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New PARP targets for cancer therapy

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Abstract

Poly(ADP-ribose) polymerases (PARPs) modify target proteins post-translationally with poly(ADP-ribose) (PAR) or mono(ADP-ribose) (MAR) using NAD^+ as substrate. The best-studied PARPs generate PAR modifications and include PARP1 and the tankyrase PARP5a, both of which are targets for cancer therapy with inhibitors in either clinical trials or preclinical development. There are 15 additional PARPs, the majority of which modify proteins with MAR, and their biology is less well understood. Recent data identify potentially cancer relevant functions for these PARPs, indicating that we need to understand more about these PARPs in order to target them effectively.

Introduction

The 17 member poly (ADP-ribose) polymerase (PARP) family of proteins, also known as ADP-ribosyltransferase diphtheria-toxin-like proteins (ARTD1-17; referred to here as PARPs according to standard nomenclature for the cancer field) has garnered much attention over the past decade as a target for cancer therapy due to the success of PARP inhibitors in preclinical trials[1]. The primary function of PARPs is to post-translationally modify target proteins with ADP-ribose using NAD^+ as substrate[2]. The four best-studied family members, PARP1 and PARP5a along with their close functional homologs PARP2 and PARP5b respectively, all generate poly (ADP-ribose) (PAR). However, most PARPs do not generate PAR, and instead attach ADP-ribose as a monomer (MAR) onto target proteins[3]. Recent data has shown that many of these MAR-generating PARPs might have cancer relevant functions (Table 1). Therefore, understanding the distinction between PAR and MAR synthesis is important as they function by different mechanisms that will likely impact the efficacy of current and novel PARP inhibitors.

In this Perspective Opinion article, we describe the key functional differences between MAR and PAR and discuss recently discovered PARP functions that may be cancer-related. The majority of these functions involve MAR-generating PARPs, identifying this class of PARP proteins as potentially important targets for cancer therapy.

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MAR versus PAR

Multiple characteristics of the PARP catalytic domain are important in determining whether a PARP generates PAR or MAR modifications. These include the specific amino acid residues that bind to NAD^+ and catalyze the transfer reaction as well as structural elements that define the substrate and acceptor binding pockets (Figure 1 and Table 1). PAR-generating PARPs contain an H-Y-E motif in which the histidine and tyrosine are involved in NAD^+ binding and coordination whereas the glutamate is required for PAR transfer and elongation activity[4]. The majority of PARP family members lack this glutamate and instead contain leucine, isoleucine or valine and are predicted or experimentally demonstrated to generate MAR using automodification reactions containing purified PARP and labeled NAD^+ (Table 1). In addition, PARPs 9 and 13, which lack the histidine, are predicted to be enzymatically inactive and do not exhibit automodification activity (Table 1)[3, 5]. Structural characteristics of the substrate and acceptor binding pockets that impact enzymatic activity include the Donor loop (D-loop) which makes contacts with the substrate NAD^+ and is thought to act as a "lid" to hold NAD^+ within the catalytic pocket[6] (Figure 1). Additionally, the acceptor pocket is partly lined by the loop between β sheets 4 and 5, referred to as the acceptor loop (Figure 1). This loop is implicated in the binding of protein substrate for MAR- and PAR-generating PARPs, or an incoming ADP-ribose unit for PAR-generating PARPs[7, 8].

Both PAR and MAR act as traditional post-translational modifications that can alter the function of target proteins. However, PAR has a unique chemistry and structure compared to MAR that further influences its biological function (Figure 2). PAR is composed of ADP-ribose residues connected via glycosidic bonds, imparting characteristics of both nucleic acids and polysaccharides. PAR can contain both linear and branched linkages although branched linkages are less frequent (~one per 20–50 linear linkages)[9] (Figure 2). When generated *in vitro*, PAR can be sizeable, containing up to 200 ADP-ribose residues[10]. In cells, polymers of such size are likely not found constitutively since PAR purified from tissue contains a maximum of 30 residues[11]. However, they can exist transiently as treatment with DNA damaging agents results in lengths comparable to those produced *in vitro*[12]. Thus the chemistry, high negative charge density, and size of PAR results in a molecule that can function as a high density protein binding scaffold[13] (Figure 2). Several examples of this function exist. DNA repair proteins are recruited to sites of DNA damage by binding directly to PAR attached to PARP1 and histones[14]. Similarly, PAR scaffolds have been implicated in regulation of NF-κB signaling[15], cajal body function[16] and cytoplasmic stress granule assembly[17], and they are also present at the mitotic spindle pole[18].

Although both PAR and MAR can bind proteins, the complexity of the recruitment signal, the number of binding proteins, the number of identified binding domains, and the amount of protein that can bind to PAR greatly exceeds that of MAR. There are four known high affinity PAR binding domains – tryptophan-tryptophan-glutamate (WWE)[19], poly(ADP-ribose) binding zinc finger (PBZ)[20], and 'macro'[21] domains as well as a loosely defined PAR binding motif (PBM)[22] (Figure 2; see REFs [13 and 23] for reviews); collectively, these domains are found in over 800 proteins some of which include the PARPs themselves

(Table 1)[20, 22, 24, 25]. In contrast, the only MAR binding domain identified thus far is the macro domain, shown to bind both free[21] and protein-attached[26, 27] MAR and PAR, although binding affinities for the two types of ADP-ribose modifications varies among different macro domains[28]. However, although many functions for MAR are now identified[29], the biological relevance of protein binding to MAR has not been extensively studied and is therefore unclear.

As a regulatory molecule, MAR is thought to be evolutionarily ancient because viruses such as T4 bacteriophage and certain pathogenic bacteria encode mono ADP-ribosyltransferases (mARTs) that modify host proteins with MAR to mediate pathogenicity[30–32]. In addition to PARPs, eukaryotes contain multiple MAR-generating enzymes, all of which require NAD^+ as substrate. These include two members of the sirtuin family, SIRT4[33] and SIRT6[34], and the eukaryotic ADP-ribosyltransferase (ART) family[35]. In mammals, 3 of the 5 ARTs are active as arginine-ADP-ribosyltransferases[35]. Although sirtuins can generate MAR intracellularly, the ARTs found in humans likely do not since they are either glycosylphosphatidylinositol-anchored or secreted ecto-enzymes[35].

Intracellular MAR modifications in humans have long been identified, although in many cases the specific enzymes responsible for their synthesis are unknown. Known targets of MAR modification include the cytoskeletal proteins actin[36, 37] and desmin[38], the protein folding chaperone GRP78 (also known as BiP)[39–42] and heterotrimeric G-proteins[43–47]. Each of these proteins is MARylated on arginines instead of the canonical lysine, glutamate or aspartate residues known to be PARylated by PARPs[48–50]. However, as the amino acid targets of most MARylating PARPs have not been identified, it is possible that among these PARPs are the proteins responsible for arginine modification of the above targets. In fact, several new functions ascribed to MAR-generating PARPs, including actin cytoskeletal regulation, membrane regulation and regulation of the unfolded protein response (UPR) could involve modification of the above proteins[51, 52] (Table 1).

New PARP functions relevant to cancer

Recently several new functions have been identified for PARPs that demonstrate their importance in diverse physiological and stress-dependent pathways. (summarized in Figure 3 and reviewed in REFs[13, 29, 53–55]). The majority of these functions involve MAR-generating PARPs (Table 1), making the development of MAR-generating PARP inhibitors an important priority as current PARP inhibitors primarily target PAR-generating PARPs[6]. Here we focus on new functions that are cancer relevant, including the regulation of the endoplasmic reticulum (ER) unfolded protein response (UPR)[51], the cytoplasmic stress response[17], miRNA-mediated post-transcriptional gene regulation[17, 56], cancer-related signal transduction pathways[57–59] and cell migration[52, 60] (Figure 3). Additional functions identified for PARPs 4[61], 6[62], 7[63, 64] and 8[52] will not be discussed since less is known about their direct relevance to cancer.

Unfolded Protein Response

The UPR is a cellular adaptation to ER stress triggered by an increase in misfolded proteins within the ER lumen, or by extracellular stressors such as nutrient or oxygen deprivation[65].

Because of the cytoprotective function of the UPR, its up-regulation is a hallmark of many cancers, due in part to the highly oxidative tumor microenvironment and the high rate of protein synthesis found in cancer cells[66]. During severe stress or prolonged UPR activation, the UPR activates a distinct transcriptional program to induce UPR-dependent apoptosis[65]. Activation of this apoptotic program makes the UPR a particularly attractive target for cancer therapies[54].

In humans two highly homologous transmembrane kinases – protein kinase RNA-like endoplasmic reticulum kinase (PERK) and inositol-requiring enzyme 1α (IRE1α) - act as ER stress sensors that regulate separate but interconnected signaling networks in the UPR[65]. A third ER stress sensor, ATF6 also exists but is not regulated by PARP activity. UPR activation by these kinases results in a general decrease in translation and while transcription and translation of stress-specific proteins is increased to restore ER homeostasis[65]. Both PERK and IRE1α are targets for cancer therapies[67–69].

PARP16 is an ER transmembrane protein with a cytoplasmic catalytic domain that exhibits MAR activity[51, 70]. During UPR activation, PARP16 enzymatic activity is highly upregulated resulting in modification of IRE1α, PERK and PARP16 itself with MAR[51]. Karyopherin-β1, part of the nuclear trafficking machinery, has also been identified as a target of PARP-16[70] suggesting that PARP16 has additional non UPR dependent functions. MARylation of IRE1α and PERK is sufficient to activate these enzymes *in vitro* and knockdown of PARP16 in HeLa cells results in defective UPR activation with PERK and IRE1α signaling dramatically reduced[51]. Together these results suggest that PARP16 is critical for activating these enzymes in vertebrates and/or maintaining their “on” state[51]. In addition, PARP16 is phosphorylated by PERK i*n vitro*[51] suggesting that PARP16 activation could be regulated by PERK phosphorylation, similar to PARP1 activation by ERK phosphorylation[71, 72] and PARP5a activation by GSK3 phosphorylation[73]. Thus PERK and PARP16 appear to regulate each other via positive feedback.

Since PARP16 regulates UPR activation and PERK and IRE1α signaling, it is an attractive candidate for the therapeutic inhibition of UPR signaling in cancers[54] with or without known UPR activating agents such as HSP90[74] and 26S proteasome inhibitors[75]. Data suggests that this approach is feasible as siRNA-mediated knockdown of PARP16 renders HeLa cells highly sensitive to UPR activation resulting in increased cell death of UPR activated cells relative to non-treated PARP16 knockdowns[51]. Therefore, the requirement of PARP16 function for UPR activation makes it an attractive candidate to target cancers that upregulate UPR (Table 1).

Cytoplasmic stress response

Cytoplasmic stressors including viral infection, oxidative stress, heat shock, hypoxia, and ER stress result in eIF2α phosphorylation, inhibition of cap dependent mRNA translation, and the assembly of stress granules (SG) — large ribonucleoprotein complexes that contain mRNA, RNA binding proteins and 40S ribosomal subunits[76]. PAR, 5 different PARPs and poly(ADP-ribose) glycohydrolase (PARG), an enzyme specific for hydrolysis of PAR, are enriched in SGs on stress induction and PAR synthesis and turnover dynamics regulate the kinetics of SG formation and disassembly[17]. Of the SG-PARPs, only PARP5a has PAR

synthesis activity whereas PARPs 12, 14 and 15 generate MAR and PARP13 is inactive, but present[3, 17].

Under hypoxic or oxidative stress, SGs inhibit the induction of apoptosis through the JUN N-terminal kinase (JNK)-MAPK signaling pathway via the sequestration of RACK1, a mediator of the MAPK pathway[77]. Similarly, sequestration of the mTORC1 component Raptor in SGs in the presence of oxidative stress prevents apoptosis induced by mTORC1-hyperactivation[78]. Astrin, a protein that is upregulated in cancer cells, mediates the localization of Raptor to SGs and oxidative stress induced-apoptosis is increased in cancer cells in which SG assembly is inhibited or expression of Astrin is knocked down using siRNAs[78].

Cancer cells in solid tumors are subject to multiple SG-inducing stresses, such as hypoxia and oxidative stress, both of which are associated with chemoresistance[79]. For example, solid tumors are largely resistant to apoptosis induction mediated by bortezomib, a 26S proteasome inhibitor which is effective in treatment of multiple myelomas and hematological tumors[80]. Interestingly, bortezomib treatment was shown to induce SG assembly in multiple cancer cells lines and inhibition of SG formation promoted bortezomib-mediated apoptosis, further supporting the protective effects of SGs in cancer cell survival[81]. Therefore, targeting the PARPs that function in SG assembly could be a strategy to sensitize solid tumors to chemotherapy (Table 1).

microRNA-Ago2 silencing pathway

MicroRNAs are small, non-coding RNAs that regulate gene expression via post-transcriptional mechanisms. MicroRNA function is mediated by the RNA induced silencing complex (RISC), core components of which are Argonaute proteins that bind to the microRNA–mRNA duplex and mediate post-transcriptional silencing[82]. Argonaute proteins are modified by PAR during normal conditions, but the level of PAR modification increases during stress conditions including viral infection and oxidative stress, resulting in decreased microRNA-dependent silencing activity[17, 56]. PARP13 seems to be important for regulation of Ago2 function, as PARP13 knockdown upregulates Ago2 silencing activity under stress and non-stress conditions[17, 56]. Although PARP13 is enzymatically inactive, it contains 4 RNA-binding CCCH Zinc finger domains and binds to Ago2 in an RNA dependent manner suggesting that it either binds to RNA attached to Ago2, or that RNA binding to Ago2 results in a conformational change that mediates PARP13 binding. PARP13 is a target for PAR modification and therefore could also target Ago2 for modification by recruiting other PARPs[17].

The role of Ago in cancer progression is complex. Profiling of Ago family members in human colon cancer tissue identified overexpression of Ago2 in cancerous tissue compared with adjacent non-cancer tissue[83] and Ago2 was similarly found to be upregulated in human hepatocellular carcinoma, promoting tumor growth and metastasis[84]. In contrast, other reports show that Ago2 overexpression inhibits tumorigenesis by silencing genes required for proliferation[85, 86] and that Ago2 expression is downregulated in melanoma[87] and lung adenocarcinoma[86]. Thus, the role of Ago2 and other argonaute proteins in tumorigenesis may depend on tumor specificity, the tumor microenvironment and the genetic alterations of

the cancers in question. Because of the complex role of Ago2 in cancer, further investigation will be required to determine if inhibition of Ago2 ADP-ribosylation will have therapeutic benefits. Perhaps one of the most straight-forward benefits of modulating miRNA activity via PARP inhibition might be to increase the effectiveness of siRNA or miRNA therapies, since PAR modification of Ago2 inhibits its miRNA-mediated silencing activity.

Signal Transduction

PARP10, a MAR-generating PARP[3] with RNA and ubiquitin binding domains, has functions in multiple signaling pathways. It was initially identified as a MYC interacting protein that inhibits transformation of rat embryo fibroblasts when coexpressed with MYC and HRAS, but its effect was independent of its ADP-ribosylase activity[88]. This was the fist indication of a potential tumor suppressive role for PARP10 because MYC, a transcription factor that regulates many cellular processes including cell proliferation, is frequently deregulated in cancer cells and is associated with tumor progression[89].

Recently, PARP10 was also shown to regulate NF-κB signaling in a manner dependent both on PARP10 interacting with poly-ubiquitin chains on proteins that regulate NF-κB activity and its ADP-ribosylase activity. Exogenous PARP10 expression in both HeLa and U20S cells resulted in the inhibition of downstream NF-κB target gene expression in response to interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) by altering the poly-ubiquitylation state of several NF-κB signaling intermediates and preventing the translocation of the NF-κB transcription factor p65-RelA to the nucleus[57]. Additionally, PARP10 overexpression in HeLa cells inhibited cell proliferation through the induction of apoptosis[90, 91], although the contribution of altered NF-κB and/or MYC signaling to apoptosis induction was not investigated. PARP10 function in NF-κB signaling regulation is physiological relevant as shRNA and siRNA mediated knock down of endogenous PARP10 increased expression of NF-κB targets in HeLa and U2OS cell lines[57].

PARP10 is enriched in cytoplasmic poly-ubiquitin containing foci that can interact with autophagosomes marked by p62, a ubiquitin-binding autophagy adaptor protein[92]. Although the role of PARP10 in autophagy has not been investigated, this association is particularly interesting because autophagy is activated in cancer cells and might represent another mechanism to cope with cellular stress[93–95]. Inhibition of autophagy can sensitize cancer cells to chemotherapy[96] or inhibit tumour growth[97]. The autophagy pathway exerts cytoprotective effects on cancer cells by inhibiting apoptosis and necrosis in response to metabolic stress[98, 99]. Since NF-κB signaling can regulate autophagy, PARP10 may represent a important link between these two pathways[100]. Further study of the PARP10 function in NF-κB signaling will be important to understand its role in normal physiology and disease and determine if it does indeed have a function in autophagy regulation.

PARP14 (also known as BAL2 on the basis of its homology to PARP9 (BAL1)), is a MAR-generating PARP that contains three macro domains (Table 1). PARP14 regulates interleukin-4 (IL-4) signaling by acting as a transcriptional co-activator of the transcription factor signal transducer and activator of transcription 6 (STAT6) in a mechanism that is dependent on its catalytic activity[59, 101]. B cell proliferation and survival is compromised in splenocytes from *Parp14*$^{-/-}$ mice due to an impaired response to IL-4[102]. Furthermore,

whereas IL-4 exerts an anti-apoptotic effect on *ex vivo* cultured B cells from wild type mice, the response is attenuated in B cells from *Parp14* $^{-/-}$ mice[102]. Moreover, *Parp14*$^{-/-}$ mice have delayed MYC-induced B cell lymphomagenesis, highlighting the role of PARP14 in B cell lymphoma development[102, 103]. Recently, PARP14 has also been implicated in mediating JNK pro-survival signaling in multiple myeloma cells and is highly expressed in these cells compared with normal plasma cells[58]. Therefore, PARP14 is a new candidate for therapeutic intervention in hematological malignancies due to its functions in B cell development (Table 1).

Cell Migration

PARP9 and PARP14 are members of the macro PARP subfamily, containing 2 and 3 macro domains respectively. The macro domains of PARP9 can bind to both free MAR and PAR whereas PARP14 macro domains specifically bind to MAR-modified proteins[21, 27]. Both are involved in the regulation of cell migration[52, 60], a highly complex process requiring the coordinated activity of multiple proteins that is necessary for the development of metastases[104, 105]. The discovery of regulatory functions for PARPs 9 and 14 in cell migration suggests that they could be important targets for cancer therapy.

PARP9 was originally identified as BAL1 (B-aggressive lymphoma 1) because it is expressed at higher levels in high-risk diffuse large B-cell lymphomas when compared to low risk tumors[60]. PARP9 overexpression promotes the migration of B-cell lymphoma cells, suggesting a function in regulation of cell motility[60]. Consistent with this observation, PARP9 knockdown results in defects in the actin cytoskeleton[52]. Although PARP9 is constitutively expressed in cells, its expression can be induced by interferon-γ (IFN-γ)[106], an immunostimulatory cytokine which has been previously implicated in activating B cell motility[107, 108]. IFN-γ has tumor suppressive effects by increasing tumor immunogenicity and is used clinically as a cancer treatment, however many studies also report pro-tumorigenic effects of IFN-γ treatment[109]. This contradiction seems to be a consequence of dosage. Treatment of a low grade bladder cancer cell line with high concentrations of IFN-γ had anti-proliferative effects, whereas low doses of IFN-γ resulted in resistance to TNFα-mediated cytotoxicity and was associated with an increase in cell migration[110]. Additionally, mammary adenocarcinoma cells expressing low levels of IFN-γ were more metastatic than those expressing high levels when evaluated in BALB/c mice after tail vein injections of cells[111]. Finally, low surface expression of IFN-γR2, a component of the IFN-γ receptor, on T cells results in a proliferative effect on treatment with IFN-γ, which switches to an apoptotic effect if the levels of IFN-γ R2 are increased through exogenous expression[112]. One possible model that integrates these disparate findings is that low amounts of IFN-γ induce PARP9 expression, resulting in upregulation of cell motility and metastasis, whereas higher levels overcome the effects of PARP9 expression and result in anti-proliferative and pro-apoptotic effects. Therefore, the expression levels of PARP9 and other IFN-γ dependent genes following low or high doses of IFN-γ treatment should be evaluated.

PARP9 is catalytically inactive based on automodification activity[3, 113] and how PARP9 functions in cell migration is unknown. It will be important to determine whether binding to MAR or PAR regulates PARP9 function. If PARP9 is a contributing factor to the pro-

metastatic effects of IFN-γ treatment, inhibition of PARP9 function in conjunction with IFN-γ could potentially overcome the tumorigenic effects of low levels of IFN-γ.

PARP14 associates with focal adhesions, identified by both biochemical purification of focal adhesion complexes from human foreskin fibroblast cells[114] and by co-immunostaining with focal adhesion proteins in HeLa cells[52]. PARP14 knockdown results in defects in cell migration in adherent cells in which cells are unable to effectively retract protrusions and have increased adhesiveness to a fibronectin substrate[52]. These findings indicate that PARP14 regulates focal adhesion turnover[52]. Although metastasis requires the loss of cell-cell contacts, metastatic cells are able to bind to extracellular matrix components that are not bound by cells in primary tumors[115]. Fibronectin and integrin interactions have long been implicated in the promotion of tumor cell invasion and metastasis[116]. Further mechanistic investigation of the function of PARP14 in focal adhesion regulation will be important to determine whether PARP14 is a useful target for the inhibition of metastasis.

Concluding Remarks

Recent analysis examining the binding of 185 known PARP inhibitors to bacterially expressed catalytic domains of 14 of the 17 human PARPs showed that almost none of the inhibitors bind to MAR-generating PARPs and the handful that bind do so with low affinity[6]. These results suggest that selective inhibition of MAR generating PARPs is possible, and provide an explanation as to why MAR dependent phenotypes do not occur on treatment with current PARP1 and 2, and PARP5a and 5b inhibitors.

Within the past several years, data identifying important cellular functions for MAR generating PARPs have emerged. Many of these functions are disease relevant and could be attractive targets for the therapeutic inhibition of cancer. Much remains unanswered regarding the mechanism of MAR function, the potential functional interactions between MAR and PAR and the potential regulatory interactions between PARPs. Identifying PARP-specific activating signals and targets, and determining the manner in which protein function is altered upon modification will be critical steps for our understanding of MAR. This information will also allow us to better evaluate the therapeutic relevance of MAR inhibition for the treatment of cancer.

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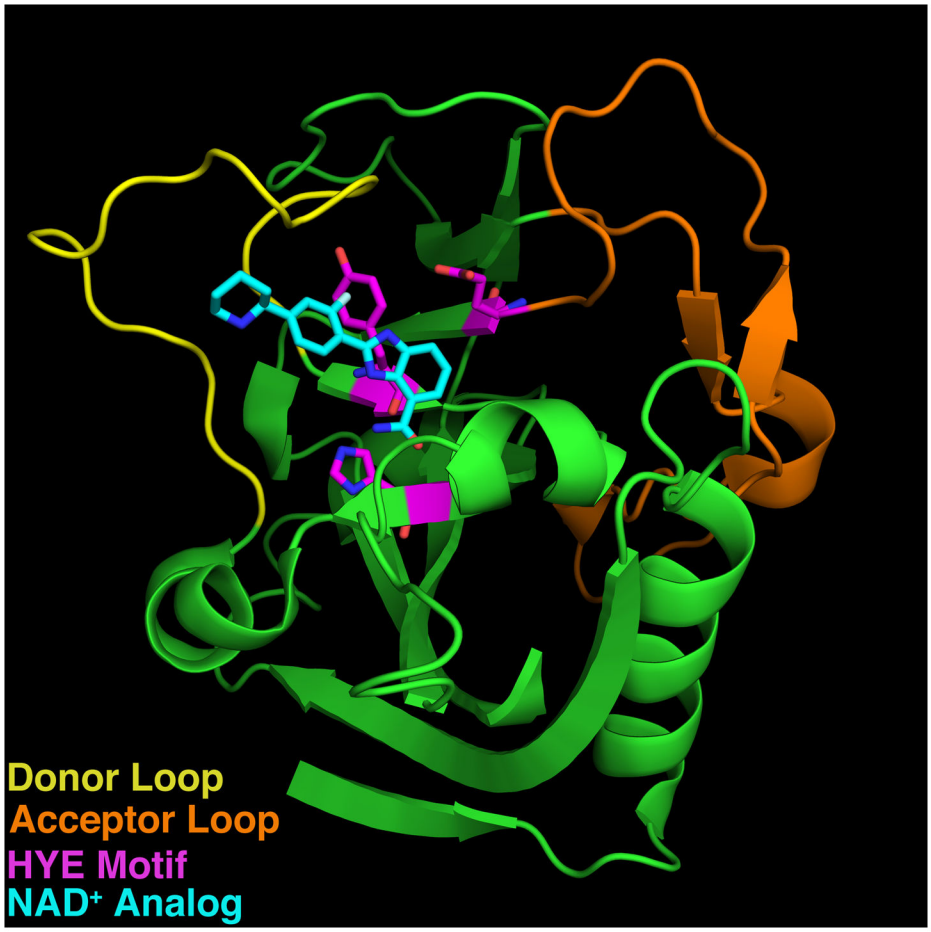

Figure 1. Sequence and Structural Elements of the PARP catalytic domain

The Donor (yellow) and acceptor (orange) loops of PARP1 (3L3M[117]), which shape the substrate and acceptor binding pockets respectively, are indicated. H-Y-E motif is shown in magenta. A co-crystallized NAD^+ analog inhibitor (A927929) is shown in cyan.

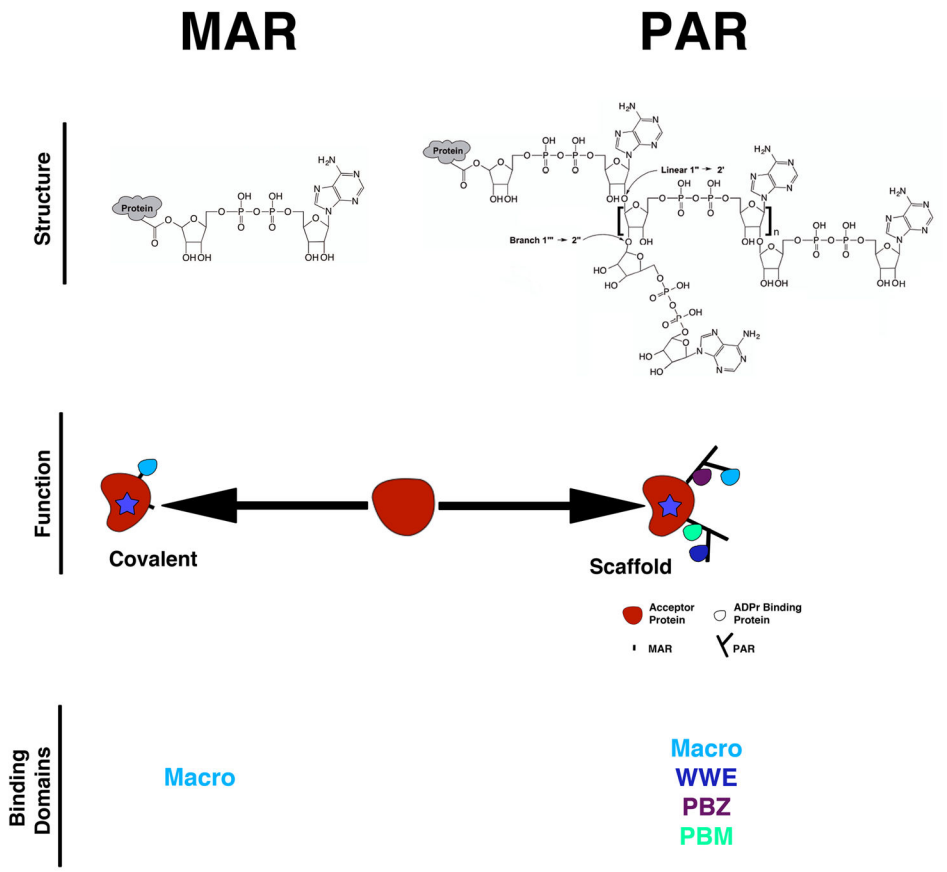

Figure 2. Two forms of ADPr modifications

PARPs synthesize either mono(ADP-ribose) (MAR) or poly(ADP-ribose) (PAR) modifications. Both can alter target protein function through covalent modification. PAR can also function as a scaffold to recruit proteins containing macro, WWE, PBZ and PBM domains. In contrast, MAR is only recognized by macro domains and does not act as a scaffold since it only contains a single binding site for proteins. Therefore, the structural distinction between MAR and PAR has important consequences of the mechanism of function of the modification.

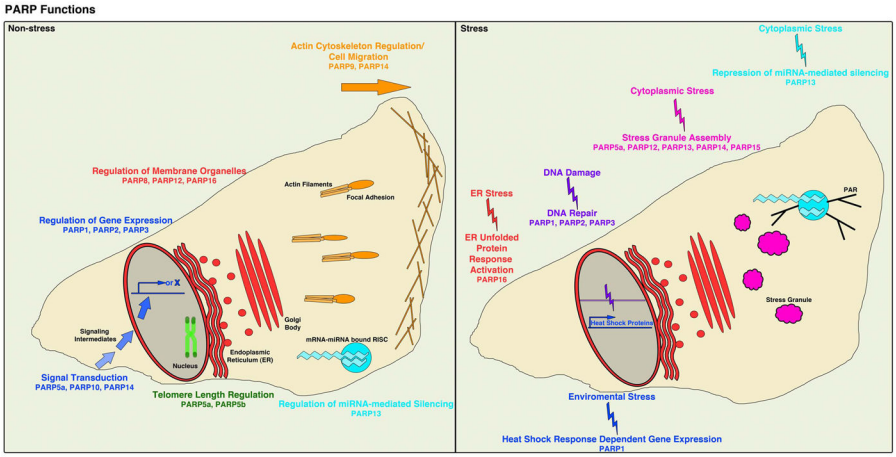

Figure 3. Cellular Functions of the PARP Family

PARPs have multiple diverse in functions in physiological pathways including cell migration, transcriptional regulation, signal transduction, miRNA-mediated gene silencing, regulation of membrane organelles and telomere length regulation. Additionally, PARPs function in stress-responsive cellular pathways upon DNA damage, cytoplasmic stress, environmental stress and ER stress, activating DNA damage repair, stress granule assembly, the heat shock response and the ER unfolded protein response pathways in response. Many of these physiological and stress response pathways are misregulated in cancer, raising the possibility that inhibition of these PARP functions could have therapeutic benefits.

Table 1

Enzymatic activity and cancer relevant functions of PARPs.

PARP	Other Names	Demonstrated Activity*	Predicted Activity	ADPr Binding Domains	Cancer Related Functions	Cancers to target
1	"PARP" ARTD1	PAR[10]			DNA Repair[14], ERK/ NF-kB signaling[118], Heat shock response[119]	HR deficient Elevated ERK/NF-kB signaling
2	ARTD2	PAR[120]			DNA Repair[120]	HR deficient
3	ARTD3	MAR[121]			DNA Repair[122]	
4	vPARP ARTD4	MAR[61]				
5a	TNKS1 ARTD5	PAR[123]			Telomere Maintenance[124], Wnt Signaling[125], Proteasome Regulation[126], Stress Granule Assembly[17], Cell Division[127]	Elevated Wnt Signaling Telomerase Dependent Stress Granule Positive Solid Tumors
5b	TNKS2 ARTD6	PAR[128]			Telomere Maintenance[128], Wnt Signaling[125]	Elevated Wnt Signaling, Telomerase Dependent
6	ARTD17		MAR[3]		Negative Regulator of Proliferation[62]	Potential Tumor Suppressive Functions
7	tiPARP ARTD14	MAR[64]		WWE		
8	ARTD16		MAR[3]			
9	BAL1 ARTD9	No automodification activity[113]	Inactive[3]	Macro (2)	Cell Migration[60]	Metastatic Cancers
10	ARTD10	MAR[3]			Inhibits Myc[88] and NF-kB[57] signaling Pro-apoptotic[91]	Potential Tumor Suppressive Functions
11	ARTD11		MAR[3]	WWE		
12	ARTD12	MAR[17]		WWE	Stress Granule Assembly[17]	Stress Granule Positive Solid Tumors
13	ZAP ZC3HAV1 ARTD13	No automodification activity[3]	Inactive[3]	WWE	Stress Granule Assembly[17], miRNA-RISC regulation[17, 56]	Stress Granule Positive Solid Tumors
14	BAL2 ARTD8	MAR[3]		Macro (3) WWE	B cell survival[102], Cell Migration[52], Stress Granule Assembly[17]	Hematopoeitic malignancies, Metastatic Cancers
15	BAL3 ARTD7	MAR[17]		Macro (1)	Stress Granule Assembly[17]	Stress Granule Positive Solid Tumors
16	ARTD15	MAR[51, 70]			ER Unfolded Protein Response[51]	UPR dependent

*Catalytic activity is based on ability of PARPs to automodify when incubated with NAD^+. PAR: poly(ADP)-ribose; MAR: mono(ADP-ribose); HR: Homologous Recombination; ER: endoplasmic reticulum