Emerging proteins involved in castration-resistant prostate cancer via the AR-dependent and AR-independent pathways (Review)

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Abstract. Despite achieving optimal initial responses to androgen deprivation therapy, most patients with prostate cancer eventually progress to a poor prognosis state known as castration-resistant prostate cancer (CRPC). Currently, there is a notable absence of reliable early warning biomarkers and effective treatment strategies for these patients. Although androgen receptor (AR)-independent pathways have been discovered and acknowledged in recent years, the AR signaling pathway continues to play a pivotal role in the progression of CRPC. The present review focuses on newly identified proteins within human CRPC tissues. These proteins encompass both those involved in AR-dependent and AR-independent pathways. Specifically, the present review provides an in-depth summary and analysis of the emerging proteins within AR bypass pathways. Furthermore, the significance of these proteins as potential biomarkers and therapeutic targets for treating CRPC is discussed. Therefore, the present review offers valuable theoretical insights and clinical perspectives to comprehensively enhance the understanding of CRPC.

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Abbreviations: PCa, prostate cancer; CRPC, castration-resistant prostate cancer; AR, androgen receptor; ADT, androgen deprivation therapy; DHT, dihydrotestosterone; BPH, benign prostatic hyperplasia; ADPC, androgen-dependent prostate cancer; GR, glucocorticoid receptor; PRMT5, protein arginine methyltransferase 5; 4-1BBL, 4-1BB ligand; YB-1, Y-box binding protein-1; RSK1, ribosomal protein S6 kinase A1; Twist1, twist basic helix-loop-helix transcription factor 1; LIMK2, LIM-domain kinase-2; EMT, epithelial-to-mesenchymal transition; AURKA, aurora A kinase; Mdm2, mouse double minute-2; Siah2, seven in absentia homolog 2 (drosophila); RNF6, ring finger protein 6; FKBP4, FK506 binding protein 4; HNPC, hormone-sensitive prostate cancer; GRB10, growth factor receptor bound protein 10; LCN2, lipocalin 2; AKR1C3, ido-keto reductase family 1 member C3; ERRα, estrogen-related receptor α; DHX15, DEAH-box RNA helicase family member 15; TXNDC5, thioredoxin domain-containing protein 5; OCT1, octamer transcription factor 1; NCoA2, nuclear receptor coactivator 2; PI3K, phosphatidylinositol-3 kinase; STAT3, signal transducer and activator of transcription 3; FOXA1, forkhead box protein A1; YAP1, yes-associated protein 1; MST1, macrophage stimulating 1; NEPC, neuroendocrine prostate cancer; IRE1α, inositol-requiring enzyme 1 α; FGG, serum fibrinogen γ; PSA, prostate specific antigen; NKX3.1, NK3 homeobox 1; IRF8, interferon regulatory factor 8; RGS2, G-protein signaling proteins 2; MYSM1, Myb-like SWIRM and MPN domains 1; HOXB13, Homeobox B13; ATTs, androgen targeted therapies; NE, neuroendocrine; DNPC, double-negative prostate cancer; RTKs, receptor tyrosine kinases; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; ERK, extracellular regulated protein kinase; TGF, transforming growth factor; FGFR1, growth factor receptor 1; Hh, hedgehog; Cav-1, caveolin-1; ZBTB46, zinc finger and BTB domain-containing protein 46; LIF, leukemia inhibitory factor; SSTR2, somatostatin receptor 2; GPR30, G protein coupled receptor 30; PSMA, prostate-specific membrane antigen; TUBB3, class III β-tubulin; RHAMM, hyaluronan-mediated motility receptor; CaSR, calcium-sensing receptor; SPAG5, sperm-associated antigen 5; MED12, mediator complex subunit 12; SMAD3, mothers against decapentaplegic homolog 3; NRP1, neuropilin-1; OPRK1, k-type opioid receptor; WLS, wntless; NSD2, nuclear receptor binding SET domain2; SRRM4, serine/arginine repetitive matrix 4; PPFIA4, fraction of tyrosine phosphatase receptor type F polypeptide interacting protein α 4; MTHFD2, methylenetetrahydrofolate dehydrogenase 2; MDH2, malate dehydrogenase 2; JNK, c-Jun N-terminal kinase; ATF, activating transcription factor; ER, endoplasmic reticulum; THEM6, the ER membrane-associated protein, thioesterase superfamily member 6; ACAT1, elevated acetyl-coenzyme A acetyltransferase 1; PIM, serine/threonine-protein kinase; ERG, ETS-related gene 1; Notch1, nuclear notch homolog 1; AMPK, adenosine monophosphate-activated protein kinase; ACO2, aconitase 2; SMO, smoothened; HepaCAM, hepatocyte cell adhesion molecule; AKT, Ak strain transforming

Key words: castration-resistant prostate cancer, androgen receptor, protein, signaling pathway, biomarker, therapeutic target

Contents

1. Introduction

The incidence of prostate cancer (PCa) remained stable from 2014 to 2018 but contributed to 27% of all cancer cases in the USA (1). However, the incidence of advanced PCa in the USA has been increasing by 4-6% annually since 2011. PCa has remained the second leading cause of death in males with cancer over the past decade, and this has been attributed to the development of castration-resistant prostate cancer (CRPC) (1). At present, the treatment and management of CRPC is challenging and most patients have a poor prognosis (2,3). Like normal prostate cells, PCa cells require androgens for continued growth (4). Therefore, the primary treatment for advanced or metastatic PCa is androgen deprivation therapy (ADT) by surgical or pharmacological castration (5).

The androgen receptor (AR), a ligand-dependent nuclear transcription factor, binds to testosterone or dihydrotestosterone (DHT), leading to the transcription of AR-responsive genes, which drive the proliferation and survival of prostate cells (6). Compared with benign prostatic hyperplasia (BPH), the AR is upregulated in primary PCa and is even upregulated throughout the progression to CRPC during ADT (7). The mechanisms by which androgen-dependent prostate cancer (ADPC) progresses to CRPC remain largely unknown. However, the AR is the most researched molecular factor in the context of PCa research and is reported to promote CRPC. The mechanisms underlying the development of CRPC are divided into AR-dependent and AR-independent pathways (also termed bypass ways) (8).

The AR-dependent pathways include: i) High affinity for ligands by translated AR gene mutants; ii) AR splice variants that are constitutively active without ligand; iii) AR gene locus amplification; iv) ectopic biosynthesis of androgens from adrenal steroids and cholesterol or paracrine biosynthesis from mesenchymal cells; and v) non-canonical induction of AR signaling, such as the IL-6/STAT3 pathways, in the absence of ligand (9-12). Including AR V7 and Arv567es, >20 AR variants have been identified. A dedicated review that discusses these AR mutations is already available (13), and therefore, AR variants will not be discussed in the present review. In addition, alternative signaling pathways supporting the growth and viability of CRPC cells have been demonstrated to bypass the AR absolutely (14). For instance, the glucocorticoid receptor (GR) binds to androgen response elements to sustain PCa cell proliferation. In previous studies, it was demonstrated that inhibiting the GR or glucocorticoid-regulated kinase 1, a target gene of both the AR and GR, delayed castrate-resistant tumor formation (15-17).

Regardless of the aforementioned mechanisms, proteins are the executors of the biological functions in CRPC progression (18). Therefore, identifying new proteins or studying their functions in CRPC will lead to the identification of new treatment targets, biomarkers for early stages of PCa and markers for predicting recurrent or treatment response. This will lead to an improvement in prognosis for patients with CRPC. Mass spectrometry is a powerful method that enables increasingly comprehensive insights into changes in the proteome, allowing for high-throughput analysis of clinical patient samples (19). In addition, studies involving large-scale, mass spectrometry-based proteomics of human cancer have recently been published (20,21). Researchers have found and validated many differentially expressed proteins from primary PCa and CRPC clinical tissue samples (22). Emerging proteins in CRPC have been identified from various sources, including human tissues, mouse xenografts, cell lines and human serum or urine samples (23). Therefore, the present review focuses on the expression and function of proteins in patients with CRPC, particularly whether they can regulate AR expression or translation activity. In addition, their clinical applications in the management of CRPC are outlined, which were identified or validated using immunohistochemistry (IHC). These proteins are expected to be potential diagnostic markers, therapeutic monitoring indicators and therapeutic targets for CRPC.

2. Proteins involved in AR-dependent pathways

Proteins promoting CRPC progression in AR-dependent pathways

Proteins contributing to AR expression. Although CRPC is androgen-independent, AR gene amplification or upregulation is observed in up to 80% of samples from patients with CRPC(24). Various proteins, such as epigenetic modification factors, promote ectopic AR expression, contributing to CRPC (25,26). Protein arginine methyltransferase 5 (PRMT5), an epigenetic activator, is upregulated in CRPC and activates AR transcription by recruiting pICln to the AR promoter (25). In addition, PRMT5 or pICln induces CRPC tumor growth in mice (25). Moreover, 4-1BB ligand (4-1BBL, also termed CD137L), a transmembrane glycoprotein belonging to the tumor necrosis factor family, has been found to be upregulated during the progression of PCa to CRPC, thereby promoting the expression of AR (26). However, the process by which 4-1BBL promotes AR expression is yet to be identified. In addition, 4-1BBL augments the proliferation and invasion abilities of PCa cells in an androgen-deprived environment (26).

Similarly, several transcription factors that induce AR expression at the transcriptional level are upregulated in patients with CPRC (27). Y-box binding protein-1 (YB-1) is one of the transcription factors that regulate AR transcription by binding to the Y-box in the AR promoter. In addition, YB-1 modulates the expression of AR variants at the transcription and splicing levels (28-30). Moreover, another transcription factor, twist basic helix-loop-helix transcription factor 1 (Twist1) was reported to upregulate AR gene expression by binding to E-boxes in the AR promoter region (31). Notably, Twist1 enhances CRPC cell proliferation, leading to cisplatin and taxane resistance by increasing YB-1 expression. YB-1 also regulates the expression of Twist1, suggesting a strong functional crosstalk between the two proteins (32).

Kinases responsible for the phosphorylation of transcription factors also play critical roles in CRPC progression. During ADT, YB-1 phosphorylation is induced by ribosomal

protein S6 kinase A1 (RSK1) phosphorylation, which regulates full-length AR and AR V7 splicing (28,29). In addition, Twist1 is stabilized by LIM-domain kinase-2 (LIMK2) via phosphorylation to prevent its degradation (33). The feedback loop between Twist1 and LIMK2 increases PCa cell migration and promotes epithelial-to-mesenchymal transition (EMT) (33). Moreover, LIMK2 degradation is decreased by its phosphorylation via aurora A kinase (AURKA). It has also been shown that AURKA is upregulated by LIMK2 and is also positively regulated by the androgen-induced AR, which binds in its intronic region (34). In conclusion, YB-1, Twist1, RSK1, LIMK2, AURKA and AR are significantly upregulated in CRPC samples, and are involved in a positive feedback loop that synergistically promotes CRPC progression.

Proteins contributing to AR transcriptional activity. In addition to alterations in AR expression or structure, many factors contribute to AR activation despite castrate levels of serum androgens. These alterations include changes in AR stability, steroid metabolism, coactivator expression/activity and cell signaling (35). Furthermore, the modulation of AR activity through various posttranslational modifications, such as ubiquitination and phosphorylation, has been extensively studied (36-38).

As a transcription factor, the AR is regulated by E3 ubiquitin ligases of the ubiquitin-proteasome pathway, such as mouse double minute-2 (Mdm2), seven in absentia homolog 2 (Siah2) and ring finger protein 6 (RNF6), which have been implicated in the control of AR stability and activity (36,39,40). The expression level of Siah2 is significantly upregulated in CRPC tissues and is required for the growth of CRPC tumors in mice (39). Notably, Siah2 binds to the corepressor, NCOR1, to remove the transcriptionally inactive AR from chromatin, enhancing AR transcriptional activity (39). In addition, the expression of another ubiquitin E3 ligase, RNF6, was found to be upregulated during PCa progression (36). Furthermore, RNF6 assumes a critical role in promoting PCa cell growth under androgen-depleted conditions by ubiquitinating AR at K845. This ubiquitination event serves as a scaffold for the recruitment of coactivators such as ARA54 (36).

The expression of non-receptor tyrosine kinase is upregulated in CRPC samples and correlates with AR Y534 phosphorylation. Studies have shown that phosphorylation of the AR, induced by Src interacting with the AR through its Src homology 2 domain, profoundly affects the stability and turnover of the AR. As a result, this interaction may prevent the association of the AR with Mdm2 (37). FK506 binding protein 4 (FKBP4, also termed FKBP52), is another protein that promotes phosphorylation of the AR to enhance its transcriptional activity. A previous study analyzing >500 PCa samples revealed that FKBP4 expression is upregulated in CRPC, when compared with hormone-sensitive prostate cancer (HNPC) (38). Growth factor receptor bound protein 10 (GRB10) also phosphorylates the AR at S81, which is critical for AR transcriptional activity (41). GRB10 is the most significantly and consistently upregulated gene during CRPC progression and markedly induces PCa cell growth (42).

Several studies have demonstrated that steroidogenic enzymes involved in androgen biosynthesis are upregulated in PCa tissues, promoting CRPC development (43-45). The AR becomes more sensitive due to the tumor's own *de novo* androgen production, thereby promoting the progression of PCa. Notably, increased expression of lipocalin 2 (LCN2) was detected in CRPC tissues, when compared with patients with PCa or BPH (43). LCN2 upregulation leads to upregulation of the AR downstream gene, SLC45A3, without affecting AR levels, suggesting that LCN2 enhances AR transcriptional activity and thereby contributes to CRPC progression (43). Similarly, ido-keto reductase family 1 member C3 (AKR1C3) is a critical enzyme for catalyzing the biochemical reduction of 5α-Adione to DHT in PCa cells (44). In addition, AKR1C3 promotes EMT during PCa metastasis by activating extracellular regulated protein kinase (ERK) signaling (44). Moreover, the expression of AKR1C3 is significantly higher in CRPC tissues than in HNPC tissues of the same patients (46). Estrogen-related receptor α(ERRα) was also reported to be upregulated in metastatic CRPC (mCRPC) (45). In addition, ERRα enhances intra-tumoral androgen biosynthesis by regulating the transcription of AKR1C3 (45). ETS-related gene 1 (ERG) and AKR1C3 are co-expressed in human prostate tumor tissue specimens, and they predict a lower probability of survival (47).

Evidence from previous studies has indicated that the dysregulation of AR cofactors contributes to the development and progression of CRPC (48-52). DEAH-box RNA helicase family member 15 (DHX15) is an AR coactivator that forms a complex with the AR and Siah2 to increase their stability and enhance the E3 ubiquitin ligase activity of Siah2 (48). The expression of DHX15 is also upregulated in human CRPC tissues compared with HNPC tissues (53). Thioredoxin domain-containing protein 5 (TXNDC5) is another AR cofactor upregulated in CRPC. TXNDC5 directly interacts with the AR protein to increase its stability, and thus enhances its transcriptional activity through hypoxia inducible factor-1α in a miR-200b-dependent manner (49). Moreover, octamer transcription factor 1 (OCT1) is an AR-interacting protein that regulates target gene expression in PCa cells and has been shown to enhance AR transcriptional activity to induce the growth and migration of 22Rv1 cells (50). Notably, the expression of OCT1 and disks large-associated protein 5 was found to be upregulated in CRPC specimens (50). Nuclear receptor coactivator 2 (NCoA2, also termed SRC-2), is a well-studied coactivator of the AR. NCoA2 is often found to be upregulated in patients with metastatic PCa and plays a key role in driving the development of CRPC (51). When androgen levels are reduced due to deprivation therapy, NCoA2 levels increase. This heightened NCoA2 expression, in turn, triggers activation of the phosphatidylinositol-3 kinase (PI3K) signaling pathway, thereby promoting the metastasis of prostate cancer (51). Based on quantitative protein results, forkhead box protein A1 (FOXA1) was identified to be elevated in PCa tumor-node-metastasis stage 3 (including both Gleason grade 3 and Gleason grade uncertain) and CRPC despite ADT treatment (54,55). FOXA1 is a pioneer factor facilitating AR transcription and PCa growth (52,56) and possesses an AR-independent role in regulating EMT (52). Notably, the expression of Yes-associated protein 1 (YAP1) is upregulated and activated in CRPC and enzalutamide-resistant cells but is downregulated in neuroendocrine prostate cancer (NEPC) (57,58). YAP1 binding to the AR in the nucleus is regulated by macrophage stimulating 1 (MST1) signaling,

which may play a prominent role in the emergence of advanced PCa (59). Moreover, YAP1 silencing attenuates the growth and invasion of PCa cells *in vitro* (59). Functional analyses have uncovered that YAP1 positively regulates numerous genes involved in cancer stemness and lipid metabolism (60). In addition, YAP1 interacts with chicken ovalbumin upstream promoter transcription factor 2 to form a transcriptional complex.

Studies have shown that several growth factors and cytokines, such as epidermal growth factor, transforming growth factor (TGF)α, IL-6 and their downstream tyrosine kinases, including erbB2, Src and focal adhesion kinase, can activate the AR and minimize or possibly even negate the requirement for ligand (61-63). During ADT, the AR is inactive, however, in compensation, IL-6 and STAT3 induce activation of the AR in a ligand-independent manner (64). Moreover, the upregulation of nuclear AR expression by IL-6 has been demonstrated (65). In addition, both IL-6 and phosphorylated STAT3 (pSTAT3) are upregulated in bone metastases tissues from patients who died from CRPC (66). The downstream target genes and relevant signaling pathways regulated by IL-6 interweave into a vast signaling network that could promote the progression of CRPC. For instance, inositol-requiring enzyme 1α (IRE1α), a key regulator of the unfolded protein response, is associated with CRPC development and promotes the castration-resistant growth of PCa cells in an IL-6/AR-mediated manner (67).

Protocadherin B9, which is involved in cell adhesion and migration, promotes nuclear AR translocation in LNCaP cells (68). The expression of protocadherin B9 is associated with the preoperative prostate specific antigen (PSA) concentration, the Gleason score, lymphatic invasion and seminal vesicle invasion in PCa cases (68). In addition, the expression of nuclear CDK19 and CDK8 is upregulated during PCa progression to CRPC (69). A study demonstrated that CDK8/CDK19 inhibition reduced cell migration and increased collagen I-dependent adhesion (70). It also demonstrated that combining CDK8/CDK19 inhibitors with anti-androgens lead to synergistic antiproliferative effects and sensitized androgen-independent cells to bicalutamide. It was therefore suggested that CDK8/CDK19 partially mediates its pro-oncogenic effects via the AR axis.

Proteins repressing CRPC progression in AR-dependent pathways. Proteins that upregulate AR expression or activity have been extensively examined, but there are limited reports on proteins that suppress AR expression or activity. The expression of orphan nuclear receptor, TLX (also termed nuclear receptor subfamily 2, group E, member 1), is upregulated in mCRPC and it directly binds to the AR promoter and represses AR transcription by recruiting histone modifiers, including histone deacetylase (HDAC)1, HDAC3 and lysine-specific demethylase 1, inducing resistance to androgen deprivation in PCa cells (71). NK3 homeobox 1 (NKX3.1), a prostate-specific homeodomain-containing transcription factor, is negatively associated with the initiation and progression of PCa and the progression of CRPC (72). NKX3.1 downregulates Ak strain transforming (AKT) activation and decreases AR and ARv7 levels in CRPC cells, and NKX3.1 can be degraded following phosphorylation via LIMK2 in CRPC (72).

A study has suggested that Mdm2, an E3 ubiquitin ligase, can induce polyubiquitination of the AR, which results in AR nuclear degradation (40). In addition, Mdm2 is downregulated in CRPC cell lines compared with the hormone sensitive prostate cancer cell lines (40,73). Unlike Mdm2, interferon regulatory factor 8 (IRF8) directly combines with the AR and promotes its degradation by activating the ubiquitin/proteasome systems (74). It is also of note that IRF8 expression was upregulated in primary PCa tissues but downregulated in CRPC tissues, compared with normal prostate tissues (74). By contrast, G-protein signaling protein 2 (RGS2) regulators are downregulated at the early stages of PCa (75). However, late or advanced stages of PCa are associated with RGS2 upregulation, which correlates with a poor survival rate and high metastasis (75-77). Both the AR and RGS2 inhibit each other and RGS2 may suppress androgen-independent AR activity by inhibiting ERK activity in PCa cells (77). In addition, Myb-like SWIRM and MPN domains 1 (MYSM1) acts as a histone H2A deubiquitinase and a study has shown that MYSM1 expression is downregulated in CRPC compared with localized PCa (78). In addition, MYSM1 interacts with the AR and reduces AR activity by inhibiting AKT/c-Raf/GSK-3β signaling (78). Homeobox B13 (HOXB13) is one of the 39 HOX homeodomain proteins. A reporter transcription assay demonstrated that HOXB13 significantly suppressed hormone-mediated AR activity in a dose-responsive manner, and suppression was specific to the AR, with which HOXB13 physically interacts (79). Another study has shown that HOXB13 regulates AR action on endogenous target genes (80). HOXB13 is a bifunctional regulator of AR transcriptional activity, demonstrating the hallmarks of both an activator and a repressor (80). Notably, the upregulation of HOXB13 led to the suppressed proliferation of LNCaP cells (79). In addition, interference with HOXB13 expression with small interfering RNA also resulted in the inhibition of LNCaP cell proliferation (80). Collectively, these observations suggest a pivotal role of HOXB13 in LNCaP cell proliferation (80). The relationship between AR and the aforementioned proteins is outlined in Fig. 1 and Table I.

3. Proteins involved in AR-independent pathways

Proteins contribute to CRPC progression in AR-independent pathways

AR-independent pathways. Once PCa cells undergo androgen targeted therapies (ATTs), either AR signaling is reactivated as previously described or AR pathways are bypassed, probably by transdifferentiating neuroendocrine (NE) or by switching to an AR-null NE-null phenotype termed double-negative prostate cancer (DNPC) (81,82). The process by which AR bypassing promotes PCa progression to CRPC includes dysregulated receptor tyrosine kinases (RTKs; receptors of growth factors) and downstream effectors comprising mitogen-activated protein kinase (MAPK), mitogen-activated extracellular signal-regulated kinase (MEK) and ERK, TGF-β/mothers against decapentaplegic (SMAD) signaling, the PI3K/AKT/mTOR pathway, Wnt/β-catenin signaling, activation of the NF-κB pathway by cytokines and GR upregulation (83-86). This process was reviewed by Makino *et al* (83) and Saraon *et al* (84). Some pathways form intricate connections with AR signaling by directly regulating AR, while others completely circumvent AR to facilitate the survival,

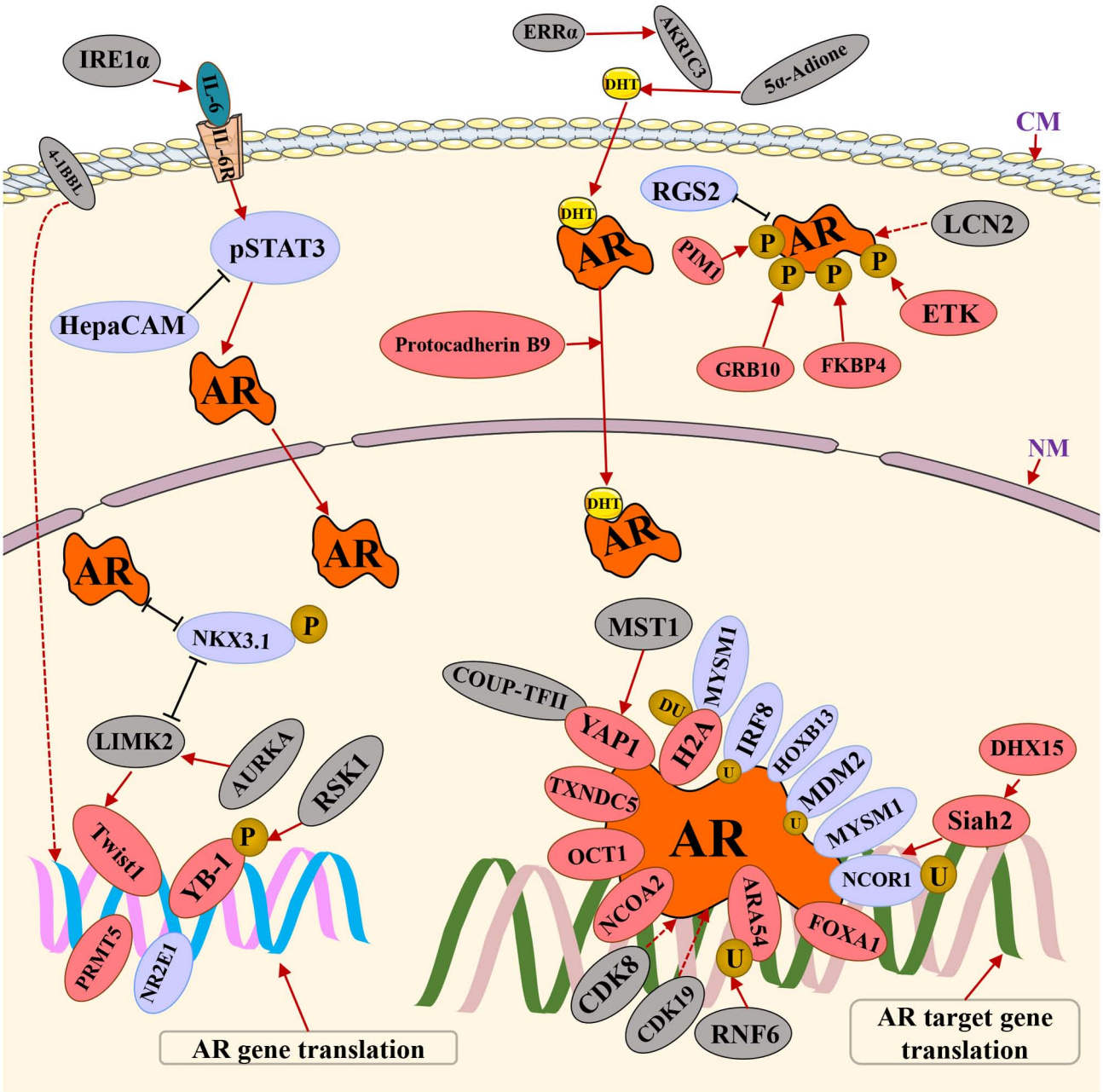

Figure 1. Proteins involved in AR-dependent pathways. These proteins are divided in two groups: One group comprises proteins that regulate AR expression, such as PRMT5, 4-1BBL, LIMK2, YB-1, Twist1, RSK1, AURKA and NR2E1, and another group contains proteins that modulate AR transcriptional activity, such as IRE1α, ERR1α, AKR1C3, RGS2, PIM1, GRB10, FKBP4, ETK, LCN2, MST1, COUP-TFH, YAP1, IL-6, HOXB13, TXNDC5, OCT1, NCOA2, CDK8, CDK19, RNF6, FOXA1, Siah2, DHX15, MYSM1, IRF8, MDM2 and HepaCAM. Proteins presented with a red background are those that directly activate the AR, whereas those marked in gray indirectly activate the AR. Proteins presented in light blue background decrease the expression or activity of the AR. The arrowhead indicates positive regulation of the target protein, whereas the blunt head indicates negative regulation of the target protein. Likewise, the full lines show direct regulation and dotted lines indicate indirect regulation. CM, cytomembrane; ETK, non-receptor tyrosine kinase; NM, nuclear membrane; PRMT5, protein arginine methyltransferase 5; 4-1BBL, 4-1BB ligand; LIMK2, LIM-domain kinase-2; YB-1, Y-box binding protein-1; Twist1, twist basic helix-loop-helix transcription factor 1; RSK1, ribosomal protein S6 kinase A1; AURKA, aurora A kinase; NR2E1, nuclear receptor subfamily 2, group E, member 1; IRE1α, inositol-requiring enzyme 1 α; FGG, serum fibrinogen γ; AKR1C3, ido-keto reductase family 1 member C3; RGS2, G-protein signaling proteins 2; GRB10, growth factor receptor bound protein 10; FKBP4, FK506 binding protein 4; LCN2, lipocalin 2; MST1, macrophage stimulating 1; YAP1, yes-associated protein 1; HOXB13, Homeobox B13; TXNDC5, thioredoxin domain-containing protein 5; OCT1, octamer transcription factor 1; NCoA2, nuclear receptor coactivator 2; RNF6, ring finger protein 6; FOXA1, forkhead box protein A1; Siah2, seven in absentia homolog 2 (drosophila); DHX15, DEAH-box RNA helicase family member 15; MYSM1, Myb-like SWIRM and MPN domains 1; IRF8, interferon regulatory factor 8; Mdm2, mouse double minute-2; HepaCAM, hepatocyte cell adhesion molecule.

proliferation, migration and invasion of CRPC cells (84). Consequently, the abnormal expression of proteins involved in these pathways plays a significant role in driving the progression of CRPC.

RTKs/MAPK/MEK/ERK signaling pathway. The RTKs/MAPK/MEK/ERK signaling network is a canonical pathway that is essential to the carcinogenesis of various human tumors since it is closely related to cell growth,

Table I. Functions and clinical values of proteins involved in AR-dependent pathways.

Protein	Expression	Function	Clinical value	(Refs.)
PRMT5	Increased	Promotes AR expression	Therapeutic target	(24)
4-1BBL	Increased	Promotes AR expression	-	(25)
YB-1	Increased	Promotes AR expression	Prognostic marker, therapeutic target	(27-29)
TWIST1	Increased	Promotes AR expression	-	(30)
LIMK2	Increased	Promotes AR expression	Therapeutic target	(32)
AURKA	Increased	Promotes AR expression	Diagnostic marker, therapeutic target	(33)
Siah2	Increased	Inhibits polyubiquitination of AR	-	(35)
RNF6	Increased	Inhibits polyubiquitination of AR	Diagnostic marker	(36)
Etk	Increased	Phosphorylates AR	-	(37)
FKBP4	Increased	Phosphorylates AR	Diagnostic marker, prognostic marker	(38)
GRB10	Increased	Phosphorylates AR	Prognostic marker	(39,40)
LCN2	Increased	Facilitates androgen synthesis	-	(41)
AKR1C3	Increased	Facilitates androgen synthesis	Prognostic marker, therapeutic target	(42,43,45)
ERRα	Increased	Facilitates androgen synthesis	Therapeutic target	(44)
DHX15	Increased	AR cofactor	Prognostic marker	(46,47)
TXNDC5	Increased	AR cofactor	-	(48)
OCT1	Increased	AR-interacting protein	-	(49)
NCoA2	Increased	AR coactivator	Prognostic marker	(50)
FOXA1	Increased	Facilitates AR transcription	-	(51-53, 54)
YAP1	Increased	Binds to AR	Diagnostic marker, therapeutic target	(55-58)
IL-6	Increased	Promotes AR activity	Therapeutic target	(62,64)
STAT3	Increased	Promotes AR activity	-	(62,64)
IRE1α	Increased	Promotes AR activity	-	(65)
Protocadherin B9	Increased		Prognostic or predictive marker	(69)
CDK8/CDK19	Increased		Prognostic marker, therapeutic target	(70,71)
TLX	Increased	Represses AR transcription	-	(72)
NKX3.1	Decreased	Downregulates AR transcription and inhibits AKT signaling	-	(73)
MDM2	Decreased	Induces polyubiquitination of AR	Therapeutic target	(74,75)
IRF8	Decreased	Promotes AR degradation	Therapeutic target	(76)
RGS2	Increased	Inhibits ERK activity	Prognostic marker	(77-79)
HepaCAM	Decreased	Inhibits the IL-22/p-STAT3 axis and Notch signaling	Prognostic marker	(165,166)
MYSM1	Decreased	Reduces AR activity	-	(80)

PRMT5, protein arginine methyltransferase 5; 4-1BBL, 4-1BB ligand; YB-1, Y-box binding protein-1; TWIST1, twist basic helix-loop-helix transcription factor 1; LIMK2, LIM-domain kinase-2; AURKA, aurora A kinase; Siah2, seven in absentia homolog 2 (drosophila); RNF6, ring finger protein 6; FKBP4, FK506 binding protein 4; GRB10, growth factor receptor bound protein 10; LCN2, lipocalin 2; AKR1C3, ido-keto reductase family 1 member C3; ERRα, estrogen-related receptor α; DHX15, DEAH-box RNA helicase family member 15; TXNDC5, thioredoxin domain-containing protein 5; OCT1, octamer transcription factor 1; NCoA2, nuclear receptor coactivator 2; FOXA1, forkhead box protein A1; YAP1, yes-associated protein 1; STAT3, signal transducer and activator of transcription 3; IRE1α, inositol-requiring enzyme 1 α; TLX, orphan nuclear receptor; NKX3.1, NK3 homeobox 1; MDM2, mouse double minute-2; IRF8, interferon regulatory factor 8; RGS2, G-protein signaling proteins 2; HepaCAM, hepatocyte cell adhesion molecule; MYSM1, Myb-like SWIRM and MPN domains 1.

survival, differentiation, invasion, metastasis, extracellular matrix degradation and angiogenesis (85). Consequently, any RTK ligand, such as growth factors or proteins, can regulate any of the signal factors that lead to CRPC (87-89). A study has shown that gremlin1, a fibroblast growth factor receptor 1 (FGFR1) ligand, promotes CRPC by activating the FGFR1/MAPK signaling pathway, and that the transcription of GREM1 is suppressed by AR and released following ADT (90). MET, the hepatocyte growth factor receptor, is almost exclusively expressed in CRPC (91). Moreover, MET overexpression in DU145 cells enhances cell migration, cell invasion and the acquisition of a stem-like phenotype (91). The hedgehog (Hh) ligands, sonic and desert, have been reported to be elevated in castration-induced CRPC (92). The expression of Hh promotes CRPC progression by eliciting paracrine effects on epithelial growth and differentiation (93).

Target genes of Hh signaling include several growth factors, such as insulin-like growth factor binding protein (Igfbp)-6 and Igfbp-3 (93), indicating that Hh signaling may activate RTK pathways in CRPC.

Caveolin-1 (Cav-1) expression has been shown to be upregulated in immunohistochemical assays of biopsies from patients with CRPC, compared with primary PCa samples (94). Moreover, Cav-1 promotes the invasion and migration of CRPC cells by activating the H-Ras/phospholipase Cε signaling pathway in the cell membrane caveolae (94). IL-6 exhibits the capability to enhance not only the activity and expression of the AR but also to activate the ERK1/2-MAPK signaling pathway (64,65,95). Upon binding to IL-6, Janus kinase (JAK) phosphorylates Src homology 2 domain-containing tyrosine phosphatase 2 (95). This event triggers the activation of Ras, setting off a cascade of reactions that lead to the sequential activation of Raf, followed by MEK and culminating in the activation of ERK. Additionally, the levels of zinc finger and BTB domain-containing protein 46 (ZBTB46) and leukemia inhibitory factor (LIF) are associated with PCa progression (24,96). LIF-induced androgen-independent proliferation, invasion and NE transdifferentiation via activation of ZBTB46 expression further activates the JAK/STAT and Ras/MAPK pathways in CRPC cells (24,96,97). Although diminished or lost somatostatin receptor 2 (SSTR2) expression is consistent with advanced tumor grade (98), SSTR2 expression is elevated following hormone depletion in PCa and contributes to NEPC via modulating MAPK through G protein-dependent mechanisms (99). In addition, patients with mCRPC have higher G protein coupled receptor 30 (GPR30) expression compared with primary PCa (100). Moreover, GPR30 is also upregulated in stromal cells, promoting PCa cell invasion (100,101). Notably, GPR30 induces the growth of breast and ovarian cancer cells, whereas the activation of GPR30 by a selective agonist, G-1, inhibited the growth of androgen-dependent and androgen-independent PCa cells *in vitro* and *in vivo* via continuous activation of ERK1/2 and c-jun/c-fos (102). GPR30 can also promote the proliferation and migration of PCa cells in a paracrine manner (101). Considering the contradictory effect of GPR30 in stromal and epithelial cells on PCa development, there is a need for further studies to investigate the underlying mechanism.

PI3K/AKT/mTOR signaling pathway. PI3K/AKT/mTOR pathway dysregulation facilitates CRPC progression (86). The diversity of proteins involved in PI3K/AKT/mTOR signaling and CRPC is associated with enhancing the activation of the PI3K/AKT/mTOR pathway (103,104). For example, prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that dysregulates AR signaling (105). PSMA is positively correlated with PCa progression by redirecting MAPK to activate the PI3K/AKT pathway (106). PSMA expression is upregulated in higher tumor grades and in the development of castration resistance (107). The use of PSMA radioligand in diagnosing and treating PCa has been under studied (108-110). However, the expression of PSMA in PCa biopsies is highly variable both within one patient and between different patients, which restricts the application of PSMA scans and PSMA-targeted therapies (111).

A study has shown that the tumor suppressor gene, PTEN, is downregulated in PCa, inhibiting the activation of the PI3K/AKT/mTOR pathway (112). Consequently, the expression levels of class III β-tubulin (TUBB3) and PTEN are inversely regulated, suggesting that TUBB3 is related to PTEN deficiency, and that TUBB3 may activate the PI3K/AKT pathway (112). TUBB3, a primarily neural isoform of β-tubulin, is significantly upregulated when ADPC progresses to CRPC (113). In addition, TUBB3 is an adverse prognostic factor in patients with mCRPC treated with docetaxel (114). Moreover, the TUBB3 protein is stabilized by Src-mediated tyrosine phosphorylation, promoting the stabilization of mitotic spindles in dividing cells and resulting in resistance to taxane therapy (115).

The hyaluronan-mediated motility receptor (RHAMM) signal transduction pathway not only activates cell cycle genes but also plays a fundamental role in cell growth, differentiation and motility (116). ADT upregulates the expression of RHAMM in patients with PCa (116). In addition, the expression of RHAMM is upregulated when tumor cells progress to a castration resistant stage. Hyaluronan binds to RHAMM and activates its downstream proteins, including ROK1, GRB2-associated binding protein-1, PI3K*p110α and eukaryotic translation initiation factor 4E family member 3, to facilitate cell motility and accelerate cell invasion and metastasis of CRPC cells, compared with ADPC cells (117). IL-6 possesses the ability to not only activate ERK but also initiate signal transduction via the PI3K signaling pathway (95). Activation of PI3K leads to the recruitment of the protein kinase, AKT, to the plasma membrane and subsequent binding, and the complex crosstalk between the PI3K/AKT/mTOR pathway and multiple interacting cell signaling cascades can further promote CRPC progression (86,95).

The calcium-sensing receptor (CaSR) is a receptor for several ligands, including Ca^{2+}, amino acids, vitamin D and IL-6 (118). The expression of CaSR is upregulated in mCRPC and NEPC and is associated with shorter overall survival (119,120). CaSR is a potential NE marker that promotes NE differentiation in PCa (119). CaSR enhances the proliferation and migration of PCa cells by both ERK and AKT signaling pathways (121,122). Similarly, sperm-associated antigen 5 (SPAG5) expression is markedly upregulated in primary PCa (compared with normal tissues), metastatic PCa (compared with primary PCa), CRPC (compared with HNPC) and NEPC (compared with prostate adenocarcinoma) (123). SPAG5 promotes colony formation, migration and invasion of PCa cells and increases both the tumor volume and weight in mice xenograft models (123). In addition, targeting the PI3K/AKT/mTOR signaling pathway leads to the downregulation of SPAG5 in LNCaP cells, indicating that SPAG5 is involved in the AKT/mTOR pathway (124).

TGF-β/SMAD signaling pathway. Both Mediator complex subunit 12 (MED12) and MED15 are components of the Mediator complex, which modulates TGF-β receptor signaling (125). A study has shown that nuclear MED12 is upregulated in 40% of distant mCRPC and 21% of local recurrent CRPC, inconsistent with the low frequencies (11%) in HNPC and the lack of expression in BPH tissues (126). Similar to MED12, MED15 is upregulated in both distant mCRPC (76%) and local recurrent CRPC (70%), compared with HNPC or BPH tissues (127). In addition, expression of nuclear MED12 was significantly correlated with the nuclear

localization of phosphorylated SMAD3, whereas MED12 knockdown reduced levels of the TGF-β target gene, vimentin, and promoted the expression of p27 (126). It was also found that MED15 expression is upregulated in CRPC tissues after ADT (72%) and the CRPC cell line, PC3 (128). Moreover, inhibition of MED15 expression reduced viability and induced apoptosis in LNCaP cells after ADT. The expression of MED15 is positive correlated with the phosphorylation level of both AKT and SMAD3 (128).

A study has shown that the transmembrane co-receptor, neuropilin-1 (NRP1), promotes cancer progression via TGF-β/SMAD signaling (129). NRP1, which is repressed by androgen, is upregulated in mCRPC, and the inhibition of NRP1 expression significantly restores the invasive and metastatic ability of PC3 cells (130). Similarly, the κ-type opioid receptor (OPRK1) is a G protein-coupled receptor repressed by the AR in androgen-containing medium (131). OPRK1 expression is significantly induced by ADT and is upregulated during CRPC progression. OPRK1 supports the androgen-independent growth of VCaP cells, and the SMAD6 pathway is downregulated by OPRK1 blockade under castrated conditions (131).

Wnt/β-catenin signaling pathway. A study has shown that the Wnt secretion mediator, Wntless (WLS), is a significant driver of NEPC and promotes the growth of NEPC cells by activating the receptor tyrosine kinase-like orphan receptor 2/protein kinase Cδ/ERK signaling pathway (132). However, the expression of WLS is repressed by the AR in HNPC cells. It was also revealed in the same study that the expression of WLS is enhanced in both CRPC and NEPC tumors.

NF-κB signaling pathway. It is well-known that histone modifications are essential in gene transcription and participate in tumor progression. Nuclear receptor binding SET domain 2 (NSD2, also termed MMSET), a histone methyltransferase, catalyzes the mono- and di-methylation of H3K36 (133). Analysis of clinical samples demonstrated that NSD2 expression was increased in CRPC samples compared with HNPC (134). In addition, NF-κB is constitutively activated by the cytokine autocrine loop mediated via NSD2 binding to the chromatin of NF-κB, which improves survival and promotes the proliferative capacity of tumor cells (135).

HOXB13 was significantly upregulated in hormone-refractory tumors compared with tumors without PSA after initial treatment (136). Additionally, heightened expression of HOXB13 was correlated with an increased growth advantage in PCa cells under conditions of low or absent androgen levels. This effect was linked to the activation of the retinoblastoma tumor suppressor (RB)/E2F signaling pathway and the suppression of c-Jun N-terminal kinase (JNK)/c-Jun expression, which was achieved through the inhibition of the $p21^{waf}$ tumor suppressor (136,137) Furthermore, another study found that HOXB13 promotes PCa invasion and metastasis by reducing intracellular zinc levels, consequently stimulating NF-κB signaling (138). This suggests that HOXB13 plays a pivotal role in enhancing the malignant characteristics of PCa. By contrast, in ~30% of mCRPC cases, hypermethylation and subsequent downregulation of the HOXB13 gene were observed (139). The loss of HOXB13 was associated with lipid accumulation in PCa cells, leading to increased cell motility and enhanced xenograft tumor metastasis. Therefore, the impact of HOXB13 on the proliferation and migration of PCa cells in various cellular contexts and under different androgen level environments has yielded conflicting research findings. These conflicting results underscore the complexity of the involvement of HOXB13 in PCa and emphasize the importance of further research to gain a comprehensive understanding of its effects.

Other proteins. Numerous studies have demonstrated that some PCa cells can survive ATTs via lineage transition, such as transforming to NEPC cells for survival (140-142). NEPC is an aggressive subtype of CRPC with poor overall survival (142). Several proteins have been reported to participate in NE lineage transition, such as the previously mentioned SSTR2 (99), CaSR (118) and SPAG5 (123). However, the mechanisms of certain other proteins, such as splicing factor serine/arginine repetitive matrix 4 (SRRM4) (143) and the DNA topology modulator, DEK (24), detected in NEPC are unknown or do not involve the aforementioned RTKs/MAPK/MEK/ERK, PI3K/AKT/mTOR, TGF-β/SMAD and Wnt/β-catenin, NF-κB pathways. The expression of SRRM4 and DEK, are both upregulated in NEPC (143,144). SRRM4 is a vital driver gene that not only promotes PCa cell survival, proliferation and tumorigenesis but also alters cellular morphology and transforms ADPC cells into NEPC xenografts *in vivo* (24). SRRM4 crosstalks with other signaling pathways, such as the AR, p53 and RB1 pathways, to modulate the phenotypical reprogramming of PCa cells (145). DEK induces tumorigenesis and neoplastic progression by promoting cell division, inhibiting cell differentiation, senescence and apoptosis, and cooperating with transforming oncogenes (146). Inhibition of DEK significantly reduces cell proliferation, migration and invasion in PC3 cells (143).

The development of treatment resistance in cancer cells is accompanied by metabolic adaptations that enhance their survival under stress-inducing conditions (147). Both the mitochondria and the endoplasmic reticulum (ER) play a pivotal role in modulating stress-signaling pathways. In a previous study, a fraction of tyrosine phosphatase receptor type F polypeptide interacting protein α4 (PPFIA4) interacted with methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), a critical enzyme for one-carbon metabolism (148). PPFIA4 was located in the mitochondria, and its expression was significantly upregulated in CRPC samples compared with localized PCa. ADT induced PPFIA4 translocation into the mitochondria, where it subsequently bound to MTHFD2, promoting the phosphorylation of MTHFD2 (148). Subsequently, the production of NADPH was upregulated, promoting the survival of tumor cells in androgen deprivation-induced mitochondrial dysfunction. The expression of malate dehydrogenase 2 (MDH2), another mitochondrial tricarboxylic acid cycle enzyme, is significantly upregulated in CRPC compared with PCa and BPH (149). Moreover, inhibition of MDH2 further increases the docetaxel-induced phosphorylation of JNK, activating transcription factor (ATF) 2 and c-Jun (150). Consequently, the anti-apoptotic protein, B-cell lymphoma 2, is inactivated by the phosphorylated JNK, which promotes the initiation of mitochondria-based apoptosis. In addition, the ER membrane-associated protein, thioesterase superfamily member 6 (THEM6), is an ADT-induced protein that is significantly increased in CRPC cells and that alters ER

function, promoting *de novo* sterol biosynthesis and mediating lipid-mediated activation of ATF4 to maintain the growth and survival of CRPC cells (151). Metabolic pathways, such as lipogenesis, cholesterol biosynthesis and ketogenesis, play essential roles in PCa progression (152-154). The expression of acetyl-coenzyme A acetyltransferase 1 (ACAT1) is upregulated in patients receiving ADT and during CRPC progression, with metastatic bone lesions containing the most prominent expression patterns (154,155).

The three oncogenic PIM family kinases, PIM1-3, have been implicated in the development of PCa. In CRPC biopsies, both PIM1 and PIM2 expression levels were significantly upregulated compared with primary PCa samples (156). The expression of the PIM family members was also positively correlated with ERG and MYC oncoproteins. Notably, ERG directly binds to the promoter of all PIM genes, upregulating both gene and protein expression levels of the PIMs (156). Serum fibrinogen γ (FGG) is a downstream target gene regulated by the IL-6/STAT3 pathway. The expression of FGG was significantly higher in patients with CRPC than in patients with localized PCa (157). In addition, FGG knockdown resulted in the inhibition of proliferation, migration and invasion capabilities while inducing the apoptosis of PCa cells (157). Nonetheless, there is a requirement for additional research to explore the downstream pathways associated with PIM and FGG that contribute to the progression of CRPC. Expression of the nuclear Notch homolog 1, translocation-associated (Notch1) receptor intracellular domain, is significantly upregulated in high Gleason score (8-10) cases of HNPC and in almost all mCRPC samples, but not in benign samples or low Gleason score (<8) localized PCa (158). Furthermore, there is a synergistic effect among Notch1 with the AKT, Myc and Ras/Raf/MAPK pathways, promoting the prostate castration-resistant phenotype (158). However, Notch1 contradictorily plays both a suppressive and oncogenic role in PCa development, which requires further investigation (159).

Proteins repressing CRPC progression in AR-independent pathways. Repressors, unlike the extensively examined proteins that drive CRPC through AR-independent pathways, have not received adequate research attention. Two examples of repressors are adenosine monophosphate-activated protein kinase (AMPK) and aconitase 2 (ACO2). AMPK restrains CRPC progression by inhibiting both fatty acid and cholesterol synthesis (160). In a previous study, AMPK was found to be downregulated in CRPC specimens compared with HNPC specimens due to phosphorylation, which promoted CRPC progression (161). Notably, ACO2 expression was higher in PCa than in BPH but lower in CRPC than in PCa (149). ACO2 promoted *in vivo* prostate cancer progression through promoting mitochondrial citrate synthesis to facilitate *de novo* lipogenesis. Sirtuin 3, which acetylates ACO2, is upregulated following ATT (162). However, the role and exact mechanism by which ACO2 expression is downregulated in CRPC remains unknown.

The G protein-coupled receptor smoothened (SMO) plays an important role in the Hh pathway and the loss of SMO was observed in all NEPC specimens but only in 9% (2 of 22) of high-grade ADPC samples (163). Moreover, the loss of SMO attenuated AR signaling, indicating that the Hh pathway is inhibited during the pathogenesis of NEPC. Previously, it was reported that activation of the IL-6/STAT3 pathway and the downstream target genes of this pathway could promote the progression of CRPC (64). However, hepatocyte cell adhesion molecule (HepaCAM) is a tumor suppressor that is downregulated in CRPC tissues compared with matched primary PCa tissues (164), and it suppresses the proliferation, migration and invasion of PCa cells by decreasing the expression of pSTAT3, G1/S-specific cyclin-D1, MYC proto-oncogene bHLH transcription factor, matrix metallopeptidase (MMP) 2, MMP9 and vascular endothelial growth factor (165). More notably, HepaCAM inhibits the metastasis of CRPC cells from the prostate to the lungs (165). These AR-independent signaling proteins and their associated pathways are described in Fig. 2 and Table II.

4. Clinical value of CRPC-related proteins

Diagnostic markers. In an earlier discussion, the proteins exhibiting changes in expression within CRPC clinical samples were explored, highlighting their potential clinical significance, including roles as diagnostic markers, indicators for therapeutic monitoring and targets for CRPC treatment, as detailed in Tables I and II. Conventional methods like elevated PSA, bone scans, biopsies and positron emission tomography (PET) imaging are commonly employed for detecting CRPC recurrence or new metastases (166). However, the diagnostic accuracy of these methods is low and there are relatively few diagnostic markers for CRPC. Since all of the aforementioned proteins are significantly increased or decreased in CRPC tissues, they can serve as diagnostic markers for CRPC. However, unfortunately most of these proteins have low specificity for CRPC. PSMA-PET, a new sensitive imaging tool for PCa, has been developed to help clinicians determine the appropriate treatment strategy for advanced PCa (111). In addition, CRPC samples from a tissue microarray exhibited elevated FKBP4 protein expression levels with an average FKBP4 histoscore of 87.1, compared with a score of only 14.4 for HNCP (Wilcoxon rank sum test, $P=2.301x10^{-7}$) (38), suggesting that FKBP4 may serve as a CRPC diagnostic marker. Additional proteins that could be used as markers for the diagnosis of NEPC include WLS (132), SRRM4 (144), DEK (143), SSTR2 (98), CaSR (120), SPAG5 (167) and SMO (163). Among them, CaSR has been found to be highly expressed in all cases of NEPC (119).

Prognostic markers. The upregulated expression of certain proteins in PCa tissues, such as GRB10 (41), AKR1C3 (44), DHX15 (48), NCoA2 (51), protocadherin B9 (68), CDK19 (70), MED15 (128), DEK (146) and THEM6 (151), is associated with a poorer patient outcome. By contrast, the downregulation of HepaCAM is strongly correlated with a worse progression-free survival (164). High expression levels of YB-1 (30), RGS2 (76) and CaSR (120) predict a poor cancer-specific survival rate in patients with CRPC. Furthermore, high expression of Cav-1 in CRPC specimens indicates an increased risk of HNPC progression to CRPC and is correlated with a shorter recurrence-free survival time in patients with CRPC (94). However, high FKBP4 protein expression exhibited a lower survival rate (38%) compared with low expression (79%) for patients with

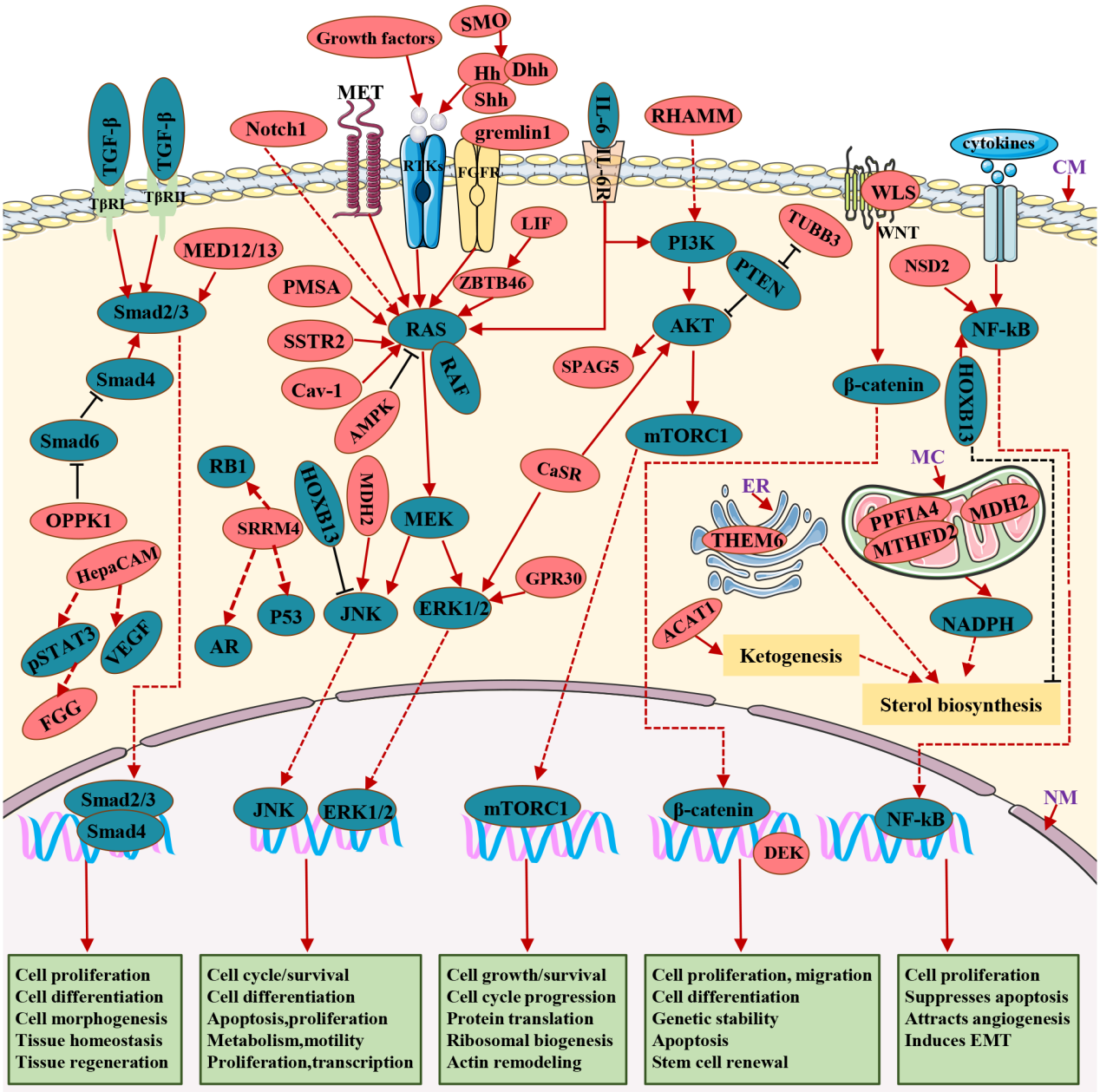

Figure 2. Proteins involved in AR-independent pathways. Proteins dysregulated in CRPC tissues and that bypass the AR during CRPC development are mainly associated with five pathways: RTKs/MAPK/MEK/ERK, TGF-β/SMAD, PI3K/AKT/mTOR, Wnt/β-catenin and the NF-κB pathway (activated by cytokines). These dysregulated proteins establish a complex network in the five signaling pathways, which promote the progression of CRPC. Proteins shown in red or blue background are those described in the present article or other studies, respectively. In addition, the arrowhead indicates positive regulation of the target protein and the blunt head indicates negative regulation of the target protein. Full lines indicate direct regulation and dotted lines indicate indirect regulation. MEK, mitogen-activated extracellular signal-regulated kinase; ERK, extracellular regulated protein kinase; TGF, transforming growth factor; FGFR, growth factor receptor; Hh, hedgehog; Cav-1, caveolin-1; ZBTB46, zinc finger and BTB domain-containing protein 46; LIF, leukemia inhibitory factor; SSTR2, somatostatin receptor 2; GPR30, G protein coupled receptor 30; TUBB3, class III β-tubulin; RHAMM, hyaluronan-mediated motility receptor; CaSR, calcium-sensing receptor; SPAG5, sperm-associated antigen 5; MED12, mediator complex subunit 12; SMAD3, mothers against decapentaplegic homolog 3; WLS, wntless; NSD2, nuclear receptor binding SET domain2; SRRM4, serine/arginine repetitive matrix 4; PPFIA4, fraction of tyrosine phosphatase receptor type F polypeptide interacting protein α 4; MTHFD2, methylenetetrahydrofolate dehydrogenase 2; MDH2, malate dehydrogenase 2; JNK, c-Jun N-terminal kinase; THEM6, the ER membrane-associated protein, thioesterase superfamily member 6; ACAT1, elevated acetyl-coenzyme A acetyltransferase 1; Notch1, nuclear notch homolog 1; AMPK, adenosine monophosphate-activated protein kinase; SMO, smoothened; HepaCAM, hepatocyte cell adhesion molecule; AR, androgen receptor; HOXB13, Homeobox B13; PI3K, phosphatidylinositol-3 kinase; AKT, Ak strain transforming; PTEN, tumor suppressor gene; DEK, the DNA topology modulator; SMAD, mothers against decapentaplegic homolog; RTKs, receptor tyrosine kinases; OPPK1,ovarian pelvic pain killer 1; VEGF, vascular endothelial growth factor; JNK, c-jun N-terminal kinase; PMSA, prostate-specific membrane antigen; NF-kB, nuclear factor-kappa B; mTORC1, mammalian target of rapamycin complex 1; NADPH, nicotinamide adenine dinucleotide phosphate; MET, mesenchymal-epithelial transition factor; pSTAT3, phosphorylated signal transducer and activator of transcription 3; CM, cytomembrane; ER, endoplasmic reticulum; MC, mitochondrion; NM, nuclear membrane.

HNPC but not with CRPC (38). Besides, increased expression of CaSR in mCRPC can accurately indicate poorer survival outcomes (120).

Predictive markers. Protocadherin B9 and NRP1 serve not only as biomarkers for predicting the overall survival of patients with PCa but also as predictive indicators for non-recurrence

Table II. Signaling pathways and clinical values of proteins involved in AR-independent pathways.

Protein	Expression	Signaling pathway	Clinical value	(Refs.)
Gremlin1	Increased	Activates RTKs/MAPK/MEK/ERK signaling	Therapeutic target	(91)
MET	Increased	Activates RTKs/MAPK/MEK/ERK signaling	-	(92)
Shh/Dhh	Increased	Activates Hh signaling	Therapeutic target	(93)
Cav-1	Increased	Activates H-Ras/PLCε	Diagnostic or prognostic marker, therapeutic target	(95)
IL-6	Increased	RTKs/MAPK/MEK/ERK and PI3K/AKT/mTOR signaling	Therapeutic target	(96)
ZBTB46	Increased	Promotes NE differentiation	-	(23,98)
LIF	Increased	Activates JAK/STAT and RAS/MAPK	-	(97)
PSMA	Increased	Activates MAPK to PI3K/AKT signaling	Diagnostic marker, therapeutic target	(107-112)
TUBB3	Increased	Activates PI3K/AKT signaling	Predictive marker	(114-117)
RHAMM	Increased	Activates ROK/PI3K signaling	-	(118,119)
CaSR	Increased	Activates ERK and AKT signaling	Prognostic marker, therapeutic target	(120-123)
SPAG5	Increased	Involved in the AKT/mTOR pathway	Diagnostic marker	(125-127)
MED12/MED15	Increased	Activates TGF-β/SMAD signaling	Prognostic marker	(128-131)
NRP1	Increased	Activates TGF-β/SMAD signaling	Predictive marker	(132,133)
OPRK1	Increased	Activates TGF-β/SMAD signaling	-	(134)
WLS	Increased	Activates ROR2/PKCδ/ERK signaling	Diagnostic marker, therapeutic target	(135)
NSD2	Increased	Activates NF-κB signaling	-	(136-138)
SRRM4	Increased	Promotes NE transdifferentiation	Diagnostic orprognostic marker	(144,146,147)
DEK	Increased	Regulates DNA damage response signaling and repair	Diagnostic or prognostic marker	(145,148)
PPFIA4	Increased	Increases NADPH synthesis	-	(150)
THEM6	Increased	Stabilizes the endoplasmic reticulum	Prognostic marker, therapeutic target	(153)
ACAT1	Increased	Promotes fatty acid and ketone body synthesis	Prognostic marker	(156,157)
AMPK	Decreased	Inhibits fatty acid or cholesterol synthesis	-	(161,162)

JAK, Janus kinase; MET, mesenchymal-epithelial transition factor; Cav-1, caveolin-1; ZBTB46, zinc finger and BTB domain-containing protein 46; LIF, leukemia inhibitory factor; PSMA, prostate-specific membrane antigen; TUBB3, class III β-tubulin; RHAMM, hyaluronan-mediated motility receptor; CaSR, calcium-sensing receptor; SPAG5, sperm-associated antigen 5; MED12/MED15, mediator complex subunit 12/15; NRP1, neuropilin-1; OPRK1, k-type opioid receptor; WLS, wntless; NSD2, nuclear receptor binding SET domain2; SRRM4, serine/arginine repetitive matrix 4; DEK, the DNA topology modulator; PPFIA4, fraction of tyrosine phosphatase receptor type F polypeptide interacting protein α 4; THEM6, the ER membrane-associated protein, thioesterase superfamily member 6; ACAT1, elevated acetyl-coenzyme A acetyl-transferase 1; AMPK, adenosine monophosphate-activated protein kinase.

in those undergoing ATT (68,130). Moreover, patients exhibiting low TUBB3 expression experience a significant decline in PSA levels of at least 10% in 89% of cases, whereas this reduction is seen in only 65% of patients with high TUBB3 expression (P=0.0267). It is suggested that patients with PCa with low TUBB3 expression will have a good response to ATT (114).

Therapeutic targets. Notably, inhibition of proteins involved in AR signaling can suppress AR^+ CRPC cell proliferation *in vitro* and tumor growth *in vivo*. These proteins include ERRα (45), PRMT5 (25), LIMK2 (33), AURKA (34), YAP1 (59) and CDK8/CDK19 (70). Either one or a combination of these proteins with an androgen signaling inhibitor can inhibit CRPC cell growth (90,92,94,121,148). A total of 156 out of 180 kinase phosphorylation sites, including ERK and RSK, were activated in CRPC cells, leading to increased phosphorylation of YB-1, which is a key molecule in the progression to CRPC (28). YB-1 signaling regulated AR V7 expression, and YB-1 inhibition augmented the anticancer effect of enzalutamide. Targeting proteins associated with AR-independent pathways has also shown promising effectiveness. The use of PSMA-PET in combination therapy is a viable option in second-line treatment for CRPC, and ^{177}Lu-PSMA is utilized

for radioligand therapy in select patients with CRPC (168). Notably, the MTHFD2 inhibitor, DS18561882, combined with enzalutamide caused a significant restraint of the proliferation and growth of CRPC cells (148). In addition, calcilytics, NPS2143 and Calhex 231, decreased CaSR expression to inhibit CRPC cell proliferation and migration (94). Similarly, downregulation of Cav-1 expression by simvastatin promoted the antitumor effects of AR antagonists (121). Treatment with TAK-441 (an SMO antagonist) restricted paracrine Hh signaling in tumor stroma disrupting the castration-resistant progression of LNCaP xenografts (92). Finally, inhibition of the Wnt signaling by LGK974 delayed the growth of NE prostate tumor xenografts in mice (132). To target DNPC cells, a monoclonal antibody against Gremlin1 inhibits the proliferation and sphere formation of PC3 and LNCaP cells as well as PC3 xenografts (90). Moreover, Gremlin1-specific antibody combined with enzalutamide exerts a synergistic tumor-inhibitory effect.

5. Conclusions

Collectively, the present review summarizes the proteins dysregulated in CRPC tissues and highlights the expression levels and distribution patterns of these proteins in HRPC, compared with CRPC, together with the mechanisms they regulate in CRPC development. The expression levels of these proteins were verified through IHC tests on tissues from clinical patients. Proteins that were only detected in cell lines, xenograft mice, serum or succus prostaticus were not included in the present review. In addition, fusion proteins generated by gene rearrangements, such as PTEN and ER and protein variants, including AR-splice V7 were not described in the present study.

Certain proteins may exert their influence during the progression of CRPC through both AR-dependent and AR-independent molecular mechanisms. For instance, IL-6 and its downstream tyrosine kinases not only directly activate the AR but also promote CRPC through the RTKs/MAPK/MEK/ERK and PI3K/AKT/mTOR AR-independent pathways. Another example is HOXB13, which is strategically positioned at the reprogrammed AR binding sites within PCa tissues (80). HOXB13 serves as a multifaceted regulator of AR biology, either activating or inhibiting the transcription of distinct AR target genes via the AR-dependent pathway, thereby impacting disease progression. Simultaneously, HOXB13 has been reported to promote the progression of CRPC through the AR-independent NF-κB and JNK/c-Jun pathways. However, it is evident that there exist conflicting research findings regarding the precise impact of HOXB13 on CRPC progression. These discrepancies underscore the need for a more comprehensive and in-depth research approach to provide a clearer understanding of the role of HOXB13 in CRPC. Furthermore, certain proteins influence not just a single signaling pathway, but they concurrently engage multiple pathways, resulting in a complex tumorigenesis regulation network. For instance, IL-6 activates the Ras and PI3K signaling pathways in the development of CRPC, while CaSR activates the ERK and AKT signaling pathways in CRPC progression.

Targeting a single protein might not yield an effective treatment for CRPC, as inhibiting one pathway could potentially trigger compensation through another pathway. Notably, studies have illustrated that ADT plays a role in regulating cancer cell adaptation through the modulation of protein expression and epigenetic modifications. Cancer cells activate novel pathways in an ongoing process of adaptation and evolution, which consequently results in the development of drug resistance, an almost inevitable outcome (169). Certain studies have unveiled an array of distinct mechanisms underpinning cancer drug resistance. Resulting mutations can arise within the same protein or across different proteins (170,171), as well as within the same pathway or parallel pathways (172), effectively circumventing intercepted signaling cascades (173). Additionally, ADT triggers the activation of various proteins, including Gremlin1, MET, ZBTB46, SSTR2, RHAMM, NRP1, OPRK1, ACAT1 and ACO2. These proteins contribute to tumor cells acquiring heightened capabilities in proliferation, invasion and migration, along with increased resistance to apoptosis, ultimately culminating in the progression towards CRPC.

In recent decades, there has been extensive research focused on AR^+ CRPC and NEPC, while the interest in DNPC has been steadily growing. It is anticipated that additional proteins will continue to be discovered and characterized in DNPC. Given the high heterogeneity of tumors, it is imperative to explore new proteins and molecular mechanisms that underlie the development of CRPC. This will yield new insights for the development of precision therapeutics.

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Authors' contributions

KF and CL wrote the manuscript and abstract; PK wrote the conclusion section and revised the paragraph structure of the manuscript; WW completed the figures and tables; ZT participated in revising and editing the manuscript; WL provided constructive feedback and guidance, completed critical revisions and proofread the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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