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The comings and goings of PARP-1 in response to DNA damage

John M. Pascal

Université de Montréal, Department of Biochemistry and Molecular Medicine, 2900 Boulevard Edouard-Montpetit, Roger-Gaudry Pavilion, D-347, Montréal, Qc H3T 1J4 Canada

Abstract

Poly(ADP-ribose) polymerase (PARP) enzymes are broadly involved in the cellular response to DNA damage. PARP-1 is the chief human PARP enzyme involved in the DNA damage response, acting as a first responder that detects DNA strand breaks, and contributes to repair pathway choice and the efficiency of repair through modulation of chromatin structure and through interaction with and modification of a multitude of DNA repair factors. This perspective summarizes our knowledge of PARP-1 involvement in DNA repair pathways, and highlights recent structural and functional data regarding the activation of PARP-1 upon detecting DNA damage, and the release and trapping of PARP-1 at sites of DNA damage.

Keywords

poly(ADP-ribose); PARP; DNA damage response

The PARP family of enzymes

The poly(ADP-ribose) polymerase (PARP) family of enzymes regulates virtually every aspect of human cell biology through the production of an ADP-ribose posttranslational modification of proteins using NAD^+ [1,2]. The majority of the 17 family members create a mono(ADP-ribose) modification on the acceptor amino acids of target proteins, and a subset of family members extend the initial modification site to form poly(ADP-ribose), or PAR. The structures and activities of the catalytic domains of PARP family enzymes are related to each other and to the bacterial toxins that also use NAD^+ to ADP-ribosylate proteins [3]; indeed, the PARP family members are also known as ADP-ribosyl transferase diphtheria toxin-like (ARTD) enzymes [4]. In contrast to the related catalytic domains, distinct regulatory domains of the 17 members of the PARP family of enzymes specify their cellular functions. Three human PARP enzymes, PARP-1, and PARP-2 and PARP-3, are regulated through interaction with DNA damage, and each of these DNA damage response PARPs are implicated in different aspects of the cellular response to DNA damage [5,6]. The Tankyrase

john.pascal@umontreal.ca.

Conflict of Interest Statement

The author claims no conflict of interest.

enzymes (PARP-5a/PARP-5b) are perhaps best known for their contribution to genome stability through the regulation of telomeres and mitosis [7,8], and there is also growing evidence for other PARP family members involvement in the DNA damage response [6]. This Perspective will focus on PARP-1, for which there is the most advanced understanding of structure, mechanism, and biological function. Moreover, PARP-1 is the major source of poly(ADP-ribose) produced during the cellular response to DNA damage.

PARP-1 and the cellular response to DNA damage

PARP-1 plays an expansive and multifaceted role in the cellular response to DNA damage, with growing evidence for participation in multiple pathways of DNA damage repair and genome maintenance [5,6]. The currently appreciated roles within repair pathways can be summarized in three categories: (i) detection of DNA damage, (ii) poly(ADP-ribose) mediated recruitment of repair factors, and (in) poly(ADP-ribose) mediated regulation of biochemical activities. Early literature centered on PARP-1 involvement in single strand break repair (SSBR) and base excision repair (BER) [9–16], where critical events are the detection of single-stand break damage and the poly(ADP-ribose)-mediated recruitment of the scaffolding factor XRCC1 to DNA strand breaks. PARP-1 has now been implicated in the regulation of nucleotide excision repair (NER) [17,18], classical non-homologous end-joining (cNHEJ) [19–21], alternative non-homologous end-joining (aNHEJ) [22–28], microhomology-mediated end-joining (MMEJ) [29,30], homologous recombination (HR) [31,32], DNA mismatch repair (MMR) [33], and maintenance of replication fork stability [34–38]. The emerging details for the roles of PARP-1 in the various pathways has been the subject of two recent reviews [5,6]. Several representative roles for PARP-1 regulation of DNA repair are summarized in Table 1.

An additional and perhaps more general role of PARP-1 in the response to DNA damage is the regulation of chromatin structure and composition. This role is carried out in part through the poly(ADP-ribose)-mediated recruitment and regulation of chromatin remodeling factors [39–42], but also through PARP-1 modification of histones [43]. Furthermore, poly(ADP-ribose) has been proposed to seed the formation of subnuclear structures through the principle of liquid demixing, a phase separation phenomenon that endows special physical properties for granting access to certain protein factors and excluding others [44]. Thus, in addition to specific roles in repair pathways, PARP-1 can be viewed as a general organizer of nuclear architecture [45].

Cells with defects in homologous recombination DSB repair due to BRCA1/2 loss are exquisitely sensitive to chemical inhibition of PARP activity [46,47]. PARP inhibition and HR deficiency exemplify the concept of synthetic lethality, in which two deficiencies that are not individually lethal are rendered lethal in combination. PARP inhibitors are the first example of synthetic lethality that has shown success in the clinic, and they have heralded the potential of targeting DNA damage repair for the treatment of cancer [48,49]. Given PARP-1 connections to multiple repair pathways, there have been several different proposals to explain the sensitivity of HR-deficient cells to PARPi-mediated deficiencies in repair pathways [5]: (i) deficiency in SSBR: elevated number of unrepaired single strand breaks that are converted to a DSB end after encountering a replication fork, (ii) deficiency in

aNHEJ: eliminates another pathway of DSB repair in addition to HR, and (iii) deficiency in stability of replication forks: further reduces the capacity to cope with unstable replication forks. There is a growing appreciation for the importance of PARP-1 contribution to repair pathways outside of SSBR/BER, and this shift in understanding has also shifted the focus to alternate explanations for the underlying mechanism of PARPi sensitivity. A Perspective from Alan D'Andrea in this issue further explores the mechanisms of PARP inhibitor sensitivity and resistance.

PARP-1 detecting and signaling DNA damage

The structural analysis of PARP-1 has provided the most keen insights into how PARPs recognize DNA damage and into how DNA damage detection allosterically leads to robust production of poly(ADP-ribose) [50–57]. PARP-1 has a multi-domain architecture composed of six domains (see Fig. 1 schematic). Although the structure of full-length PARP-1 has yet to be determined, a composite model based on X-ray and NMR structures of fragments and biophysical and biochemical analysis of full-length protein provides a rather complete view of PARP-1 in the act of detecting DNA damage and being primed for poly(ADP-ribose) production (Fig. 1; see legend for model details).

There are several key aspects of the PARP-1 structural model. First, the domains are organized through interaction with DNA damage, and the domains that contact DNA directly (Znl, Zn2, Zn3, and WGR) have mutually compatible binding sites. This aspect is particularly important for a single-strand break that presents two DNA ends, the key feature recognized by PARP-1 zinc fingers Zn1 and Zn2 [50]. A composite NMR/x-ray structure of the Zn1-Zn2 fragment of PARP-1 bound to a model single-strand DNA break illustrated that the zinc fingers are partitioned to specific ends of the DNA structure (Znl to the 5' end, Zn2 to the 3' end), rather than competing for the same DNA end or forming a mixed population [50]. This specific arrangement presents the Zn1 to form essential contacts with the WGR domain, which binds near the 5' end of the DNA. The Zn1 domain has particular sequence features that allow it to communicate with the WGR domain and which are not present in the Zn2 domain [52,58]. It is also noteworthy that the extended linker region connecting the Zn1 and Zn2 domains is likely to allow the Zn1-Zn2 fragment to accommodate greater distances between the two ends of the DNA, for example on a single-strand break with a multi-nucleotide gap. The precise composition of the DNA structure could thus influence the efficiency with which the PARP-1 domains are assembled, and could thereby regulate the catalytic output (e.g. single-strand break *versus* stalled replication fork structure).

A second feature of the model is that PARP-1 binds to DNA damage as a monomer, thus indicating an intramolecular mechanism of activation. This aspect of the model is supported by both structural data and biophysical analysis [50,58–60]. The organization of domains positions a heavily modified region of PARP-1, the linker residues following the BRCT fold [61], in close proximity to the catalytic domain. The structural model thus can explain PARP-1 preference for automodification, and biochemical analysis using PARP-1 variants of different size and using defined DNA substrates has indicated a preference for *in cis* modification [50]. Recent cell-based studies using different tagged versions of PARP-1 have also supported the intramolecular activation mechanism of PARP-1 [62].

A third important aspect of the model concerns the mechanism of allosteric activation. A structural distortion in the regulatory helical domain (HD) of PARP-1 was observed in the crystal structure of the essential Zn1, Zn3, WGR, and CAT domains in complex with a DNA double strand break [58]. Along with supporting protein mutagenesis and biochemical analysis, it was expected that a conformational change in the HD, promoted through contacts with the Zn1, Zn3, and WGR domains, was the underlying trigger for an increase in poly(ADP-ribose) production [53]. However, the mechanism was not clear. An analysis of PARP-1 structural dynamics in the absence and presence of DNA strand break damage using hydrogen-deuterium exchange with mass spectrometry (HXMS) indicated that the DNA damage-dependent structural distortion of the HD is actually much more severe than what was captured in the crystal structure, leading to the unfolding of specific HD regions that are held in a helical conformation in the absence of DNA [51]. Deletion of the HD domains from PARP-1, PARP-2, and PARP-3 leads to constitutively active PARP enzymes, thus indicating that the HD is an autoinhibitory domain for each of the DNA damage-dependent PARPs [51]. A recent study using a non-hydrolyzable NAD^+ analog has provided the final important step of the mechanism, indicating that the folded conformation of the HD acts to block NAD^+ access to the PARP-1 catalytic domain; HD unfolding allows unrestricted access to NAD^+ [54].

The full potential of PARP-1 catalysis of poly(ADP-ribose) production is remarkably robust. Indeed the HD-deleted, constitutively active forms of PARP-1 produced for biochemical and structural analysis require special considerations for production in E. coli, including the presence of PARP inhibitors and sortase-mediated joining of PARP fragments [51,63]. The HD provides a mechanism to keep PARP-1 inactive by restricting access to the key requirement for poly(ADP-ribose) synthesis: NAD^+. Interaction with DNA damage acts to distort the structure of the HD, increasing the frequency of the active site being in the “open” state. Thus, the HD can be viewed as a throttle for the PARP-1 active site, regulating access to the NAD^+ fuel.

PARP-2 and PARP-3 also exhibit HD autoinhibition [51], and are predicted to form similar WGR contacts with the HD [64]. Their WGR contacts with the DNA are likely to differ somewhat from what has been observed with the WGR of PARP-1, based on the fact that PARP-2 and PARP-3 are most potently activated by DNA single strand breaks and DNA phosphorylated on the 5’ terminus [64–66]. Thus, the nature of the damaged DNA structure (i.e. gapped or nicked single-strand break) can influence the catalytic output. A more complete understanding of how the DNA structure influences PARP-2 and PARP-3 allosteric activation will require structural information for DNA-bound enzymes.

Regulation of the PARP-1 complex with DNA damage

The presented structural model represents the expected state of PARP-1 immediately following DNA damage detection and just prior to the burst in production of poly(ADP-ribose). The DNA damage activated complex is dependent on a quite elaborate network of protein-DNA and protein-protein contacts, likely providing points of regulation through posttranslational modifications (including ADP-ribose) and through the binding of partner proteins. As an example, the protein HPF1 (Histone PARylation Factor 1) was recently

identified as a binding partner of PARP-1 that regulates catalytic output [67]. The mechanistic details for how this is accomplished are still unknown, but HPF1 could potentially act by adjusting the organization of PARP-1 domains, and thereby controlling the catalytic output. Timeless is another binding partner of PARP-1, for which a complex of the Timeless PARP-1 binding domain has been determined in complex with the PARP-1 catalytic domain [68]. There is no apparent affect of this interaction on PARP-1 catalytic output. In this case, the repair factor Timeless might simply use the PARP-1 protein as an anchoring site to promote homologous recombination [68]. PARP-1 is an abundant nuclear protein and an ever-present chromatin-associated factor. As such, there are likely to be more repair factors with interfaces designed to engage or associate with PARP-1, similar to the transcription-related proteins that are influenced by PARP-1 [69].

Another mechanism of regulating PARP-1 assembly on DNA is automodification with poly(ADP-ribose). Automodification eventually leads to PARP-1 release from DNA and a concomitant drop in catalytic output. The balance between the cellular level of PARP-1 automodification that can contribute to repair factor recruitment, and the level of automodification that can lead to PARP-1 release from cellular sites of DNA damage is not clear. One challenge to investigating the function and mechanism of PARP-1 automodification is the sheer number of automodification sites that have been identified, which is likely to reflect some level of redundancy and the importance of PARP-1 automodification to the DNA damage response. However, the key sites required for regulation of PARP-1 have not been definitively established.

Interestingly, a recent study from the Van Houten and Wilson groups analyzed the mobility of unmodified and ADP-ribose-modified forms of PARP-1 on DNA tight ropes containing abasic site DNA damage using single molecule imaging and quantum dot-labeled PARP-1 [59]. Unmodified PARP-1 was stably associated with the DNA damage sites, whereas an automodified form of PARP-1 exhibited constrained motion around the DNA damage site, suggesting that there could also be an intermediate state of modification that regulates PARP-1 function, rather than just an on/off switch for interaction with DNA.

PARP inhibitors compete for the NAD^+ binding site of PARP-1, thus preventing poly(ADP-ribose) production and its contribution to the recruitment and regulation of repair factors, and also its contribution to PARP-1 release from DNA damage. Pommier and colleagues have noted that certain PARP inhibitors are more efficient at “trapping” PARP-1 and PARP-2 in a tight complex with chromatin, and that the inhibitors with the higher trapping potential are more efficiently able to kill HR-deficient cells [70,71]. The differences in inhibitor trapping ability were proposed to arise from potential differences in their ability to invoke reverse allostery, in which the mode of inhibitor binding might influence PARP-1 structure in a way that would propagate to the DNA binding domains. However, there has been no evidence that this actually occurs with clinically used PARP inhibitors [72]. A recent study using a non-hydrolyzable NAD^+ analog showed clear evidence of reverse allostery, where the presence of the NAD^+ analog invoked a 10-fold increase in PARP-1 affinity for single-strand break damage and a resistance for PARP-1 to release from DNA in a competition experiment [54]. Moreover, there was a change in the dynamics of the DNA binding domains of PARP-1 in response to analog binding as measured by hydrogen/

deuterium exchange mass spectrometry [54]. The study indicates the potential for substrate NAD^+ to influence PARP-1 stability and residence time on DNA damage, and also indicates the design principles that should lead to inhibitors that can invoke reverse allostery and potentially lead to enhanced trapping.

Emerging topic: ADP-ribose modification of serine residues

PARP enzymes modify a variety of amino acid side chains with ADP-ribose. Glutamate and aspartate residues have been most frequently reported as the key residue type for modification by PARP-1. However, recent studies have discovered the ADP-ribose modification of serine residues mediated by PARP-1 [73]. Interestingly, HPF1 (histone PARylation factor 1) is essential for ADP-ribose-serine modification [74], in effect changing the specificity of PARP-1 from glutamate-directed modification to serine-directed modification. HPF1 also influences the target of PARP-1 catalysis toward histone modification, rather than almost exclusively being directed toward PARP-1 automodification [67]. The mechanism of HPF1 influence on PARP-1 catalytic output and the target amino acid specificity switch are not known. It is also not known whether HPF1 exerts its influence over other PARP enzymes, besides just PARP-1 and PARP-2. The enzyme ADP-ribosylhydrolase 3 (ARH3) reverses the ADP-ribose modification of serine residues [75,76], and the ADP-ribose-serine modification has recently been reported to be the major type of ADP-ribose modification in response to DNA damage [77]. A specificity switch is an attractive mechanism to create a different pattern of ADP-ribose modification in stress conditions versus normal physiological conditions.

Emerging topic: ADP-ribose modification of DNA

It has recently been reported that human PARP-1, PARP2 and PARP3 can modify DNA with ADP-ribose [78–81]. The ADP-ribose modification of DNA bases occurs through the action of certain toxins [82]. In contrast, the recent reports indicate modification of the 5’phosphoiylated end of a DNA strand in the context of duplex DNA. 5’phosphorylated DNA is the same structure that maximally activates PARP2 and PARP3 through a WGR contact with the 5’ terminus [64]. Thus, it is unclear whether the same 5’ phosphate feature serves as both a binding site and a point of modification. The biochemical analysis indeed has required DNA structures bearing at least two 5’ phosphoiylated breaks. Despite the current uncertainties in the reaction mechanism, the biochemical activity appears to be robust *in vitro,* and there is evidence that the reaction takes place in cellular extracts [79]. The biological relevance of the modification is still unclear. Whether the ADP-ribose modified DNA represents a *bona fide* signaling modification or repair pathway intermediate has yet to be determined. Alternatively, the modification could represent an unwanted side reaction that occurs in the context of excessive DNA damage and PARP over-activation, akin to the abortive DNA ligation reaction that leaves an AMP nucleotide on the 5’ phosphate group of DNA, which can be reversed by the enzyme aprataxin [83,84]. ADP-ribosylhydrolase 3 (ARH3) is able to reverse the ADP-ribose modification of DNA [81], suggesting a pathway to reverse either a signaling event or an unwanted side reaction. DNA modification could represent an interesting extension of the use and prevalence of the ADP-ribose modification.

Conclusion

PARP-1 has long been appreciated as important for DNA repair [85], but the role of PARP-1 has been fairly enigmatic and difficult to clearly define and categorize. The understanding of PARP-1 contribution to DNA damage repair continues to grow in more specific and mechanistic ways. Collectively, we can start to appreciate that PARP-1 and the other DNA response PARPs have a pervasive influence on the nuclear environment in which repair processes take place, and we gain an even greater appreciation for the mechanisms by which the ADP-ribose modification can influence the cellular response to DNA damage

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Abbreviations:

PAR	poly(ADP-ribose)
PARP	PAR polymerase
PARylation	poly(ADP-ribosylation)

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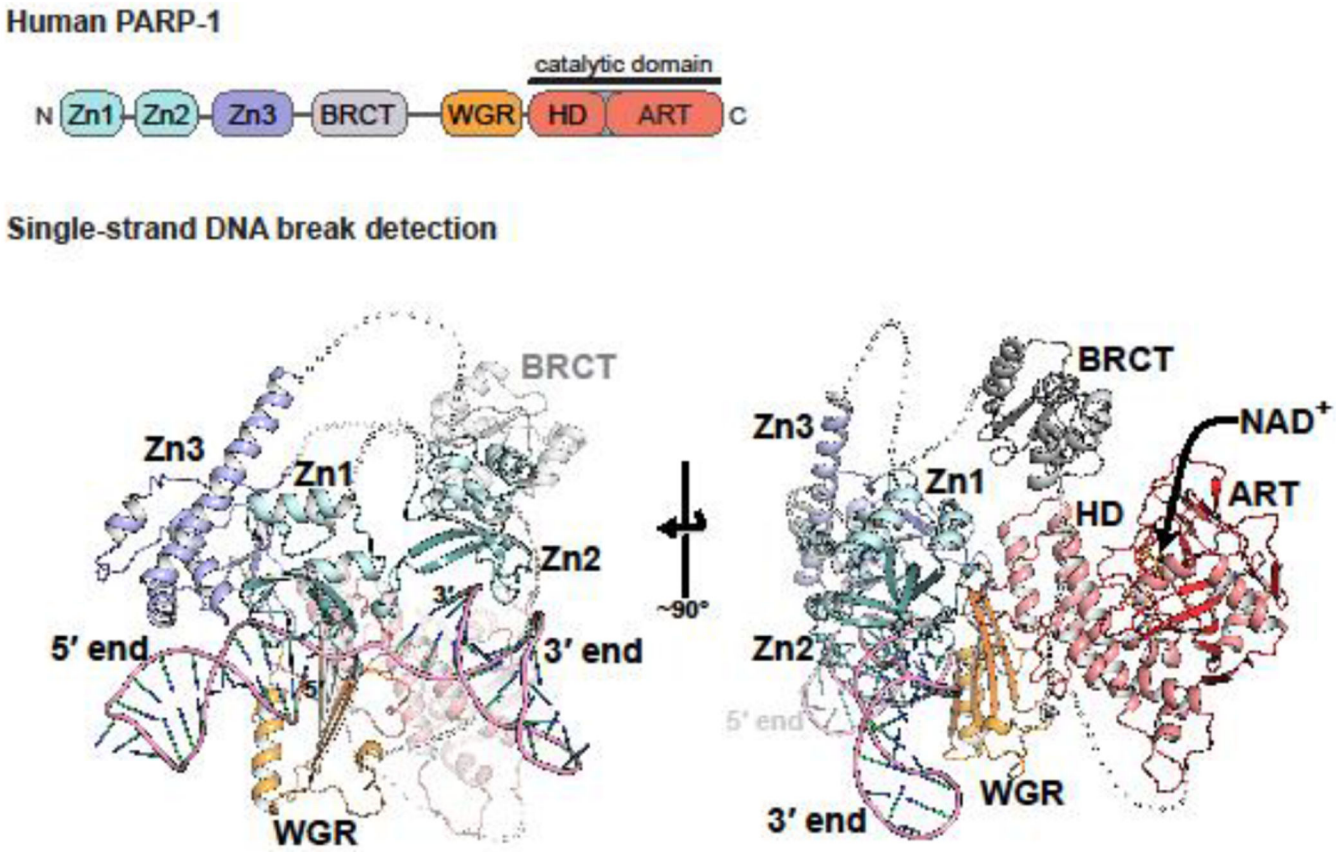

Figure 1. PARP-1 detecting DNA damage and primed for poly(ADP-ribose) production

Human PARP-1 domain names and organization, and a structural model for PARP-1 interaction with single-strand break DNA damage. PARP-1 binding to the ends of DNA strand break damage is achieved through coordinated action of two zinc finger domains, Zn1 and Zn2, located at the N-terminus of the protein. The Zn1 domain binds to the side of the DNA break with a terminal 5' strand (5' end), and the Zn2 domain binds to the side of the DNA break with a terminal 3' strand (3' end). A structurally unrelated third zinc binding domain, Zn3, and the WGR (Trp-Gly-Arg) domain also make contacts with DNA. The catalytic domain (CAT) is composed of an ADP-ribosyl transferase (ART) fold and a helical subdomain (HD). The linker residues (each residue represented by an individual sphere) and the BRCT (BRCA1 C-terminus) domain were manually positioned based on linker lengths and the domain termini. The NAD^+ binding site is noted. The combined crystallographic and NMR model is shown in two orientations that are related by an approximately 90-degree rotation about a vertical axis in the plane of the page. The left view highlights the structure of the DNA break and PARP-1/DNA contacts, with the CAT domain and the BRCT in the background. The right view highlights the HD contacts with the domains that are assembled on DNA.

Table 1.

Examples of PARP-1 participation in DNA repair pathways

Role of PARP-1/poly(ADP-ribose)	Repair factor	Pathway(s)
recruitment	XRCC1, scaffold protein	SSBR, BER
damage detection	DNA damage-binding protein 2 (DDB2)	NER
recruitment and activation	ALC1, chromatin remodeller	NER
recruitment and inhibition	RECQ1, helicase	replication fork reversal
recruitment	POLΘ, polymerase	aNHEJ
recruitment	MRE11, nuclease	HR, aNHEJ, replication fork stability
recruitment	CHD2, chromatin remodeller	cNHEJ
recruitment	BRCA1, scaffold protein	HR

Note: refer to text for references linking these PARP-1/PAR functions to repair pathways.