

## Phosphoprotein phosphatase 1-interacting proteins as therapeutic targets in prostate cancer

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### Abstract

Prostate cancer is a major public health concern worldwide, being one of the most prevalent cancers in men. Great improvements have been made both in terms of early diagnosis and therapeutics. However, there is still an urgent need for reliable biomarkers that could overcome the lack of cancer-specificity of prostate-specific antigen, as well as alternative therapeutic targets for advanced metastatic cases. Reversible phosphorylation of proteins is a post-translational modification critical to the regulation of numerous cellular processes. Phosphoprotein phosphatase 1 (PPP1) is a major serine/threonine phosphatase, whose specificity is determined by its interacting proteins. These interactors can be PPP1 substrates, regulators, or even both. Deregulation of this protein-protein interaction network alters cell dynamics and underlies the development of several cancer hallmarks. Therefore, the identification of PPP1 interactome in specific cellular context is of crucial importance. The knowledge on PPP1 complexes in prostate cancer remains scarce, with

only 4 holoenzymes characterized in human prostate cancer models. However, an increasing number of PPP1 interactors have been identified as expressed in human prostate tissue, including the tumor suppressors TP53 and RB1. Efforts should be made in order to identify the role of such proteins in prostate carcinogenesis, since only 26 have yet well-recognized roles. Here, we revise literature and human protein databases to provide an in-depth knowledge on the biological significance of PPP1 complexes in human prostate carcinogenesis and their potential use as therapeutic targets for the development of new therapies for prostate cancer.

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**Key words:** Prostate cancer; Reversible phosphorylation; Phosphoprotein phosphatase 1; Phosphoprotein phosphatase 1-interacting proteins; Protein complexes; Therapeutic targets

**Core tip:** Protein kinases and phosphatases are challenging and valuable therapeutic targets for cancer. Here, we revise the relevance of phosphoprotein phosphatase 1 and its interactors for prostate carcinogenesis. Although only 4 complexes are characterized in human prostate cancer models, 81 additional interactors are expressed in human prostate tissue and, at least, 29 of which are involved in prostate carcinogenesis. This complex network has promising roles in the development of new therapies for prostate cancer. Therefore, efforts should be made in order to characterize their biological significance in prostate carcinogenesis.

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## INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed non-cutaneous cancer and a leading cause of cancer-related death in men worldwide<sup>[1]</sup>. In spite of the recent advances in early diagnosis and therapeutic management of the disease, prognoses are still poor once the disease progresses to castration-resistant and metastasizes, mainly to bone<sup>[2,3]</sup>. The urgent need for a panel of reliable biomarkers that could overcome the lack of cancer-specificity of prostate-specific antigen (PSA), as well as alternative therapeutic targets is challenging the scientific community<sup>[4]</sup>.

Reversible phosphorylation of proteins regulates more than 70% of all eukaryotic cellular processes<sup>[5]</sup>. Phosphorylation at serine (Ser) and threonine (Thr) residues is accomplished by protein Ser/Thr kinases (PSTKs) and reversed by protein Ser/Thr phosphatases (PSTPs)<sup>[6]</sup>. Deregulation of the counterbalanced action between PSTKs and PSTPs is frequently associated with system-wide disruption of signal transduction and malignant transformation of cells<sup>[7,8]</sup>. For this reason, emergent studies have been focused on large-scale examination of PCa phosphoproteome<sup>[9-12]</sup>. Androgen receptor (AR), for instance, is a phosphoprotein vital to the development and progression of PCa that presents, at least, 15 Ser and Thr phosphorylated residues. Phosphorylation of such residues modulates the transcriptional activity, subcellular localization, and stability of the AR<sup>[13]</sup>.

The mammalian genome encodes considerably more PSTKs than PSTPs-nearly 10 to 1<sup>[14]</sup>. Hence, the success of the protein reversible phosphorylation system depends on the ability of PSTPs to form stable complexes with other proteins, giving rise to a huge number of distinct holoenzymes. This is particularly true for phosphoprotein phosphatase 1 (PPP1), a major PSTP of eukaryotic cells that controls a myriad of processes: glycogen metabolism, muscle contraction, RNA splicing, apoptosis, protein synthesis, cell cycle, among others<sup>[15-18]</sup>. PPP1 exhibits an effective catalytic machinery, but lacks substrate specificity. Therefore, a number of regulatory subunits, also known as PPP1-interacting proteins (PIPs), have been associated with the spatiotemporal regulation of PPP1 activity<sup>[19]</sup>. Given the key roles of PIPs, efforts have been made to characterize PPP1 interactomes in human tissues and to identify disease relevant PIPs<sup>[20-24]</sup>.

In contrast to PSTKs, whose therapeutic benefits have been largely explored, PSTPs had been considered not “drug-targetable” for years and, thus, remain understudied<sup>[25,26]</sup>. In the case of PPP1, this vision is changing due to the increasing number of PPP1 holoenzymes that have been described, and which seem to be attractive targets for the development of new therapies<sup>[27]</sup>. In fact, pharmaceutical companies are being encouraged to pursue approaches that aim the inhibition or activation of PPP1 holoenzymes.

Here, we revise literature and human protein databases to provide an in-depth knowledge on the relevance of PIPs, expressed in human prostate tissue, for prostate

carcinogenesis. Moreover, we address the biological significance of their interaction with PPP1 and consider their potential use as therapeutic targets for the management of human PCa.

## RESEARCH

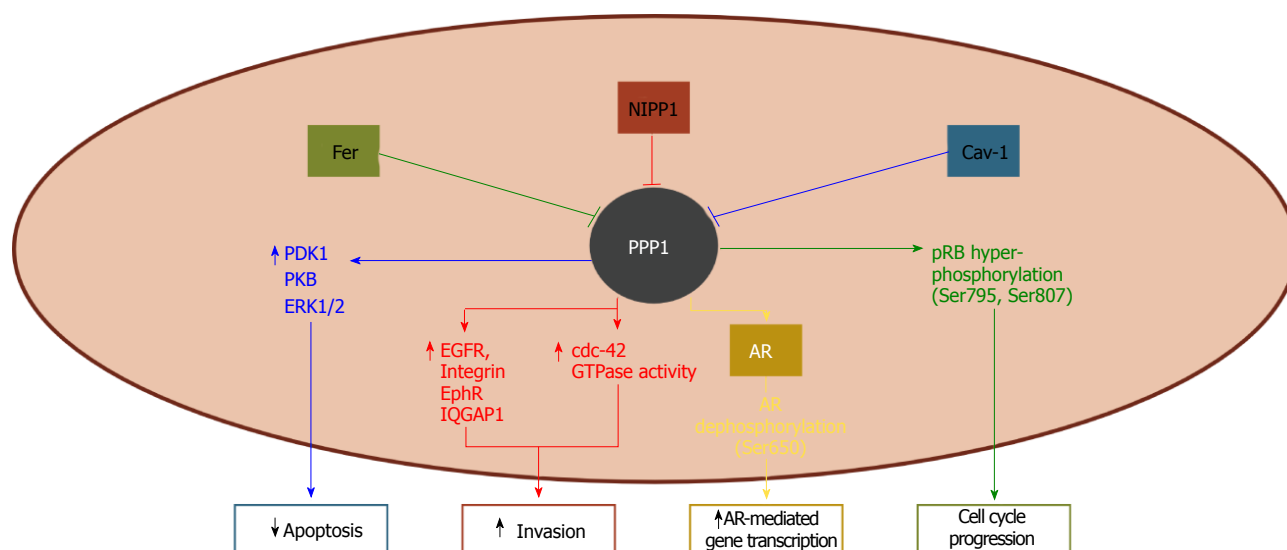
A comprehensive literature search of studies involving human samples or human cell lines was performed to identify articles on PPP1 and its interactors in human PCa. The Pubmed database was searched until May 2014 using the Medical Subject Heading (MeSH) whenever possible-for terms not included in MeSH (*e.g.*, “PP1-interacting protein” or “PP1 interactor”) a basic Pubmed search was employed instead. MeSH terms included: (“protein phosphatase 1” or (“PIP abbreviation) protein, human”) and (“prostate” or “prostatic neoplasms”). Reference lists of included studies and review articles were manually searched. The search was restricted to English-language literature.

For the sake of completeness, databases were reviewed: TissueNet and HIPPIE were used to identify additional PIPs expressed in human prostate tissue; BioGPS and The Human Protein Atlas were used to assess mRNA and protein expression levels, respectively; Gene Ontology Consortium was used to identify the biological processes in which proteins are involved; and, ScanProsite was used to identify PPP1 binding motifs for each PIP.

## OVERVIEW OF PHOSPHOPROTEIN PHOSPHATASE 1 STRUCTURE

PPP1 is one of the most conserved proteins in eukaryotic species<sup>[28,29]</sup>. In mammals, three genes encode the catalytic isoforms of the enzyme-PPP1CA, PPP1CB, and PPP1CC-which are ubiquitously expressed. Additionally, *PPP1CC* gene can generate two splice variants-PPP1CC1 and PPP1CC2-with the latter one being testis-enriched. This catalytic core is analogous, both in terms of structure and mechanism of action, to all members of the phosphoprotein phosphatase superfamily<sup>[30]</sup>. The major divergences among PPP1 isoforms are found at NH<sub>2</sub>- and COOH-terminal sequences<sup>[13]</sup>. Interestingly, the N-terminal was shown to influence the properties of the active site and, consequently, the function of the enzyme and its sensitivity to inhibitors<sup>[31,32]</sup>.

PPP1 catalytic isoforms are not found freely in cells. PPP1 catalytic subunit (PPP1C) interacts with diverse regulatory subunits, known as PIPs, thus enabling the formation of distinct PPP1 multimeric holoenzymes. The nature of the relationship between PPP1 and PIPs greatly varies: (1) PIPs can be substrates for PPP1, with their functions being directly controlled through dephosphorylation by PPP1; (2) PIPs can determine the substrate specificity of PPP1 by either targeting PPP1C to specific subcellular compartments or enhancing/suppressing PPP1C activity towards different substrates; and



**Figure 1 Phosphoprotein phosphatase-1 complexes described in human prostate cancer.** Phosphoprotein phosphatase-1 (PPP1) dephosphorylates pRb at Ser795 and Ser807 and contributes to its hypophosphorylated and activated state. The activity of Fer tyrosine kinase leads to the inhibition of PPP1 and consequent hyperphosphorylation of pRb, which culminate in poor G1-S transition control. The inhibition of PPP1 by the nuclear inhibitor of protein phosphatase 1 (NIPP1) increases the expression of epidermal growth factor receptor (EGFR), integrin, ephrin receptor (EphR), and Ras GTPase-activating-like protein IQGAP1, as well as enhances the activity of cdc-42 GTPase. This, in turn, promotes invasiveness of tumor cells. Caveolin-1 (Cav-1) inhibits PPP1 and potentiates the activity of phosphoinositide-dependent kinase-1 (PDK1), protein kinase B (PKB), and extracellular signal-regulated kinase 1/2 (ERK1/2), increasing cell survival. PPP1 specifically dephosphorylates androgen receptor (AR) at Ser650, thus inhibiting AR nuclear export and enhancing AR-mediated gene transcription.

(3) some PIPs are simultaneously substrates and regulators of PPP1<sup>[15,19]</sup>. More than 200 holoenzymes have already been identified and characterized, but thousand more remain unknown<sup>[15,33]</sup>.

PPP1 is not able to recognize a consensus sequence near the phosphorylated residue of its phosphotarget. Instead, PPP1C binding is mostly mediated by a short sequence (usually four to eight residues long), remote from the active site, commonly referred to as docking motif<sup>[19]</sup>. A number of novel PPP1 binding sites have been mapped in PIPs, such as SILK and MyPhoNE, but the RVxF motif (x = any amino acid except proline) is still the most frequent, described for more than 70% of PIPs<sup>[34,35]</sup>. It was also reported that some PIPs display isoform-specificity, suggesting that they possess isoform-specific docking motifs with putative location at the N- or C-terminal<sup>[19]</sup>.

## PHOSPHOPROTEIN PHOSPHATASE 1 COMPLEXES CHARACTERIZED IN HUMAN PROSTATE CANCER

Imbalances in the protein phosphorylation system strongly contribute to carcinogenesis. In addition to the constitutive activation of oncogenic protein kinases, there is also evidence that the gain and loss of phosphorylation sites in relevant signaling proteins occur in human cancers<sup>[36,37]</sup>.

PPP1 has been shown to take part of various complexes that control cancer hallmarks<sup>[24,38]</sup>. However, whether the role of PPP1 is pro- or anti-cancer largely depends on its interacting partners and cellular context. For instance, the interaction between PPP1CA and tensin1 impairs the

migration and invasion of cancer cells, and the interaction between PPP1CC and hScrib downregulates extracellular signal-regulated kinase (ERK) signaling, thus suppressing oncogene-induced transformation of primary rodent cells<sup>[39,40]</sup>. On the other hand, the interplay between PPP1 and transforming growth factor- $\beta$  (TGF $\beta$ ) drives malignant transformation of premalignant oral lesion cells<sup>[41]</sup>.

The knowledge on the involvement of PPP1 complexes in human PCa remains scarce. Few complexes have actually been characterized and even those are not fully understood; nonetheless, such complexes seem to have central roles in prostate carcinogenesis (Figure 1).

### Androgen receptor/Phosphoprotein phosphatase 1

AR plays a key role in the development of PCa and, accordingly, androgen deprivation therapy is the standard hormonal treatment for the disease<sup>[42,43]</sup>. AR is regulated by phosphorylation at multiple Ser residues and PPP1CA was shown to specifically reverse phosphorylation at Ser650<sup>[44]</sup>. Since phosphoSer650 mediates AR nuclear export, PPP1CA dephosphorylation increases the stability and the transcriptional activity of the AR (Figure 1)<sup>[44,45]</sup>. Besides being a substrate for PPP1, AR may also regulate the phosphatase activity by targeting it to chromatin, where PPP1 can modulate transcription and splicing events<sup>[44]</sup>.

### Nuclear inhibitor of protein phosphatase 1 / Phosphoprotein phosphatase 1

Nuclear inhibitor of protein phosphatase 1 (NIPP1) is a ubiquitously expressed scaffold protein that was firstly identified as a PPP1 inhibitor<sup>[46]</sup>. The interaction between NIPP1 and PPP1 was shown to orientate cell migration

by regulating the expression of integrin and growth factor receptors, and the activity of Cdc42 GTPase (Figure 1). Genetic disruption of this complex decreases the directional migration of PC-3 cells and impairs their migratory potential<sup>[47]</sup>.

#### ***Fer tyrosine kinase /Phosphoprotein phosphatase 1***

Fer tyrosine kinase is highly expressed in human malignant prostate tissues compared to normal or benign tissues, which suggests its involvement in PCa progression<sup>[48]</sup>. Fer interacts with signal transducer and activator of transcription 3 (STAT3) and phosphorylates AR at Tyr223, thus contributing to interleukin-6 (IL-6)-mediated AR activation and cell growth<sup>[49,50]</sup>. Downregulation of Fer results in the activation of PPP1CA and consequent hypo-phosphorylation and activation of retinoblastoma protein (RB1), which, in turn, leads to cells arrest at the G<sub>0</sub>/G<sub>1</sub> phase (Figure 1)<sup>[51]</sup>. Accordingly, downregulation of Fer impairs the proliferation of PCa cells and their ability to form colonies in soft agar<sup>[48]</sup>.

#### ***Caveolin-1 /Phosphoprotein phosphatase 1***

Caveolin-1 (Cav-1) is overexpressed in human PCa and correlates positively with Gleason score, thus being suggested as a potential prognostic marker<sup>[52-55]</sup>. It has also been proposed as biomarker to monitor the response to treatments with dasatinib and sunitinib<sup>[56]</sup>. Cav-1-mediated cell survival depends on its interaction with and inhibition of PPP1 (and also PPP2), leading to the increased activity of phosphoinositide-dependent kinase-1, v-akt murine thymoma viral oncogene homolog (AKT), and ERK1/2 (Figure 1)<sup>[57]</sup>.

### **ADDITIONAL PHOSPHOPROTEIN PHOSPHATASE 1-INTERACTING PROTEINS EXPRESSED IN HUMAN PROSTATE TISSUE**

In spite of the limited number of PPP1 complexes experimentally characterized in human PCa models, several additional PIPs have already been identified as expressed in human prostate tissue. The human prostate proteome includes a total of 81 hitherto experimentally detected PIPs (Table 1)<sup>[58,59]</sup>, but many more may remain unknown. None of the interactors is prostate-specific; however, 28 are highly expressed in prostate tissue, namely BAD, BCL2, CCND1, CUEDC2, GABARAPL2, HCFC1, HDAC1, HDAC10, HEYL, IKBKB, LMTK2, MAP1LC3B, MYC, NOM1, PPP1R3D, PPP1R7, PPP1R11, PPP1R13B, PPP1R37, RB1, RRP1B, RYR2, SH2D4A, STAM, STAU1, SYTL2, TRIM28, and ZFYVE9 (Table 1)<sup>[60]</sup>.

Of the interactions identified, 67 were described for a specific PPP1 isoform, while 6 seem to be common to all isoforms (Table 1)<sup>[58,59]</sup>. In the vast majority, binding to PPP1 is assured *via* RVxF motif, although less described SILK, MyPhoNE, RARA, and other motifs (*e.g.*, apop-

totic signature motifs and inhibitor-2 degenerate motif) are also present in some PIPs (Table 1).

### **INTERACTORS OF PHOSPHOPROTEIN PHOSPHATASE 1 IN PROSTATE CARCINOGENESIS: VALUABLE TOOLS FOR CANCER MANAGEMENT**

PIPs expressed in human prostate tissue are key mediators of several signaling pathways and cellular processes, such as apoptosis, transcription, cell cycle, development/differentiation, and immunology/inflammation.

In the context of human prostate carcinogenesis, only 31 of these proteins have well-recognized functions. In this section, we revise the contribution of these PIPs to prostate carcinogenesis, focusing on studies involving human tissue samples or cell lines.

#### ***Apoptotic protease-activating factor 1***

Apoptotic protease-activating factor 1 (APAF1) is responsible for the cleavage of procaspase-9 and mitochondria-mediated activation of caspases-9, being a major effector of apoptosis<sup>[61]</sup>.

An alternative splicing product of APAF1, known as APAF1-ALT, was found in LNCaP cells. APAF1-ALT exhibits a defective pro-apoptotic function and its expression was shown to be increased under infective conditions. Therefore, this spliced form may be particularly involved in inflammation and carcinogenesis, since it compromises the apoptotic pathway<sup>[62]</sup>.

Resveratrol, sulforaphane, and vitamin D3 exert their tumor suppressive functions through changes in the gene that encodes for APAF1, at least in part<sup>[63-65]</sup>. APAF1 apoptosome is also involved in malignant cells-selective induction of apoptosis by apoptin<sup>[66]</sup>.

#### ***Ataxia telangiectasia mutated kinase***

Ataxia telangiectasia mutated (ATM) is a ubiquitously expressed Ser/Thr kinase with a wide spectrum of downstream targets involved in cell-cycle control, DNA repair after radiation-induced damage, and apoptosis<sup>[67]</sup>.

The expression levels of ATM are similar or higher in PCa samples compared to normal prostate tissue; however, its activation is higher in precursor stages of prostate tumorigenesis, like PIN<sup>[68,69]</sup>.

Variants of the *ATM* gene have been associated with the risk of PCa development, and might be useful predictive markers of adverse responses to radiotherapy<sup>[70-72]</sup>. ATM maintains telomeres' length and mediates tumor surveillance<sup>[68,69,73]</sup>.

Downregulation of ATM increases LNCaP, DU-145, and PC-3 cells' sensitivity to radiation-induced apoptosis<sup>[74-77]</sup>. The molecular events that arose from ATM inhibition include increased mitotic index, augmented expression of E2F transcription factor and proliferating cell nuclear antigen, and inhibition of G<sub>2</sub> arrest in response



**Table 1** Interactors of phosphoprotein phosphatase-1 expressed in human prostate tissue

PIP	Uniprot ID	Biological processes	PPP1 specificity	PPP1 binding motif
AKAP11	Q9UKA4	Intracellular signal transduction	PPP1CB, PPP1CC	RVxF, other motifs
APAF1	O14727	Apoptosis	PPP1CA	RVxF, other motifs
ATM	Q13315	Cell cycle; response to DNA damage; protein phosphorylation	PPP1CA	RVxF, SILK
AXIN1	O15169	Intracellular signal transduction; apoptosis; regulation of protein phosphorylation; transcription	PPP1CA	-
BAD <sup>1</sup>	Q92934	Apoptosis	PPP1CA	other motifs
BCL2 <sup>1</sup>	P10415	Apoptosis; response to DNA damage; transmembrane transport	PPP1CA, PPP1CB	RVxF, other motifs
BCL2L2	Q92843	Apoptosis	PPP1CA	RVxF, other motifs
BRCA1	P38398	Cell cycle; DNA repair; lipid metabolism	PPP1CA, PPP1CB, PPP1CC	RVxF, other motifs
CCND1 <sup>1</sup>	P24385	Cell cycle; response to DNA damage; transcription	PPP1CB	-
CCND3	P30281	Cell cycle; intracellular signal transduction; protein phosphorylation	PPP1CB	-
CDC5L	Q99459	Cell cycle; transcription; mRNA splicing	PPP1CA	RVxF
CDC34	P49427	Cell cycle; protein ubiquitination; intracellular signal transduction	PPP1CB	other motifs
CDK2	P24941	Cell cycle; DNA repair; meiosis; mitosis; intracellular signal transduction; cell proliferation	PPP1CA	-
CDK4	P11802	Cell cycle; protein phosphorylation; cell proliferation	PPP1CA	-
CSRN2	Q9H175	Apoptosis; transcription; protein phosphorylation	PPP1CA	RVxF, SILK
CUEDC2 <sup>1</sup>	Q9H467	Intracellular signal transduction	PPP1CA	-
CUL1	Q13616	Host-virus interaction; intracellular signal transduction	PPP1CA	-
EED	O75530	Transcription	PPP1CA	RVxF
EIF2AK2	P19525	Transcription; immunity; host-virus interaction	PPP1CA	other motifs
GABARAP	O95166	Apoptosis; autophagy; transport	PPP1CC	other motifs
GABARAPL2 <sup>1</sup>	P60520	Autophagy; transport	PPP1CC	-
GRB2	P62993	Host-virus interaction	PPP1CB	RVxF
GSK3B	P49841	Carbohydrate metabolism; differentiation; intracellular signal transduction	PPP1CA	-
HCFC1 <sup>1</sup>	P51610	Cell cycle; host-virus interaction	PPP1CA	RVxF, RARA
HDAC1 <sup>1</sup>	Q13547	Transcription; host-virus interaction; biological rhythms	PPP1CC	RVxF
HDAC6	Q9UBN7	Transcription; autophagy	PPP1CC	RVxF
HDAC8	Q9BY41	Transcription	PPP1CC	-
HDAC10 <sup>1</sup>	Q96958	Transcription	PPP1CC	-
HEY1 <sup>1</sup>	Q9NQ87	Transcription; intracellular signal transduction	PPP1CA	RVxF
HSPA8	P11142	Host-virus interaction; mRNA processing; transcription	PPP1CA	other motifs
IKBK <sup>1</sup>	O14920	Intracellular signal transduction	PPP1CA	other motifs
IKBK <sup>1</sup>	Q9Y6K9	Transcription; host-virus interaction	PPP1CB, PPP1CC	RARA
LMTK2 <sup>1</sup>	Q8IWU2	Protein phosphorylation; intracellular transport; receptor recycling	PPP1CA	RVxF, other motifs
MAP1LC3A	Q9H492	Autophagy; intracellular signal transduction	PPP1CC	other motifs
MAP1LC3B <sup>1</sup>	Q9GZQ8	Autophagy; intracellular signal transduction	PPP1CC	-
MAP3K3	Q99759	Intracellular signal transduction; protein phosphorylation	PPP1CA, PPP1CC	RVxF
MAX	P61244	Transcription	PPP1CA, PPP1CB	-
MDM4	O15151	Cell cycle; cell proliferation; apoptosis; response to DNA damage and hypoxia; protein stabilization; protein complex assembly	PPP1CA, PPP1CB, PPP1CC	-
MPHOSPH10	O00566	Ribosome biogenesis; RNA processing	PPP1CA	RVxF
MYC <sup>1</sup>	P01106	Transcription	PPP1CA	RVxF
NCL	P19338	Transcription; angiogenesis	PPP1CB	other motifs
NCOR1	O75376	Transcription	PPP1CA, PPP1CB, PPP1CC	RVxF, other motifs
NOC2L	Q9Y3T9	Apoptosis; transcription	PPP1CA	RVxF
NOM1 <sup>1</sup>	Q5C9Z4	Targets PPP1CA to the nucleolus	PPP1CA	RVxF, SILK
PAK6	Q9NQ55	Transcription; protein phosphorylation; cytoskeleton organization; apoptosis	-	Other motifs
PLCL2	Q9UPR0	Intracellular signal transduction; lipid metabolic process	PPP1CA	RVxF
PPP1R2	P41236	Regulation of phosphoprotein phosphatase activity; regulation of signal transduction; carbohydrate and glycogen metabolism	PPP1CB, PPP1CC	SILK, other motifs
PPP1R3B	Q86X16	Carbohydrate and glycogen metabolism	PPP1CA	RVxF
PPP1R3D <sup>1</sup>	O95685	Regulation of protein dephosphorylation; carbohydrate and glycogen metabolism	PPP1CC	RVxF
PPP1R7 <sup>1</sup>	Q15435	Regulation of protein dephosphorylation; regulation of catalytic activity	PPP1CB	other motifs
PPP1R10	Q96QC0	Regulation of catalytic activity; transcription; protein import into nucleus	PPP1CA	RVxF
PPP1R11 <sup>1</sup>	Q60927	Regulation of catalytic activity	PPP1CB	RVxF
PPP1R12A	O14974	Regulation of catalytic activity; intracellular transport; cell cycle; regulation of cell adhesion; protein dephosphorylation; intracellular signal transduction	PPP1CB	RVxF, MyPhoNE
PPP1R13B <sup>1</sup>	Q96KQ4	Cell cycle; apoptosis	PPP1CA	RVxF
PPP1R14B	Q96C90	Regulation of phosphorylation; regulation of catalytic activity	PPP1CC	RVxF
PPP1R15A	O75807	Apoptosis; regulation of translation; stress response	PPP1CA, PPP1CB, PPP1CC	RVxF, RARA
PPP1R15B	Q55WA1	Regulation of translation; stress response; dephosphorylation	PPP1CA	RVxF, other motifs
PPP1R26	Q5T8A7	Regulation of phosphatase activity	PPP1CA	RVxF

PPP1R37 <sup>1</sup>	O75864	Regulation of phosphatase activity	PPP1CA	RVxF
PTEN	P60484	Lipid metabolism; apoptosis; neurogenesis	PPP1CA	RVxF
PTK2	Q05397	Angiogenesis	PPP1CB	SILK
RB1 <sup>1</sup>	P06400	Transcription; cell cycle; host-virus interaction	PPP1CA	RVxF, SILK, other motifs
RIPK3	Q9Y572	Necrosis	PPP1CB, PPP1CC	RVxF
RPAP2	Q8IXW5	Transcription	PPP1CA	RVxF
RPAP3	Q9H6T3	Alternative splicing; polymorphism	PPP1CA	other motifs
RRP1B <sup>1</sup>	Q14684	Regulation of phosphatase activity; RNA processing	PPP1CA	RVxF, other motifs
RUVBL2	Q9Y230	DNA repair; growth regulation; transcription	PPP1CA	-
RYR21	Q92736	Intracellular transport	PPP1CA, PPP1CB, PPP1CC	RVxF, other motifs
SF3A2	Q15428	mRNA processing and splicing	PPP1CA	-
SH2D4A <sup>1</sup>	Q9H788	Regulation of phosphatase activity	PPP1CB	RVxF, MyPhoNE
SKP1	P63208	Intracellular signal transduction	PPP1CA	RVxF
SMARCB1	Q12824	Transcription; cell cycle; host-virus interaction; neurogenesis	PPP1CA, PPP1CB, PPP1CC	RVxF
SPRED1	Q7Z699	Regulation of protein phosphorylation; regulation of protein deacetylation; response to DNA damage; development	PPP1CA	RVxF
STAM <sup>1</sup>	Q92783	Protein transport	PPP1CA	RVxF
STAU1 <sup>1</sup>	O95793	Intracellular mRNA localization	PPP1CA	RVxF, other motifs
SYTL2 <sup>1</sup>	Q9HCH5	Intracellular transport; exocytosis; regulation of phosphatase activity	PPP1CA	RVxF, SILK, other motifs
TMEM33	P57088	-	PPP1CB	-
TP53	P04637	Apoptosis; cell cycle; host-virus interaction; necrosis; transcription	PPP1CA	-
TP53BP2	Q13625	Intracellular signal transduction; apoptosis; cell cycle; embryo development; heart development; response to ionizing radiation	PPP1CA, PPP1CC	RVxF, other motifs
TRIM28 <sup>1</sup>	Q13263	Transcription; DNA repair; protein ubiquitination; protein sumoylation; protein oligomerization; gene expression; epithelial to mesenchymal transition; innate immune response; regulation of viral release from host cell	PPP1CA, PPP1CB, PPP1CC	RVxF
TUSC3	Q13454	Intracellular transport	PPP1CA	RVxF, other motifs
USF1	P22415	Transcription	PPP1CC	RVxF, other motifs
ZFYVE9 <sup>1</sup>	O95405	Intracellular signal transduction	PPP1CA, PPP1CB, PPP1CC	RVxF, other motifs
ZFYVE16	Q7Z3T8	Intracellular signal transduction; regulation of endocytosis; protein targeting	PPP1CA	RVxF, other motifs

<sup>1</sup>Highly expressed in human prostate (criteria selection: prostate mRNA expression higher than the mean mRNA expression taking into account all tissues analyzed). Other motifs include apoptotic signature motifs and inhibitor-2 degenerate motif. PPP1: Phosphoprotein phosphatase-1; ATM: Ataxia telangiectasia mutated; GSK3B: Glycogen synthase kinase-3  $\beta$ ; SMARCB1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; BRCA1: Breast cancer type 1 susceptibility protein.

to DNA damage<sup>[78]</sup>. Therefore, *ATM* gene therapy and the use of *ATM* inhibitors have been explored as adjuvants to radiation therapy in PCa.

### Axis inhibition protein 1

Axis inhibition protein 1 (AXIN1) is a tumor suppressor that integrates the  $\beta$ -catenin destruction complex, along with adenomatous polyposis coli protein and glycogen synthase kinase-3  $\beta$  (GSK3B).

Wnt/ $\beta$ -catenin signaling pathway has been extensively explored due to its impact on development, proliferation, and tumorigenesis<sup>[79]</sup>. Mutations in the signaling mediators of such system are reported in several types of cancer. For instance, 7 variations in the DNA sequence of axin-1 were found in specimens with abnormal  $\beta$ -catenin immunohistochemistry and 4 different polymorphisms were observed in LNCaP, DU145, PC-3, 22Rv1, and P69SV40T cell lines, as well as in the sublines M12, M2182, M2205<sup>[80]</sup>.

### Bcl-2 family members: BCL2, BCL2L2 and BAD

Members of the Bcl-2 family of proteins are pivotal regulators of apoptosis. Bcl-2 (BCL2) and Bcl-2-like pro-

tein 2 (BCL2L2) are anti-apoptotic proteins, while Bcl-2 antagonist of cell death (BAD) has proapoptotic functions<sup>[81]</sup>.

The expression of BCL2 is not observed in normal prostate epithelial cells, but is found in PIN and increases in advanced PCa (further details in Catz *et al.*<sup>[82]</sup>). Higher BCL2 expression is also found in patients that underwent radiotherapy before surgery than those who received surgical treatment as first choice<sup>[83]</sup>. BCL2 upregulation is required for the acquisition of castration-resistance, in part by suppressing TGF $\beta$  and dihydrotestosterone-mediated induction of caspase-1 expression and activation<sup>[84,85]</sup>.

In conformity with BCL2, the expression of BAD is found elevated in highly proliferative states, in spite of not being helpful in the discrimination between benign and malignant prostate tissues<sup>[86]</sup>. The overexpression of proapoptotic proteins in highly proliferative states seems paradoxical since cancer cells normally take advantage of the molecular machinery to evade apoptosis. However, BAD overexpression was shown to stimulate PCa cells proliferation and enhance tumor growth<sup>[87]</sup>. On the other hand, overexpression of BAD in LNCaP cells, which are resistant to tumor necrosis factor-related apoptosis-

inducing ligand (TRAIL)-induced apoptosis, renders the cells sensitive to TRAIL effects<sup>[88]</sup>.

Several studies have reported the great value of targeting apoptotic molecules in order to increase the sensitivity to apoptosis-inducing agents. Polygene therapy and other combinatorial approaches are receiving increased attention due to their effectiveness<sup>[89]</sup>. Since BCL2 is associated with increased resistance to androgen deprivation in LNCaP cells, a number of approaches aim to decrease its expression and phosphorylation state<sup>[90,91]</sup>. The targeting of BCL2 has been explored not only in already settled castration-resistant cases, but also to delay the progression to this advanced state<sup>[92,93]</sup>. In the case of BCL2L2, it was shown to be a target of miR-205-modulated chemosensitivity<sup>[94]</sup>. Pharmacological interventions targeting BAD intent to increase its expression and decrease its phosphorylation state<sup>[95-97]</sup>.

### Breast cancer type 1 susceptibility protein

Breast cancer type 1 susceptibility protein (BRCA1) has long been described as a tumor suppressor that regulates gene transcription and DNA damage repair<sup>[98]</sup>. In spite of the relevance of BRCA1 mutations in other types of cancers, evidences of their association with PCa development have been inconsistent and at times contradictory. While some studies point to their irrelevance in PCa development, others state that carriers of BRCA1 mutations have more aggressive phenotype and are more prone to develop distant metastasis<sup>[99-102]</sup>.

The expression profile of BRCA1 during PCa progression is also very heterogeneous, although it tends to be higher in PCa compared to normal prostate epithelium<sup>[103,104]</sup>. Some works actually suggest that its expression correlates with increased tumor proliferative index and development of lethal cancer, being, therefore, considered a potential prognostic marker<sup>[105]</sup>.

The mode of action of BRCA1 in PCa is complex and seeks clarification<sup>[102]</sup>. BRCA1 mediates apoptosis, cell-cycle arrest, and the response to doxorubicin treatment in PC-3 cells by targeting a wide variety of genes (*e.g.*, *CCND1*, *BLM*, *BRCA2*, *DDB2*, *FEN1*, *H3F3B*, *CCNB2*, *MAD2L1*, and *GADD153*)<sup>[106]</sup>. It was also shown to negatively regulate the transcription of insulin-like growth factor I receptor in an AR-dependent manner<sup>[104]</sup>.

The use of anticancer drugs that inhibit poly ADP-ribose polymerase (PARP), such as niraparib and olaparib, has demonstrated efficacy in PCa patients with BRCA1 mutations<sup>[107,108]</sup>.

### Cyclins D1 and D3

Cyclins are key mediators of the cell cycle. Cyclin D1 (CCND1) is scarcely found in non-neoplastic tissues, but its levels are increased in the majority of localized tumors, where distinct subcellular localizations are observed according to tumor grading<sup>[109]</sup>. Likewise, CCND3 displays higher expression in PCa than in BPH and its expression correlates positively with PSA serum levels<sup>[110]</sup>.

In addition to the roles of cyclins in the regulation

cell cycle, CCND1/3 interact with AR. CCND1 suppresses the activity of the AR either directly, with the main mediator being the repressor domain of CCND1, or indirectly *via* histone deacetylases<sup>[111]</sup>. In this fashion, CCND1 differentially regulates the expression of several androgen-sensitive genes-it represses some genes, such as *KLK3/PSA*, while induces the transcription of others, as *CDC6* and *MCM2*. Further effects of CCND1 include alteration of transcription factor-chromatin interactions, restraining of TGF $\beta$ , Snail, Twist, and Goosecoid signaling pathways, enhancement of *Wnt* and *ES* gene expression, and enlargement of a prostate stem cell population<sup>[112,113]</sup>. The association between CCND3 and the AR represses ligand-dependent activation through cyclin-dependent kinase 4 (CDK4)-independent mechanisms and appeases androgen-dependent proliferation<sup>[114]</sup>.

CCND1 has been proposed as a prognostic marker for poor clinical outcome in PCa biochemical-free recurrence. A number of strategies targets CCND1, including miR-153 and perhaps miR-449a, piperine, and L-mimosine, with the effect of the latter being only observed in PC-3 cells<sup>[115-118]</sup>.

### Cyclin-dependent kinases 2 and 4

CDK family of proteins regulates cell cycle progression and is involved in AR-mediated cell proliferation. CDK2 mRNA levels decrease after castration, increase after testosterone propionate treatment, and are expressed at high levels in recurrent human xenograft CWR22 tumors<sup>[119]</sup>. The expression of CDK2 and CDK4 is up-regulated within hours of androgen treatment; nevertheless, castration-resistant PC-3 cells, which do not respond to androgen stimulation, show constitutively high basal expression of both kinases<sup>[120]</sup>.

The activity of CDK2 kinase is stimulated by androgen<sup>[119,120]</sup>. Increased CDK2 activity correlates with PCa cells insensitivity to TGF- $\beta$ 1, while even modest depletion of CDK2 in LNCaP cells results in strong growth repression<sup>[121,122]</sup>.

CDK4 protein expression was not found elevated in localized prostate tumors, but its overexpression overcome 3,9-dihydroxy-2-prenylcoumestan-induced G<sub>0</sub>/G<sub>1</sub> arrest in castration-resistant cells<sup>[123]</sup>.

Decreased expression and inhibition of the activity of CDK2 and CDK4 are observed upon treatment with anti-proliferative agents, such as resveratrol, BZL 101, and inositol hexaphosphate<sup>[124-126]</sup>. As phosphorylation of CDK2 on Thr160 is essential for the kinase activity, the manipulation of this phospho-residue has also been analyzed<sup>[127]</sup>.

### GSK3B

The multifunctional GSK3B exhibits potent tumor suppressor qualities and is upregulated in many types of tumor, including PCa. The expression pattern of GSK3B differs between normal prostate and PCa cells - nuclear GSK3B is higher in normal prostate, whereas cytoplasmic GSK3B is higher in PCa. Increased GSK3B cytoplasmic

levels might determine PCa development and progression due to their correlation with high Ki-67 labeling index, low apoptotic index by TUNEL, high levels of AR and phosphorylated AKT, extracapsular extension, high Gleason score, lymph node metastasis, and biochemical recurrence-free survival<sup>[128]</sup>.

GSK3B mediates both estrogen and AR signaling (for details see Mulholland *et al.*<sup>[129]</sup>). GSK3B phosphorylates AR and represses AR-mediated transcription and growth<sup>[130,131]</sup>. GSK3B/AR complex, which locates within the cytoplasm and nucleus, contributes to AR stability, nuclear translocation, and consequent modulation of PCa cells' response to androgen<sup>[132]</sup>. The signaling pathway AKT/GSK3B is also involved in nuclear factor  $\alpha$  (NF $\alpha$ )-induced epithelial-mesenchymal transition (EMT) in PC-3 cells by contributing to Snail stability<sup>[133]</sup>. On the other hand, suppression of GSK3B sensitizes PCa cells to TRAIL-induced apoptosis, which might suggest its involvement during resistance acquisition<sup>[134]</sup>. The suppression of GSK3B expression or phosphorylation state has also demonstrated positive results in inhibiting proliferation of PCa cells<sup>[135,136]</sup>.

AKT/GSK3B signaling pathway has been targeted by a number of antiproliferative and apoptosis-induced agents, namely thiazolidinediones and isoflavone, as well as agents that impair cell migration and invasion, such as fenretinide<sup>[137-139]</sup>.

### Histone deacetylases-1, -6 and -8

Histone deacetylases (HDACs) are a large family of enzymes that regulates the nucleosomal histone acetylation. Members of HDACs' family are divided into four classes (classes I-IV), according to their homology with yeast proteins, with class II being further subdivided into class IIa and IIb. HDAC1 and -8 belong to the class I histone deacetylases, whereas HDAC6 belongs to the class IIb. All members of class I were found to be deregulated in many types of cancers (for review see<sup>[140]</sup>).

HDAC1 is expressed in normal prostate tissues, where it locates exclusively in the nucleus, cancer precursor lesions, and PCa, and its expression was shown to be lower in stromal cells<sup>[141,142]</sup>. Conversely, HDAC8 is primarily found in the cytoplasm of stromal cells<sup>[142]</sup>.

HDAC1 expression levels correlate with tumor dedifferentiation, high Gleason score, high pT stage, and high biochemical recurrence rates<sup>[141,143]</sup>. HDAC1 is a major repressor of AR and E-cadherin, thereby regulating AR-transcriptional activity, cell proliferation and motility, and invasion<sup>[144-146]</sup>.

HDAC6 deacetylates and activates HSP90 chaperone protein, which, in turn, binds to AR<sup>[147]</sup>. Indeed, HDAC6 regulates AR hypersensitivity to androgens, nuclear localization, and attenuation of its degradation<sup>[147,148]</sup>. HDAC6 might establish important interactions with other proteins since its decrease is also observed in PC-3 cells, which are castration-resistant<sup>[149,150]</sup>.

The use of HDAC inhibitors in the prevention and treatment of cancer has become an area of intense re-

search. The repression of HDAC1 expression by miR-449a induces growth arrest in PCa and its inhibition by maspin prevents pathologic gene silencing, increasing tumor cell's sensitivity to drug-induced apoptosis<sup>[151,152]</sup>. The deacetylase activity of HDAC6 decreases after sulforaphane treatment and it might be responsible for the selective effects of this agent in both hormone-sensitive and castration-resistant cells, while normal cells remain intact<sup>[149,150]</sup>.

### Heyl

Heyl is a member of the hairy/enhancer-of-split-related with YRPW-like motif family of transcriptional repressors. Of the three members of the referred protein family, Heyl is the more potent AR corepressor and reduces the growth of LNCaP cells. The repression of AR activity by Heyl occurs through HDAC1/2-independent mechanisms. Heyl was shown to be excluded from the nucleus in malignant cells but not in benign tissue, thus nuclear exclusion of the protein might be involved in tumor progression<sup>[153]</sup>.

### Inhibitor of nuclear factor- $\kappa$ B kinase subunit beta and gamma

Inhibitor of nuclear factor- $\kappa$ B (NF- $\kappa$ B) kinase subunit  $\beta$  and  $\gamma$  (IKBKB and IKBKG, respectively) are involved in the activation of NF- $\kappa$ B<sup>[154]</sup>, a transcription factor that regulates cell growth, apoptosis, inflammation, angiogenesis, and metastasis (for review see<sup>[155]</sup>).

Studies on human prostate cell lines have not revealed significant differences between primary prostate cells, hormone-sensitive, and castration-resistant PCa cells<sup>[156]</sup>. However, IKBKB expression is higher in PCa tissue than in benign non-atrophic and atrophic glands<sup>[157]</sup>.

The effects of sulforaphane and phenethyl isothiocyanate are mediated, at least in part, through the inhibition of IKBKB phosphorylation<sup>[158]</sup>. The loss of IKBKB and IKBKG are also involved in proteasome inhibitors-induced apoptosis<sup>[159]</sup>.

### Lemur tyrosine kinase 2

Lemur tyrosine kinase 2 (LMTK2) is a Ser/Thr transmembrane protein kinase mainly involved in endosomal membrane trafficking<sup>[160]</sup>. In LNCaP cells, this function is achieved, at least in part, by the interaction with myosin VI and consequent recruitment of this protein to the surface of endosomes<sup>[161]</sup>. Interestingly, the gene that encodes for LMTK2 is one of the novel common alleles associated with PCa<sup>[162]</sup>. LMTK2 is underexpressed in PCa tissue compared to non-malignant BPH tissue due to alterations in intron 9; however, the mechanism by which this alteration leads to the increased risk of PCa is not properly understood<sup>[163]</sup>. LMTK2 functions depend on its interaction with other proteins, which includes CDK/P35 complex and PPP1, besides the already mentioned myosin VI<sup>[164,165]</sup>.

### MYC family of proteins: MYC and MAX

MYC deregulation is a well-established mechanism in car-



cinogenesis<sup>[166]</sup>. The role of MYC in PCa, nevertheless, is not fully understood. MYC overexpression is frequently observed in PCa, which can be partially explained by locus amplification, mainly in advanced cancers<sup>[167]</sup>. MYC stabilizes the length of telomeres and is required for EMT<sup>[168,169]</sup>. MYC and MAX interact with and regulate the AR<sup>[170]</sup>.

MYC amplification status and its overexpression have been suggested as a valuable prognostic tool<sup>[171,172]</sup>. The existence of a panel of markers that encompass MYC, PTEN, and Ki67 shown benefits in predicting progression-free survival in men receiving adjuvant docetaxel after prostatectomy<sup>[173]</sup>. Cells that exhibit resistance to treatment with docetaxel have constitutive activation of MYC signaling<sup>[174]</sup>.

### Nucleolin

Nucleolin (NCL) is an abundant nucleolar phosphoprotein involved in various stages of ribosome synthesis. The expression and phosphorylation of NCL are extremely sensitive to androgens-with both decreasing following androgen deprivation. Thus, the control of NCL expression and phosphorylation by androgens may be an important nucleolar control mechanisms involved in the growth of prostate cells<sup>[175]</sup>. NCL can also be found in the cell surface, where it may function as a hepatocyte growth factor receptor. Cell surface NCL was shown to be upregulated during PCa progression<sup>[176]</sup>.

### Nuclear corepressor 1

Nuclear corepressor 1 (NCOR1), an AR co-repressor, is overexpressed in PCa cell lines compared to normal prostate cells. NCOR1 expression is confined to the S phase of cell cycle; therefore, during this time NCOR1 represses the expression of AR target genes<sup>[177]</sup>. In PCa cells, the activity of NCOR1 is positively regulated by protein kinase A (PKA)<sup>[178]</sup>.

The increased expression and activity of NCOR1 impair peroxisome proliferator activated receptor  $\alpha/\gamma$ -mediated expression of key target genes, such as *CDKN1A* and *TGFBRAP1*, thus contributing to the loss of ligands anti-proliferative responsiveness in PCa cells<sup>[179]</sup>. NCOR1 might also be important during the process of castration-resistant acquisition<sup>[180]</sup>.

### Serine/threonine-protein kinase PAK 6

The expression of PAK6 is increased in primary and metastatic PCa, and correlates with cells' sensitivity to androgens<sup>[181,182]</sup>. PAK6 co-localizes with AR in the cytoplasm of normal prostate epithelium and translocates into the nucleus in malignant phenotypes, where it represses both AR- and ER-mediated gene transcription<sup>[181,183,184]</sup>. It was also shown that PAK6 phosphorylates the AR at Ser578, promoting the association of AR-E3 ligase murine double minute-2 (Mdm2) and guiding AR degradation<sup>[185]</sup>.

The knockdown of PAK6 impairs PCa growth and improves chemosensitivity of docetaxel and sensitivity to radiation<sup>[186,187]</sup>.

### Phosphatase and tensin homolog

Phosphatase and tensin homolog (PTEN) is a dual speci-

ficity phosphatase and a recognized tumor suppressor. Inactivation of *PTEN* has been associated with many different types of cancer, including PCa, and assumes preponderant roles (further details on<sup>[188,189]</sup>). A number of molecules have been recently shown to contribute to PTEN downregulation, including lamin A/C and a subset of microRNAs (*e.g.*, miR-19b, miR-23b, miR-26a, miR-92a, and miR-153)<sup>[117,190,191]</sup>. Loss of PTEN determines PCa progression through several downstream effectors and signaling pathways, including PI3K/AKT, BIM1, CXCL12/CXCR4, and PDGF D/ $\beta$ -PDGFR<sup>[192-195]</sup>. The loss of PTEN is also associated with increased risk of capsular penetration<sup>[196]</sup>. Interestingly, it was recently shown that PTEN is incorporated in the cargo of exosomes prevent from cancer cells, but not in those derived from non-malignant cells. Exosomes are able to transfer PTEN to other cells, which in turn recover the tumor-suppressor activity<sup>[197]</sup>.

Recent evidences support the usefulness of PTEN in PCa management. Blood exosomes of PCa patients contain PTEN, contrarily to the exosomes isolated from normal subjects, which may indicate exosomal PTEN as a putative diagnostic tool<sup>[197]</sup>. The loss of cytoplasmic PTEN was shown to accurately distinct intraductal carcinoma from prostatic intraepithelial neoplasia, since the latter does not manifest PTEN loss at all<sup>[198]</sup>. PTEN status might also be useful in the prognostic evaluation of men with localized PCa<sup>[199,200]</sup>.

Moreover, a phase II clinical trial reported that the activity of PTEN determines the improvement of progression-free survival and is potentially required for the efficacy of cetuximab in metastatic castration-resistant PCa<sup>[201]</sup>. PTEN expression is enhanced by resveratrol-mediated AR inhibition<sup>[202]</sup>.

### Protein tyrosine kinase 2

Protein tyrosine kinase 2 (PTK2) regulates adhesion and motility of cells. Its upregulation and activation was observed in localized and castration-resistant PCa, in spite of being more evident in the latter case<sup>[203,204]</sup>. The complexes that PTK2 forms with paxillin and p50csk are mainly observed in metastatic PCa and contribute to the metastatic behavior<sup>[204]</sup>. PTK2 is also involved in the migration and invasion mediated by IL-8 and CXCL13-CXCR5<sup>[205,206]</sup>.

Treatments with FTY720 and the combinatorial therapy with curcumin and methylseleninic acid compromises PTK2 activity, and PTK2 inhibition was shown to delay the progression of PCa<sup>[203,207]</sup>. PTK2 is also a target of genistein-mediated morphologic changes<sup>[208]</sup>.

### Tripartite motif-containing protein 28

Tripartite motif-containing protein 28 (TRIM28) is a substrate of ATM kinase involved in the maintenance of chromatin in condensed states<sup>[209]</sup>. The expression of TRIM28 is observed in prostate cancer lines, despite being lower in castration-resistant cell lines<sup>[210]</sup>. TRIM28 was recently identified as an activator of the AR and is also

involved in the response of prostate cells to DNA damage<sup>[210,211]</sup>.

### **Tumor suppressor pathways: RB1 and TP53**

Retinoblastoma-associated protein (RB1) and cellular tumor antigen p53 (TP53) are major tumor suppressors whose functions in PCa have been broadly explored. Loss of RB1 and TP53 is strictly associated with AR misregulation and progression to castration-resistant disease. Both their mechanism and their potential roles in managing PCa are extensively revised in Aparicio *et al.*<sup>[212]</sup>, Dean *et al.*<sup>[213]</sup> and Lee *et al.*<sup>[214]</sup>.

### **Ryanodine receptor 2**

Ryanodine receptor 2 (RZR2) is expressed in PWR-1E non-tumor cells, as well as in LNCaP and DU145 PCa cells, with the latter registering the lowest expression<sup>[215,216]</sup>. RZR2 mobilizes Ca<sup>2+</sup> from intracellular stores, which is essential to the regulation of apoptosis<sup>[215]</sup>.

### **SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1**

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) is a core subunit of the SWI/SNF family of nucleosome-remodeling complexes<sup>[217]</sup>. In aggressive PCa, the expression of SWI/SNF target genes is impaired by the binding to SchLAP1, which was shown to be aberrantly upregulated<sup>[218]</sup>.

## **BIOLOGICAL SIGNIFICANCE OF INTERACTIONS: PPP1 REGULATORS OR SUBSTRATES?**

The relationship between PPP1 and the majority of the PIPs here referred, as well as possible alterations in the dynamics of such complexes during prostate carcinogenesis, require further elucidation.

Some of the PIPs are already characterized as PPP1 regulators, substrates, or both (Figure 2). For a significant number of PIPs identified in protein-protein interaction screenings, nevertheless, the functional significance of their interaction with PPP1 remains poorly understood. Therefore, efforts should be made in order to understand PPP1 interaction with CCND1, CCND3, CDC5L, CDC34, CDK4, EED, EIF2AK2, GABARAP, GABARAPL2, GRB2, HDAC8, HDAC10, HSPA8, HEYL, MAX, NCL, IKBKB, IKBKG, MAP1LC3A, MAP1LC3B, MAP3K3, MPHOSPH10, MYC, NCOR1, NOC2L, PAK6, PLCL2, PPP1R3B, PPP1R12A, PPP1R13B, PTEN, RIPK3, RPAP2, RPAP3, RRP1B, RUVBL2, SF3A2, SH2D4A, SKP1, SPRED1, STAM, STAU1, SYTL2, and USF1.

In other cases, the biological significance of the complex is partially known, although it is not established whether the PIP is the regulator or the substrate (or even both). For instance, HDAC6 directly binds to PPP1 and the complex controls microtubule dynamics by maintaining

$\alpha$ -tubulin in a deacetylated state, but the exact mechanism remains poorly understood<sup>[219]</sup>.

### **Phosphoprotein phosphatase 1 regulators**

AKAP11 acts as a targeting subunit of PPP1 and it can also inhibit the phosphatase activity<sup>[220,221]</sup>. BCL2L2 and CUEDC2 target PPP1 to protein complexes: BCL2L2 recruits PPP1 to BAD, forming a complex that is involved in the control of apoptosis<sup>[222]</sup>, and, CUEDC2 targets PPP1 to IKK, thereby promoting the dephosphorylation and inactivation of the kinase<sup>[223]</sup>. NOM1 acts as a PPP1 nucleolar targeting subunit, PPP1R10 targets PPP1 to the nucleus, and PPP1R15A targets PPP1 to the endoplasmic reticulum<sup>[224-227]</sup>. PPP1R10/PPP1 holoenzyme is known to regulate chromosome decondensation and apoptosis in response to cellular stresses<sup>[226,228]</sup>.

PPP1C positive regulators include ATM, GSK3B, and SMARCB1. In response to ionizing radiation, PPP1 is dephosphorylated and activated by ATM<sup>[229]</sup>. ATM-mediated activation of PPP1 could occur, at least, *via* two mechanisms: (1) phosphorylation of I-2 and consequent dissociation of the complex I-2/PPP1; or, (2) dephosphorylation of PPP1C at Thr320 to amplify its activity<sup>[230]</sup>. As a result, PPP1 dephosphorylates HDAC1, leading to the dissociation of the HDAC1-PPP1-Rb complex<sup>[231,232]</sup>. In similar way to ATM, GSK3B activates PPP1 *via* phosphorylation of I-2 and consequent disruption of the I-2/PPP1 complex<sup>[233]</sup>. SMARCB1 forms a tricomplex with PPP1R15A and PPP1, and weakly stimulates PPP1 activity<sup>[234]</sup>.

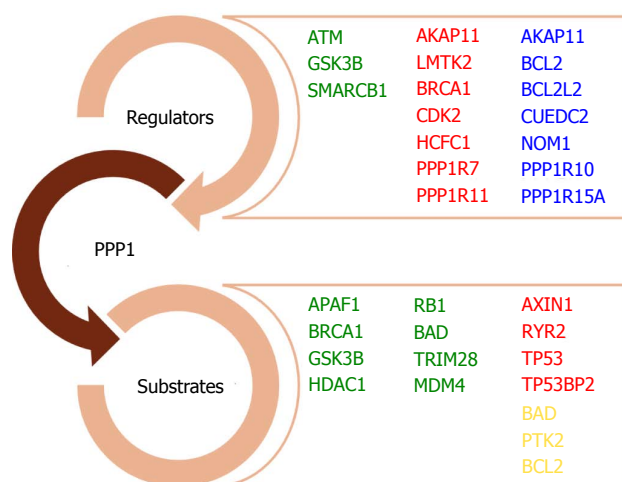
AKAP11, BRCA1, CDK2, LMTK2, HCFC1, PPP1R7, PPP1R11, and TP53BP2 inhibit the activity of PPP1<sup>[229,235-239]</sup>.

### **Phosphoprotein phosphatase 1 substrates**

PPP1C is a key regulator of the two major tumor suppressors: it inhibits TP53 and activates RB1 (further details on<sup>[24]</sup>). The apoptotic process is strictly controlled by reversible phosphorylation<sup>[240]</sup>. The phosphorylation of APAF1 by the 90-kDa ribosomal S6 kinase (RSK) compromises the formation of the apoptosome, impairs cells' sensitivity to cytochrome c, and inhibits apoptosis. PPP1CA was shown to reverse the RSK-mediated phosphorylation of APAF1, thus enhancing its pro-apoptotic activities<sup>[241]</sup>. BAD is also dephosphorylated by PPP1CA in a dependent way of the anti-apoptotic members BCL2, BCL2L2, and BCL-XL<sup>[222,242,243]</sup>. While BAD overexpression provides proliferative advantage to tumor cells, BAD dephosphorylation increases their sensitivity to apoptosis<sup>[87]</sup>.

PPP1 exerts a positive control on Wnt signaling through dephosphorylation of AXIN1. As a result,  $\beta$ -catenin destruction complex dissociates, the free phospho- $\beta$ -catenin accumulates in the cytoplasm, and the transcriptional activity of  $\beta$ -catenin is promoted<sup>[244]</sup>.

In addition of being regulators, BRCA1 and GSK3B are also substrates for PPP1C. PPP1C dephosphorylates BRCA1 and enhances its DNA repair function<sup>[235,245,246]</sup>. GSK3B is also dephosphorylated and disinhibited by PPP1-mediated dephosphorylation<sup>[247]</sup>.



**Figure 2** Phosphoprotein phosphatase 1 interacting proteins can be regulators, substrate or both. Green represents positive regulation of phosphoprotein phosphatase 1 (PPP1) (in case of regulators) or PPP1-mediated upregulation of substrates. Red represents negative regulation of PPP1 (in case of regulators) or PPP1-mediated downregulation of substrates. Blue characterizes PPP1-interacting proteins (PIPs) exhibiting PPP1 targeting ability. Yellow corresponds to proteins that are identified as substrates, but whose interaction with PPP1 are not fully understood. ATM: Ataxia telangiectasia mutated; GSK3B: Glycogen synthase kinase-3  $\beta$ ; SMARCB1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; BRCA1: Breast cancer type 1 susceptibility protein.

HDAC1 activity is promoted through dephosphorylation of Ser133 by PPP1, which leads to dissociation of HDAC1-PP1-Rb complex, and consequent increase of HDAC1 activity<sup>[232,248]</sup>. Similarly, HDAC6 and -8, which can be phosphorylated, might also be PPP1 substrates, although this fact has not been confirmed yet.

RYYRs are regulated through reversible phosphorylation, and PPP1 reverts PKA-mediated phosphorylation and activation of RYYR2<sup>[249-251]</sup>. PPP1 dephosphorylates TRIM28 (Ser824), enhancing its sumoylation state, and MDM4 (Ser367), enhancing its stability and leading to the consequent inhibition of TP53 activity<sup>[252]</sup>. PPP1 also reverts the phosphorylation of PTK2 and BCL2<sup>[253-255]</sup>.

## CHALLENGE OF TARGETING PPP1 ACTIVITY

Since PPP1 is a Ser/Thr phosphatase with major roles in several pathological processes, the manipulation of its activity is a valuable therapeutic tool that had been misjudged for years. PPP1 activity could be manipulated through direct or indirect inhibition of the catalytic site (for review see<sup>[27]</sup>).

The dissociation of PPP1 complexes through the targeting of PIPs is challenging and might overcome the problems that arise from direct inhibition of PPP1C. However, this area remains understudied and only two complexes are currently being targeted: PPP1C/HDAC and PPP1C/PPP1R15A. Trichostatin A disrupts PPP1C/HDAC and is used in the treatment of glioblastoma and PCa cells. LBH589, an inhibitor of HDAC, was also shown to be

able to dissociate this complex<sup>[256]</sup>. As a consequence, AKT is dephosphorylated and its activity decreases. PPP1C/PPP1R15A complex is disrupted upon salubrinal treatment, thereby dephosphorylating eIF2 $\alpha$ <sup>[257,258]</sup>.

The increasing number of PPP1 docking motifs identified offers excellent opportunities for targeting specific complexes. In fact, the docking motif found in Bad has inspired the designing of a peptide that interferes with PPP1/BAD complex and is able to induce cell death<sup>[259]</sup>. Also, the PPP1 docking motif R/Kx(0,1)V/IxFxxR/KxR/K, a new PPP1C-dependent apoptotic signature, might be a useful tool for drug design<sup>[260]</sup>.

The disruption or enhancement of several other complexes might contribute to the enhancement of PCa management, enabling more efficient therapies for advanced castration-resistant PCa. Therefore, the identification of PPP1 complexes in human prostate and their characterization in prostate carcinogenesis is imperative for the search of new therapeutic targets.

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