) and to abiraterone acetatate/enzalutamide treatment (26-month progression-free survival) [24].

2.3. CHD1

The *CHD1* gene encodes the chromo-domain helicase DNA-binding protein 1, which is involved in several biological processes, including chromatin remodeling, recruitment of HRR proteins to double-strand DNA breaks and AR-dependent transcriptional control. Five-ten percent of PCas display loss of *CHD1*, which is usually associated with *SPOP* mutations and *MAP3K7* and *PTEN* deletion, while inversely correlating with *TMPRSS2:ERG* gene fusion [25,26]. Notably, *CDH1* loss appears to sensitize tumor cells to DNA damage and PARP inhibition in both preclinical and clinical settings [27].

2.4. p53

p53 is one of the most commonly mutated genes in tumors. It is known as "the guardian of genome", due to its ability to induce S phase cell cycle arrest and subsequent apoptosis in human cells. In early PCa, a relatively low incidence (10–20%) of *p53* gene mutations has been found, while it increases in the late phases of disease (42%), correlating with high Gleason score, reduced survival and metastases to the bones [28–30]. In particular, experiments performed on different PCa mouse models have recently elucidated the role of *p53* in tumor evolution: on one side, mutations in this gene transiently potentiate androgen-independent cell growth and facilitate the occurrence of genome instability [31,32]; on the other side, they cooperate with *RB1* and/or *PTEN* loss in promoting lineage plasticity, metastasis and antiandrogen resistance [33]. Based on this evidence, p53 has emerged as a promising stratification factor. Indeed, in a cohort of 168 CRPC patients *p53* mutational status allowed to predict abiraterone acetate or enzalutamide outcomes [34]. Similarly, immunohistochemistry conducted on localized PCa specimens has evidenced a positive correlation between the presence of *p53* abnormalities and biochemical/metastatic relapse and tumor-associated mortality [35].

It is important to highlight that the association between *p53* alterations and tumor-infiltrating T-cell density has been recently explored in surgically-excised primary PCas, by exploiting three independent tissue microarray sets, namely a group of tumors from grade-matched patients of European American or African American ancestry, a retrospective case-cohort of intermediate- and high-risk patients enriched for adverse outcomes and a group of carcinomas with Gleason score 5. In a pooled analysis of all sets, adjusted for clinicopathological variables, $CD3^+$ and $CD8^+$, but not FOXP3+, T-cell densities resulted to be significantly higher in cancers with p53 nuclear accumulation than in those without. This might be relevant for future immunotherapy studies on PCa [36].

2.5. Rb

Retinoblastoma protein (Rb) suppresses DNA duplication, blocking cell cycle progression from G1 to S phase. *Rb* mutations frequently occur in both local and advanced PCas, with almost 50% of them found in metastatic CRPCs [32,37]. In particular, it has been demonstrated that *Rb* loss does not affect PCa growth; nonetheless, upon castration, Rb-null cells are more proliferative, probably due to increased AR expression [38]. Moreover, alterations in *Rb* gene have been shown to drive cytoskeleton reorganization, EMT and migration in various *in vitro* and *in vivo* PCa models, promoting the tumor cell spread induced by *PTEN* mutation [31,32,39]. Additional loss of *p53* has been found to confer anti-androgen resistance [32,39].

2.6. PTEN

5–30% of localized PCas and 30–60% of advanced carcinomas are characterized by *phosphatase and tensin homolog* (*PTEN*) mutations [40]. This gene encodes a phospholipid phosphatase that suppresses the PI3K/Akt/mTOR pathway, crucially involved in cell proliferation [40]. Particularly, loss of *PTEN*, together with *TMPRSS:ERG* fusion, *c-myc* upregulation and *NKX3.1* alteration, promotes prostate tumorigenesis [41–44]. Furthermore, it suppresses androgen-responsive gene expression by directly downregulating endogenous AR levels and modulating their transcription factor activity [45]. In terms of prognosis, *PTEN* deletion correlates with reduced response to anti-androgens, limited progression-free survival and high risk of relapse and metastases [40].

In addition to *PTEN* mutations, loss of *MAGI2* gene, encoding for a PTEN-interacting protein, has been detected in PCa [46]. This genetic signature correlates with NKX3.1 overexpression and Akt phosphorylation. Intriguingly, MAGI2 levels are higher in high-grade prostatic intraepithelial neoplasia (HGPIN) than in normal or benign prostatic tissue, while decreasing again during PCa progression [47,48]. In the clinical context, MAGI2 reduction is predictive of tumor relapse [48].

It should be emphasized that abnormalities in other members of the PI3K cascade, including *PI3KCA* (13%), *PIK3R1* (6%), *NF2* (3%), *AKT1* (1.5%), and *NF1* (1.5%), are commonly found in PCa [49]. In advanced tumors, PI3K signaling mutations correlate with *p53* and *AR* alter-

ations, thereby promoting castration resistance after androgen deprivation therapy [50,51]. For these reasons, PI3K/Akt/mTOR inhibitors are under extensive study for the treatment of CRPC [52].

2.7. SPOP

Speckle-type PO2 protein (SPOP) is a tumor suppressor protein and substrate adaptor of the cullin 3-RING-ubiquitin ligase (CUL3). *SPOP* mutations prevent substrate binding and ubiquitination, resulting in the upregulation of oncogenic targets. Among them, c-myc, DEK and TRIM24 have been found to be stabilized in *SPOP*-mutant cells, leading to tumor growth and invasion. Moreover, a dual link between SPOP and AR pathway has been recently disclosed: on one hand, SPOP inactivation disrupts the degradation of the AR coactivator SRC3 and of its suppressive activity on AR cascade [53,54]; on the other hand, *SPOP* mutants cannot bind to AR and mediate its elimination [55].

SPOP mutations identify a subclass of PCas with poor prognosis [56]. They define the 6–15% of total tumors, although a recent report has shown that more than 35% of malignancies exhibit loss of this gene [56,57]. Intriguingly, in early PCas an inverse relationship between *SPOP* and *PTEN* mutations has been observed, while they generally co-occur in advanced carcinomas [56]. In addition, *SPOP*-mutated PCas frequently exhibit *CDH1* loss and are highly responsive to abiraterone acetate treatment [58]. However, *SPOP* alterations significantly affect BET protein stability, promoting resistance to BET inhibition [59]. Interestingly, recent findings suggest that *SPOP*-mutant tumor cells are unable to degrade PD-L1 through poly-ubiquitination, supporting the use of immune checkpoint inhibitors for the management of these carcinomas [60].

2.8. Myc

The *myc* family is composed of three genes: *c-myc*, *l-myc (MYCL)* and *n-myc (MYCN)*. *C-myc* amplification and overexpression have been found in both early and metastatic PCas; such upregulation generally correlates with high Gleason grade and poor prognosis [61]. Remarkably, *MX11*, a c-myc upstream inhibitor, is also frequently mutated in PCa [62]. *MYCL* and *MYCN* are differentially modulated based on clinical stage: while *MYCL* amplification is usually detected in premalignant lesions and primary tumors, *MYCN* is overexpressed in 40% of aggressive CRPCs [63,64].

Several molecular mechanisms seem to be responsible for myc upregulation in PCa. The first of them is protein stabilization, apparently related to myc ability to directly interact with Rho-associated kinase 1 (ROCK1): this results in protein phosphorylation and activation of its transcriptional activity [65]. Furthermore, IRE1α-XBP1-mediated endoplasmic reticulum (ER) stress, a pro-survival process activated in case of limited oxygen and nutrient supply, promotes PCa growth via c-myc signaling, indicating that its targeting may offer novel therapeutic approaches [66]. Finally, in myc-driven tumors, enhancer of zeste homolog 2 (EZH2) histone methyltransferase is overexpressed and downregulates interferon-gamma receptor 1 (IFNGR1), with consequent inhibition of apoptosis; in this context, the combination of EZH2 and IFNG targeted therapies might be promising in the management of PCa [67].

Data about the interplay between myc and AR signaling are still controversial: while Barfold et al. have shown that myc antagonizes AR transcriptional activity via co-occupation of several AR-binding enhancer-like sites, it has been recently proposed that this oncogene can stabilize and upregulate both the full-length hormone receptor and its variants [68,69]. Further studies are needed to verify the utility of targeting myc as an adjuvant to AR-directed therapy.

2.9. TMPRSS2:ERG

Transmembrane serine protease 2 (*TMPRS2*) is an androgen-responsive gene encoding a prostate-specific cell-surface serine protease, whose function relies on gene fusion with ETS transcription factors, such as ERG. Notably, the *TMPRSS2:ERG* gene fusion is present in the majority of both primary and metastatic PCas, leading to an ERG upregulation-related increase in tumor growth. In this setting, TMPRSS2:ERG transcripts have recently emerged as promising urinary biomarkers in PCa [70]. Many studies have also investigated the prognostic value of TMPRSS2:ERG in PCa patients with discording results: while some of them have not found any correlation between the expression of this fusion gene and PCa recurrence and mortality, other studies have shown that ERG hyperactivation is associated with a poor prognosis [71–73]. It should be underlined that AR activation triggers *TMPRSS23:ERG* rearrangement; according to this evidence, *TMPRSS2:ERG* fusions are more frequent in young patients, known to display increased AR levels [74]. On the other hand, TMPRSS2:ERG expression leads to the activation of several pathways crucially involved in oncogenesis, including EZH2 and myc [42,75,76]. In this regard, it is important to evidence that PCas characterized by *PTEN* loss exhibit *TMPRSS2:ERG* fusion, while not all of the *TMPSS2:ERG*-positive carcinomas display *PTEN* deletion, indicating that the latter generally occurs after *ERG* rearrangements [77,78].

It has been recently reported that ERG overexpression in *PTEN/p53*-mutated PCa-bearing mice induces AR re-expression, Rb hypophosphorylation and downregulation of mesenchymal regulators, thus maintaining anti-androgen sensitivity and decreasing tumor plasticity [79]. This evidence indicates that ERG fusion might represent a promising biomarker to define the optimal therapeutic approach for treating PCas with *PTEN/p53* alterations [80].

TMPRSS2:ERG-positive PCas are endowed with specific hormonal features. Indeed, patients affected by *TMPRS2:ERG* fusion display increased androgen-mediated gene expression and altered intratumoral androgen metabolism with respect to *TMPRS2:ERG*-negative subjects, resulting in decreased testosterone levels and enhanced DHT/testosterone ratio [81]. Thereby, these men could benefit from inhibition of DHT biosynthesis.

ETV1 is another member of the ETS transcription family, which fuses not only with *TMPRSS2* but also with other androgen-responsive genes, such as *SCL45A3* and *ACSL3*. This triggers a tumorigenic program, often accompanied by *PTEN* loss [82]. In particular, subjects showing high *ETV1* levels commonly develop metastases and have a poor prognosis, with even inferior disease-free survival in case of concomitant *PTEN* mutation [82].

Notably, 2–4% of PCas exhibit mutations in the ETS transcriptional repressor *ERF*, irrespective of ERG upregulation [83]. These alterations lead to ERF loss, which – similar to *ERG* gain – results in AR pathway stimulation, often in cooperation with *PTEN* deletion [83]. Nevertheless, since ERF abnormalities are significantly rarer than ERG activation, it is suggested that ERG may have further gain-of-function activities supporting its tumorigenic ability [84].

2.10. NKX3.1

Homeobox protein NKX3.1 is a transcription factor that downregulates prostate-specific antigen (PSA) after binding to DNA. Deletion or loss of function of this gene occur early in PCa, characterizing almost 5% of localized malignancies, 20% of advanced carcinomas, 35% of castration-resistant tumors and 80% of metastases [85,86]. Copy loss of NKX3.1 is an interesting marker of poor prognosis after surgery or radiation therapy; in combination with myc activation, the prognostic value of both proteins for tumor recurrence is even higher [87,88]. Additionally, NKX3.1 directly regulates the expression of AR, p53 and Akt [89,90].

2.11. PCA3

Prostate cancer antigen 3 (PCA3) is a lncRNA transcribed from an intronic region at the long arm of human chromosome 9q21-22 [91]. It has been reported to promote PCa cell growth and survival, by regulating AR signaling through upregulation of several androgen responsive genes, including PSA, PMEPA1, FGF8, GREB1, NDRG1 and CdKs. In addition, it can control the expression of various EMT markers, such as E-cadherin, Twist, Snail and cytokeratin-18, and miRNAs, namely miR-1261 and miR-218–5p [91].

Since its discovery, PCA3 has gained great interest from clinicians due to its overexpression in PCa. In particular, PCA3 molecular tests have been proposed, based on its detection by quantitative real-time PCR (qPCR) in body fluids and urinary sediments after digital rectal examination [92,93]. In this context, PCA3 has been recently approved as an auxiliary diagnostic biomarker for PCa [91]. On the other hand, the potential use of PCA3 as a prognostic biomarker is still under investigation, with ongoing studies showing contradictory results in linking its expression with tumor aggressiveness [91].

2.12. PSMA

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein, whose levels gradually increase from normal epithelium to PCa [94]. In particular, its expression inversely correlates with androgen production, with enhanced synthesis detected in castration-resistant tumors [94]. Interestingly, the potential of PSMA in positron emission tomography-computed tomography (PET-CT) has been recently assessed in a prospective study conducted on 314 patients with recurring PCa, highlighting that 68Ga-PSMA PET-CT displays a higher diagnostic yield and a better safety profile than 18F-choline PET-CT [95].

3. Molecular mechanisms and genetic alterations in prostate cancer: therapeutic implications

As illustrated above, various therapeutic options exist for men diagnosed with PCa (Fig. 2). Active surveillance is the preferred approach for patients with non-aggressive tumors, especially for those with a PSA level <10 ng/mL and a $3 + 3$ Gleason score [1]. Prostatectomy and radiation continue to be effective against localized diseases, while androgen deprivation therapy still represents the standard treatment for hormone-naïve carcinomas [1,2]. For CRPC, the use of AR antagonists and chemotherapeutics is usually recommended, with radium-223 being particularly indicated in the case of bone metastases [1]. Remarkably, the progress in the elucidation of the gene mutations implicated in PCa development has resulted in the identification of novel molecular targets, eventually defining new targeted strategies (Table 1).

3.1. Anti-androgen therapy

Given the key role of AR in regulating PCa onset and evolution, current research has been consistently revolving around the screening and testing of new agents targeting this signaling. This has led to the approval of first- and second-generation anti-androgens, as well as to the development of novel approaches, including the use of antisense oligonucleotides, bipolar androgen therapy and EZH2 and BET inhibitors.

Abiraterone acetate is an irreversible inhibitor of CYP17A1, a member of the CYP450 family converting pregnanes into steroids, including androgen precursors. Thus, it is able to block androgen synthesis not only in testes and adrenal cortex but also in PCa itself [96]. The main side effects (*i.e.* hypokalemia, hypertension and fluid retention) of abiraterone acetate correlate with the rise in mineralocorticoid levels due to CYP17A1 inactivation; therefore, prednisone or prednisolone are usually concomitantly administered [97]. In 2011, abiraterone acetate received approval by the Food and Drug Administration (FDA) for patients with CRPC; the next year, its use was also recommended prior to chemotherapy [96]. It is now being investigated in combination with different treatments, and it has recently shown improved effectiveness, including increased overall survival and radiographic progression-free survival, when given together with hormonal therapy in patients with locally advanced PCa [97,98]. Other CYP17A1 inhibitors (*i.e.* galeterone and orteronel) have been tested in various clinical trials but their primary endpoint was not reached [99].

Enzalutamide is a new-generation, competitive, orally-administered AR antagonist commonly employed in the management of CRPC both post- and pre-chemotherapy [100]. Interestingly, it substantially increases metastasis-free survival in patients with high-risk non-invasive CRPC [100]. Adverse events (*i.e.* headache, confusion, dizziness, insomnia, anxiety/depression) due to drug penetration in the brain have been reported [100]. Co-treatments with enzalutamide and other therapeutics already in use for localized or advanced PCa, including abiraterone acetate, docetaxel or radium-223 dichloride, are currently under inten-

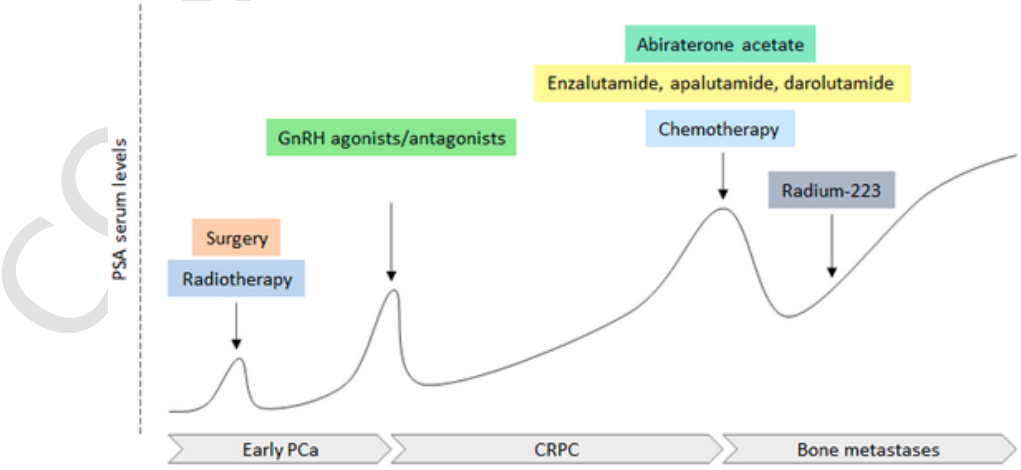

Fig. 2. Traditional therapies for prostate cancer (PCa). When localized, PCa can be eradicated by surgery or radiation therapy. Nonetheless, many patients experience disease progression; in this phase, in which tumor growth depends on androgens, hormonal therapy with GnRH analogs and anti-androgens represents the treatment of choice. Unfortunately, after good initial results, recurrence is frequently observed, with the tumor reaching a condition of castration resistance (CRPC) for which current therapeutic options, including androgen receptor (AR) antagonists, chemotherapy and radium-223, offer a short progression-free survival.

Table 1
Emerging targeted therapies for prostate cancer.

Drug	Therapeutic class	Clinical development	References
Abiraterone acetate	CYP17A1 inhibitors	FDA approval, phase III trials (combination)	[96–98]
Enzalutamide, apalutamide, darolutamide	AR antagonists	FDA approval, phase III trials (combination)	[100–106]
EZN-4176	AR antisense oligonucleotides	Phase I trials	[109]
Testosterone	Bipolar androgen therapy	Pilot studies/phase II trials	[111, 112]
CPI-1205	EZH2 inhibitors	Phase I/II trials	[115]
ARV-771	BET inhibitors	Preclinical studies	[118]
Olaparib, rucaparib, niraparib and talazoparib	PARP inhibitors	FDA approval (Olaparib, rucaparib), phase III trials (niraparib, talazoparib)	[120, 121]
Ipatasertib	Akt inhibitors	Phase II trials	[124]
177Lu-PSMA J591, 177Lu-PSMA 617	Anti-PSMA therapy	Phase I/II trials	[125–129]
Ipilimumab	Anti-CTLA4 antibodies	Phase I trials	[131]
Pembrolizumab	Anti-PD1 antibodies	FDA approval	[132, 133]
Avelumab, durvalumab and atezolizumab	Anti-PDL1 antibodies	Phase I trials	[135]
ERG and NOTCH inhibitors	Anti-TMPRSS2: ERG therapy	Preclinical studies	[135, 136]

sive study [101]. In particular, the recent ARCHES trial has highlighted the promise of the combination of enzalutamide and androgen deprivation therapy in reducing the risk of metastasis and death versus pharmacological castration alone in men with hormone-sensitive PCa, with a safety profile comparable to that observed in CRPC patients [102].

Apalutamide is an enzalutamide-like oral AR antagonist, that is recommended for the management of non-metastatic CRPC [103]. Common toxic effects include rash, weight loss, fatigue, arthralgia and fracture [103]. Several clinical studies are currently investigating the efficacy and safety of combinations of apalutamide with standard androgen deprivation therapy [104].

Darolutamide is a competitive, oral and structurally novel example of second-generation AR antagonists [105]. Unlike previous drugs, it does not penetrate the blood-brain barrier, displaying low toxicity [105]. Phase III trials are now ongoing to test darolutamide with hormonal therapy and taxanes in CRPC [106].

Antisense oligonucleotides present the unique advantage of targeting both the full-length transcript and the splice variants of a gene. Therefore, antisense oligonucleotides targeting exon-1, intron-1 and exon-8 of AR pre-mRNA have been recently designed to suppress both the receptor and its variants in PCa, demonstrating high anti-tumor activity in enzalutamide-resistant cell lines and xenografts [107]. Furthermore, combination of EZH2 inhibitors and antisense oligonucleotides has shown promise in the treatment of CRPC preclinical models, additively inhibiting tumor xenograft growth [108]. However, administration of EZN-4176, a third-generation antisense oligonucleotide able to bind to the hinge region of AR mRNA, to 22 CRPC patients was followed by limited drug response in a first phase I study [109].

Bipolar androgen therapy has been developed based on the consideration that supraphysiological doses (≅1500 ng/dL) of testosterone could exert significant anti-tumor effects in CRPC animal models [110]. Although the mechanisms of this growth-suppressing activity are still unclear, a pilot clinical trial was conducted in 2015: among the 16 CRPC patients treated with 400 mg of intramuscular testosterone monthly, 50% exhibited marked PSA decline and radiographic response and 100% displayed high sensitivity to androgen deprivation therapy [111]. Similar findings have been obtained in a phase II study, where bipolar androgen therapy susceptibility was evaluated in CRPC patients experiencing disease progression post-enzalutamide treatment: 30% of them had a ≥50% PSA decrease and 52% of them achieved a PSA response when rechallenged with enzalutamide [112]. Further studies are needed to define the appropriate method for alternating androgen and anti-androgen therapies in CRPC to maximize patient outcomes.

EZH2 is one of the key components of the Polycomb Repressive Complex 2, which controls gene expression through the methylation of H3 via its methyltransferase activity. In PCa, EZH2 not only acts as a transcriptional coactivator of AR but also disrupts the negative feedback loop regulated by the AR repressor CCN3 [113,114]. In this context, a randomized phase Ib/II study (ProSTAR) is evaluating the efficacy of the EZH2 inhibitor CPI-1205 with enzalutamide or abiraterone/prednisone in CRPC patients [115].

BET proteins (BRD 2/3/4) are important coactivators of AR-mediated gene transcription. Recently, Asangani et al. have shown that the BRD4 inhibitor JQ1 suppresses CRPC cell proliferation [116]. Importantly, JQ1 treatment not only determines AR repression but also c-myc downregulation [117]. However, despite these encouraging results, clinical application of this drug is limited due to high toxicity and numerous off-target effects. For this reason, more specific drugs binding to both E3 Ubiquitin-ligase Cereblon (CRBN) and BET proteins have been designed. This is the case of ARV-771, a small-molecule pan-BET degrader based on proteolysis-targeting chimera technology, that has demonstrated improved anti-tumor activity in CRPC cells with respect to classical BET inhibition [118]. It is important to underline that both first- and second-generation BET inhibitors act as competitors of the transcription factor GATA2, blocking the expression of AR splicing variants [119].

3.2. PARP inhibitors

Poly ADP ribose polymerases (PARP) are a family of proteins involved in DNA repair. Once active, they recruit a number of targets implicated in HRR, including BRCA1, BRCA2, ATM and PALB2. Thus, mutations in HRR genes confer sensitivity to PARP inhibition, resulting in synthetic lethality [120]. Based on this rationale, PARP inhibitors have shown great promise in PCa treatment. Indeed, in 2020 olaparib and rucaparib have received FDA approval for the treatment of CRPC patients with a somatic mutation in any HRR gene or any germline mutation in *BRCA1*, *BRCA2* and *ATM* genes [120]. Similarly, niraparib and talazoparib have been tested in phase II trials in patients with *BRCA*-mutated metastatic disease previously treated with antiandrogens and docetaxel: the relative risk of niraparib was 41%, while that of talazoparib was 54%, with both therapeutics found to prolong progression-free survival [120]. Phase III trials are currently underway [121].

3.3. PI3K/Akt/mTOR inhibitors

Activation of PI3K/Akt/mTOR pathway following *PTEN* loss has been strongly linked with PCa growth and progression [52]. Early efforts at suppressing this cascade were focused on mTOR inhibition. However, rapamycin, a TORC1 inhibitor, and its derivatives, temsirolimus and everolimus, lacked significant efficacy, while dual blockade of TORC1 and TORC2 with drugs like dactolisib (BEZ2350) and MLN0128 have been followed by severe toxic effects [52]. Parallelly, buparlisib (BKM-120), the most extensively investigated PI3K inhibitor in PCa, failed in reverting castration resistance when given in combination with antiandrogens [122,123]. On the other hand, a combination of abiraterone and ipatasertib, an oral small molecule able to bind to the ATP-binding pocket of all three Akt isoforms, has been demonstrated to prolong radiographic progression-free survival over abiraterone alone, with even greater effects in patients with PTEN-null PCas with respect to those with the intact protein [124]. Thereby, several clinical trials with ipatasertib and other Akt inhibitors are ongoing.

3.4. Anti-PSMA therapy

Anti-PSMA therapy is based on the use of radiolabeled small molecules containing glutamate-urea-lysine residues able to bind to the glutamate carboxypeptidase II pocket of PSMA or of monoclonal antibodies directed against the extracellular enzymatic domain. Among them, the monoclonal antibody 177Lu-PSMA J591 selectively targets the PSMA extracellular domain, generating a complex that releases the radionuclide once internalized into cancer cells. This molecule can be given in a single dose, and it has demonstrated great efficacy in phase I-II trials when given to CRPC patients [125,126]. Similar encouraging results have been obtained with 177Lu-PSMA 617, which has demonstrated high response rates, low toxicity and reduction of pain in men with metastatic PCa that has progressed after conventional strategies [127–129].

3.5. Checkpoint inhibitors

PCa is characterized by a relatively low number of cancer-specific neoantigens, indicating that it may be unresponsive to immune checkpoint inhibitors [130]. However, based on the benefits demonstrated by these therapeutics in several cancer types, their potential has also been explored in PCa. The anti-CTLA4 antibody ipilimumab has shown promising activity in terms of PSA rate decline in PCa patients, causing a complete tumor remission in some cases, although no improvement of overall survival was evidenced in larger studies [131]. Long-lasting responses (*i.e.* median duration of response of 13.5 months, median progression-free survival of 3.5 months and overall survival of 7.9 months, respectively) to pembrolizumab, an anti-PD-1 antibody, have been observed in CRPC patients [132]. Notably, this drug has been recently approved for the treatment of mismatch repair-deficient solid tumors, allowing CRPC patients belonging to this group to undergo immunotherapy [133]. Regarding anti-PD-L1 antibodies, clinical trials with avelumab, durvalumab and atezolizumab are ongoing for CRPC management [134].

3.6. Anti-TMPRSS2:ERG therapy

Androgen deprivation therapy is commonly followed by TMPRSS2:ERG suppression; however, upon development of castration resistance, TMPRSS2:ERG expression is generally restored. In this context, the TMPRSS2:ERG fusion protein represents an attractive therapeutic target. Recently, novel ERG inhibitors have been engineered: these peptides can selectively interact with the DNA-binding domain of the transcription factor and promote its proteolytic degradation, eventually culminating in reduced tumor growth and invasion [135].

Other studies have been focused on the identification of the specific molecular features of *TMPRSS2:ERG*-positive PCas. In this regard, it has been reported that both NOTCH1 and 2 are direct transcriptional targets of ERG [136]. Interestingly, tumor treatment with the NOTCH γ-secretase inhibitor GSI-1 resulted in an enhanced responsiveness to anti-androgens (*i.e.* abiraterone and enzalutamide), raising the possibility that combinatorial strategies directed against NOTCH and AR signaling may be effective in the eradication of *TMPRSS2:ERG*-bearing advanced PCas [136].

4. Conclusions

The identification of diagnostic/prognostic markers as well as the development of targeted therapies for PCa have exploited various elements of prostate biology. While emerging evidence points to a key role of a wide range of gene mutations in PCa pathogenesis and progression, the androgen-dependent growth of PCa is still the focus for the screening of new therapeutics, with novel androgen deprivation approaches showing the greatest effect on cause-specific and overall survival. On the other hand, small molecules designed to inhibit oncogenic signaling pathways have been recently subjected to clinical trials with encouraging results. Finally, prostate epithelial cells express a number of tissue-specific proteins that have been explored as a target for antibody-directed therapies, as in the case of PSMA. However, the application of targeted therapies to PCa management is still limited, since no common dominant oncogenic mutations have been completely identified yet; the combination of targeted treatments with pharmacological castration and chemotherapy also remains to be assessed. In the future, we expect that pinpointing the molecular mechanisms and genetic alterations of PCa would allow for early detection and increasingly specific diagnosis/staging as well as for the continued development of more effective therapeutic strategies.

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Declaration of interest statement

The authors declare no competing interest.

Author contributions

Writing – original draft preparation, F.F.; writing – review and editing, F.F., M.A. and P.L.; funding acquisition, P.L.

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