Am J Clin Exp Urol 2015;3(1):1-12
www.ajceu.us /ISSN:2330-1910/AJCEU0006714

Review Article

Role of PARP-1 in prostate cancer

Dhanraj Deshmukh, Yun Qiu

Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Maryland, 21201

Received February 4, 2015; Accepted March 30, 2015; Epub April 25, 2015; Published April 30, 2015

Abstract: Poly (ADP-ribose) polymerase-1 (PARP-1) is an enzyme that catalyzes the covalent attachment of polymers of ADP-ribose (PAR) moieties on itself and its target proteins. PARP1 activity is frequently deregulated in various cancers and therefore it has emerged as a new drug target for cancer therapy. The role of PARP-1 in DNA repair has been well documented and BRCA mutations are implicated for determining the sensitivity to PARP inhibitors. Recent studies also point to a role of PARP-1 in transcription regulation which may contribute to oncogenic signaling and cancer progression. Given that efficacy of PARP inhibitors are also seen in patients not harboring BRCA mutations, some other mechanisms might also be involved. In the present review, we highlight the mechanisms by which PARP-1 regulates gene expression in prostate cancer and provide an overview of the ongoing clinical trials using PARP inhibitors in various cancers including prostate cancer.

Keywords: PARP-1, PAR, prostate cancer

Introduction

Prostate cancer, incidence and current therapy

Prostate cancer is one of the most commonly diagnosed cancers in men worldwide [1]. Metastatic disease is diagnosed in about 10 to 20 percent of prostate cancer patients and metastases could also develop from latent disseminated tumor cells years later after treatment of surgery and radiotherapy [2]. For these patients, Androgen Deprivation Therapy (ADT) is the first line of treatment [3]. Men with localized prostate cancer invariably respond to Androgen Deprivation Therapy (ADT) initially, but progress to a Castration Resistant Prostate Cancer (CRPC) disease after approximately 2-3 years [4]. Prostate cancer deaths are usually due to metastatic castration-resistant prostate cancer (mCRPC) and the median survival of men with mCRPC is less than two years. The first line of treatment for mCRPC is usually Docetaxel combined with a glucocorticoid like prednisone [5]. This treatment modality was based on the results of two clinical trials viz; the Southwest Oncology Group (SWOG) and Taxotere (TAX) studies [2, 6, 7]. However, the Overall Survival (OS) compared to comparator treatments was found to be a modest 2-3 months. Other treatments for mCRPC include Sipuleucel-T, an immunotherapy and abiraterone acetate which is an inhibitor of androgen biosynthesis [8, 9]. The improvement in OS for Sipuleucel-T was found to be 4.1 months and that for abiraterone was 4.6 months. Other therapies for docetaxel resistant mCRPC include cabazitaxel, a second generation tubulin inhibitor and enzalutamide, an AR antagonist [10-12]. The current therapies for mCRPC offer a modest increase in OS of about 2-5 months and have significant toxicities. Moreover, resistance to taxol and anti-androgen therapy is rampant. Therefore, treatment options which offer increased OS, better Quality of Life, less toxicity and reduction in metastases are the need of the hour.

PARP-1 structure and functions

PARP-1 domains and PARP-1/PAR interactions

Poly (ADP-ribose) polymerase-1 (PARP-1) is an abundant and ubiquitous enzyme found predominantly in the nucleus. It catalyzes the covalent attachment of polymers of ADP-ribose (PAR) moieties on itself and other target nuclear proteins from donor nicotinamide adenine dinucleotide (NAD^+) molecules. PARP-1 is a 116 kDa

protein with six well characterized functional domains (**Figure 1**). The DNA binding domain of PARP-1 has two zinc finger motifs which are instrumental in the binding of PARP-1 to DNA. These zinc finger domains from different PARP-1 molecules co-operate in detecting DNA damage and trans-automodify each other in response to DNA strand breaks [13] thereby participating in a number of DNA repair pathways. There is a third zinc finger domain which has a distinct function and a nuclear localization signal located between the second and third Zn finger domains. The DNA binding domains show preferential binding to DNA structures like single-strand breaks, double-strand breaks, cruciform and crossovers and to nucleosomes [14, 15].

The central automodification domain contains a leucine zipper motif and a BRCA1 C-termins (BRCT) domain and is the primary site of post translational modifications. The leucine zipper motif might be instrumental in PARP homo-dimerization or hetero-dimerization [16]. The BRCT domain is a protein-protein interaction domain which interacts with the BRCT domain of XRCC1 and DNA ligase III [17, 18]. The catalytic domain located on the C-terminus includes the WGR and ART subdomain which is conserved across other ADP-ribosyl transferases and is required for NAD^+ binding and catalysis of PAR synthesis [19, 20]. Non-covalent binding of PAR with other proteins is affected through the motif *hxbxhhbbhhb* (where *h* stands for hydrophobic, *b* stands for basic and *x* for any other amino aicd) identified by Pleschke *et al* [21]. The auto-modification domain is the target of several covalent automodifications like PARylation, phosphorylation, SUMOylation, acetylation and ubiquitination (**Figure 1**). ADP-ribosylation or Poly (ADP) ribosylation is by far the most important post-translational modification that PARP-1 uses to affect a number of cellular processes. PARP-1 uses nicotinamide adenine dinucleotide (NAD^+) as a donor to polymerize and add either linear or branched chains of ADP-ribose (ADPR) on itself (major acceptor) or target nuclear proteins with the help of its c-terminal catalytic domain. Poly (ADP-ribosyl) ation (PARylation) occurs on a variety of target proteins and plays an important role in a variety of cell processes such as stress response, DNA repair and transcriptional regulation [22, 23]. PARP-1 is also a target for phosphorylation which serves as an important DNA-independent stimulus for PARP-1 activation. In breast cancer cells, CDK2 was found to phosphorylate PARP-1 on serine residues 785/786 located in the catalytic domain in response to PR stimulation by progestin [24]. Extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylates PARP-1 thereby leading to its activation and consequent neuronal cell death in response to neurotoxins [25]. Acetylation of PARP-1 is required for NF-κB mediated inflammatory response [26]. On stimulation of primary Mouse Embryonic Fibroblasts (MEFs) with LPS, p300/CBP acetylates PARP-1 on a number of lysine residues thereby activating NF-κB driven gene transcription. SUMOylation of PARP-1 is another post-transcriptional modification implicated in the transcription of the Hsp70.1 gene [27]. K48 polyubiquitination of PARP-1 was also observed which might be involved in regulating PARylation and/or degradation of PARP-1 [28].

PARP-1 in DNA repair

In DNA damage repair, PARP-1 functions as a sensor and also initiates repair. DNA damage due to oxidation, alkylation and ionizing radiation leads to a massive increase in PARylation. The Zn finger domains act as sensors of single-strand breaks (SSBs) and double-strand breaks (DSBs) and activate PARP-1. When the DNA damage is within physiological limits, PARP-1 initiates repair but when it is too high, it leads to cell death [29]. This decision between repair and suicide is probably determined by the available pool of NAD^+ [30]. When DNA damage is repairable, PARP-1 recruits various proteins involved in DNA repair pathways by direct interaction or through PAR and thereby participates in SSB, DSB and base excision repair (BER) pathways [31-33]. Inhibition of PARP which is key to DNA SSB repair, leads to stalling of the replication forks [34] ultimately leading to DSBs. BRCA1 and BRCA2 are important repair proteins for DNA DSB repair by homologous recombination [35]. Thus inhibiting PARP-1 in cancer patients with BRCA mutations leads to chromosomal instability, cell cycle arrest and apoptosis. Therefore, PARP-1 is an important therapeutic target in cancer therapy including prostate cancer, especially in patients harboring the BRCA mutations.

PARP-1 in transcriptional regulation

All the different domains enable PARP-1 to interact with genomic DNA and chromatin and

modulate transcription [36, 37]. PARP-1 affects transcription in a number of ways. PARP-1 opens up the chromatin by denying access to the demethylase enzyme KDM5B, to histone H3K4 methylation marks [38, 39] and by eviction of histone H1 from promoter nucleosomes [40] thereby enabling access to the transcriptional machinery (**Figure 2**). Ctcf induces PARP1 activity and PARP1 PARylates Ctcf thereby enabling Ctcf to prevent certain DNA regions from *de novo* methylation [41]. In the *Drosophila melanogaster hsp70* promoter, the histone variant H2Av (mammalian equivalent H2A.X/H2A.Z) co-localizes with PARP-1. Phosphorylation of H2Av in response to genotoxic stress was found to activate PARP-1 [42]. In HeLa cells, the histone variant mH2A1.1 colocalizes with PARP-1 to form a repressive nucleosome complex at the Hsp70.1 and Hsp70.2 promoters. Activation of PARP-1 led to the release of both mH2A1.1 and PARP-1 from this promoter thereby leading to transcription of Hsp70 [42]. Thus the two different mechanisms identified might be organism specific. It was also found that eviction of the histone H1 by PARP-1 at active promoters was essential for gene expression in MCF7 cells [40]. PARP-1 was found to promote transcriptional activation of the FOS promoter in response to ERK signaling by replacing the histone H2A with H2A.Z [36, 44].

An important consequence of PARylation of PARP-1 and the enrichment of variant histones at PARP-1 target gene promoters is de-compaction of the chromatin leading to assembly of basal transcription machinery at these promoters [38]. PARP-1 binds to E2F-1 through its automodification domain thereby increasing the binding of E2F-1 to its promoter and promotes its transcription when cells progress from G1/G0 to S phase [45]. PARP-1 was also shown to regulate FOXO-1 mediated transcription further underscoring its importance in transcriptional regulation by orchestrating transcription factors [46]. PARP-1 is also understood to regulate heterochromatin by interacting with UHRF1 an E3 ligase which plays an important role in G1/S transition by regulating TopoIIα and Rb gene expression [47]. PARP-1 also has an important say in transcriptional regulation of p16 and IGF2/H19 Imprinting Control Region (ICR). Upstream of the p16 locus, CTCF creats a heterochromatin boundary. This boundary is effective only when CTCF is PARylated by PARP-1. When CTCF is not PARylated, the chromatin is converted to a repressed state thereby silencing p16 [48]. The maternal IGF/H19 ICR is maintained in a repressed state by PARP-1 PARylation of CTCF and likely involves non-covalent interaction of PARP-1 with DNMT-1 via the PAR moieties [49]. Thus, PARP-1 is involved in either the positive or negative regualation of a number of important genes involved in oncogenesis. Thus, it is important to take into consideration the non-DNA repair properties of PARP-1 when therapeutically targeting PARP-1 in cancer.

PARP-1 and nuclear hormone receptor signaling

PARP-1 is involved in transcriptional regulation of a number of Nuclear Hormone Receptors. The most intriguing thing is that the mechanisms of PARP-1 function are very diverse (**Figure 3**). PARP-1 was found to be essential for Retinoic Acid Receptor (RAR) activation [50]. The catalytic domain of PARP-1 and hence Poly-ADP-Ribosylation was dispensable for PARP-1 activity whereas the BRCT domain was found to be essential. PARP-1 localized to the RARE along with RAR/RXR and mediator. In the inactive state, the promoter is populated by the corepressor complexes (NCoR, SMRT), the Pre-initiation complex (PIC), Pol II and the Cdk8 module with RAR/RXR interacting with mediator via PARP-1. On Retinoic Acid (RA) binding to RAR, it undergoes a conformational change leading to the release of the co-repressor complexes and the recruitment of the co-activator complexes which de-condenses the chromatin at the promoter. Next, mediator and PARP-1 directly interact with RAR releasing the cdk8 module which leads to activation of mediator and transcription initiation. PARP-1 protein was also found to directly bind the nuclear receptor binding partner RXR [51]. In gel retardation assays, PARP-1 was found to bind to the Thyroid Receptor (TR) RXR dimer and the DNA binding domain of RXR was found to be essential for this interaction. Further, PARP-1 inhibited the transcriptional activity of TR in the presence of its ligand T3. In MCF7 breast cancer cells, nuclear PAR levels increased dramatically on treatment with a synthetic progesterone analog R5020 [24]. This increase in PAR levels was due to CDK2 dependent phosphorylation of PARP-1 on S785/S786. Phosphorylation of PARP-1 was essential for affecting progestin

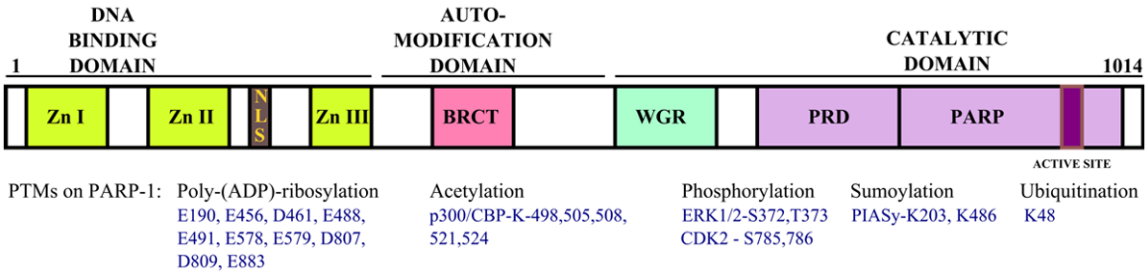

Figure 1. PARP-1 domains and post-translational modifications.

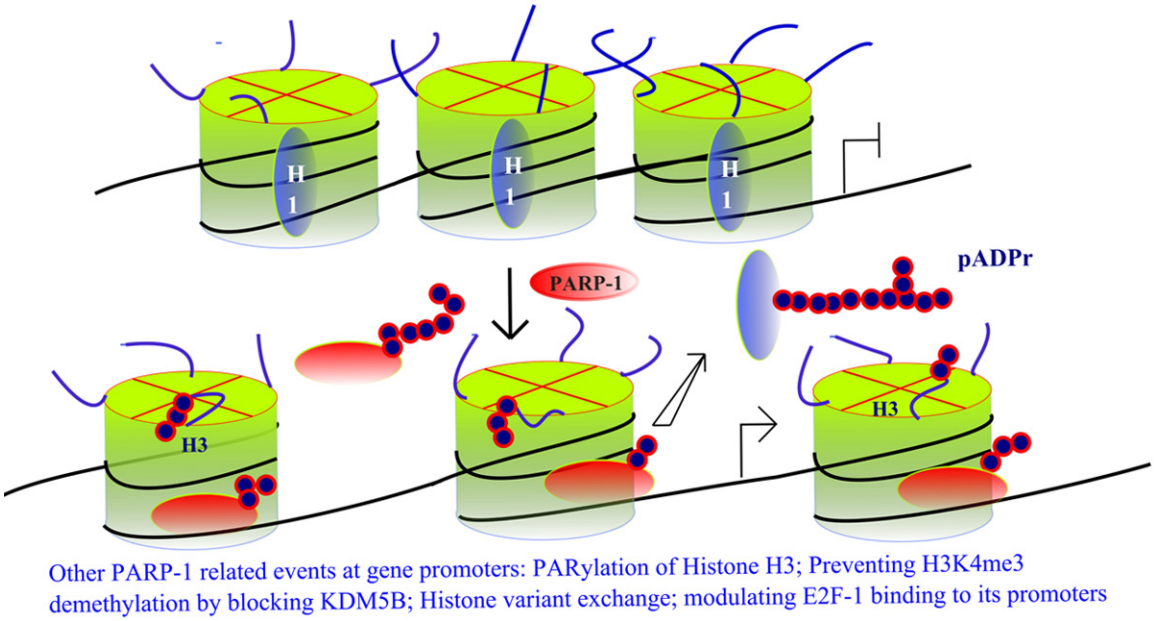

Figure 2. Role of PARP-1 at target gene promoters.

dependent Progesterone Receptor regulated gene expression. An inhibitor of either PARP-1 or CDK2 effectively blocked 85% of target genes regulated by progestin. One mechanism which stands out is the estrogen-regulated TFF1 (pS2) gene promoter where PARP-1 functions as a co-activator [52]. In the absence of 17β-estradiol (E2), this promoter was bound by basal levels of PARP-1, TopoIIβ and co-repressor complex containing N-CoR and HDAC3. On E2 treatment, there was an increase in PARP-1 and TopoIIβ recruitment with a concomitant eviction of N-CoR and HDAC3 at the promoter. Other components involved in DNA repair namely DNA-PK, Ku86/Ku70 were also recruited to the promoter region of the pS2 gene promoter. The underlying mechanism was that estrogen exposure leads to a transient dsDNA break which probably leads to a favorable topological conformation of the promoter region. PARP-1 also affected the release of histone H1 on a single nucleosome containing the ERE and concomitant recruitment of of the high mobility group B (HMGB1/2). The authors found evidence of similar recruitment of TopoIIβ complex to promoters of androgen receptor (AR), retinoic acid receptor (RAR), thyroid receptor (T3R) and activating protein 1 (AP-1) thereby underscoring a widely used mechanism of gene transcription.

PARP-1 and prostate cancer

The data on the role of PARP-1 in gene regulation in prostate cancer is scant. Most of the available data is either in the housefly *Drosophila melanogaster* or in breast cancer cell line MCF7. However, two recent publica-

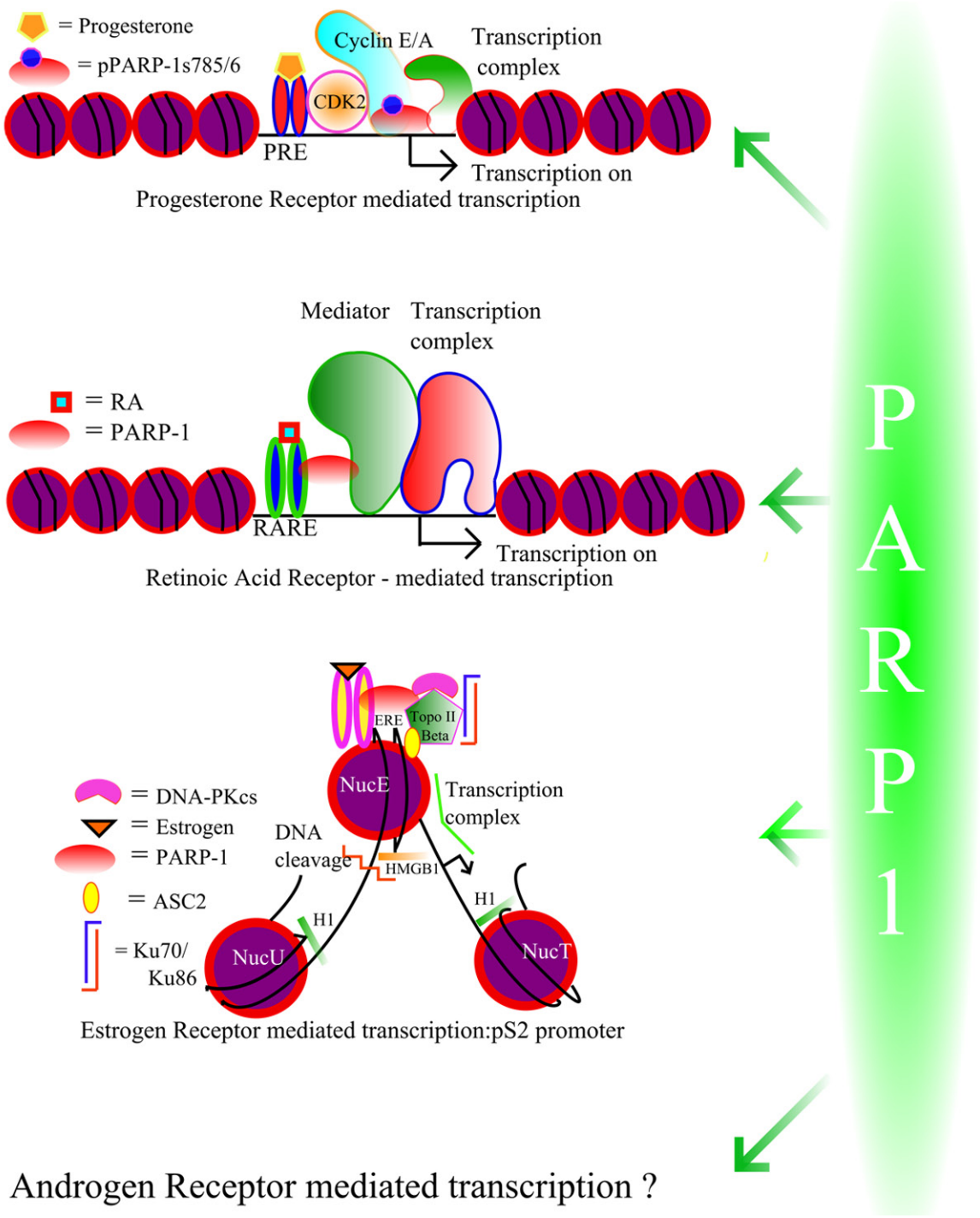

Figure 3. Role of PARP-1 in Nuclear Hormone Receptor Signaling.

tions shed some light on the role of PARP-1 in gene regulation in prostate cancer cells. In one study, it was shown that PARP-1 has a role in regulating AR target genes [53]. In this study, a number of PARP-1 target genes viz; TMPRSS2, KLK3 and FKBP5 were shown to be down-regulated by PARP-1 inhibitor ABT-888 in AR positive cell lines LNCaP and VCaP. PARP-1 inhibition led to a decrease in AR recruitment to the promoters of its target genes KLK3 and TMPRSS2. Moreover, AR and PARP-1 were found to occupy distinct sites on the loci to

Table 1. Ongoing Clinical Trials (Phase II/III) with PARP-1 inhibitors for various cancers (www.clinicaltrials.gov)

Agent(s) [Phase]	Cancer (Patient stratification)	Identifier
BMN-673 [I/II]	Ovarian, peritoneal, Breast, other solid tumors (BRCA)	NCT01989546
BMN-673 + TMZ [I/II]	Leukemia, Ewing sarcoma, Neuroectodermal, solid tumors	NCT02116777
BMN-673; Physician's choice [III]*	Breast (BRCA)	NCT01945775
BMN-673 [II]	Endometrial cancer	NCT02127151
Niraparib [III]	Ovarian	NCT01847274
	Breast (HER2, BRCA)	NCT01905592
Olaparib [II]	Ovarian Neoplasms (BRCA)	NCT00494442
Olaparib [II]	Breast (BRCA)	NCT00494234
Olaparib [II]	Non-small cell lung cancer	NCT01788332
Olaparib + Arbiraterone [II]	Metastatic castration resistant prostate cancer	NCT01972217
Olaparib; Doxorubicin [II]	Ovarian (BRCA)	NCT00628251
Olaparib [II]	Ewing's sarcoma	NCT01583543
Olaparib + Paclitaxel [II]	Gastric cancer	NCT01063517
Olaparib + Paclitaxel + Carboplatin [II]	Ovarian cancer	NCT01081951
Olaparib [II]	Colorectal cancer (microsatellite instability)	NCT00912743
Olaparib + Cediranib maleate [II]	Ovarian, fallopian, peritoneal cavity, triple-negative breast	NCT01116648
Olaparib [II]	Ovarian, breast (BRCA)	NCT00679783
Olaparib [III]*	Ovarian (BRCA)	NCT01874353
Olaparib [II]	Ovarian, breast, prostate, pancreatic, advanced tumors (BRCA)	NCT01078662
Carboplatin + Paclitaxel +/-Veliparib [III]*	Non-small cell lung cancer	NCT02106546
Carboplatin + Paclitaxel +/-Veliparib [III]*	Metastatic Breast Cancer (HER2 –ve, BRCA)	NCT02163694
Veliparib + Temozolomide [I]	Prostate Cancer	NCT01085422
Veliparib + Temozolomide [II]	Colorectal	NCT01051596
Veliparib + Cyclophosphamide [II]	Fallopian tube, triple-negative breast, non-Hodgkin's lymphoma	NCT01306032
Veliparib + Temozolomide [II]	Breast (BRCA)	NCT01009788
Veliparib + Temozolomide [II]	Small cell lung cancer	NCT01638546
Veliparib + Topotecan [I/II]	Solid tumor, ovarian, peritoneal cavity tumors	NCT01012817
Veliparib [II]	Fallopian tube, ovarian, peritoneal cavity cancer	NCT01540565
Veliparib + TMZ; Veliparib + Carbo + Pacli [II]	Breast (BRCA)	NCT01506609
Veliparib [II]	Ovarian	NCT01472783
Veliparib + 5-FU; Oxaliplatin + Leucovorin [I/II]	Pancreatic	NCT01489865
Veliparib + TMZ [II]	Hepatocellular	NCT01205828
CEP9722 [I/II]	Solid tumors	NCT01311713
Cisplatin + Rucaparib[II]	Breast -triple negative (BRCA)	NCT01074970
Rucaparib [II]	Metastatic breast, advanced ovarian	NCT00664781
Rucaparib [III]*	Ovarian, fallopian tube, peritoneal	NCT01968213
Rucaparib [II]	Pancreatic	NCT02042378
E7449; E7449 + TMZ; E7449 + Carbo + Pacli [I/II]	Solid tumor, ovarian, breast, melanoma, B-cell malignancy	NCT01618136

TMZ = Temozolomide; Carbo = Carboplatin; Pacli = Paclitaxel; * = Phase III; Bold = prostate cancer.

which they were recruited. PARP-1 was also found to reduce the expression of UBE2C, a gene involved in cell cycle progression. UBE2C is involved in cyclin B degradation and in mitotic spindle checkpoint control and is found to be overexpressed in CRPC [54]. Thus PARP-1 was found to inhibit AR target gene expression at least in part by preventing recruitment of AR to its target gene loci. This phenomenon was observed in AR positive cells irrespective of their TMPRSS2:ETS gene rearrangement status. TMPRSS2:ERG gene fusions are found in approximately 50% of prostate cancer cases [55, 56]. In a study by Brenner et al., it was observed that PARP-1 and DNA-dependent protein kinase, catalytic subunit (DNA-PKcs) which is involved in NHEJ-dependent DNA repair interacted with the predominant TMPRSS2:ETS gene fusion product, ERG. Inhibition of either DNA-PKcs or PARP-1 led to a decrease in ERG-mediated transcription. The interactions of both the proteins DNA-PKcs and PARP-1 with ERG were not DNA dependent. Pharmacological inhibition of PARP-1 led to a decrease in ETS-

positive cancer xenograft growth but not ETS-negative cancer xenograft growth [57]. ERG was also found to disrupt the AR driven lineage-specific differentiation program in the prostate and to initiate an EZH2 driven de-differentiation program akin to embryonic stem cells (ESC) [58]. EZH2 was also found to be the most highly expressed gene in metastatic prostate cancer [59]. From the available literature to date it thus appears that PARP-1 might regulate gene expression either via chromatin remodeling or by affecting transcription factors like ERG. There could be other mechanisms at play like modulating the expression of AR chaperone proteins like Heat Shock Protein 70 (Hsp70) and Hsp90. In the 1980s it was discovered that the 90 kDa Hsp was found to be associated with the v-Src tyrosine kinase as well as the avian progesterone receptor [60]. It was subsequently found that the heat shock proteins function as chaperones and assist in folding and assembly of various proteins [61]. Now, it's known that most steroid receptors like AR, GR, PR and ERα are found associated with Hsp90 and other chaperone proteins in the absence of a ligand. These chaperone proteins might play an important role in the nuclear receptor stabilization in the absence of a ligand. In a study by Holley et al., the mammalian retinoid receptor activity, especially signal transduction was severely affected in a *Saccharomyces cerevisiae* strain expressing almost 20-fold lower levels of the Hsp90 homologue [62]. One study found that on heat shock, the SUMO E3 ligase PIASy sumoylates PARP-1 and PARP-1 ADPribosylates PIASy. On SUMOylation, PARP-1 leads to the transcriptional activation of the HSP70.1 gene [27]. In the *Drosophila*, the histone variant H2Av (mammalian homologues H2Ax/H2A.z) recruits PARP-1 to specific gene promoters, one of which is the Hsp70 gene. Subsequent phosphorylation of the H2Av histone activates PARP-1 thereby leading to the decondensation of the chromatin and Hsp70 gene activation [42]. In a PARP-1 interactome study using Affinity Purification-Mass Spectrometry (AP-MS) in HeLa (cervical carcinoma) and SK-N-SH (neuroblastoma), a number of Heat Shock Proteins include Hsp90-β and Hsp70 were found to interact with PARP-1 [63]. Thus, PARP-1 might play an important role in AR and GR activation via modulation of the Heat Shock Proteins. However, further studies need to be done to provide more concrete evidence. A recent study found that the Glucocorticoid Receptor (GR) was responsible for resistance to the antiandrogen Enzalutamide [64]. GR expression was found to be higher in Enzalutamide resistant human tumor samples. Further, GR was found to drive the expression of AR target genes in Enzalutamide resistant tissues. There was a significant overlap between AR and GR specific genes. When Enzalutamide resistant LNCaP cells were treated with either DHT or Dexamethasone, about 52% of AR binding sites identified on DHT treatment were common with GR binding sites after Dexamethasone treatment. Moreover, the AR/GR overlap peaks were enriched for the FoxA motif. These observations were independently corroborated by another group [65]. Some of the pathways affected by PARP-1 directly impinge on the GR regulated pathways. PARP-1 was found to interact with Smad which is the effector of TGF-β signaling thereby preventing Smad-driven gene regulation by ADP-ribosylating Smad3 and Smad4 [66]. PARP-1 was also found to regulate NFκB, an important transcription factor in immune and inflammatory responses which is also regulated by GR [67]. Another pathway which overlaps with GR and is also activated by PARP-1 is the ERK pathway [68, 69]. Based on the role of PARP-1 in Hsp gene expression, modulation of some pathways in common with GR and the overlap between the AR and GR transcriptomes, a potential for targeting PARP-1 in antiandrogen resistant tumors cannot be ruled out. A recent study has pointed out to AR splice variants (AR-V) as the cause of resistance to antiandrogen therapy in CRPC [70]. A number of AR splice variants have been identified so far which have distinct functions. For example, the splice variant AR3 is localized to the nucleus and is involved in regulating a set of genes distinct from the canonical AR while AR8, another splice variant is localized to the cell membrane [71, 72]. It would be interesting to study if PARP-1 has a role in regulating any of the AR splice variants especially those like AR3 which localize to the nucleus. Thus, a number of lines of evidence, point to a potential role of PARP-1 in diverse mechanisms, from cancer progression to resistance in prostate cancer.

Therapeutic potential of targeting PARP-1 in prostate cancer

The concept of synthetic lethality which targets DNA repair defects in patients with BRCA mutations has been utilized for treatment of pros-

tate cancer patients [34]. Till recently, it was believed that PARP inhibitors elicit their effects by inhibiting their catalytic activities. However, a recent paper shows that these inhibitors additionally trap PARP-1 and PARP-2 enzymes at damaged DNA. The trapped PARP-DNA complexes were believed to be more cytotoxic than unrepaired SSBs which ultimately result in DSBs. Moreover, niraparib was found to be more potent in trapping PARP when compared with olaparib and eliparib was the least potent agent out of three [73]. In a study published by Schreiber *et al* in 1995, it was found that the over-expression of just the DNA binding domain (DBD) of PARP-1 led to a dominant negative effect as it prevented the endogenous PARP-1 from binding to DNA. This loss of catalytic activity rendered the cells more sensitive to the genotoxic agent MNNG [74]. Thus, small molecules which affect the catalytic activity of PARP-1 might be an interesting therapeutic option. So far, many clinical trials have been conducting in treatment of various types of cancers (**Table 1**). Some promising efficacy has been observed in trials on prostate cancer treatment. In a Phase I clinical trial with Olaparib, a PARP inhibitor, three patients with prostate cancer was recruited of which one had a BRCA2 mutation [75]. This patient had a more than 50% decrease in serum PSA levels and a resolution of bone metastases. In a follow up Phase II study (American Society for Clinical Oncology 2013 Annual Meeting), eight prostate cancer patients with BRCA1/2 mutations were recruited and treated with Olaparib monotherapy. Of these there was a Partial Response (PR) in 4 patients and 2 patients had stable disease for more than eight weeks. In another study a combination of veliparib (ABT-888) and temozolomide (alkylating agent) was used in metastatic castration-resistant prostate cancer (mCRPC) patients pre-treated with docetaxel [76]. This combination had modest activity over temozolomide monotherapy. Only one patient had the TMPRSS2:ERG gene fusion and this patient achieved stable disease with a Progression Free Survival (PFS) of 70 days and and Overall Survival (OS) of 277 days. Another PARP-1 and PARP-2 inhibitor Niraparib (MK4827) was evaluated in 23 patients with CRPC. Out of 23 patients only one had BRCA mutation. This patient had a more than 50% decrease in PSA. Nine out of 23 patients had a decrease in circulating tumor cells and a stable disease for more than 6 months. The authors did not see any correlation between ETS gene rearrangements or PTEN loss and time to disease progression or potential markers of antitumor activity like decrease in circulating tumor cells [77]. The patients without BRCA mutations that responded to PARP inhibitor therapy point to other factors at play that might influence PARP inhibitor therapy in CRPC patients. These factors might include mutations in other genes involved in DNA repair (e.g. ATM, CHEK2) and transcriptional regulation of AR target genes by PARP-1. Further mechanistic studies in patients might throw light on these pathways.

Conclusions

Given its versatility, therapeutic targeting of PARP-1 might negatively impact a number of cellular processes. More mechanistic data is required to make informed decisions in using PARP inhibitors for cancer therapy. On the other hand, PARP inhibitors that are selective catalytic inhibitors could offer better therapeutic value and modalities that target PARP-1 catalytic activation could have a therapeutic advantage. Current literature and some of the already concluded clinical trials of PARP-1 inhibitors show some promise in prostate cancer therapy. A systems approach to understanding the various functions of PARP-1 would help in better targeting therapy in prostate cancer. Based on its effect on AR function, it could serve as an important therapeutic modality in managing anti-androgen resistant CRPC.

Acknowledgements

The authors thank Kamalika Saha and Yang Xi for their critical reading of the manuscript. This work was partially supported by NIH grants (CA169524 and CA106504) to Y.Q.

Address correspondence to: Yun Qiu, Department of Pharmacology, University of Maryland School of Medicine, 655 W Baltimore St, BRB Rm 4-002, Baltimore, MD 21201. Tel: 410-706-4535; Fax: 410-706-0032; E-mail: yqiu@som.umaryland.edu

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