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Review Article

PARP-1 and PARP-2: New players in tumour development

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Abstract: Poly(ADP-ribose) polymerase-1 (PARP-1) and PARP-2 belong to a family of enzymes that, using NAD^+ as a substrate, catalyze poly(ADP-ribosyl)ation of proteins. PARP-1 and PARP-2 catalytic activity is stimulated by DNA-strand breaks targeting mainly proteins involved in chromatin structure and DNA metabolism, providing strong support for a dual role of both PARP-1 and PARP-2 in the DNA damage response as DNA damage sensors and signal transducers to downstream effectors. The DNA damage response has important consequences for genomic stability and tumour development. In order to manipulate DNA damage responses to selectively induce tumour cell death, a considerable effort is centred on defining the molecular mechanisms that allow cells to detect, respond to, and repair DNA damage. PARP inhibitors that compete with NAD^+ at the highly conserved enzyme active site are arisen as new potential therapeutic strategies as chemo- and radiopotentiation and for the treatment of cancers with specific DNA repair defects as single-agent therapies. In the present review, we highlight emerging information about the redundant and specific functions of PARP-1 and PARP-2 in genome surveillance and DNA repair pathways. Understanding these roles might provide invaluable clues to design new cancer therapeutic approaches. In addition, we provide an overview of ongoing clinical trials with PARP inhibitors and the value of PARP-1 and PARP-2 expression as prognostic biomarkers in cancer.

Keywords: Poly(ADP-ribose) polymerases, poly(ADP-ribosyl)ation, DNA repair, genomic instability, therapeutic approaches, prognostic markers, cancer

Introduction

Poly(ADP-ribose) polymerase-1 (PARP-1) and PARP-2 belong to a family of enzymes (PARP) that, using β-NAD^+ as a substrate, synthesize and transfer ADP-ribose polymers onto glutamate, aspartate or lysine residues of acceptor proteins, modifying their functional properties. Poly(ADP-ribose) (PAR) molecules covalently attached to acceptor proteins vary greatly in size, up to several hundred ADP-ribose residues with branching and large negative charges [1,2]. This protein modification by poly(ADP-ribosyl) ation, first detected over 40 years ago in nuclear extracts [3], is a dynamic process as indicated by the short half-life of the ADP-ribose polymer, which is rapidly subjected to degradation by the poly(ADP-ribose) glycohydrolase (PARG) [4] and the poly(ADP-ribose) hydrolase 3 (ARH3) [5] enzymes (**Figure 1**). PARP family members share a conserved catalytic domain that contains the *PARP signature* motif, a highly conserved sequence that forms the active site [6,7]. Recently, a unified nomenclature referring to this family of proteins as ADP-ribosyl transferases (ARTs) has been proposed to recognize that not all family members have PARP activity and some are likely to function as mono(ADP-ribosyl) transferases (mARTs). PARPs 1-5 are bone fide PARPs containing a conserved glutamate (Glu-988 in PARP-1) that defines the PARP catalytic activity; PARPs 6-8, 10-12, and 14-16, which are confirmed or putative mARTs; and PARPs 9 and 13, which lack key NAD^+-binding residues and the catalytic glutamate, and are likely inactive [8].

Among the members of the PARP family, PARP-1 and PARP-2 are, so far, the only known members whose activity is stimulated by DNA strand interruptions targeting mainly proteins involved in chromatin structure and DNA metabolism as well as PARP-1 and PARP-2 themselves [1,2]. Poly(ADP-ribosyl)ation mediated by PARP-1 and PARP-2 causes chromatin decondensation around damage sites, recruitment of repair ma-

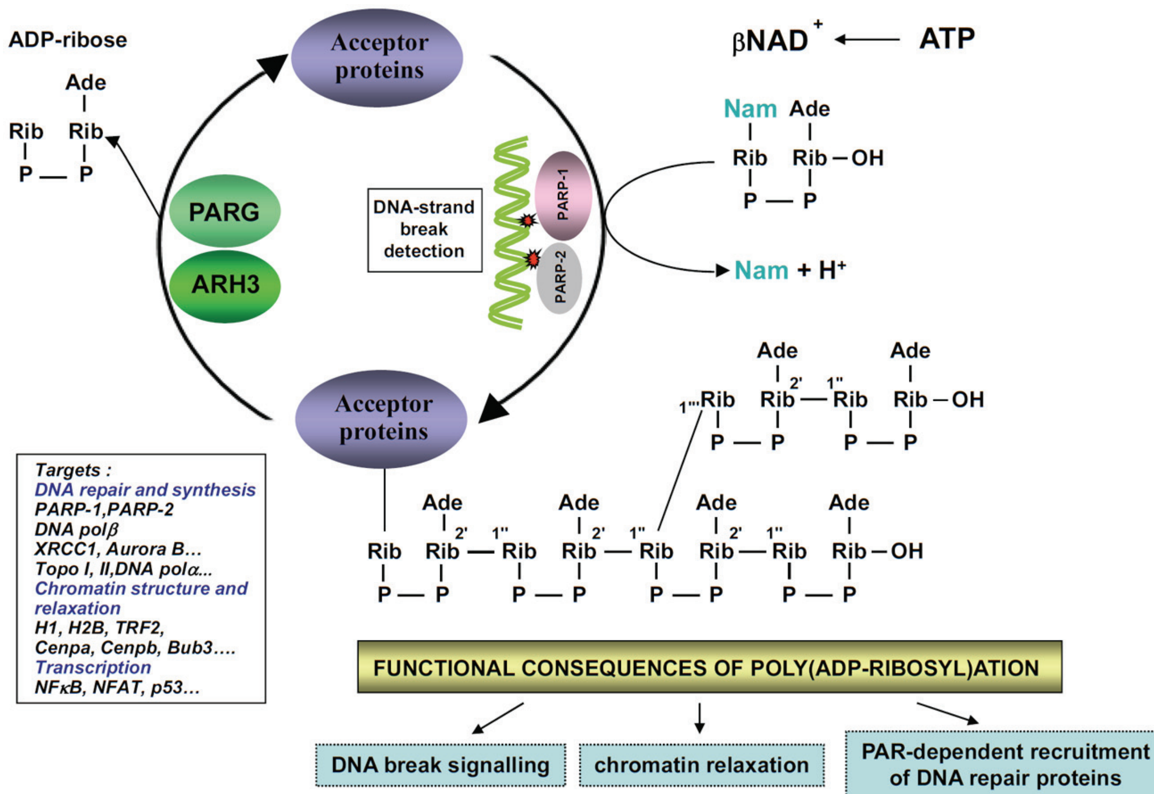

Figure 1. Poly(ADP-ribosyl)ation reaction activated by DNA strand breaks. PARP-1 and PARP-2, rapidly recognizes DNA-strand breaks generated by genotoxic agents leading to their activation. Activated PARPs hydrolyse βNAD^+, releasing nicotinamide (Nam) and one proton (H^+) and catalyse the transfer of ADP-ribose moiety onto aminoacid residues of acceptor proteins. The proteins targeted are involved in numerous biological processes, including DNA repair, chromatin structure and transcription. Poly(ADP-ribosyl)ation of aceptor proteins has functional consequences such as DNA-break signalling, chromatin relaxation and recruitment of DNA repair proteins. The reaction is reversed by the activities of poly(ADP-ribose) glycohydrolase (PARG) and poly(ADP-ribose) hydrolase-3 (ARH3) that hydrolyse poly(ADP-ribose) into ADP-ribose units.

chineries, and accelerates DNA damage repair, indicating a dual role of PARP-1 and PARP-2 in the DNA damage response as DNA damage sensors and signal transducers to down-stream effectors (**Figure 1**) [1,2]. DNA repair pathways and cell cycle control processes have important consequences for genomic stability and tumour development. Indeed a considerable effort is centred to manipulate DNA damage responses to selectively induce tumour cell death [9]. Radiotherapy and chemotherapeutic agents are the most prevalent cancer treatment by which DNA damage induces tumour cell death and there are efforts to understand and to improve the response to current cytotoxic chemotherapeutic agents. Accordingly, PARP inhibitors that compete with β-NAD^+ at the highly conserved enzyme's active site are arisen as new potential therapeutic strategies as chemo- and radiopotentiation and for the treatment of cancers with specific DNA repair defects as single-agent therapies acting through the principle of synthetic lethality [10]. However, PARP-1 and PARP-2 have different targets both in DNA and in proteins, suggesting that they might play specific biological functions [2]. Indeed, it has previously shown that the genetic disruption of PARP-2, but not of PARP-1, in mice affects various differentiation processes, including spermatogenesis [11], adipogenesis [12], and the survival of thymocytes [13].

The aim of this review is to update the redundant and specific functions of PARP-1 and PARP

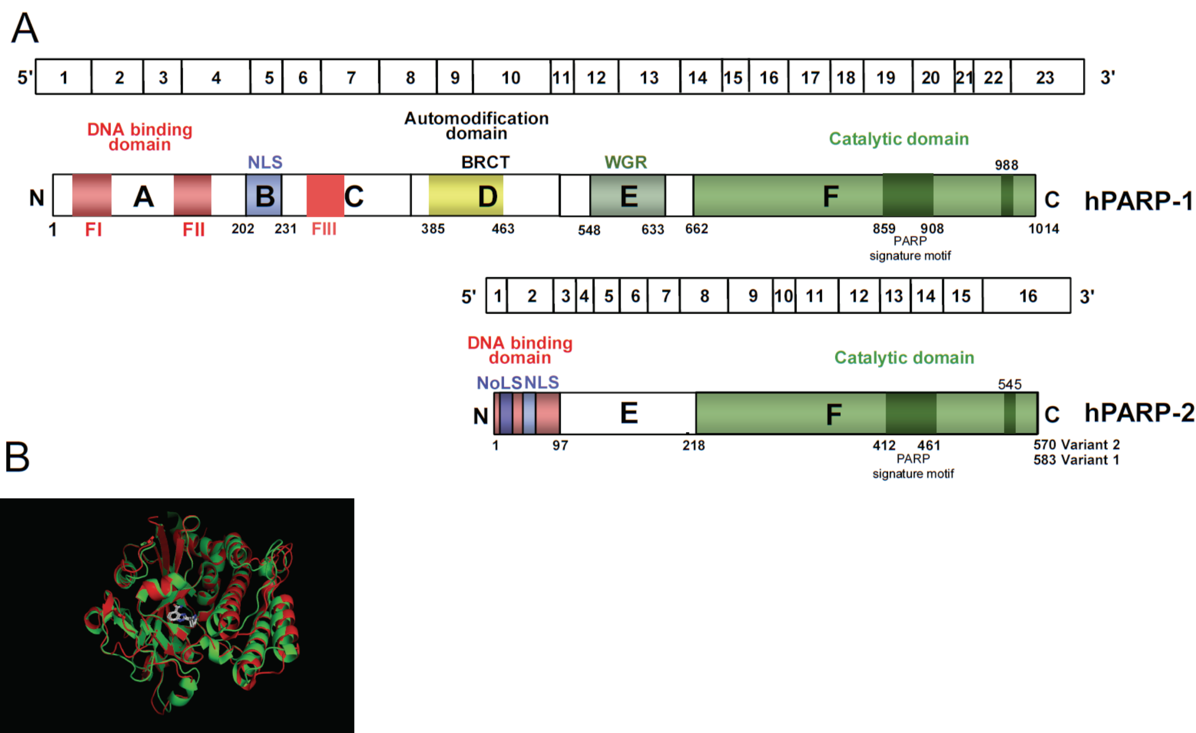

Figure 2. Structural characteristics of human PARP-1 and PARP-2. (A) Schematic representation of human PARP-1 and PARP-2 gene organisation and protein domains. The region that is homologous to the PARP signature (residues 859-908 of PARP-1 and 412-461 of PARP-2 in variant 2) as well as the crucial residue for polymerase activity (glutamic acid 988 of PARP-1 and glutamid acid 545 of PARP-2 in variant 2) are indicated as darkened green box within the catalytic domain. FI, FII: zinc fingers motifs; FIII: zinc ribbon domain; BRCT: BRCA1 C-terminus motif; WGR: domain with unknown function; NLS: nuclear localization signal; NoLS: nucleolar localization signal. (B) Superposition of the catalytic domain structures of human PARP-1 (red) and human PARP-2 (green) in complex with PARP inhibitor ABT-888 [159] (www.pdb.org).

-2 in genome surveillance and DNA repair pathways. A comprehensive understanding of the mechanistic involvement of PARP-1 and PARP-2 proteins in DNA repair and genomic instability is expected to provide invaluable clues to the rational development and exploitation of specific inhibitor drugs in a clinical setting and the design of new therapeutic approach in cancer. Ongoing clinical trials with PARP inhibitors and the value of PARP-1 and PARP-2 expression as prognostic biomarkers in cancer are also discussed.

PARP-1 and PARP-2: The two DNA-damage dependent PARP enzymes

The dramatic PAR formation stimulated by DNA-damage has been associated with PARP-1 and PARP-2 enzymatic activity, with PARP-1 being the most active protein, responsible for about 90% of cellular PAR formation observed under these conditions [14]. In fact, PARP-2 was discovered as a result of the presence of residual DNA-dependent PARP activity in PARP-1-deficient (Parp-1$^{-/-}$) mouse embryonic fibroblasts (MEFs) [15].

The human PARP-1 (hPARP-1) protein (113 kDa) is a highly conserved nuclear protein organized into six domains, encoded by a gene located at position 1q41-42, which consists of 23 exons spanning ~43 kb (**Figure 2A**) [1]. The amino-terminal DNA binding domain (DBD) contains two zinc fingers that define a DNA-break-sensing motif [16]. A third zinc finger motif has been identified in the PARP-1 C-domain, dispensable for DNA binding, but important for coupling damage-induced changes in the DBD to alterations in PARP-1 catalytic activity [17,18]. The B domain contains a nuclear localization

signal and a caspase-3 cleavage site. The central automodification domain comprises a BRCA1 carboxy-terminal (BRCT) motif via which PARP-1 participates in protein-protein interactions. The C-terminal catalytic domain contains the *PARP signature* motif, a highly conserved sequence in PARP family proteins that forms the active site [1].

Human PARP-2 (hPARP-2) is a nuclear protein of 62 kDa encoded by a gene located at position 14q11.2, that consists of 16 exons spanning about 13 kb (Figure 2A) [1]. Interestingly, two isoforms of the hPARP-2 protein generated by alternative splicing have been described, although its functional significance is unknown. The variant 2 lacks an internal segment of 13 amino-acid in the 5´ coding region, as compared to variant 1. The N-terminal domain of PARP-2 does not contain zinc-finger motifs but a highly basic DBD, and nuclear and nucleolar localization signals [1]. The PARP-2 DBD is structurally different from that of PARP-1 likely reflecting differences in the DNA structures recognized by each enzyme [15,19]. Accordingly, in contrast to PARP-1, PARP-2 binds less efficiently to DNA single-strand breaks (SSB) but instead recognizes gaps and flap structures [20]. A caspase-3 cleavage site defines the border between the DBD and domain E, homologous to the E domain of PARP-1. PARP-2 domain E acts both as the interacting interface with various partners and as an automodification domain [14]. A caspase-8 cleavage site marks the border between PARP-2 domains E and the C-terminal catalytic domain which display approximately 69% of similarity with the PARP-1 catalytic domain [15].

Analysis of the crystal structures of the catalytic domains of hPARP-1 and hPARP-2 (www.pdb.org) revealed a conserve structure and the mode of NAD^+ cofactor binding is rather similar. Although the overall fold of PARP-2 catalytic domain is very similar to that of PARP-1, small structural feature differences between PARP-1 and PARP-2 catalytic domains could reflect specificities in the substrate proteins ADP-ribosylated by these enzymes (Figure 2B).

PARP-1 and PARP-2 as components of the DNA-damage response

The cellular genome is continuously exposed to different genotoxic agents, both exogenous (irradiation, genotoxic drugs, etc) and endogenous (reactive oxygen species, eroded telomeres, intermediates of immune and meiotic recombination, etc) that introduce damage to DNA. To combat this continuous threat to genomic integrity, cells have evolved mechanisms to detect DNA lesions, signal their presence and promote their repair. Concomitant to the repair of the DNA breaks, a rapid signalling cascade must be also coordinated at the lesion site that leads to the activation of cell cycle checkpoints and/or apoptosis. Cells defective in these mechanisms display accumulation of DNA damage that could lead to oncogenic chromosomal translocations and, eventually, to cancer [21]. PARP-1 and PARP-2, through their physical association with, or by the poly(ADP-ribosyl)ation of their partner proteins, are playing a dual role in the DNA damage response as DNA damage sensors and signal transducers to down-stream effectors (Figure 1).

Although *Parp-1*$^{-/-}$ cells and *Parp-2*$^{-/-}$ cells shown increased spontaneous genomic instability [22-24], Parp-2$^{-/-}$ mice do not exhibit a propensity for the development of spontaneous tumours [24,25] while Parp-1$^{-/-}$ mice develop spontaneous mammary and liver tumours only with long latency and at a low incidence [26,27]. However, both PARP-1 and PARP-2 deficiency accelerated spontaneous tumour development in p53 null mice, suggesting a synergistic functional interaction between PARPs proteins and p53 in tumour suppression through the role of PARP-1 and PARP-2 in the DNA damage response and genome integrity surveillance [23,24]. In addition, *Parp-1*$^{-/-}$ mice and *Parp-2*$^{-/-}$ mice are very sensitive to ionizing radiation and alkylating agents, although to different extents. Altogether, these data support a role for these proteins in the cellular response to DNA damage [25]. Indeed, different studies provided strong support for key shared functions of PARP -1 and PARP-2 in the cellular response to DNA damage: both proteins heterodimerize [25], share several common nuclear binding partners [28] and mice double deficient for PARP-1 and PARP-2 are not viable and die at the onset of gastrulation demonstrating the crucial role of poly(ADP-ribosyl)ation during embryonic development [25]. However, PARP-1 and PARP-2 have different targets both in DNA and in proteins, suggesting that they might also play specific functions in the response to DNA damage which are starting to be clarified [2].

PARP-1, PARP-2 and base-excision repair

In base-excision repair (BER), a damaged base is often recognized by a DNA glycosylase enzyme that mediates base removal, creating apurinic/apyrimidinic (AP) site. The repair of AP sites is initiated through strand incision by the AP endonuclease 1 (APE1) and polymerase and ligase proteins complete the repair [29]. The involvement of PARP-1 and PARP-2 in BER has long been recognized [1]. PARP-1 and PARP-2 were shown to accumulate with different kinetics at laser induced DNA damaged sites: while PARP-1 accumulated fast and transiently, PARP-2 showed a delayed and persistent accumulation at repair sites [30]. PARP-2 accumulation relies on the activity of PARP-1. Likewise, PARP-1 and PARP-2 interact with X-ray repair cross-complementing I (XRCC1), a crucial scaffold protein that interacts with and stimulates most of the SSBR/BER factors. Interestingly, the recruitment at damaged sites of XRCC1 was shown to be dependent on PARP-1 activity [31-33], but not on PARP-2 [30]. Taken together, these observations are in favour for an implication of PARP-2 at later steps of the repair process. This is strengthened by the fact that, as mentioned above, unlike PARP-1 which binds to SSB, PARP-2 has higher affinity for gaps or flaps, structures that correspond to more advanced repair intermediates. Thus, PARP-1 and PARP-2 have key but distinct roles in the spatial and temporal organization of SSBR/BER processes. In addition, both PARPs interact also with the other SSBR/BER factors DNA polymerase β and DNA ligase III [14]. Recently, Khodyreva et al. have demonstrated a new role for PARP-1 in the regulation of the BER process through its interaction at the AP site. PARP-1 interaction at the AP site could protect the site until APE1 becomes available to initiate strands incision and BER [34].

PARP-1, PARP-2, nucleotide excision repair and mismatch repair

Others DNA strand breaks repair pathways include the nucleotide excision repair (NER) pathway and the mismatch repair (MMR) pathway [29]. The NER pathway, which recognizes helix-distorting base lesions, is a multistep process that serves to repair a variety of DNA damage, including DNA lesions caused by ultraviolet (UV) radiation, mutagenic chemicals, or chemotherapeutic drugs [29]. UV-induced activation of PARP-1 has been reported and some evidence indicated a role of PARP-1 in the lesion recognition steps of the NER pathway, although the mechanistic details of this role remain elusive [35-37]. However, it is interesting to point out that while Parp-1$^{-/-}$ mice show increased susceptibility to carcinogenesis induced by alkylating agents [38], there is no such susceptibility regarding carcinogenesis induced by a heterocyclic amine, IQ (2-amino-3-methylimidazo[4,5-f] quinoline) and 4-nitroquinoline 1-oxide (4NQO), both of which give rise to bulky DNA adducts [39,40]. Alkylation damage to DNA bases may be repaired mainly by BER, while bulky DNA adducts may be targeted by NER, suggesting in those experimental models a minor role of PARP-1 in NER.

The MMR pathway plays an important role in repairing base-base mismatches and insertion/deletion loops that are formed during DNA replication [29]. MMR has important roles in both the predisposition to cancer and also the response to therapy. However, the role of PARP-1 and PARP-2, if any, in this pathway remain largely unknown.

PARP-1, PARP-2 and DNA double-strand breaks repair

Ataxia telangiectasia mutated (ATM) is an early signaling protein kinase that initiates the transduction cascade at DNA double-strand breaks (DSBs) sites. The early embryonic lethality of Parp-1$^{-/-}$Atm$^{-/-}$ (**Table 1**) [41] and Parp-2$^{-/-}$Atm$^{-/-}$ [42] mice (**Table 2**) is likely the consequence of the inefficient SSBR/BER of spontaneous lesions arising in highly proliferative embryonic cells due to the absence of PARP-1 or PARP-2, leading to the conversion of unrepaired SSB to DSB during replication. The absence of ATM then compromises the efficient processing of these DSB by repair processes. However, evidence is accumulating that PARP-1 and PARP-2 are playing a direct and important role in the DSB repair pathways.

DSB repair can be mediated by two major repair pathways depending on the context of the DNA damage, non-homologous end-joining (NHEJ) or homologous recombination (HR) [29]. In NHEJ, the major repair pathway for DSBs in mammalian cells, DSBs are recognized by Ku proteins (Ku70 and Ku80) that then binds and activates the protein kinase DNA-PKcs, leading to recruit-

Table 1. Parp-1$^{-/-}$ mouse models

Genotype	Development defects	Fertility defects	Spontaneous tumorigenesis	Refs.
Parp-1$^{-/-}$	None	None	Mammary and livers tumours with long latency and at low incidence	[26,27]
Parp-1$^{-/-}$Parp-2$^{-/-}$	Early embryonic lethality	NA	NA	[25]
Parp-1$^{-/-}$DNA-PK$^{-/-}$	None	None	T-cell lymphoma	[143]
Parp-1$^{-/-}$Ku80$^{-/-}$	Early embryonic lethality	NA	NA	[27]
Parp-1$^{-/-}$Ku80$^{+/-}$	None	None	Hepatocellular carcinoma	[27]
Parp-1$^{-/-}$Atm$^{-/-}$	Early embryonic lethality	NA	NA	[41]
Parp-1$^{-/-}$WRN$^{Dhel/Dhel}$	None	None	Early onset of different tumours	[144]
Parp-1$^{-/-}$p53$^{-/-}$	None	None	Early onset of lymphoma Other carcinomas (breast, lung, prostate, skin, brain) Medulloblastomas Suppresion thymic lymphoma	[23,145, 146]

NA, not applicable

Table 2. Parp-2$^{-/-}$ mouse models

Genotype	Development defects	Fertility defects	Spontaneous tumorigenesis	Refs.
Parp-2$^{-/-}$	Impaired thymopoiesis, adipogenesis and spermatogenesis	None	None	[11, 12, 13]
Parp-2$^{-/-}$Parp-1$^{-/-}$	Early embryonic lethality	NA	NA	[25]
Parp-2$^{-/-}$Atm$^{-/-}$	Early embryonic lethality	NA	NA	[42]
Parp-2$^{-/-}$p53$^{-/-}$	Partial embryonic lethality	None	Early onset of T cell lymphoma	[24]

NA, not applicable

ment and activation of end-processing enzymes, polymerases and DNA ligase IV. Functional interaction of PARP-1 with different NHEJ proteins has been described (**Table 1**), suggesting a role of PARP-1 in NHEJ. For instance, recent studies that investigated the interaction between PARP-1 and DNA-PK in the cellular response to ionizing radiation suggest that PARP-1 and DNA-PK cooperate within the same pathway to promote DSB repair [43]. In the mean time, the role of PARP-2 in NHEJ, remains elusive. A less-well-characterized Ku-independent NHEJ pathway called microhomology-mediated end-joining, which is biased toward microhomology usage, also exits [44]. This alternative NHEJ pathway has a significant contribution in the resolution of AID-induced DNA breaks during class switching recombination (CSR) [45]. Recently, it has been shown that PARP-1 is required for the alternative Ku-independent end-joining [46-49] and PARP-1, but not PARP-2, favours repair of switch regions through this microhomology-mediated pathway [50].

HR is a multistep process that requires several proteins and is generally restricted to S and G2 because it uses sister-chromatid sequences as the template to mediate faithful repair [29]. HR is initiated by SSB generation, which is promoted by various proteins including the Mre11-Rad50-NBS1 (MRN) complex. SSBs persisting into S-phase produce replication fork collapse, requiring BRCA1 and BRCA2-mediated HR repair for resolution [21]. PARP-1 and PARP-2 detect disrupted replication forks and attract Mre11 for end processing that is required for

subsequent recombination repair and restart of replication forks [51]. Recently, has also been reported that disruption of PARP-1 can inhibit HR by suppressing expression of BRCA1 and RAD51 [52].

PARP-1, PARP-2 and chromatin structure

It is becoming increasingly clear that chromatin structure is modulated in response to DNA damage and has an impact in the recognition of DNA strand breaks and accessibility to damage sites of the DNA-repair machinery [53]. Dynamic chromatin structures are governed in part by posttranslational modifications of histones and non-histone DNA-binding proteins [54]. Indeed, the earliest characterized effects of PARP-1 on the genome were the modulation of chromatin structure by poly(ADP-ribosyl)ation of histones providing the first clue to the function of poly (ADP-ribosyl)ation as an epigenetic modification [55-57]. Several laboratories identified glutamic acid residues in histone H1 and histone H2B to be modified by poly(ADP-ribosyl)ation [58-59]. Recently, it has also been shown that PARP-1, but not PARP-2, covalently modifies the tails of all four core histone on specific lysine residues [60]. In addition to histone modifications by poly (ADP-ribosyl)ation, non-histone chromosomal proteins, including HMGP and the heterochromatin proteins HP1a and HP1b have also been demonstrated to be poly(ADPribosyl)ated [61,62]. In addition to covalent modifications, a number of chromatin-modifying enzymes have been identified that are recruited to PARP-1-associated PAR in a non-covalent way, representing a new mechanism by which poly(ADP-ribosyl)ation orchestrates chromatin-related functions [63].

One of the best characterized examples of chromatin modulation in response to DNA damage is ATM/ATR/DNA-PK mediated phosphorylation of the histone variant H2AX on chromatin flanking DSB sites. This serves as a signal for the recruitment of DNA damage response factors plus other chromatin-modifying components which, together, are though to promote DSB repair and amplify DSB signalling [64]. The H2AX-associated factors promote both integration and dissociation of H2AX and exchange with conventional H2A histone. These factors include FACT (Spt16/SSRP1), DNA-PK and PARP -1. It has been shown that FACT, involved in the H2AX exchange process, is stimulated by phosphorylation and inhibited by ADP-ribosylation [65]. More recently, it has been shown that the chromatin-remodeling enzyme ALC1 (Amplified in Liver Cancer 1) is rapidly recruited to DNA damage sites via an interaction with poly(ADP-ribosyl)ated PARP-1, activating its ATPase and chromatin remodelling activities and catalyzing PARP-1-stimulated nucleosome sliding [66,67].

Likewise, through its role in chromatin remodelling PARP-1 also play a role in transcription regulation [68]. The deregulated expression of genes, which occur through both genetic and epigenetic mechanisms are known to promote tumorigenesis and tumour progression. Biochemical and in vivo studies showed that PARP-1 contributes to either the compaction or decondensation of the chromatin depending on the physiological conditions. For instances, it has been suggested that PARP-1 sets up a transient repressive chromatin structure at sites of DNA damage to block transcription and facilitate DNA repair [69]. On the other hand, PARP-1 localizes to the promoters of almost all actively transcribed genes [70], which suggests that it plays a role in promoting the formation of chromatin structures that are permissive to transcription. However, PARP-1 only regulates a subset of the genes to which it binds, and it has both positive and negative effects of transcription [70-72]. Thus, gene regulation by PARP-1 is a complex process that is likely to involve multiple mechanisms and be modulated by additional inputs. Meanwhile, the role of PARP-2 in transcription regulation remains largely elusive.

Recent studies have begun to link PARP-1-dependent poly(ADP-ribosyl)ation with DNA methylation, a stable epigenetic mark that can be passed to daughter cells upon cell division and is associated with the repression of gene expression [73,74]. The chromatin insulator CTCF plays an essential role in the effects of PARP-1 on DNA methylation. CTCF is an activator of PARP-1 automodification that in turn inhibits DNA methyltransferase Dnmt1 activity with consequences on the methylation state of both genomic DNA and in CpG island regions [75]. Recently, Krishnakumar and Kraus have also shown that PARP-1 regulates chromatin structure and transcription through the histone demethylase KDM5B-dependent pathway [76].

Other mechanisms link PARP-1 and PARP-2 with genome surveillance and cancer

Defects in other biological processes such as

chromosome segregation and loss of telomeres could lead to genomic instability, a hallmark of most cancer [77].

PARP-1, PARP-2 and chromosome segregation

Segregation of sister chromosomes during the metaphase to anaphase transition is a dramatic event that results in the inheritance of a complete set of chromosomes by each daughter cell undergoing cell division. In essence, duplicated chromosomes are condensed and then lined up at the metaphase plate, where the sister chromatids are subsequently pulled apart by microtubules attached to the kinetochores [78]. This process requires the temporal and spatial coordination of a myriad of proteins in order that genomic stability is maintained over successive rounds of cell division. Indeed, chromosomal missegregation and centrosome amplification frequently occur in cancer cells [79].

PARP-1 and PARP-2 associate with functional mammalian centromeres in a cell-cycle dependent manner and interacts with the kinetochore proteins centromere protein A (CENPA), centromere protein B (CENPB) and mitotic spindle checkpoint protein BUB3 [80,81]. Interestingly, BUB3 is suggested to act as a regulator of the Anaphase-Promoting Complex or Cyclosome (APC/C) complex which is largely associated with cell cycle progression and sister chromatid separation [82]. Recently, it has been shown that PARP-1 interacts with eight of the twelve proteins belonging to the APC/C complex, suggesting a role of PARP-1 in mitotic progression [28]. Unlike PARP-1, which binds to a broad centromeric-pericentromeric heterochromatic region [83], PARP-2 appears to transiently associate with the outer kinetochore at centromeres in prometaphase and metaphase cells [81]. Interestingly, this centromeric accumulation of PARP-2 is increased when microtubule dynamics are disrupted, behaviour reminiscent of that observed with spindle checkpoint proteins. In line with this observation, Parp-2$^{-/-}$ cells exhibit DNA-damage-induced kinetochore defects resulting in chromosome mis-segregation in mitotic cells [25]. In addition, Parp-2$^{-/-}$ male mice display meiotic chromosome mis-segregation, which is related to defective centromeric heterochromatin and/or abnormal spindle configurations [11]. All together, these observations argue for essential roles of PARP-1 and/or PARP-2 in accurate chromosome segregation through the maintenance of centromeric heterochromatin structure and/or mitotic spindle integrity.

PARP-1, PARP-2 and telomeres

Telomeres are specialised DNA–protein complexes that cap the end of chromosomes to protect them from being recognised as DSBs needing repair [84]. Human telomeres consist of double stranded tandem repeats of the hexanucleotide sequence TTAGGG and a protective, specific protein complex (shelterin/telosome) with associated nontelomere-specific proteins [85,86]. Telomeres can fold into t-loops that may result from the invasion of the 30 overhang into duplex DNA [87] or into G-quadruplex (G4) DNA, an unusual DNA conformation based on guanine quartets [88].

The existing evidence of the involvement of PARP-2 in telomere integrity comes from the identification of a physical and functional interaction of PARP-2 with telomeric repeat binding factor 2 (TRF2), a key player in telomere protection through its ability to interact with DNA-damage signalling and repair factors [89–91]. PARP-2 regulates the DNA-binding activity of TRF2 via both a covalent heteromodification of the dimerisation domain of TRF2 and a non-covalent binding of poly(ADP-ribose) to the TRF2 DNA-binding domain. Both possible ways of TRF2 regulation act to open the t-loop structure in response to DNA damage to facilitate access of the repair machinery. Accordingly, primary Parp-2$^{-/-}$ MEFs show normal telomere length and telomere capping but display a spontaneously increased frequency of chromosome ends lacking detectable T_2AG_3 repeats [89]. Together, these observations describe PARP-2, through its regulation of TRF2, as an additional central component of telomere integrity. PARP-1 also interacts with TRF2 and controls TRF2 DNA-binding activity in response to DNA damage [92].

Recently, it has been reported that upon telomere damage induced by the G-quadruplex ligand RHPS4 [93], PARP1, but not PARP2, is recruited at the telomeres and forming several ADP-ribose polymers that co-localize with the telomeric repeat binding factor 1 protein. This process is inhibited by PARP inhibitors, suggesting the beneficial effect of PARP inhibitors in telomere-based therapy [94].

Targeting PARP-1 and PARP-2 in cancer

PARP inhibitors first emerged 30 years ago as potential anticancer drugs, showing an exquisite cytotoxicity in proliferating cells, but only after treatment with genotoxic agents [95]. Three generations of inhibitors later, increased potency and suitable pharmacokinetic properties have allowed preclinical studies to evaluate the benefit of these inhibitors in cancer [96]. This academic and industrial effort has made PARP inhibitors headway in clinical trials (**Table 3**). However, current PARP inhibitors target the catalytic site of PARP enzymes which is highly similar amongst PARPs family members and no isoform-specific PARP inhibitors are available [10, 96].

So far, PARP inhibitors have two therapeutic applications in cancer: (i) as chemo/radio-potentiator and (ii) as a stand-alone therapy for tumour types that are already deficient in certain types of DNA repair mechanisms (**Table 3**). In the first application, the combination of PARP inhibitors with DNA damaging chemotherapeutics or radiation could compromise the cancer cell DNA repair mechanisms, resulting in genomic dysfunction and cell death [96]. Indeed, the first phase I clinical trial of a PARP inhibitor was carried out between 2003 and 2005 with AG014699 in combination with the methylating agent temozolomide in patients with advanced solid tumours [97]. Phase I, Phase II and phase III clinical trials with other PARP inhibitors in combination with chemotherapeutic agents are ongoing (**Table 3**).

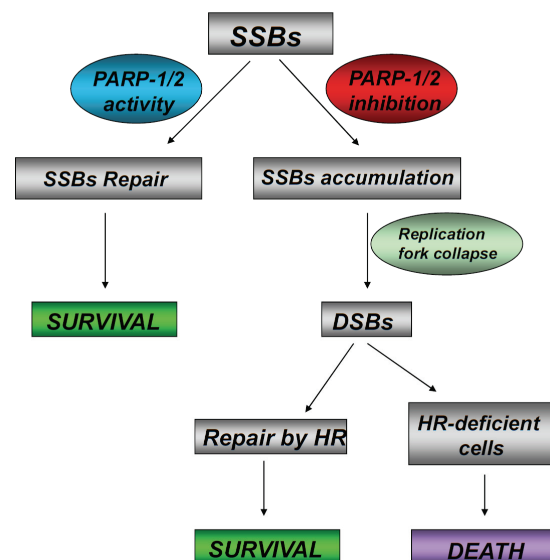

Figure 3. A model for the selective effects of PARP inhibitors on HR-deficient cells. PARP-1 and PARP-2 promote the repair of DNA single-strand breaks (SSBs) that result from various genotoxic insults such as oxidative damage by base excision repair (BER). When PARP-1 and PARP-2 are inhibited, these lesions are unresolved and large numbers of DNA SSBs persist and are encountered by DNA replication forks. These lead to replication fork arrest associated with DNA double-strand breaks (DSBs). Such DSBs are effectively repaired by homologous recombination (HR) in normal cells but not in HR-deficient cells (i.e. BRCA1- or BRCA2-deficient cells). Accordingly, PARP inhibition in these HR-deficient cells causes a high degree of genomic instability and cell death.

A major breakthrough in the field of PARP inhibitors coming out in 2005 when two independent groups demonstrated the sensitivity of BRCA1 and BRCA2-deficient cell lines toward PARP inhibitors, supporting for the first time the potential use of PARP inhibitors as single therapeutic agents in cancer cell types with deficiency in certain types of DNA repair mechanisms [98,99]. This approach is based on the concept that PARP inhibition will lead to an increase in SSB will eventually lead to DSB via replication fork collapse [100], and the repair of these DSB will be compromised in tumour cells that have lost BRCA1 and BRCA2, critical components of the HR pathway, leading to chromosomal aberrations and instability of the genome resulting in cell death (**Figure 3**). This synthetic lethal approach, defined as the situation when mutation in one gene will result in cell susceptibility (i.e. loss of a PARP enzyme or a BRCA protein) but the loss of both is lethal [101], seems to be a promising approach in the development of cancer treatment. Different clinical trials have been initiated to test the efficacy of this approach. Indeed, a trial with the orally active PARP inhibitor olaparib showed clinical benefit in BRCA1 or BRCA2-mutant tumours [102,103]. In addition, any tumour with deficiency in other homologous recombination pathway proteins will be sensitive to PARP inhibitors. For instance, recent results have shown that cells harbouring PTEN (phosphatase and tensin homologue) mutations are sensitive to PARP inhibitors [104-106]. Similarly, PALB2-deficient cells are also sensitive to PARP inhibitors [107]. In addition, it had been shown that ATM deficiency sensitizes mantle

Table 3. Clinical trials with PARP inhibitors in cancer

Inhibitor	Company	Indications	In combination with	Clinical phase	Route	Refs
AZD2281 (olaparib)	AstraZeneca	Breast neoplasms in BRCA1/2 mutation carriers Ovarian neoplasms in BRCA1/2 mutation carriers Avanced or metastatic solid tumours Avanced serous ovarian cancer Solid tumours Ovarian cancer, triple-negative breast cancer Malignant solid tumours Melanoma neoplasm Avanced solid tumours	- - - Paclitaxel and Carboplatin Cisplatin and Gemcitabine - Topotecan Dacarbazine Bevacizumab	II II I II I II I I I	Oral	[102,147-149]
ABT-888 (Veliparib)	Abbott	Metastatic breast cancer in BRCA1/2 mutation carriers Non-hematologic malignancies and metastatic melanoma Adult refractory solid tumours and lymphomas Adult refractory solid tumours and lymphomas	Temozolomide Temozolomide - Metronomic Cyclophosphamide	II I I I	Oral	[150-152]
BSI-201 (Iniparib)	Sanofi-Aventis	Non-small cell lung cancer stage IV BRCA1/2 associated advanced epithelial ovarian, Fallopian tube or primary peritoneal cancer Triple-negative metastatic breast cancer Platinum-sensitive recurrent ovarian cancer	Gemcitabine and Cisplatin - Gemcitabine and Carboplatin Gemcitabine and Carboplatin	II II III II	Intravenous	[153,154]
AG014699	Pfizer	Advanced solid tumours Ovarian cancer, breast cancer in BRCA1/2 mutation carriers	Temozolomide -	I II	Intravenous	[97,155]
CEP-8983/ 9722	Cephalon	Advanced solid tumours	Temozolomide	I	Subcutaneous	[156]
MK-4827	Merck	Advanced solid tumours, BRCA1/2 mutant tumours	-	I	Oral	[157]
INO-1001	Inotek	Stage III or IV melanoma	Temozolomide	Ib	Intravenous	[158]

cell lymphoma cells to PARP inhibitors [108].

As PARP inhibitors move as therapeutic drugs in cancer, several major challenges should be addressed: (i) To develop isoform-specific PARP inhibitors; (ii) To understand the specific involvement of the PARP-1 and the PARP-2 proteins in the DNA damage response and genome surveillance that will provide a basis for the rational exploitation of isoform-specific PARP inhibitors; (iii) To examine the potential long-term effects of PARP inhibitors as PARP-1 and PARP-2 have been implicated in tumour suppression [23,24]; (iv) To elucidate the details of the DNA damage response pathways to overcame PARP inhibitor resistance [109] due to reactivation of BRCA1 or BRCA2 by secondary mutations [110,111]. High-resolution crystal structures of inhibitors bound to PARP catalytic sites (**Figure 2A**) are essential for an in-depth understanding of the binding mode of these compounds, evaluation of the risks and mechanisms of their potential side effects, and optimization of compound selectivity and specificity.

PARP-1 and PARP-2 as prognostic biomarkers in cancer

PARP-1 over-expression both at mRNA and protein levels has been observed in various human tumour types and frequently correlated with a poor outcome, while the expression of PARP-2 in cancer samples and its linkage with evolution of the disease is largely unknown. For instance, increased expression of PARP-1 has been reported in Ewing´s sarcomas [112], malignant lymphomas [113], the early stage of colorectal carcinogenesis [114], intestinal adenomas of patients with familial adenomatous polyposis [115], hepatocellular carcinoma [116], nonatypical and atypical endometrial hyperplasia [117], breast, uterine, lung, and ovarian cancers [118]. Interestingly, no significant differences in PARP-2 expression were observed between normal tissues and breast, uterine, lung, and ovarian cancers [118].

In a recent meta-analysis performed in a large public retrospective gene expression data set from breast cancers, PARP-1 mRNA expression correlated with high grade, medullary histological type, tumour size, worse metastasis-free survival and overall survival [119]. In cutaneous malignant melanomas over-expression of PARP-1 correlated with recurrence and/or progression of the disease [120]. Similarly, PARP-1 overexpression in ovarian serous carcinomas was correlated with poor outcome [121]. Furthermore, it has also been reported a positive correlation between PARP-1 protein expression and response to neoadjuvant chemotherapy [122, 123]. Altogether, these data indicated that PARP-1 expression level may serve as a promising new biological marker of aggressive tumour behaviour with prognostic value.

Polymorphisms in the promoter region of PARP-1 gene may influence PARP-1 protein expression. A microsatellite polymorphism consisting of a variable number of CA nucleotide repeat has been identified in the PARP-1 promoter [124]. Additionally, 4 sequence variations have been identified in the 5´flanking sequence of the PARP-1 gene: C410T, poly$(A)_n$, C1362T, and G1672A [125]. However, Zaremba et al. did not find any correlation between the level of PARP-1 expression and length of the CA-repeats in several tumor cell lines [126]. In addition, the T2444C single-nucleotide polymorphism (SNP) that results in an amino-acid substitution V762A in the PARP-1 activity domain [127] reduces PARP-1 catalytic activity by 30-40% [128,129]. This variant form has been found to be associated with prostate cancer, oesophageal, lung and thyroid cancer [128,130,131]. Two additional SNP that results in M129T and E251K substitutions have been described in human germ cell tumor cell lines although its relevance remains unknown [132]. Overexpression of PARP-1 in tumours could be also associated with a genomic gain/amplification of PARP-1 gene. For instance, it has been reported an association between mRNA overexpression and gain/amplification at the PARP-1 locus in breast cancer [119].

Interestingly, in human tumour cell lines there was no significant correlation between PARP activity, PARP-1 protein expression and/or a polymorphism in the DNA sequence encoding the enzyme active site, suggesting the complexity of PARP-1 regulation [126]. However, it has been observed that PARP-1 is hyperactivated in replicating BRCA2-defective cells, suggesting that the presence of PAR polymers could be used to identify HR-defective cells that are sensitive to PARP inhibitors [133].

PARP-1 overexpression may promote tumour progression by different mechanisms that still

need to be fully elucidated. For instance, PARP-1 has been linked to inflammation and cancer through its role in the regulation of NF*k*B transcriptional activation [134,135] which is elevated in a wide spectrum of cancers and is correlated with malignancy and progression [136,137]. Indeed, it has been shown that PARP-1 play an important role in the link of DNA damage-induce nuclear events to cytoplasmic IKK activation which in turn permits NF*k*B activation to avert programmed cell death [138,139]. It has also been reported a direct implication of PARP-1 function in angiogenesis [140] and stable depletion of PARP-1 reduces *in vivo* melanoma growth and increases chemosensitivity, associated to a diminished neovasculature formation within the tumour [141]. On the other hand, as indicated above, cells with defects in DSB repair such as BRCA-deficient cells are more dependent on PARP-1 and BER to maintain genomic integrity [100]. Additionally, PARP-1 overexpression might promote tumour cell survival by coactivating hypoxia-inducible factor-1 (HIF-1)-dependent gene expression [142].

Conclusion

Although PARP-1 and PARP-2 both participate in similar biological processes controlling genome integrity, biochemical and structural studies increasingly predict that both proteins might act at different steps and/or interact with distinct protein partners. Therefore, one major challenge for the future will be to identify the specific functions of PARP-1 and PARP-2 in the genome surveillance and DNA damage response. Understanding these specific functions is expected to provide a basis for the rational development and exploitation of isoform-specific PARP inhibitors, the design of new therapeutic approaches and the identification of new target molecules.

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