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HISTONE-DEPENDENT PARP-1 INHIBITORS: A NOVEL THERAPEUTIC MODALITY FOR THE TREATMENT OF PROSTATE AND RENAL CANCERS

Peter Makhov[1], **Robert G. Uzzo**[2], **Alexei V. Tulin**[3,*], **Vladimir M. Kolenko**[4,*]

[1]Molecular Therapeutics Program, Fox Chase Cancer Center, Philadelphia, PA, USA

[2]Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

[3]University of North Dakota, Grand Forks, ND, USA

[4]Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, PA, USA

Abstract

Clinical interest in poly(ADP-ribose) polymerase 1 (PARP-1) has increased over the past decade with the recognition of its roles in transcription regulation, DNA repair, epigenetic bookmarking, and chromatin restructuring. A number of PARP-1 inhibitors demonstrating clinical efficacy against tumors of various origins have emerged in recent years. These inhibitors have been essentially designed as NAD^+ mimetics. However, because NAD^+ is utilized by many enzymes other than PARP-1, NAD^+ competitors tend to produce certain off-target effects. To overcome the limitation of NAD-like PARP-1 inhibitors, we have developed a new class of PARP-1 inhibitors that specifically targets the histone-dependent route of PARP-1 activation, a mechanism of activation that is unique to PARP-1. Novel histone-dependent inhibitors are highly specific for PARP-1 and demonstrate promising *in vitro* and *in vivo* efficacy against prostate and renal tumors. Our findings suggest that novel PARP-1 inhibitors have strong therapeutic potential for the treatment of urological tumors.

Keywords

PARP-1 inhibitors; NAD^+; histone-dependent PARP-1 regulation; renal cell carcinoma; prostate cancer

Introduction

Poly(ADP-ribose) polymerase 1 (PARP-1) is an abundant and ubiquitous nuclear enzyme. When active, it captures NAD^+ to assemble long and branching polymers of poly(ADP-ribose) (pADPr) covalently modifying itself and surrounding proteins [1]. One of the most

*Co-corresponding authors: **Corresponding authors:** Vladimir M. Kolenko, Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, PA 19111, USA, Phone: 1-215-728-5620, Fax: 1-215-728-4333, Vladimir.Kolenko@fccc.edu; Alexei V. Tulin, Department of Biomedical Sciences, School of Medicine and Health Sciences, University of North Dakota, 501 North Columbia Road Stop 9061, Grand Forks, ND 58202, USA, Phone: 1-701-777-4922, Fax: 1-701-777-2054, Alexei.Tulin@med.und.edu.

Conflict of interest

None

common and well-studied activities of PARP-1 is its role in DNA repair [2, 3]. Inhibition of PARP-1 may be lethal if combined with a loss-of-function of certain DNA repair genes, including BRCA1, BRCA2, PTEN, ATM, CHEK2, FANCA, and several others. These genes are frequently mutated in various malignancies [4–8]. Thus, tumor cells harboring defects in DNA repair pathways can be selectively targeted with PARP-1 inhibitors. In addition to its DNA repair function, PARP-1 participates in many other nuclear processes, including ribosome biogenesis, regulation of chromatin, nuclear traffic, and epigenetic bookmarking [9–11]. PARP-1 is also involved in transcriptional regulation by promoting an 'open' chromatin conformation favoring transcriptional activation [12, 13] and by serving as a cofactor of different pro-tumorigenic transcription factors, most notably NF-κB and AP-1 [14, 15].

In prostate cancer (PC), the PARP-1 function is critical for transcriptional activity of the androgen receptor (AR) [16]. PARP-1 is recruited to sites of the AR transcriptional function; PARP-1 enzymatic activity is required for the AR-driven gene expression and subsequent proliferation of androgen-dependent and castration-resistant PC (CRPC) cells [16, 17]. PARP-1 inhibition results in attenuation of the AR transcriptional activity and, therefore, interferes with androgen-dependent and -independent modes of the AR activation, whereas conventional antiandrogens, such as abiraterone (Zytiga) and enzalutamide (Xtandi), target only androgen-mediated activation of the AR [18]. PARP-1 also enhances the stability and accumulation of hypoxia-inducible factor alpha subunits (HIF-1α and HIF-2α) [19, 20], arguably the most common factors in renal carcinogenesis [19–22]. Therefore, the inhibition of PARP-1 activity represents a powerful therapeutic strategy against tumors of various origins and has been a field of intense investigation over the last two decades.

The PARP-1 pathway is aberrantly activated in several types of tumors, including prostate and kidney cancers [23–27]. Our studies reveal that the expression levels of PARP-1 and pADPr, a marker of PARP-1 activity, are significantly elevated in PC cells, relative to those in normal prostate epithelial cells. In contrast, PC cells display a loss of poly(ADP-Ribose) glycohydrolase (PARG) [27], an enzymatic antagonist of PARP-1. Furthermore, the overall pADPr levels are significantly elevated in CRPC cells compared with androgen-dependent PC cells [16]. We have also found that levels of pADPr are significantly elevated in ccRCC cell lines compared to those in normal kidney epithelial cells. pADPr expression was also augmented in the specimens of primary ccRCC tumors compared with corresponding normal kidney tissue samples. Notably, severe misregulation of PARP-1 activity was observed in all examined metastatic ccRCC tumor specimens (unpublished results). Cancer cells sensitive to PARP-1 inhibitors display a loss of PARG expression and produce excessive amounts of pADPr [26, 28]. Increased accumulation of pADPr appears to be the best predictor of tumor sensitivity to PARP-1 inhibition [2, 26, 28].

PARP inhibitors: mechanisms of action

PARP-1 activity can be regulated by three mechanisms: 1) competitive binding with nicotinamide adenine dinucleotide (NAD) [1]; 2) disruption of the interaction of PARP-1 with histones [29]; and 3) obstruction of PARP-1 binding with DNA [27]. Pharmacological PARP-1 inhibitors have been designed as NAD^+ competitors and represent various

memes of nicotinamide pharmacophore [30–32]. However, because NAD^+ is extremely abundant and ubiquitous in living cells and is utilized by many enzymes other than PARP-1, NAD^+ competitors tend to produce off-target effects. Multiple studies show that NAD-like PARP-1 inhibitors can affect distant unrelated targets, showing inter-family polypharmacology (promiscuous activities at targets of different families) and intra-family polypharmacology (non-selective activities at targets of the same family) as well as multi-signaling polypharmacology (multi-signaling activities mediated by the same target) [33–35]. Examples of off-target effects include inhibitory activities against mono-ADP-ribosyl-transferases and sirtuins, which control vital metabolic processes [34, 36, 37]. Besides binding PARP-1, most of the clinically relevant inhibitors, including olaparib, ABT-888 (veliparib,) and rucaparib, also bind to other NAD-dependent enzymes, suggesting that these compounds lack specificity and have promiscuous inhibitory activity [34, 37]. The most common dose-limiting toxicities of PARP-1 inhibitors include anemia, neutropenia, and thrombocytopenia [38]. A small number of fatal cases of myelodysplastic syndrome and acute myeloid leukemia have been reported [39–42]. In addition to the risk of undesirable off-target interactions, the polypharmacologic effects of current NAD-like PARP-1 inhibitors may interfere with the interpretation of data obtained in basic biological research and clinical outcome studies.

Screening for novel histone-dependent PARP-1 inhibitors

To overcome the limitation of NAD-like PARP-1 inhibitors, we have developed a new class of PARP-1 inhibitors that specifically targets the histone-dependent route of PARP-1 activation, a mechanism of activation that is unique to PARP-1. To establish a screening platform, we designed a PARP-1 activation assay in a 384-well ELISA plate coated with histone H4 protein-activator [43]. PARP-1 reactions were performed in each well by incubating recombinant PARP-1 enzyme and NAD^+ in the presence of a single small molecule compound or a positive and a negative control. We were able to detect compounds that could disrupt PARP-1 interaction with histone H4, compete with NAD^+, or abolish the accumulation of poly (ADP)-ribose, the product of these reactions, by measuring the levels of pADPr, which were used as an indicator of PARP-1 activity [43]. Screening a ~50,000 member small-molecule library identified 903 small molecules which inhibit PARP-1 in a cell-free system. After eliminating redundancies that displayed negligible structural differences, we reanalyzed 639 selected compounds and confirmed that all strong positive hits were 100% reproducible. A total of 373 small molecules in this list inhibited PARP-1 with the same, or better efficacy than the commonly used NAD-like PARP-1 inhibitors.

To narrow down the list of small molecules for further analysis, we used a computational approach to eliminate molecules with a structural similarity to known biologically active molecules. We identified a group of 17 small molecules that showed no significant structural similarity to known inhibitors and NAD^+. Moreover, these compounds had no obvious structural homologues among any components of eukaryotic enzymatic pathways. All these molecules showed a strong capacity to block PARP-1 interaction with histone H4 in a cell-free system. Structurally, these molecules could be split into two subgroups: the first contain N-methylpiperidin in its the core element (2-(N-methylpiperidin-1-

yl)acetate or 2-(N-methylmorpholino)acetate or 2-(N-methylpyrrolidine-1-yl)acetate); the second contains 1,3-dioxolane-4-yl)methyl, with 1-((1,3-dioxolane-4-yl)methyl)piperidine or 1-((1,3-dioxolane-4-yl)methyl)N-methylmorpholino or 1-((1,3-dioxolane-4-yl)methyl) N-methylpyrrolidine as core elements [43]. Based on anti-PARP-1 activity, ease of synthesis, and structural analysis we ultimately selected a lead hit 5F02 [18, 30]. As it was confirmed by inosine-5′-monophosphate dehydrogenase (IMPDH) activity assay, 5F02 showed no significant reduction of NADH production in contrast to olaparib, which is a structural analogue of NAD^+ and competes with NAD^+ to reduce the production of NADH in the IMPDH reaction [30]. The results of this experiment indicate that non-NAD-like inhibitors like 5F02 do not affect metabolic pathways associated with NAD^+.

Given that inhibiting PARP-1 in a cell-free system does not warrant activity of a compound in cell-based assays, we tested whether the new compounds were capable of inhibiting PARP-1 activity in a cell-based system. All 17 molecules identified by our screen potently inhibited PARP-1 in a panel of human prostate and ccRCC cell lines [30]. Dose-dependent decreases in clonogenic survival and cell viability were observed upon treatment of prostate and kidney cancer cells with histone-dependent PARP-1 inhibitors [18, 30].

Pre-clinical evaluation of the efficacy of histone-dependent PARP-1 inhibitors against ccRCC and prostate cancer

Notably, the mechanism of action of histone-dependent PARP-1 inhibitors is completely different from that of the “classical” NAD-like PARP-1 inhibitors. NAD-like PARP-1 inhibitors mediate their antitumor effect through two general mechanisms: (i) catalytic inhibition of PARP-1 and (ii) locking or ‘trapping’ PARP-1 on damaged DNA [44]. The results of our experiments are in agreement with these findings indicating that NAD-like inhibitors stabilize binding of PARP-1 to the activator histone H4 arresting PARP-1-activator complex in a transient conformation. In contrast, histone-dependent inhibitors disrupt PARP-1 binding to histone H4 and exclude PARP-1 from functional complexes [18, 30, 45]. Our experimental data support this premise, demonstrating that histone-dependent inhibitors suppress PARP-1-mediated transcription more potently than NAD-like inhibitors (unpublished results). Indeed, the expression of vascular endothelial growth factor (VEGF) was markedly suppressed in patient-derived PNX0010 ccRCC cells treated with 5F02, whereas treatment with olaparib had minimal effect on the expression of VEGF (unpublished results). Treatment with 5F02 inhibited the AR transcriptional activity and prostate-specific antigen (PSA) expression in LNCaP PC cells expressing either the wild-type AR or constitutively active AR splice variant, AR-V7 [18]. In contrast, treatment with the NAD-competing inhibitor olaparib and antiandrogen enzalutamide produced only negligible inhibitory effect on the AR transcriptional activity in LNCaP cells expressing AR-V7. Furthermore, 5F02 exerted significantly higher inhibitory effect on viability of LNCaP cells expressing AR-V7 compared with olaparib and enzalutamide. Collectively, our data demonstrate that unlike NAD-like PARP-1 inhibitors and antiandrogens that target androgen-mediated activation of the AR, histone-dependent PARP-1 inhibitors suppress the AR transcriptional function and, therefore, may be effective against both androgen-dependent and -independent routes of the AR activation. Furthermore, 5F02 demonstrated

potent antitumor activity against true castration-resistant AR-negative PC-3 and DU-145 PC cells [18, 30].

In light of these encouraging *in vitro* data, we tested the antitumor activity of 5F02 using PNX0010 renal cell carcinoma and castration-resistant AR-negative PC-3 PC xenograft animal models. Animals treated with 5F02 showed a significantly stronger inhibition of tumor growth relative to control animals and animals treated with the classical PARP-1 inhibitor olaparib [30]. Moreover, 5F02 demonstrated superior *in vivo* antitumor activity compared with clinically relevant anticancer drugs, i.e., docetaxel for prostate xenograft tumors and sunitinib for ccRCC xenograft tumors [34].

Conclusions

Clinical interest in PARP-1 has increased over the past decade with the recognition of its roles in transcription regulation, DNA repair, epigenetic bookmarking, and chromatin restructuring. Currently, over 50 clinical studies are being carried out to evaluate PARP-1 inhibitors for the treatment of solid and hematological malignancies. Given the initial promising results, the efforts are now focused on finding more effective and specific PARP-1 inhibitors. Our group was the first to identify the agents that specifically target the histone-dependent route of PARP-1 activation, a mechanism of activation that is unique to PARP-1. Greater specificity and selectivity of new inhibitors compared with the conventional NAD-like PARP-1 inhibitors is expected. The new histone-dependent PARP-1 inhibitors demonstrate higher efficacy in *in vitro* and *in vivo* settings against prostate and renal tumors compared to the classical NAD-like PARP-1 inhibitors. Taken together, our findings suggest that histone-dependent PARP-1 inhibitors have strong therapeutic potential for the treatment of urological tumors.

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