BBA - Reviews on Cancer 1880 (2025) 189282

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review Article

PARP1: A comprehensive review of its mechanisms, therapeutic implications and emerging cancer treatments

Carlota J.F. Conceição [a], Elin Moe [a,b], Paulo A. Ribeiro [c], Maria Raposo [c,*]

[a] ITQB NOVA, Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, 2780-157 Oeiras, Portugal
[b] Department of Chemistry, UiT—The Arctic University of Norway, N-9037 Tromsø, Norway
[c] Laboratory of Instrumentation, Biomedical Engineering and Radiation Physics (LIBPhys-UNL), Department of Physics, NOVA School of Science and Technology, Universidade NOVA de Lisboa, 2829-516 Caparica, Portugal

ARTICLE INFO

Keywords:
PARP1
PARP1 inhibitors
Cancer treatment
DNA repair mechanisms
Drug delivery systems

ABSTRACT

The Poly (ADP-ribose) polymerase-1 (PARP1) enzyme is involved in several signalling pathways related to homologous repair (HR), base excision repair (BER), and non-homologous end joining (NHEJ). Studies demonstrated that the deregulation of PARP1 function and control mechanisms can lead to cancer emergence. On the other side, PARP1 can be a therapeutic target to maximize cancer treatment. This is done by molecules that can modulate radiation effects, such as DNA repair inhibitors (PARPi). With this approach, tumour cell viability can be undermined by targeting DNA repair mechanisms. Thus, treatment using PARPi represents a new era for cancer therapy, and even new horizons can be attained by coupling these molecules with a nano-delivery system. For this, drug delivery systems such as liposomes encompass all the required features due to its excellent biocompatibility, biodegradability, and low toxicity. This review presents a comprehensive overview of PARP1 biological features and mechanisms, its role in cancer development, therapeutic implications, and emerging cancer treatments by PARPi-mediated therapies. Although there are a vast number of studies regarding PARP1 biological function, some PARP1 mechanisms are not clear yet, and full-length PARP1 structure is missing. Nevertheless, literature reports demonstrate already the high usefulness and vast possibilities offered by combined PARPi cancer therapy.

1. Introduction

Cancer as a multifactorial disease represents nowadays the human pathology with highest incidence and lethal consequences for the world population. This pathology is described as a disease from the genetic field, where the deregulation of tumour cells englobes multiple levels of genetic and epigenetic controls [1–3]. Common genetic alterations associated to cancer are structural alterations (e.g. inversions, translocations, among others) and numeric chromosomal alterations, punctual mutations and epigenetic variations. During cancer progression, such mutations will accumulate and be transmitted to the cell progeny [1]. This disease includes more than 200 forms, with environmental (e.g. radiation and exposure to chemical compounds), genetic and epigenetic factors being involved in its development and progression [2,3].

A comprehensive overview of the complexity involved in tumour development and progression is described by Hanahan and Weinberg, in their 2011's hallmarks of cancer [4]. In this work, the authors include the overall molecular features that provide a solid base to start to grasp the intricacy of cancer biology. However, the hallmarks are disputed and others defend the "tissue organization" theory as the most comprehensive, where: (1) cancer cells must be understood in their complex tissue environment, (2) assume cellular proliferation and motility as the cell default state, as well as realize the (3) importance of cellular microenvironment interplay [5].

Nevertheless, the stepping stone for carcinogenesis is the hallmark associated with genomic instability and mutation [4]. In this category, mutations or epigenetic alterations to specific genes may lead to the activation of oncogenes and/or silencing of genome *caretakers*. These *caretakers* are usually responsible for the maintenance of genome stability and cellular homeostasis through their intrinsic role in DNA damage detection and repair [4].

Several DNA repair mechanisms are in action in normal cells, through which cell viability is preserved and achieved by the maintenance of genomic integrity. The innate repair mechanism that operates

* Corresponding author.
E-mail addresses: cj.conceicao@itqb.unl.pt (C.J.F. Conceição), elinmoe@itqb.unl.pt (E. Moe), pfr@fct.unl.pt (P.A. Ribeiro), mfr@fct.unl.pt (M. Raposo).

https://doi.org/10.1016/j.bbcan.2025.189282
Received 22 May 2024; Received in revised form 28 January 2025; Accepted 4 February 2025
Available online 11 February 2025

to preserve genome integrity is dependent and activated based on the sustained damage type. For vertebrates, double-strand breaks (DSBs) are usually repaired by homologous repair (HR), but this is not the only repair route. Non-homologous end joining (NHEJ) (e.g. C-NHEJ and A-NHEJ) and single-strand annealing (SSA) can also repair these types of damage, however, they are error-prone mechanisms that lead to DNA loss and rearrangements. This in turn due to excessive DNA damage/alteration accumulation, can lead to cell cycle arrest and cell death [6]. As for single-strand break (SSB) repair, different mechanisms come into play, namely the base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). If not repaired in time of replication, SSB can evolve to DSB damage [6], which in turn can only be properly repaired by the HR pathway [7].

Among the extensive number of proteins involved in the repair pathways, the one in the "first line of action" and with great preponderance in cancer progression/survival belongs to the poly(adenosine diphosphate ribose) polymerase (PARP) enzyme family, more specifically the Poly (ADP-ribose) polymerase 1 (PARP1) [8].

In this work, one intends to review the multiple aspects of PARP1 performance in DNA repair and cancer and show how this protein is involved in multiple biological processes. Additionally, we want to give an overview of how PARP1 may be used as a therapeutic target for cancer therapy, and what is known, done, and available in this review. This review stands out from those in the literature because it gives a broad picture that crosses all fields of knowledge regarding PARP, PARP1, and PARP therapy. Here, both fundamental knowledge concerning biological and structural aspects of PARP1 as well as applied PARP1 knowledge will be emphasized. Additionally, the reader will find information on applied technology that takes advantage of PARP1 as a therapeutic target for cancer treatment, and what has been done in the field of nanotechnology and nano-delivery systems. Questions as to how combination therapy emerges as the next evolutionary step in PARPi therapy, with the combination of PARP1, radiation, and nano-formulations will be discussed. Moreover, the impact on the safety and long-term efficacy of PARPi therapy will be surfaced.

2. The extensive PARP protein family

The human PARP family includes a total of 17 proteins [9]. Originally, this superfamily was referred to as consisting of 18 members, however, the Tankyrase 3 protein proved to be a splice variant of Tankyrase 2 [10]. PARP homologous proteins have also been detected across the three domains (bacteria, archea, higher eukaryotes) of life and in double-stranded DNA (dsDNA) viruses (*Aeromonas phage* Aeh1, *Anticarsia gemmatalis nucleopolyhedrovirus*, *Invertebrate iridescent virus 6* and *Cellulophaga phage phi4:1*) [11]. In eukaryotes, PARP expression spans from plants to vertebrates' cells. Relatively to the human PARP family members, they have all been grouped and cataloged by their intrinsic cellular roles in the following subfamilies: DNA dependent (3 proteins), tankyrase (TNKS) (2 proteins), CCCH Zn Finger (3 proteins), MacroDomain members (3 proteins) and the unclassified members (6 proteins) [9]. Due to the homology of the CAT domain to the diphteria

Table 1
Human PARP superfamily depiction and additional information regarding cellular compartment localization, enzymatic activity, and function.

Subfamily	Protein Name	Alternative name	Cellular Compartment Localization	Enzymatic Activity	Function	References
DNA dependent	PARP1	ARTD1	Nucleus and mitochondria	MARylation PARylation, with branching	DNA repair, transcription, chromatin structure modulation - epigenetics, cell cycle, programmed cell death, membrane repair, adipogenesis, innate immunity and cell stress response	[9,13–24]
	PARP2	ARTD2	Nucleus and cytoplasm (centrosome in G_0/G_1)	PARylation, with branching	DNA repair, chromatin structure modulation - epigenetics	[9,13,17,25–28]
	PARP3	ARTD3	Nucleus and cytoplasm (centrosome in G_0/G_1)	MARylation	DNA repair regulator, DNA damage surveillance network, chromatin structure modulation - epigenetics, transcription regulation, epigenetics and link to the mitotic fidelity checkpoint	[9,12,17,26,29,30]
Tankyrase	PARP5a	TNKS1 ARTD5	Cytoplasm (centrosome)	PARylation	DNA repair and telomere length	[9,12,17,31]
	PARP5b	TNKS2 ARTD6	Cytoplasm (mitotic spindle and spindle pole)	PARylation	DNA repair, signalling pathway, telomere length and intracell vesicle traffic	[9,12,17,32–36]
CCCH Zn Finger	PARP7	tiPARP ARTD14 RM1	Nucleus and cytoplasm	MARylation	Transcription regulation, Cell structure, adhesion and motility, innate immunity, and cell stress response	[9,12,17,27]
	PARP12	ARTD12 ZC3HDC1	Cytoplasm (Golgi)	MARylation	Cell stress response	[9,12,17,27]
	PARP13	ZAP1 ARTD13 ZC3HAV1	Cytoplasm	No activity reported	Innate immunity	[9,12,17,27]
MacroDomain	PARP9	BAL1 ARTD9	Nucleus and cytoplasm (primarily)	No activity reported	Innate immunity	[9,12,17,27,37]
	PARP14	BAL2 ARTD8 CoaSt6	Nucleus and cytoplasm (primarily)	MARylation	Focal adhesion, actin cytoskeleton, transcription regulation, signal transduction pathways, cell motility and innate immunity	[9,12,17,27,37]
	PARP15	BAL3 ARTD7	Nucleus (nucleosome)	MARylation	Post-translational modification of proteins and negative regulator of transcription	[9,12,17,37,38]
Unclassified	PARP4	vPARP ARTD4	Nucleus and cytoplasm	MARylation	Cell transportation and vault particle regulation	[9,12,17,27]
	PARP6	ARTD17	Cytoplasm	MARylation	Cell structure, adhesion, motility, spindle pole regulation and cell replication	[9,12,17,27]
	PARP8	ARTD16	Nucleus (nuclear envelop and centrosome spindle poles)	MARylation	Membrane (organelles) and nuclear envelope formation	[9,12,17,27]
	PARP10	ARTD10	Cytoplasm	MARylation	Signal transduction pathways, spindle pole regulation and cell replication	[9,12,17,27]
	PARP11	ARTD11	Nucleus and cytoplasm (centriole)	MARylation	Spermatogenesis	[9,12,17,27]
	PARP16	ARTD15	Cytoplasm (endoplasmic reticulum)	MARylation	Unfolded protein response, cell stress response, membrane and nuclear envelope formation	[9,12,17,27]

toxin ART fold, PARP members are also named as ART diphteria toxin-like enzymes (ARTDs) (Table 1) [12].

Many of the PARP proteins are capable of catalyzing ADP-ribosyl post-translational modifications onto specific cellular targets [39]. The ADP-ribose is a signalling molecule that is produced by the transferase activity of PARPs while using NAD^+ as a substrate [40]. The attachment of ADP-ribose is primally done to proteins; however, evidence have shown that it can also be found on DNA/RNA ends and small chemical groups (e.g. acetate or phosphate) [40,41]. Usually, the PARPs transferase activity is linked to mono- or poly (ADP-ribosyl) modification (MARylation and PARylation, respectively), but most of these members transfer only a single ADP-ribose molecule to their targets [42], as seen in Table 1. The members 1, 2, 5a, and 5b are responsible for the addition of large polymer chains of ADP-ribose [17], but only PARP1 and 2 are capable of promoting branching points onto the PAR chain [28,40]. Fig. 1a depicts the array of possible patterns for ADP-ribosylation on target proteins.

The cofactor nicotinamide adenine dinucleotide (NAD^+) molecule is usually covalently linked to the acceptor protein, primarily to the glutamate (E) and aspartate (D) residues [9,17,41], but further studies have proved that serine (S), arginine (R), lysine (K),and cysteine (C) amino acid residues can also be involved [9,17,43–46], as seen in Fig. 1b. In the case of arginine, ADP-ribosylation has been in part or completely associated with non-PAR ARTs, such as the human arginine ADP-ribosyltransferase 1 (ART1) [46,47], that mediates mono-ADP-ribosylation, however some indications point to a possible involvement of PARP10, which still needs further validation [17]. Nevertheless, the majority of the identified ADP-ribosylation modifications in cytoplasmatic and nuclear proteins is substantially associated with the PARP family members [46]. More recently, threonine and tyrosine have also been pointed out as novel PAR acceptors [44,46,48,49]. The ADP-ribosyl modification of each amino acid residue involves a specific set of proteins [43–46,48,49], and some of these associations are depicted in Fig. 1b, as well as the acceptor (Fig. 1b1) and donor bond (Fig. 1b2) molecules involved**.** The ADP-ribose modifications are essential in the regulation of multiple cellular processes such as DNA repair, transcription, cell fate and stress response [40]. Through the addition of poly (ADP-ribose) modifications, the biochemical properties and biological activity of the target proteins are modified, facilitating processes such as protein ubiquitination and degradation [42].

Like other tightly regulated post-translational modifications, PARylation employs several players. These are classified as *writers*, *readers,* and *erasers*. The first englobes the overall PARP family members, the second includes proteins capable of recognizing and binding to the PAR chains, and the latter encompasses enzymes capable to trim and remove the ADP-ribose chains [40,51,52,54]. PARylation is known to facilitate protein-protein interactions, with the branched chains serving as scaffolds for the binding of proteins that present WWE domain (e.g. PARP14, PARP11, and PARP12), PAR-binding motif (PBM) (e.g. *Xeroderma pigmentosum* complementation group A (XPA), DNA ligase III, X-ray repair cross complementing1 (XRCC1), Ku70, ataxia telangiectasia mutated (ATM), p21 and p53), PAR-binding zinc finger (PBZ) (e.g. CHFR and APLF) or Macro domains (MacroH2A variants, PARP15 and PARP14). On the other hand, MARylation only promotes the binding of proteins that contain Macro domains [42,51–53], as depicted in Fig. 1c.

The use of the NAD^+ cofactor by PARP proteins has a profound effect at multiple cellular levels, and because of this the enzymatic activity of PARP proteins is tightly regulated in its activation, to avoid complete NAD^+ depletion from the cellular energy centers (e.g. mitochondria) [40].

In human cells, PAR and MAR modifications are reversed by a specific set of hydrolase proteins (Fig. 1c). The first is reversed by the poly (ADP-ribose) glycohydrolase (PARG) isoforms (99, 102, and 111 kDa isoforms) and ADP-ribosyl hydrolase 3 (ARH3), while single modifications are reversed by the ARH1, MacroD1, MacroD2 and terminal ADP-ribose protein glycohydrolase 1 (TARG1 or OARD1) [41,50,51]. Moreover, several evidences have shown that some phosphodiesterases (e.g. NUDT9, NUDT16 and ENPP1) present ADP-ribose *eraser* capability [50]. Further information regarding ADP-ribose hydrolases activity, specificity and cellular localization can be found in Table 2.

2.1. The DNA repair PARPs – PARP1, PARP2 and PARP3

The PARP family was first presented 60 years ago by Chambon et al., [69,70], with the first report of the immediate ADP-ribosylation response to DNA damage induced by alkylating agents, ionizing radiation, or oxygen/nitrogen radicals. Over the years, the cellular role and localization of these members were revealed to be far more complex, and wider than what was initially perceived (Table 1**)**.

Among the 17 members, PARP1, PARP2, and PARP3 are the ones more commonly associated with repair of DNA damage [40,71]. In structural terms, these proteins present several similarities in two main domains, as seen in Fig. 2. The catalytic domain (CAT) of the three PARPs includes a regulatory alpha-helical domain (HD) and an ADP-ribosyl transferase (ART) fold, which are conserved and responsible for the addition of the ADP-ribosyl molecules to the target molecules [72–75]. The PAR polymer addition is done using the NAD^+ cofactor as a substrate, and results in the subsequent release of a nicotinamide molecule per NAD^+ (Fig. 1c) [71,76]. Besides the CAT domain, PARP1, 2, and 3 share a common tryptophan (W) – glycine (G) – arginine (R) motif, which is generally called the WGR domain. This domain is capable of interacting with DNA and functions as a key regulator of DNA dependent catalytic activity [40,71,75]. Furthermore, PARP1 presents four additional domains; three zinc fingers (Zn1, 2 and 3) and a BRCA-C-terminus (BRCT) domain, while PARP2 and 3 present only a small N-terminal tail [40,73–75], as depicted in Fig. 2. This tail is not essential for PARP 2 and 3 enzymatic activity; however, it is involved in the DNA binding interface [77,78]. For these two proteins the WGR domain acts as the regulatory center for DNA binding, sensing the nature of the DNA break, and their enzymatic activity can be triggered by DNA breaks carrying a phosphate group in the 5′ end [78,79]. However, PARP3 activity appears to be most sensitive and reactive to 5′ phosphorylated single-strand nicks [78,80]. Recent crystal structure data, revealed that PARP2's WGR domain links two DNA breaks, which has led to the understanding that this protein may serve as a connecting bridge between DNA ends [80].

In the case of PARP1, the DNA binding capability is primarily triggered by the zinc finger domains, which contain zinc ions to stabilize the fold, and contrary to PARP2 and 3 the DNA binding capability and enzymatic activity is insensitive to the DNA break phosphorylation state [75,77,78]. PARP1 indiscriminately binds DNA, however, the interaction stoichiometry between these biological molecules can vary depending on the type of damage [18,81–83]. Previous reports have shown that PARP1 binding affinity/stoichiometry is dependent on DSBs, with the protein's DNA binding domain presenting a stoichiometry of two proteins to one DNA molecule to the 5′-recessed DNA end, and a 1:1 stoichiometry to the 3′-recessed end and dsDNA. Protein dimerization event was found to be a requisite for high enzymatic activity [81].

PARP1's BRCT domain is viewed as the protein centre for automodification and the WGR domain for DNA binding/interaction and allosteric activation [72–75]. It is proposed that the overall structure of PARP1 resembles a "beads-on-a-string" assembly in the absence of DNA damage [8] and the detection of strand breaks leads to the partial displacement and unfolding of the HD sub-domain [74]. In this way, access to the ART pocket is granted to NAD^+, leading to the activation of PARP1's enzymatic activity. PARP2 and 3 activation appears to be governed by the same allosteric mechanism [72].

Even though PARP1 and 2 present overlapping functions in DNA damage response, the first prevails over all the family members, since it is responsible for 80–90 % of DNA repair related PAR modifications [84,85]. Among the PARP family, PARP1 is the best characterized and studied isoform [84].

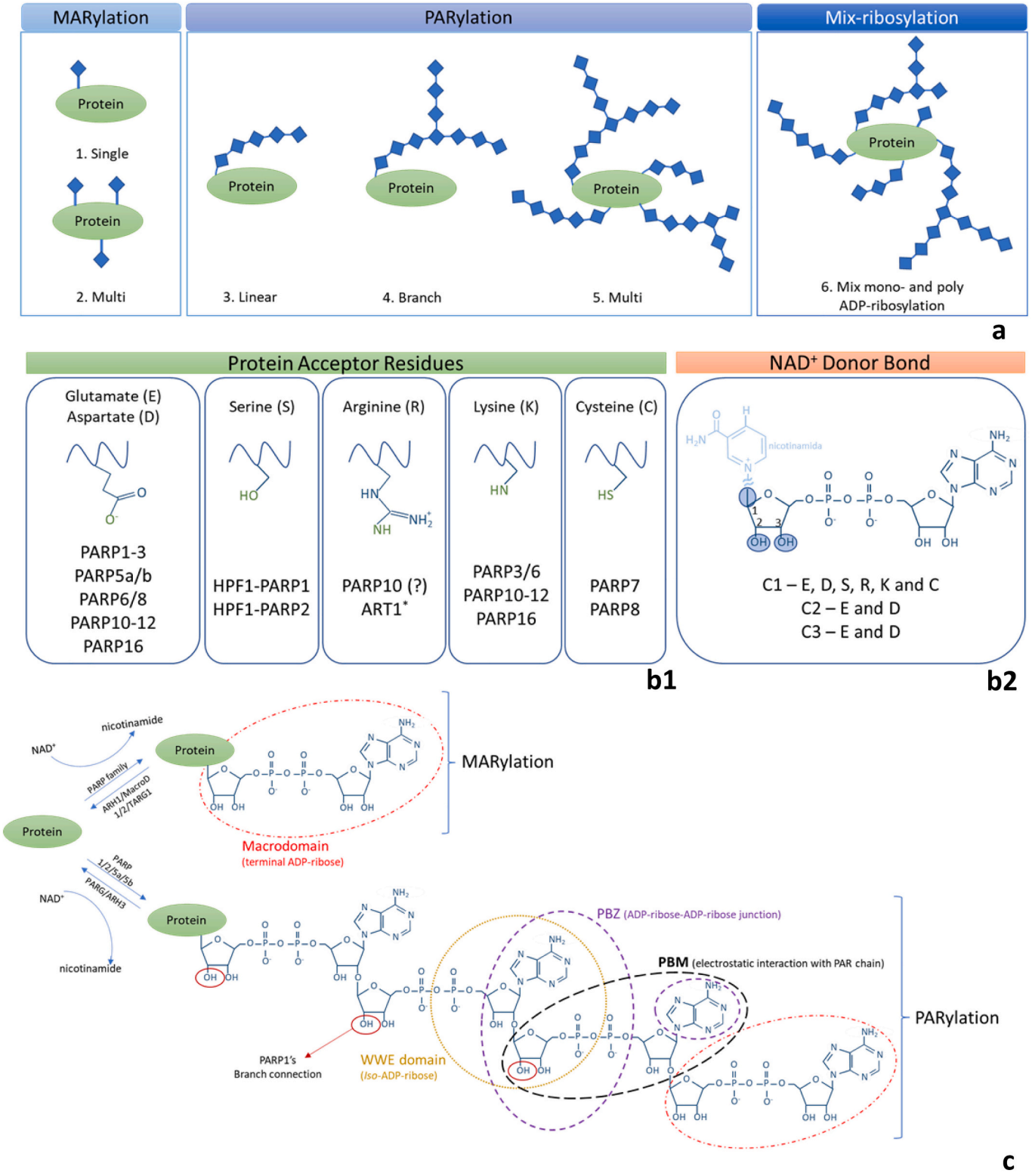


Fig. 1. Illustrations of NAD^+ polymer chain formation and NAD^+ bonding with protein residues. a) Representation of possible patterns for MARylation and chain patterns PARylation taking into consideration [50]; b) Identification of possible donor and acceptor bonds in NAD^+ (b2) and common amino acid residues (b1), that are involved in the ADP-ribosylation. PARP proteins responsible for bond formation and subsequent residue modification are identified in their respective target, taking into consideration [43–46,48,49,51]; c) Schematics of MARYlation and PARylation reactions with indication of PARP family members involved. Additional identification of *readers* domains' recognition sites in the ADP-ribosylation mono/polymer, taking into consideration [42,51–53].

Table 2
Compilation of human PAR and MARylation erasers, with information regarding cellular localization, substrate, bond, type of reversal and catalytic activity.

Name	Alternative Names	Classification	Cellular Localization	Substrate	Target bond	Type of reversal	Catalytic Activity	References
PARG (99, 102, 111 kDa isoforms)	–	Macrodomain	Nucleus (111 kDa) Cytoplasm (60, 99, 102 kDa) Mitochondrial (60, 55 kDa)	PAR	O-glycosidic	Partial	Yes (99, 102 and 111 kDa) No (55 and 60 KDa)	[50–52,55,56]
MacroD1	LRP16	Macrodomain	Nucleus Cytoplasm (primarily mitochondrial)	MAR (D/E)	Carboxyl ester	Complete	Yes	[50–52,57,58]
MacroD2	C20orf133	Macrodomain	Nucleus Cytoplasm	MAR (D/E)	Carboxyl ester	Complete	Yes	[50–52,57,58]
TARG1	OARD1 C6of130	Macrodomain	Nucleus Cytoplasm (Stress granules)	MAR PAR (D,E, OAADPr)	Carboxyl ester	Complete	Yes	[50,51,58–60]
ARH1	ADPRH	ARH fold	Cytoplasm	MAR (R)	N-glycosidic	Complete	Yes	[50,51,61]
ARH3	ADPRHL2	ARH fold	Nucleus Cytoplasm Mitochondria	MAR PAR (OAADPr, S and PAR)	O-glycosidic	Complete	Yes	[50,51,59–61]
NUDT9	ADPR-PPase IDPase	NUDIX	Mitochondria	PAR	Phosphodiester	Partial	Yes	[50,51,62]
NUDT16	U8 snoRNA-binding protein H29K	NUDIX	Nucleus Cytoplasm	MAR PAR	Phosphodiester	Partial	Yes	[50,51,63–65]
ENPP1	Plasma-cell membrane glycoprotein PC1	ENPP (PDNP)	Cell Membrane	MAR PAR	Phosphodiester	Partial	Yes	[50,51,66–68]

Note: D – aspartate; *E*- glutamate; OAADPr - *O*-acetyl-ADPr; R – arginine; S – serine; ADPRH – ADP-ribosylarginine hydrolase; ADPR-PPase – adenosine diphosphoribose pyrophosphatase; NUDIX – nucleoside diphosphates linked to moiety-X; ENPP1 – ectonucleotide pyrophosphatase/phosphodiesterase family member 1; IDPase – IDP phosphatase.

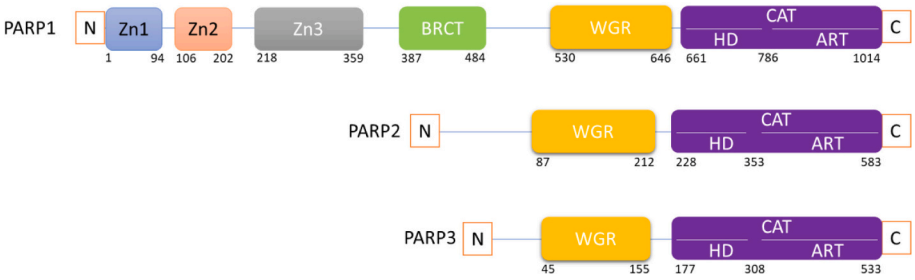


Fig. 2. Schematic illustration of DNA dependent PARP1, PARP2 and PARP3 domains, with indication of amino acid boundaries in accordance with suggestions of Suskiewicz et al., 2023 [86], van Beek et al., 2021 [71] and Steffen et al., 2015 [87].

3. PARP1 the canonical PARP

PARP1 is an abundant nuclear enzyme, which primarily acts as a transferase and is closely associated with DNA repair, mostly Base Excision Repair (BER) [9]. The key involvement of this protein in the DNA repair pathways has led to its denomination as the DNA "guardian angel" [88].

Solely in the nuclear compartment, where the PARP representation is high, PARP1 concentration values were reported to be around 7-100 μM (2×10^5–10^6 copies/nucleus), which translates into a nuclear-cell ratio of 0.08 [71]. These values are a clear indication of PARP1s great nuclear representation and its importance in maintaining genomic stability and cellular homeostasis.

PARP1, a 114 kDa multi-domain protein, orchestrates vital biological processes such as inflammation, hypoxic response, transcriptional regulation, maintenance of chromosome stability, DNA repair, and cell death [73,84]. The most extensively studied property so far is the response of this protein to DNA damage and subsequent repair of genomic anomalies. PARP1 is also capable of binding to chromatin ends in a DNA strand break, stabilizing the site, and recruiting repair and chromatin remodelling factors to the break loci [73,75]. The catalytic activity of PARP1 is 500-fold stimulated by either SSB or DSB recognition [89]. Upon damage recognition and binding, PARP1's six main domains (Fig. 2) reorganize, change its folding, and trigger enzymatic activity. This activity translates into the formation and increase of PAR chains onto specific targets (either DNA/RNA, other proteins such as histones – *trans*/hetero-modification – or PARP1 itself – *cis*/auto-modification) [71,76,84]. Through an overall change in surface charge, subsequent steps are triggered thus leading to strand break repair [74]. PARP1 auto-modification occurs predominantly on E/D and S residues, namely in E488, E491, S499, S507 and S519 [45,90–92], and promotes the release of PARP1 from the break sites through electrostatic and steric repulsion [46,74].

The removal of PAR modifications is essential to prevent the trapping of PAR-recruited proteins and permit access by downstream repair effectors to the damaged site. For the turn-over of PARP1's PAR chains, the two main human proteins involved are the PARG and ARH3, which are responsible for the cleavage of the O-glycosidic bond between ADP-ribosyl subunits [59], as depicted in Table 2 and Fig. 1c.

The inhibition of PARP1 transferase activity, and subsequent release,

in the repair of SSB is met with the accumulation of these damages, that through the collision with the replication fork will evolve into a DSB [93]. Thus, demonstrating how PARP1 auto-modification may have a profound impact on genome integrity.

The key function of PARP1's auto-modification activity is closely related to the release of the protein from the damage sites, where the bind interaction between PARP1 and DNA breaks serves as a stabilizing element until repair effectors are recruited [94,95]. As previously explained in Section 2, PAR chains also serve as a scaffold for effector recruitment and protein complex building blocks. Any type of interference with PARP1's PAR activity has profound consequences in cellular homeostasis, which leads to PARP entrapment and DNA repair prevention. This mechanism is described as the one behind clinical PARP1 inhibitors that are used in cancer therapy. These catalytic inhibitor molecules are employed to promote PARP1 trapping on the chromatin matrix, thus preventing DNA break repair and promoting cytotoxicity in cells that have their repair systems already compromised [46,59]. PARP1 is viewed as an attractive target for cancer therapy since this protein is usually upregulated in several tumours and is critical in cell survival [96]. Data regarding PARP1 inhibitors, and their therapeutic potential will be explained and discussed in another subsection.

Even though among the PARP family, the PARP1 isoform is the member that is most studied and characterized, some questions remain to be answered regarding full-length structure. Due to its flexible multi-domain nature and the presence of several linkers, only X-ray crystal structures of truncated or engineered versions of this protein have been published [75,97]. These structures comprise mainly interaction studies of CAT with known therapy inhibitors [76,97–99], as well as some interesting new potential molecules [100–116]. Besides inhibitor interactions, several attempts were made to understand PARP1 and DNA interaction at a structural level, however, all the structures remain single domain or truncated versions of PARP1 [75,117–119]. Furthermore, the structures of PARP1 bound to NAD and BAD co-factors were also determined, but still no full-length protein structure was assessed [72,103]. In other inquiries, the focus was on putative PARP1 protein interactors, where published structures include PARP1 CAT and PARP1-CAT ΔHD interacting with TIMELESS [120] and HPF1 [121], respectively. Even though attempts to determine native human PARP1 X-ray crystal structure have rendered results for single domains and truncated protein versions [122], in other organisms single domain structures have been determined from *Gallus gallus* [103] and *Rattus norvegicus* [123].

The history behind the PARP family structural unwinding can be referred to the first publishing of PARP1 in 2004 [106], followed by PARP2 in 2010 [124] and PARP3 [125], with these being the central focus for the majority of PAR transferase activity.

Structures of PARP1 domains were also determined by nuclear magnetic spectroscopy (NMR) namely the Zn1-Zn2 interacting with SSB and Zn1-Zn2-Zn3 [82,126], full-length with dumbbell DNA [72,86], the BRCT domain [86], the WGR domain [126] and CAT in complex with inhibitors (Veliparib, Olaparib and Talazoparib) [98].

In 2019, an electron density map of a dimeric form of PARP1 associated to DNA (dsDNA and nicked-dsDNA) was described using single-particle electron microscopy (EM). However, the resolution was very low (28 Å) [127]. Nevertheless, these results reinforced the hypothesis that PARP1 forms a dimer upon binding to DNA. Using the same technique, the structure of full-length PARP2 associated with the histone PARylation factor 1 (HPF1) was unveiled in 2020 [128]. The cryo-EM structure of PARP1 has yet to be determined.

In recent years, the rise of the artificial intelligence (AI) structural prediction systems AlphaFold (with its newly released AF2) [129] and RoseTTAFold [130], have presented an enormous advance in the prediction of structured and unstructured (or intrinsically disordered) protein regions. These tools can predict models of highly complex and large proteins, with an elevated degree of accuracy [129,131]. Predictions are made taking into consideration the amino acid sequence and, for example, the AF2, resort to deposited Protein Data Bank (PDB) structures and multiple sequence alignment to detect evolutionary relationships in the protein of interest [129,131].

Taking advantage of this tool, and coupling it with experimental assays, Suskiewicz et al., 2023 [86] present an in-depth analysis of PARP family structural models and unveil possible new information regarding biological functions (possible PARP14's RNA-binding and RNA ADP-ribosylation). The AF2 models of PARP1 suggest that its BRCT domain is relatively flexible and independent of the remaining domains (Fig. 3a) [86]. Moreover, the authors state that the predicted model appears to be more consistent to PARP1's multi-domain DNA-bound crystal structures [86]. However, due to the experimental analysis done by the authors, it is stated that the "free" form of PARP1 behaves as a "beads-on-a-string" (that is the consensus idea over many years) (Fig. 3b) and that it collapses into a more rigid form upon DNA binding, with BRCT being excluded from the bound form (Fig. 3c) [86].

4. PARP1s vast intracellular functions, partners and regulation

PARP1 through its ADP- ribosylation activity, either on itself and other targets, can modulate and orchestrate several intracellular pathways. In these pathways, some of the most important cellular functions include: chromatin modification, transcription regulation, DNA damage repair, and cell death [134,135]. However, due to the nature of the PAR modification, the accumulation of these chains is met with cytotoxic effects if not properly regulated. Studies in mice verified that a target disruption of PARG had lethal consequences, with activation of apoptotic cell death in blastocysts [134,136]. Thus, the PARP1 interactors are vast and can be rationalized into 3 categories: 1) PARP1 ligands and activity regulators; 2) enzymes that modify PARP1, and 3) PARP1 substrates and binding partners. In Fig. 4 all the players involved in PARP1 biological functions are summarized.

4.1. Ligands and regulators of the enzymatic activity of PARP1

One of the ligands and regulators of PARP1 activity is the nicotinamide by-product from NAD^+ consumption [134]. These molecules are known to have a mild inhibitory effect on PARP1's ADP-ribosylation transferase activity, and it is from this interference that clinical PARP1 inhibitors were first conceived and later optimized [134,137,138].

Moreover, the size of the added PAR chains helps in reducing PARP1 activity, through their excessive negative charge. When PAR chains become very long and branched, repulsion forces from DNA lead to PARP1 release, and NAD^+ consumption is thus limited [134]. Also, another negative regulator of the enzymatic activity of PARP1 is the nuclear stress protein (NUPR1), which is done by physical interaction with the protein [139].

Another off-switch of PARP1 enzymatic activity is the presence in DNA of the octamer motif 5'-RNNWCAAA-3′ (where R is adenine (A) or guanine (G), N can be any nucleotide base and W is A or timine (T)). This sequence is present in the promoters of several genes and the interaction with PARP1 suppresses the enzymatic activity and other dependent functions of the later [140]. Here it is proved that other than its affinity to and DSB/SSB dependent activity, PARP1 is regulated by other nucleotide singularities.

For example, small nucleolar RNAs were shown to affect PARP1 activity, more specifically the SNORA74A and SNORA73 [141,142]. The first was reported to interact with PARP1 and serve as a positive regulator of PARP1 activity [141], while the second restrains PARP1's auto-PARylation and leads to genome instability in hematopoietic malignancies [142].

Some proteins can be included in this section such as the nuclear nicotinamide mononucleotide adenylyltransferase (NMNAT), that enhances PARP1 activity. This protein associates with PAR chains and is capable to synthesise new NAD^+ molecules, which are fed into the transferase cycle of PARP1 [143]. Other proteins that are also involved in the regulation of PARP1's catalytic activity are the histone variant

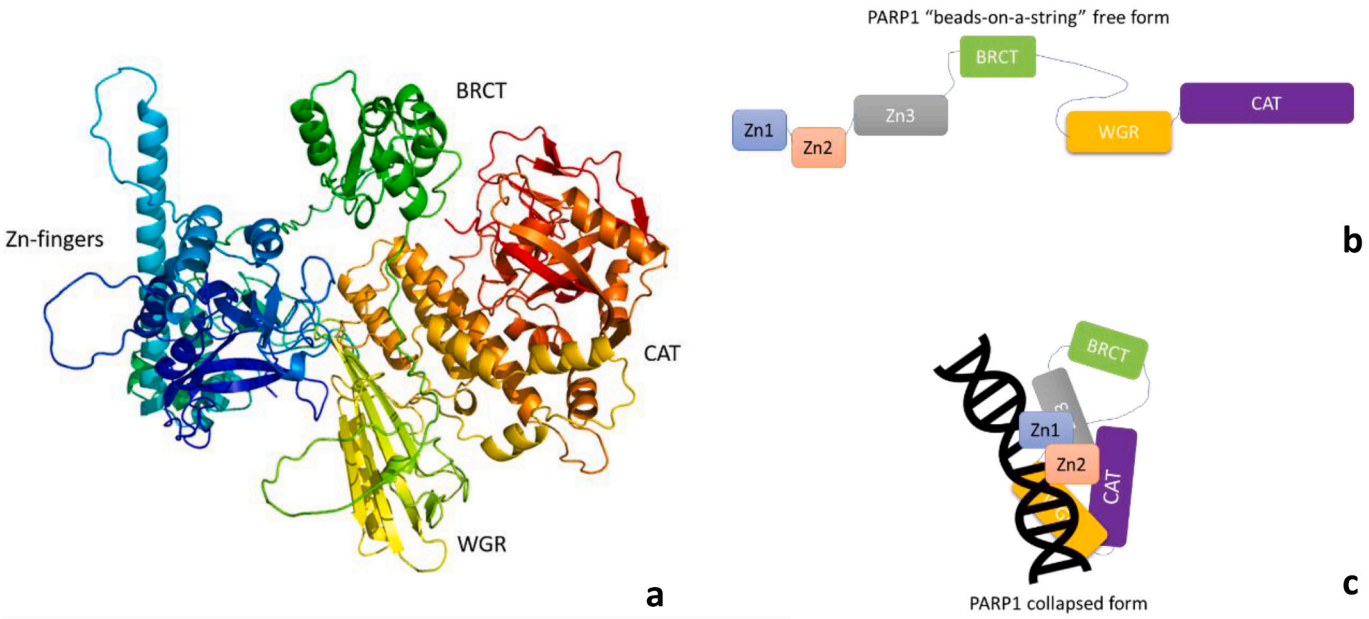


Fig. 3. Insights into PARP1 structure. a) PARP1 full-length predicted structure retrieved from AlphaFold (AF) [129,132] and figure prepared in PyMOL [133]; b) Model of PARP1 "beads-on-a-string" free form, taking into consideration [84]; c) Model of PARP1collapsed/rigid form when bound to a DNA break, taking into consideration [86].

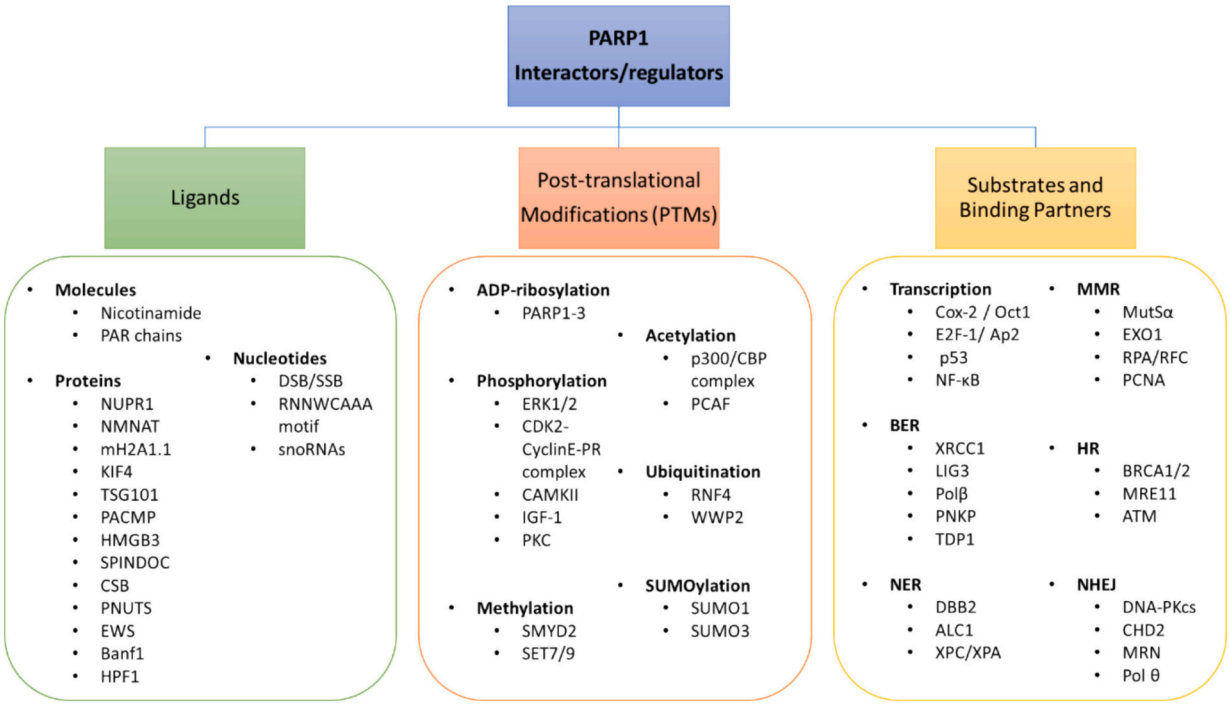


Fig. 4. Schematic summarizing the various levels of PARP1 regulation and regulator effect on multiple biological levels. The molecules that bind and regulate PARP1 activity (green box), enzymes that regulate PARP1 activity through post-translational modifications (PTMs) (orange box), and PARP1's catalytic activity targets or binding partners in transcription regulation and DNA repair pathways (yellow box) are also identified in the scheme. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mH2A1.1, KIF4, TSG101, PACMP, HMGB3, SPINDOC, and CSB [144–150]. The PNUTS protein was also reported to aid PARP1 in its DNA repair activity [151]. This protein acts as a binding partner, and it is required for the recruitment of PARP1 to DSBs and damage site PARylation in the NHEJ repair pathway [151]. Moreover, Lee et al., verified that the Ewing sarcoma protein (EWS) promoted the dissociation of PARP1 from the chromatin, thus suppressing its enzymatic activity, and leading to the prevention of excessive accumulation of PARP1 on DNA. [152]. In the case of the DNA-binding protein Banf1, Bolderson and colleagues verified that the activity of PARP1 was inhibited by direct interaction with the NAD^+ binding domain, which translated in the flawed repair of oxidative lesions [153].

One of the most important discoveries that set a new stage for PARP1 activity regulation was the description of the interactor histone

PARylation factor 1 (HPF1), which was revealed to be the major mediator of PARP1's serine target modifications [91,128,154]. HPF1 proved to be able to model the activity of PARP1 at micromolecular concentrations (in vitro assays) and to form a joint active site with PARP1/2, which leads to the aa specificity switch of PARP1/2 from E/D to S [91,92,121,128,154,155] (Fig. 1b1). HPF1 was also proved to influence the target of PARP1's enzymatic activity towards histone modification, instead of being directed mostly to auto-PARylation function [156].

4.2. Enzymes that are able to modify PARP1

Various post-translational modifications (PTMs) are known to regulate PARP1 enzymatic activity; phosphorylation, acetylation, methylation, ADP-ribosylation, SUMOylation, and ubiquitination [134,157]. Among these, disruption/dysregulation of PARP1's phosphorylation, acetylation, and methylation are met with severe cellular consequences [157].

PARP1's ADP-ribosylation is carried out by itself, PARP2, and PARP3. Even though, evidences have shown that PARP1 auto-modification occurs predominantly on E/D and S residues (E488, E491, S499, S507 and S519) [45,90–92], the K498, K521 and K524 (all within the auto-modification loop – 466-525aa), were also reported to be potential auto-modification sites [157,158]. Extensive auto-modification (chains >200 units in length) inhibits the DNA binding capability and enzymatic activity of PARP1, while less extensive chains are suggested to affect exclusively its enzymatic activity [157,158]. PARP1 and PARP2 can form a heterodimer and through this, associated PTMs are exerted onto each other. On the other hand, PARP3 promotes mono (ADP)-ribosylation of PARP1, and by direct physical interaction the first can activate PARP1's transferase activity in the absence of DNA [157].

Furthermore SIRT 6 was proved to promote mono-ADP-ribosylate PARP1 on K521, in oxidative stress conditions [159]. Mao et al. (2011) verified that in mammalian cells subjected to oxidative stress SIRT 6 is recruited to DSB sites and strongly stimulates NHEJ and HR [159]. This is promoted by its physical interaction with PARP1 leading to the activation of PARP1 enzymatic activity. Those authors proposed that SIRT 6 serves as a mediator of hormetic and acts as a regulator of oxidative stress signalling and DNA damage response [159].

Phosphorylation may have positive and negative impacts on the cellular activity of PARP1. Modification of the serine and threonine residues (S372 and T373) by the extracellular signal-regulated kinases 1/2 (ERK1/2) [160], and S785/786 by the hormone-activated kinase CDK2, cyclin E and progesterone receptor complex (CDK2-cyclin *E*-PR) [161], produces activation or further enhancement of PARP1 enzymatic activity. The phosphorylation of PARP1 in S785 and S786 results in a loosening of the NAD^+-binding pocket within the CAT domain [161], thus making indispensable the enzymatic activities of PARP1 and CDK2 for their hormone-dependent recruitment chromatin and Histone 1 (H1) displacement in the chromatin [157,161]. Similarly, phosphorylation of PARP1 by the calcium-dependent protein kinase (CAMKII) activates its enzymatic activity during neuronal development, and consequently leads to nuclear export of KIF4 [162]. On the other hand the phosphorylation of PARP1 by the insulin-like growth factor-1 (IGF-1) and protein kinase C (PKC), is linked to the inhibition of PARP1's ADP-ribosylation activity and attenuation of its DNA binding capability and enzymatic activity, respectively [157].

Methylation of PARP1 amino acids was reported in the K528 and K508 residues. The first was associated with the activity of the lysine methyltransferase SMYD2 and the second to SET7/9 [163,164]. Methylation of the mentioned lysine residues was associated to significant enhancements of PARP1 enzymatic activity [163,164]. A negative feedback on SET7/9 methylation of K508 was verified upon auto-PARylation of PARP1 [163].

Acetylation of PARP1's lysine residues (K498, K505, K508, K521 and K524) was demonstrated by Hassa et al. [165]. These modifications are conducted by the p300/CBP protein complex and are considered of the essence for PARP1 interaction and coactivation (with p300 and CDK8/MED14 complex) of the NF-κB protein complex, in inflammatory response [157,165]. On the hand, protein acetylation by lysine acetyltransferase 2B (PCAF) was reported to enhance auto- and hetero-modification activities of PARP1, and it was deemed as essential for stress-induced cell death pathways [157,166]. Deacetylation of PARP1 promotes cell survival [166] and can be conducted by sirtuin 1 (SIRT1), in the 1–214 aa region and 477–524 aa, or by histone deacetylase 1 (HDAC1) in the 477–524 aa region [165,166]. HDAC 2 and 3 were also proved efficient in PARP1 deacetylation in vivo [165].

Crosstalk between PARP1 acetylation and SUMOylation was observed, with the modifications promoted by SUMO1 and 3 contributing to the prevention of PARP1 acetylation by p300 [167]. Additionally, crosstalk between the PARP1's ubiquitination and SUMOylation hints to a possible regulation mechanism on PARP1's transcriptional role. Martin et al. [168] verified that SUMO-targeted ubiquitin ligase ring finger protein 4 (RNF4) mediates heat-shock-inducible ubiquitination of PARP1 (that is SUMOylated) and functions as a positive regulator of *HSP70.1* gene. The authors state that the results obtained pointed to a novel mechanism that regulates PARP1 transcriptional function, in response to heat shock, where the SUMOylation and RNF4-mediated ubiquitination of the protein is in rule [168].

Moreover, Zhang et al., [169,170] uncovered that the Nedd4 family member WWP2 was a specific E3 ubiquitin ligase of PARP1, contributing to the discovery of a new ubiquitin-proteasome degradation pathway of PARP1. The authors verified that WWP2 mediated-ubiquitination occurred in K418 and K249, in the myocardium tissue and cells of mouse [170].

PARP1 activity is also regulated by proteases in cell death pathways. The degradation of PARP1 is conducted by caspase 3 and 7 in apoptosis, by granzyme A and B in immune responses and several cathepsins in autophagic and necrotic cell death [134].

4.3. PARP1 protein substrates and binding partners

Over the years, many proteins were described as PARylated by PARP1 and have contributed to a better understanding of the many biological functions of PARP1. Besides proteins, nucleic acids are also depicted as PARP1's catalytic targets and a comprehensive review can be found in [171]. The focus in this section is going to be on proteins that PARP1 regulates by either physical interaction or by its PARylation activity.

Even though, PARP1's major acceptor of PAR chains is itself; this protein has long been associated with several intracellular players. The extensive PAR chains act as scaffolds to attract and assist in the assembly of large protein complexes. These are usually involved in chromatin remodelling, DNA repair and cell cycle checkpoints [134]. The role of PARP1 in chromatin remodelling is varied, where chromatin relaxation or condensation is promoted by interaction with nucleosomes and PARylation of histones H1 and H2B [135]. Also, PARP1 is closely associated with transcription regulation by direct interaction with transcription factors or by PAR activity [134,135]. In the first are included Cox-2, Oct1, E2F-1 and Ap2, and in the second are englobed p53 and RNA polymerases I/II [135]. In the case of NF-κB, PARP1 may act in both manners with p50 and p65 sub-units, thus regulating the transcriptional function of NF-κB [134].

However, one of the best-described functions of PARP1 is its role in detecting and initiating DNA repair, which will be discussed further in this section. This protein initially was associated exclusively with BER pathway, where PARP1 role is best characterized, but over the years it has been proved its involvement in other repair pathways, such as MMR, HR, NER and NHEJ [135,172,173].

Single base modifications or nucleotide damage are the most common type of damage that can be found on DNA. SSB lesions arise spontaneously, or from base modifications such as oxidated bases,

abasic sites and others [172]. On the other hand, DSBs are produced upon exposure to DNA-damaging agents, such as ionizing radiation, collapse of replication forks or genome rearrangements (e.g. class-switch recombination (CSR), V(*D*)J recombination and meiosis) [134,172].

SSBs are readily repaired by BER, with PARP1 recognizing damage loci and promoting the recruitment of effector protein complexes. However, even though it is known that DSBs are repaired either by HR or NHEJ, PARP1 mechanistic involvement in these two pathways is still not fully understood. However, the choice between HR or NHEJ is known to be ruled by cell cycle phase and chromatin context [134,172]. During the cell cycle, NHEJ is active throughout its phases, but its activation is most favoured in the G1 phase. On the other hand, the HR pathway is most prevalent after DNA replication, since an identical sister chromatid is available as a template [134,172,174]. Moreover, since DSBs occur within the complex array of chromatin structures (e.g. genes, telomeres, replication forks, intergenic regions and compact chromatin), the detection and repair of these damages have significant barriers [134,172,175]. As so, for DSB repair both post-translational modifications of nucleosomes and the concentration of DNA repair proteins at the damage site are of most importance [134,172,175]. The "access-repair-restore" model, first described by Smerdon (1991) [176], proposed the minimal steps needed for chromatin recognition and repair. In general: 1) detect damage, 2) remodel chromatin architecture, 3) reorganize the nucleosome-DNA template for processing and repair, and finally 4) restore chromatin organization and condensation after repair [134,172,175].

4.3.1. Base excision repair (BER)

BER serves as a route to repair SSBs and small lesions that may appear in DNA. The latter are first transformed into SSBs through the action of DNA glycosylases and APE1 [135,172]. The SSBs are sensed and bound by PARP1, which after auto-modification recruits the repair effector X-ray repair cross-complementing protein 1 (XRCC1) (Table 3). The rapid recruitment of XRCC1 to SSBs is dependent on PARP1 and PARP2 enzymatic activity and serves as a signal for the recruitment of other effectors such as DNA ligase 3 (LIG3), DNA polymerase β and bifunctional polynucleotide kinase 3′-phosphatase (PNKP). Only after the recruitment and formation of the protein complex is the repair process stimulated [134,135,172].

Additionally, it was shown that PARP1-mediated repair in "nick" lesions requires the involvement of tyrosyl-DNA phosphodiesterase 1 (TDP1) [177] (Table 3). TDP1 is a target of PARP1's catalytic activity and after PARylation, the protein stability and recruitment to the damaged site is enhanced. Nick lesions are known to result from the abortion of DNA topoisomerase 1 (TOP1) activity, and TDP1 hydrolyses the existing bond between TOP1 and DNA. This action helps in exposing the lesion to PARP1 and repair is carried out through BER [177].

However, some reports suggest that PARP1 may not be essential for BER repair in a specific subset of DNA lesions [178]. In the case of purine base damage repair, it has been pointed out that this event may require the presence of PARP1, however in the event of pyrimidine damage the repair may be independent of PARP1 [179].

Moreover, it is important to note that PARP1s intracellular signalling may act as a double-edged sword, since in inflammatory processes, chronically activated repair pathways can induce DNA damage [135].

4.3.2. Nucleotide excision repair (NER)

UV irradiation is known to induce distorted DNA structures (e.g. thymine dimers) and the repair of these anomalies is done through the NER pathway [134]. This repair route involves a large set of proteins that are responsible for damage recognition, damaged-DNA stretch removal, gap filling and strand ligation [135]. Also, in recent studies, it has been proved that PARP1 is involved in the initial stages of the NER sub-pathway named global genome (GG)-NER, and that PARP1's catalytic activity is triggered by UV-B radiation [180].

Table 3
PARP1 and PAR functions, regulation and protein partners in DNA repair pathways.

DNA strand break	DNA Repair Pathway	PARP1/PAR function	Repair Factors that interact with PARP1 or PAR	References
Single strand break (SSB)	Base excision repair (BER)	Bind and stabilize damage site Recruitment	XRCC1 LIG3 Polβ PNKP TDP1 (nick lesions)	[134,135,172,177]
	Nucleotide excision repair (NER)	Damage detection, recruitment and activation	XPA XPC DDB2 ALC1 MutSα	[172,180–183]
	Mismatch repair (MMR)	Interaction	EXO 1 RPA RFC PCNA	[185,186]
Double strand break (DSB)	Homologous repair (HR	Bind, stabilize and recruitment	BRCA1/2 MRE11 ATM	[173,188–192]
	Classical Non-homologous end joining (c-NHEJ)	Stimulate activity and recruitment	DNA-Pkcs CHD2	[172,190,194]
	Alternative Non-homologous end joining (alt-NHEJ)	Recruitment	POL θ MRN complex	[196–198]

The UV damages are initially recognized by the *Xerodema pigmentosum* complementation group C (XPC) and RAD23B (XPC-HHRAD23B) complex, which subsequently associates with the DNA damage-binding proteins 1 and 2 (DDB1-DDB2) complex. This induces the ubiquitylation of core histones and leads to nucleosome displacement [172]. DDB2 promotes the recruitment of PARP1, by physical interaction, and stimulates PARylation on histones [180,181] (Table 3). This results in further chromatin relaxation by the recruitment of the chromatin-remodelling helicase amplified liver cancer protein 1 (ALC1) [181,182]. Additionally, because XPC binds to PAR through its specific binding-motif (PBM), its recruitment to the damage site is further enhanced [183]. Chromatin relaxation facilitates the access of the remaining NER proteins to the UV lesions and further stimulates the repair. Moreover, PAR synthesis was also suggested to be central in the recruitment of NER damage recognition factor XPA [172] (Table 3).

Final repair steps involve: 1) DNA unwinding by the transcription factor IIH (TFIIH) and verification by XPA and RPA; 2) damaged-DNA stretch removal by endonucleases XPG and ERCC1/XPF (23–30 nt fragment); and 3) gap filling by DNA polymerases δ and ε with PCNA, RPA and RFC. Strand ligation (4) is done by DNA ligase I or DNA ligase III-XRCC1, depending on the cell cycle stage [134,184].

The role of PARP1 in the NER pathway is biologically significant, more specifically its interaction with DDB2 and ALC1 since inhibition of PARP1 activity was revealed to induce cellular sensitization to UV-irradiation [181].

4.3.3. Mismatch repair (MMR)

DNA mismatch repair is activated when single or double mismatch bases, and loops, arise from insertions or deletions in the DNA strand [134]. This pathway is initiated by the recognition heterodimer MSH2-

MSH6 (MUTSα) and recruitment of the PMS2-MLH1 heterodimer (MUTLα) [134]. The MUTSα-MUTLα complex slides and nicks DNA strands near the damage site, thus promoting Exonuclease 1 (EXO1) activity [134]. Afterwards, the recruitment of the replication clamp PCNA and the clamp loader RFC (replication factor C) to the protein complex, promotes mismatch-excision directed by 3′ or 5′ strand break [185]. In the final stages DNA polymerases δ and ε promote gap filling, and DNA ligation I leads to strand ligation [134,185].

In vitro studies revealed that PARP1 enhances mismatch dependence of 5′-directed excision in MMR and that PARP1's DNA binding and BRCT domains are involved in MMR excision specificity [185]. It was also revealed that PARP1 physically interacts with several MMR proteins such as MUTSα, EXO1, replication protein A (RPA), RFC and PCNA [185] (Table 3). Additionally, MSH6 protein was presented as a target of PARP1 enzymatic activity [186]. Even with this data, much is still uncertain about the exact role of PARP1 in MMR and further characterization studies are needed.

4.3.4. Homologous repair (HR)

HR repair is known as the high-fidelity repair route and is characterized by the usage of the sister chromatid or homologous chromosome as a DNA template for damage repair [134]. Moreover, homologous repair is required to prevent the deleterious effect of perturbed replication forks, either stalled or collapsed [180].

After DSB end recognition, the MRE11 nuclease-RAD50-NBS1 (MRN) complex jointly with the CtIP-BRCA1 complex cooperates in the generation of 3′-overhangs on DBSs blunt ends. The generated structure is then stabilized by the replication protein A1 (RPA1) and PARP1 is also pointed to help in stabilizing these DNA structures [172,180,187].

Activation of MRN complex contributes to cell cycle arrest, as well as to DNA damage repair by activation of the ataxia telangiectasia mutated (ATM) signalling through phosphorylation [187]. Afterwards, BRCA2 mediates the exchange of RPA1 for RAD51, which promotes the search for a homologous DNA template (strand invasion) for lesion repair. DNA polymerase extends the 3′-overhang strand, DNA ligase I connects the strand ends, and the intermediate Holliday junctions are resolved by resolvases [187].

If the DNA lesion is not easily repaired, the ataxia telangiectasia and Rad3-related protein (ATR) signalling route is activated by the interaction of RPA1 with ATR-interacting protein (ATRIP). This is followed by RFC-mediated loading of 9–1-1 clamp and successive activation of topoisomerase II binding protein 1 (TOPBP1) [134].

PARP1 role in the recruitment of HR proteins has been discussed over the years and it has been highlighted the importance of PAR chains in the recruitment of breast cancer type 1 susceptibility protein (BRCA1) and breast cancer type 2 susceptibility protein (BRCA2) [173,188,189] (Table 3). The first is promoted by BRCA1-binding partner BARD1, while BRCA2 recruitment is related to its own tandem oligonucleotide/oligosaccharide (OB) – folds, that help in the detection of ADP-ribose chains in the damage sites [173,188,189].

These specific interactions laid the foundations for the usage of PARP1 inhibitors in the clinical treatment of *BRCA1* or *BRCA2* mutated cancers [172]. In this line of treatment, the combined conditions (inhibitor + mutations) will expectedly result in synthetic lethality, which will help to increment therapeutic efficacy [172]. By this approach the inhibition of PARP1 leads to the accumulation of SSBs, which are further processed into DSBs during replication. Because BRCA1/2-deficient cells have their DSBs repair capabilities reduced, the synthetic lethality approach with PARP1 inhibitors will culminate in cytotoxic effects and cellular death [172].

Additionally, the role of PARP1 regarding the recruitment of MRE11, in HR, is a topic of much debate, with evidence revealing that a complex regulation system is in play at replication forks [190]. Ying et al. [190] verified that MRE11 is recruited through PARP1 activity in a small portion of stalled replication forks, particularly not easily resected forks. In the case of easily resected forks, MRE11 recruitment was considered independent of PARP1 [190]. It was also demonstrated that PARP1 could act as a replication fork protectant against MRE11-mediated resection, with a distinctive stabilization role [190]. Furthermore, the authors uncover that the resolution of unresected forks required PARP1 and DNA-dependent protein kinases catalytic subunit (DNA-PKcs) for the relocation of XRCC1 proteins [190]. In this way effective repair and replication fork restart is enabled [190] (Table 3).

Studies have also revealed that PARP1 physically interacts and PARylates with ATM, during DNA damage response [191,192] (Table 3). Additionally, PARP1-ATM interaction was considered important in the phosphorylation kinetics of downstream proteins (e.g. p53 and H2AX) [191–193]. Knockdown and inhibition of PARP1 were revealed to delay ATM activity [192].

4.3.5. Non-homologous end joining (NHEJ)

NHEJ is an error-prone mechanism that is active throughout the cell cycle, but it is the preferred mechanism in G1 phase when a DNA template is not available [172].

In classical NHEJ (c-NHEJ) the Ku heterodimer (Ku70/Ku8) ring binds to the DNA strand-break ends and recruits the DNA-dependent protein kinase (DNA-PK), XRCC4 and DNA ligase IV (LIG4). DNA-PKcs binding to DNA activates the protein and leads to a phosphorylation cascade onto ATM, p53 and itself. In the meantime, the Artemis DNA end-processing enzyme prepares DNA strands for ligation [134].

PARP1 acts in this sub-pathway (c-NHEJ) either by physical interaction with DNA-PKcs or by further stimulating protein kinase activity by PARylation [172]. Additionally, it was proved that PARP1 potentiates the efficiency of c-NHEJ repair by the recruitment of the chromodomain helicase DNA-binding protein 2 (CHD2) to DSB sites, to promote the assembly of the XRCC4-containing repair complex [194] (Table 3).

Besides c-NHEJ, several reports point to a key function of PARP1 in alternative NHEJ (alt-NHEJ) [172,180,195]. alt-NHEJ is characterized by end resection and utilizes sequence micro-homology regions, which makes it an inherently mutagenic pathway and leads to the generation of insertions and deletions [172,180,195]. This process is dependent on PARP1, XRCC1, LIG3, MRE11, NBS1 and Flap endonuclease 1 (FEN1) [195]. Strand-end ligation is independent of LIG4 and Ku complex, while DSB processing is done by the MRN complex [172,180].

PARP1 is indicated to be involved in the promotion of alt-NHEJ [169,190,191]. This is done by competing for access to DNA breaks with Ku proteins and favouring the recruitment of the MRN complex (Table 3) [169,190,191]. Additionally, PARP1 is also suggested to be involved in the recruitment of DNA polymerase θ (Pol θ), which displays a terminal transferase-like activity [196,197]. In a recent study done by Luedeman et al. [198], these authors suggest that PARylation indirectly promotes Pol θ recruitment and repair, by increasing the frequency of end resection and leading to the redirection from c-NHEJ to Pol θ-mediated alt-NHEJ in the repair of these specific ends [198] (Table 3).

The PARP1-Pol θ mediated repair thus serves as an additional justification for the synthetic lethality effect of PARP1 inhibition and *BRCA1*-mutation therapy. It was also experimentally verified that BRCA1-deficient malignancies are extremely dependent on Pol θ – mediated damage repair [196].

When DNA damage is minimal PARP1 role results in the activation of any of the repair pathways that were previously described. However, if DNA damage is too extensive to be repaired, PARP1 is rapidly cleaved by caspases [199]. The cleavage of PARP1 results in two specific fragments: a C-terminal fragment of approximately 89 kDa (comprising the catalytic domain) and a N-terminal fragment of around 24 kDa (comprising the DNA binding domains) [199]. The first fragment is known to be translocated from the nucleus to the cytosol, while the N-terminal is retained within the nucleus, irreversibly bound to DNA. The 24 kDa fragment, in its bound form, acts as a trans-dominant inhibitor of remaining active PARP1 and other repair enzymes [199]. The degradation mode of PARP1 and the intracellular localization of its fragments

is believed to be a conservation energy (cellular ATP pools) requirement for apoptosis [199].

Curiously, PARP1 is also capable of mediating a different form of cellular death, which is named parthanatos [200,201]. Under pathophysiological conditions, the over-activation of PARP1 can lead to the accumulation of PAR polymers and subsequentially to the nuclear translocation of the apoptosis-inducing factor (AIF) [200,201]. This cascade of events will then trigger this non-apoptotic programmed cell death. Parthanatos is reported to be widely involved in several pathological processes such as ischemic-reperfusion injuries, septic shock, neurodegenerative diseases (e.g. Parkinson's and Alzheimer), cardiovascular diseases, diabetes and cancer [200,201].

5. PARP1 and cancer

PARP1 has been implicated in several human pathologies, but cancer is still the disease where PARP1 has been shown to be implicated in numerous pathways. As we have shown so far, PARP1 is implicated in many of the biological functions and processes that are of essence for tumour development and growth.

This protein has been identified in the nucleus and cytoplasm of cancer cells and PARP1 expression studies have revealed that this protein is found to be upregulated in a multitude of tumours [202]. The determination of the expression levels of PARP1 is considered to be important for the determination of therapeutic potential, effect and side-effect of clinical inhibitors [202].

A study of over 8000 surgical samples from cancer and healthy patients, carried out by Ossovskaya et al. [203], revealed that *PARP1* is overexpressed in several malignant tissues. Among them significant results were verified in patients with breast, uterine, lung, ovarian, skin cancers and non-Hodgkin's lymphoma. Of these, breast cancer attracted the most attention, since the authors verified that *PARP1* overexpression was detected in over 30 % of breast infiltrating ductal carcinoma (IDC) samples, when in normal tissues values were of 2.9 % [203]. Additionally, the same study demonstrated that *PARP1* gene was up-regulated >2-fold in approximately 70 % of primary breast adenocarcinomas, including triple-negative breast cancer, where gene upregulation was consistent with increased protein expression [203]. In other assessments, high levels of PARP1 expression was related to poor prognosis and decreased survival rates in breast cancer patients, for patients with worse clinical outcome and in less aggressive clinical conditions [204].

High expression levels of PARP1 were also verified in lung carcinomas, however differences were retrieved when comparing small cell (SCLC) and non-small cell lung (NSCLC) carcinomas. mRNA and protein levels were higher in the first, than the last [205].

In Ewing's sarcoma, an aggressive malignancy that is characterized by the EWS-FLI1 or EWS-ERG genomic fusions, PARP1's expression was revealed to be maintained in a positive feedback loop by the EWS-FLI1 fusion genes [206]. The expression loop was also revealed to be required for EWS-FLI-mediated transcription. This findings led to the suggestion by the authors that EWS-FLI1:PARP1 intersection presented a therapeutic strategy to increase treatment efficacy of Ewing's sarcoma patients [206].

Zuo and colleagues verified that PARP1 mRNA levels in epithelial ovarian cancer patients (EOC) was higher in a platinum-resistant therapy group, than a platinum-sensitive group [207]. This was associated with a worse prognosis and the authors suggest that PARP1 may serve as potential biomarker to predict the resistance to platinum chemotherapy and the prognosis of EOC patients [207].

In a recent study, Puentes-Pardo et al. [208], attempted to analyse the expression of PARP1 in colorectal cancers (CRC) with different p53 status in order to evaluate the influence on the cancer stem cells (CSC) phenotype. These are a subset of cancer cells that are also considered important for cancer initiation and metastasis [208]. The authors confirmed that *PARP1* gene was overexpressed in tumour tissues from cancer patients, when compared to healthy mucosa, and that it was correlated with the differentiation grade [208]. However, this association was only upheld in tumours with wild-type p53. In patients with p53 mutation, PARP1 served as an independent prognostic survival factor [208]. The authors affirmed that PARP1 could be a clinical tool for personalized medicine, since patients with high PARP1 expression and wild-type p53 would benefit from PARP1 inhibitor therapy, while this could be adverse for patients harbouring p53 mutations [208].

Comprehensive studies were also done to understand the molecular role of PARP1 and its association with key features of cancer initiation and progress.

Demény et al. [41,209], has done a two-part review about the involvement of all PARP family members in ten hallmarks of cancer: (Part.1) 1) uncontrolled proliferation, 2) evasion of growth suppressors, 3) cell death resistance, 4) genome instability, 5) reprogrammed energy metabolism, 6) escape from replicative senescence; (Part. 2) 7) angiogenesis, 8) invasion and metastasis, 9) evasion of immune response and 10) tumour-promoting inflammation. Within Demény's review, it was extensively debated how poly (ADP-ribose) polymerases are involved in the microevolution process and survival of tumours, and how PARP1 appears again as a player with vast contribution and interconnections in all ten hallmarks. The authors also highly controversies and do an interesting introspection about open questions and future prospects related to the wide roles of PARPs in cancer biology [41,209].

Cancer survival can be regulated in several levels by PARP1 via DNA repair pathways [202]. For cancer survival, cell will activate PARP1 to repair mild damages and in this way maintain carcinogenic mutations that permit its tumour phenotype [202]. When in the presence of excessive DNA lesions, normal PARP1 activation will lead to insufficient repair and culminate in cellular apoptosis [202]. However, in the case of PARP1 overactivation, cancer cells will face further mutagenesis, metastasis, energy depletion, necrosis, and autophagy, which in turn will promote increased inflammation (cancer hallmark) [202].

As can be perceived, PARP1 is involved in multi-level biological controls, and its activity can either enhance carcinogenic features or lead to cellular death.

Additionally, PARP1 can promote tumour development through its transcriptional regulation role. This is achieved by the interaction with transcriptional factors, transcription machinery and chromatin modulators [202]. PARP1 transcriptional regulation effect, may be positive and negative. On one hand leading to the transcriptional activation of oncogenes (e.g. vascular endothelial growth factor receptor 1 (*VEGFR1*), hypoxia-inducible factor 1α (*HIF1α*) and 2 A (*HIF2A*), androgen receptor, melanocyte-lineage survival (*MITF*)), or have repressive effects on tumour suppressors (e.g. p53 and Adenomatous polyposis coli (*APC*)) [202,209]. PARP1 is also capable to influence chromatin remodelling by the activity and location of histones. This can be done by interaction with the nucleosome leading to a suppression of transcription, or by dissociation of H1 promoting RNA polymerase II-mediated gene transcription [202].

When PARP1 is hyperactivated, it promotes a positive feedback cycle that leads to the upregulation of inflammatory signal factors, such as NF-κB [202,209]. The interaction of PARP1 with NF-κB upregulates pro-inflammatory cytokines like tumour necrosis factor α (TNFα) and interleukin 6 (IL6) [202,209]. These are involved in the initiation of tumour-promoting inflammation processes. Chronic inflammation conducts to a higher degree of cell malignancy, which in turn helps with immune surveillance evasion [202,209]. It was also demonstrated that the NF-κB signal factor has a major role in cancer progression, metastasis and angiogenesis [202].

PARP1 is also capable to modulate the cell cycle of tumour cells, by regulating cellular mitosis and programmed cell death pathways [202,209]. Additionally, PARP1 can activate pro-angiogenic/metastasis factors (e.g. c-MYC, VEGF, platelet/endothelial cell adhesion molecule (PECAM1/CD31) and HIF), thus inducing angiogenesis and metastasis [202,209].

In Fig. 5 it is depicted the multifactorial roles of PARP1 in

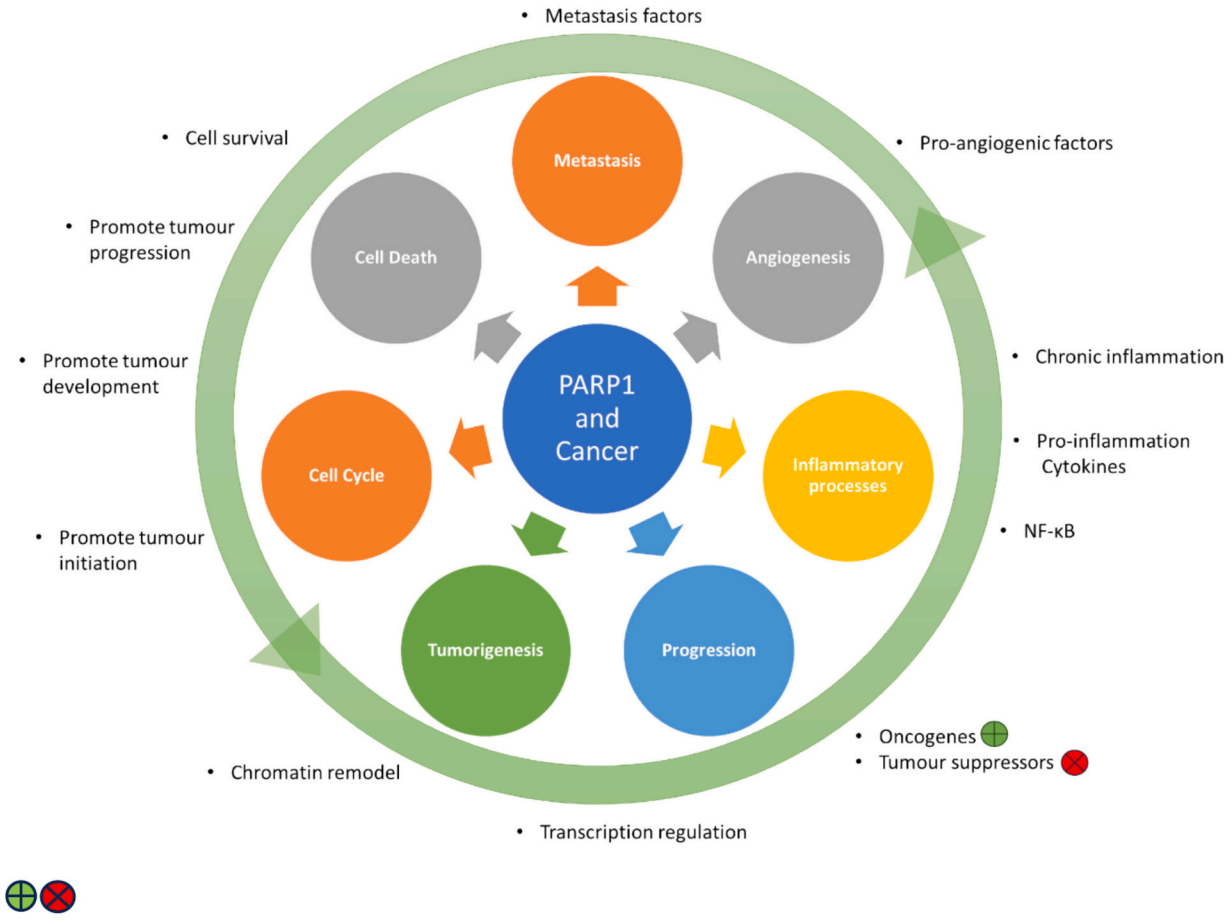


Fig. 5. Schematic summarizing the multifactorial roles of PARP1 in cancer. In the image it is depicted the way in which PARP1 is involved in tumorigenesis, tumour progression, inflammation processes, angiogenesis, metastasis, control of cell death and cell cycle. The multifaceted regulation done by PARP1 in numerous processes creates a "feed" cycle for cancer initiation, progression, malignancy, and survival ⊕ means gene expression and ⊗ means gene silencing.

tumorigenesis, giving a better image on its span in cancer biological processes.

6. PARP1 the desirable therapeutic target

PARP1 is one of the more interesting targets used in anti-cancer drug design. The abundant data proving its involvement in carcinogenesis reinforced the need for the development of better clinical inhibitors and treatments.

The therapeutic strategy behind the design of PARP1 inhibitors (PARPi) is based on the synthetic lethality theory, where cell survival is severely hindered by the simultaneous blockage of SSB repair and HR repair [210]. Since PARP1 was considered an ideal target in treating HR-deficient cancers, initial studies found that PARPis were effective in killing BRCA1/2-mutated tumours [210]. However, in more recent times it has been described that some non-mutated BRCA1/2 tumours are also sensitive to PARPi treatment [210].

Most PARP inhibitors were designed to mimic and compete with the cofactor NAD^+ for the protein catalytic domain of PARP1 [96,137,211,212]. These molecules are included in the monoaryl amides and bi−/tri−/tetracyclic lactam compound group [211], and their common pharmacophore features are the aromatic ring and carboxamide moiety [213]. The last interacts with CAT through three crucial hydrogen bonds with glycine-G863 and S904. Additionally, it was reported that the phenyl moiety of Y907 is involved in a π- π stacking interaction with the nicotinamide of NAD^+ [213].

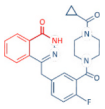
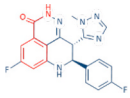
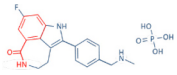
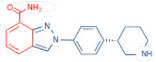
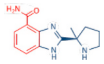
In Malyuchenko's 2015 review [137] the rationality behind the design of PARPi and how their structure has evolved from first-generation compounds until the third-generation ones is extensively explained. This last category includes the FDA-approved inhibitors: Olaparib, Rucaparib, Niraparib and Talazoparib; and Veliparib, that is currently being tested in clinical trials [138,212,214–216]. Table 4 includes pertinent information regarding these inhibitors, namely their structure (with identification in red of nicotinamide pharmacophore), alternative designation, target protein and values regarding inhibitory potential.

PARPi's unique therapeutic potential, confers great advantage in their usage in cancer treatment. They can either be used in synergistic lethal strategies, as a coadjutant to DNA damage agents (e.g. radiation or chemotherapeutics), or as mono-therapeutic agents (e.g. in tumours with specific genetic profiles) [96,210,218]. The use of PARPi, not only leads to the inhibition of PARP1's catalytic activity, but also to the prevention of its release from the damage sites. Moreover, it has been proved that chemical inhibition of PARP1 sensitizes cells to UVA, UVB and UVC treatment [180,210]. On the other hand, molecules such as Veliparib and Niraparib were also proved to be capable to bind cDNA, though intercalation in DNA grooves [219,220].

Over the years many X-ray crystal structures were determined for PARP1's CAT domain interaction with known inhibitors [76,97–99], as well as with some potential new molecules [100–116].

However, PARP therapeutic resistance has been reported in some cancers, which can be explained by the interplay effect of the c-MET membrane receptor [221]. Through the phosphorylation of PARP1's Y907 residue, the CAT-inhibitor interaction is prevented [221]. By blocking the c-MET-mediated phosphorylation of PARP1, the anti-tumour effect of PARPi is enhanced [221]. Additionally, it was

Table 4
Information regarding PARP1 clinical inhibitors. The nicotinamide pharmacophore that is common moiety among PARPi is highlighted in red.

Name	Alternative Name	Structure	Target	IC50 (nM)	K_I (nM)	References
Olaparib	AZD2281		PARP1/2	5/1	0.97/0.34	
Talazoparib	BMN673		PARP1/2	1.2/0.9	0.012/0.18	
Rucaparib	AG-014699		PARP1	1.4	0.09	[214,217]
Niraparib	MK-4827		PARP1/2	3.2/4	1.2/−−	
Veliparib	ABT-888		PARP1/2	5.2/2.9	0.96/9.9	

Note: IC50 – half maximal inhibitory concentration; K_I – inhibition/binding constant.

revealed that the cooperation between c-MET and epidermal growth factor receptor (EGFR) further enhances resistance to PARPi therapy in hepatocellular carcinoma [222].

Nevertheless, it was also verified that PARPi resistance could be circumvented by combination therapy. In NSCLC, it was established that tumour cells could be sensitized to PARPi and ionizing radiation through combination with DNA methyltransferase inhibitors [223].

Over the years a growing number of combination approaches with PARPi was assessed [41]. These include the combination with inhibitors of RTK, check-point kinase 1/2 (CHK1/2), ATR, Wee1, PI3K, HDAC, IGFR, Raf, MEK, or drugs that interfere with sex hormone synthesis [41].

Other drawbacks that have been associated with PARPi therapy, include 1) cytotoxic effects on normal cells, 2) high compound clearance rates in the organism and 3) drug interaction with plasma proteins [224,225]. Values as high as 83 % binding with human plasma protein have been reported for Niraparib, after entering the blood through the digestive system [225]. One of the best approaches to circumvent these drawbacks is by a combination therapy approach with nano-delivery systems, such as liposomes.

7. PARP1 therapy evolution – combining ionizing radiation and liposomal nano-delivery systems

As we have discussed so far, PARPi combination therapy opens new horizons in cancer treatment. Until the present day PARPi clinical efficacy is far from what is expected and some associate it to PARPi's oral administration, its relatively low accumulation in tumour mass, as well as to the complexity of the cellular microenvironment [226]. The use of nanotechnology helped to overcome most of these limitations and several nano-formulations were reported in the treatment of cancers. Among these are included liposomes, polymeric micelles, hydrogels, nano-emulsions, nano-suspensions and nanoparticles (e.g. inorganic, polymeric and solid lipid nanoparticles) [226,227]. Multiples are the advantages of using drug delivery systems in cancer therapy. It has been vastly showed that these systems are capable to carry drugs to its specific targets by enhanced permeability and retention effects [226,227]. Moreover, these systems could also be designed to control the release kinetics of drugs, thus retaining stability and drug concentration in the bloodstream, leading to the improvement of drug bioavailability and pharmacokinetics [226,227].

In this context, current PARPi monotherapy, which relies on frequent oral drug administration, can lead to several side effects such as anemia and fatigue [228]. One good example is the Olaparib drug, which due to its reduced pharmacokinetic values translates into low drug percentages that reach the tumour mass [228]. For this reason and to maintain effective drug concentrations, patients need to take up to 16 capsules per day [228]. In this way, up to 80 % of patients report one or more of the adverse effects, such as nausea, fatigue, or diarrhea [228].

Hao et al., (2021) analyzed several relevant clinical trials on patients with advanced ovarian cancer to determine the efficacy and toxicity profile of PARP inhibitors [229]. Their study indicated that the use of PARP inhibitors provided high progression-free survival (PFS) benefits, independently of BRCA mutation status [229]. However, all the patients treated exhibited higher risks of all-grade and high-grade hematological toxicities (e.g. anemia, leucopenia, neutropenia, thrombocytopenia), all-grade gastrointestinal side-effects (e.g. constipation, diarrhea, nausea, and vomiting) and high-grade nausea and vomiting [229]. Valabrega et al. (2021) also report in detail the various adverse effects due to Olaparib, Niraparib, and Veliparib administration [230]. The study states PFS rates of 3 years of 60 % and a reduction in the progression risk/death of 70 %, for BRCA-mutated patients with Olaparib treatments [230]. Furthermore, the authors state that each inhibitor presents substantial differences in their pharmacodynamic, pharmacokinetic properties, and safety profiles, which must be considered by clinicians while doing treatment administration [230].

More recently, Sun et al. (2024) revealed the benefits of maintenance therapy in ovarian cancer patients, with significant improvements in PFS, regardless of homologous recombination status. Additionally, maintenance therapy with Olaparib or Niraparib was associated with a significant extension in the overall survival of cancer patients. Nevertheless, this study has also detected that maintenance therapy significantly increases the risk of side effects, such as fatigue, nausea, anemia, neutropenia, and thrombocytopenia [231].

For these reasons, nanotechnology has been employed and set a new stepping stone in cancer therapy. When compared to conventional oral administration, the use of nano-delivery systems has the potential to reduce toxicity and improve patient recovery by decreasing administration frequency and dose [226].

The combination of PARPi with chemotherapy agents has also delivered interesting results, showing that therapies combining Olaparib increased response rates in prostate cancer patients, that no longer responded to single taxane drugs [232]. Similar data was also retrieved

for platinum-based drug-resistant tumours, where PARPi sensitized tumour cells to chemotherapeutic drugs [233]. However severe adverse events such as anemia and fatigue were reported by 20 % of patients [232]. These reports reinforce the need to employ nano-delivery systems for drug co-delivery and combination therapy.

Multiple nano-systems have been developed for the delivery of PARP1 inhibitors, with most studies and systems focusing on Olaparib and Talazoparib. These are either used per se or in combination with other chemotherapeutic drugs [226,227,234,235]. The nano-systems described involve iron oxides, hydrogels, emulsions, polymer nanoparticles, implants and micelles, metal-organic frameworks, solid lipid nanoparticles, self-assembly nanoparticles, and liposomes [226,227,234,235]. Comprehensive reviews concerning these systems and their production methods can be seen in [226,227], respectively. Besides Olaparib and Talazoparib, combination liposomal systems were also reported for Rucaparib [226] and Veliparib [236], with the first being in clinical phase trials.

More recently, we have reported a new liposomal system for the encapsulation and delivery of Rucaparib, Niraparib, and Veliparib inhibitors [237]. In that study, we have proved that 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1′-glycerol) sodium salt (DPPG) liposomes is the best lipid system to achieve high drug encapsulation efficiency (> 40 %) and elevated particle stabilization [237]. Particle characterization revealed that DPPG-encapsulating PARPi presented zeta-potential values below −30 mV and increased population homogeneity. The main population of interest presented diameter values around 130 nm [237]. We were the first to report the specific application of DPPG lipids for PARPi liposomal formulations and to uncover the preferable interaction/encapsulation mode of these inhibitors with the lipidic membrane.

Liposomes are considered efficient transport systems and present similar a structure to biological membranes, which makes them desirable for the delivery of clinical compounds through permeation [226]. Advantages related to the use of liposomes are: excellent biocompatibility, biodegradability, low toxicity, lack of immune system activation, and incorporation capability for both hydrophilic and hydrophobic molecules [238]. Several techniques can be used for their production, such as thin-film hydration, detergent depletion, ethanol injection, and reverse-phase evaporation [239]. These usually require a post-processing step, either by extrusion or sonication to achieve the required size, structure, and population heterogeneity [239]. Furthermore, liposomes can act as a protective barrier for photosensitive molecules, protecting their molecular integrity and therapeutic activity [240]. Additionally, lipidic nano-formulations may serve as a biomimetic system for interaction studies, to reduce drug cytotoxicity, and for co-loading systems to attain a higher degree of drug synergistic therapeutic effect [238]. Moreover, liposome surface can be functionalized with other molecules (e.g. polymers, polyelectrolytes, antibodies, or even conjugation with other nano-systems) [241–244], thus increasing particle biocompatibility, stabilization, control drug release and confer target specificity [242–244]. In sum, liposomes are believed to be an adequate nano-delivery system to use in PARPi-related cancer therapy, thus achieving a higher therapeutic efficacy and efficiency.

The use of nano-formulations permits to deliver clinical compounds through oral, injection, and transdermal administration, thus opening new possibilities for PARPi mono-therapy, their co-delivery with other drugs, or even combining them with radiation and photodynamic therapy [226]. Nano-systems combined with radiotherapy were previously reported with Olaparib and Talazoparib [226], while photodynamic therapy (PDT) was reported in poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles co-loading Veliparib and methylene blue [236].

In the first case, Olaparib formulations were developed in injectable nanoparticles to enhance sensitization to radiation therapy [245]. These particles presented a mean size value of 31.96 ± 1.54 nm, polydispersity index of 0.13 ± 0.01, and high radio sensitization effects (sensitization ratio of 3.81) when compared to free Olaparib (sensitization ratio of 1.66) [245]. Moreover, the combination of these formulations with radiation in mice with human non-small lung cancer xenograft tumour models showed: 1) inhibited tumour growth, 2) prolonged median survival rates (69.5 ± 11.8 days vs 31.8 ± 6.7 days), 3) increased cell numbers arrested in G2/M phase, 4) decrease angiogenesis and 5) without cytotoxicity effects on normal cells [245].

PDT resorts to light irradiation, which through the activation of photosensitizer molecules triggers the generation of reactive oxygen species (ROS) [236]. Through ROS generation cell damage is induced, which leads to cell death [236]. In this way, PARPi and nanotechnology were used to improve PDT by co-delivery of photosensitizers and PARPi. An example of this was the co-encapsulation of Veliparib and methylene blue in PLGA nanoparticles [236]. These formulations had mean size values of 90 nm and polydispersity index of 0.08. They also displayed controlled release of their cargo, with an initial burst profile and sustained release over 450 h [236]. Through the use of B16F10-Nex2 cells, it was confirmed the enhancement of photoactivity, with the release of methylene blue resulting in photodamages to the cells, while veliparib inhibited cell recovery [236]. Thus, providing further evidence for the employment of PARPi nanotechnology combination therapy with PDT.

Additionally, conventional PARPi therapy was proven to increase cell sensitization to UV irradiation [137] and positive feedback was reported when irradiation was combined with PARPi [96,210,218,246–248]. In this condition, a synergistic lethal effect is generated, leading to cancer cell death [96,210,218,246–248]. Moreover, it was verified that even low-energy sources such as UVC light were capable of activating PARylation, due to intracellular DNA damage, and in turn PARP1 inhibition sensitized cells to UVC irradiation [249].

Some preclinical evidence came to reinforce the notion that PARPi provides tumour specific radio-sensitization, in specific biological contexts, and currently, some PARPi (e.g. Olaparib, Talazoparib, Rucaparib, Veliparib, Niraparib, and Pamiparib) are in study in clinical trials while in combination with radiotherapy [248].

Considering all the data depicted, it is proved that the combination of PARPi + nano-system + irradiation therapeutic approaches (Fig. 6) constitute an evolution and alternative to conventional cancer therapy.

However, the development of nanomedicines is pointed to be faced with some challenges related to proper particle/formulation characterization, storage, manufacturing costs, and consumer compliance [227]. Nevertheless, these issues could be overcome by the advancement of scientific methodologies and techniques used as well as with the increase of the fundamental knowledge related to molecular mechanisms and interactions [227]. In this way, the strategies related to cancer treatment may evolve and possibly permit stalling, eradicating, and preventing cancer development and/or progression.

8. Conclusion and future perspectives

PARP1 is a 114 kDa multi-domain enzyme, that orchestrates vital biological processes such as inflammation, hypoxic response, transcriptional regulation, maintenance of chromosome stability, DNA repair, and cell death.

PARP1 presents multiple levels of intracellular regulation and any imbalance in its functions and biomolecular interactions, may have profound consequences at the cellular level. Moreover, PARP1's function in intracellular signalling can be considered a double-edged sword, since activated repair pathways may induce DNA damage in chronic inflammatory processes.

Even though this protein has been implicated in several human pathologies, cancer is the disease where PARP1 is more involved at multiple stages. Thus, PARP1 has been considered a desirable target for cancer therapy. Several activity inhibitors were developed along the way and currently four are FDA-approved for clinical application. However, some drawbacks are associated with conventional PARPi treatment, such as therapeutic resistance, cytotoxic side-effects, and

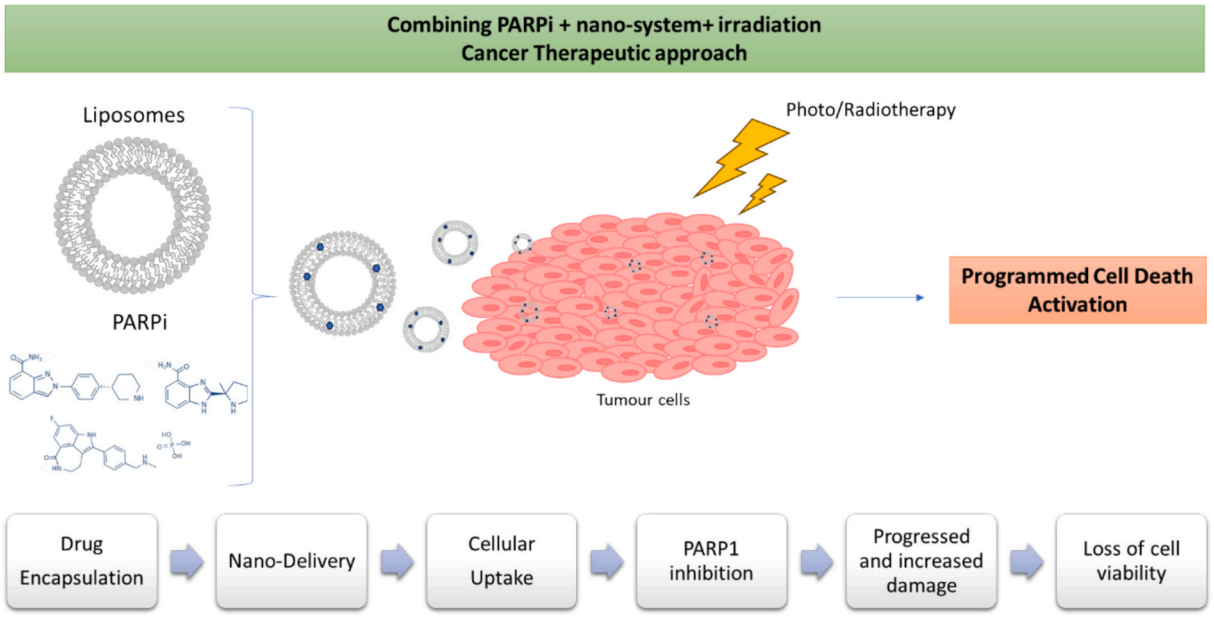


Fig. 6. Schematic representation of PARPi combination therapy with nano-system and irradiation in the tumour cells treatment. PARPi encapsulation in liposomes will increase drug circulation, protection, controlled release, and targetability to the tumour. Upon radiation exposure, DNA damage will be induced and by inhibition of PARP1 enzymatic activity, due to PARPi, damage repair will be prevented. Due to this SSB will evolve to DSB, leading to increased DNA damage, which in turn will stall replication forks. Following this event cell cycle arrest will occur, leading to loss of cell viability and activation of programmed cell death.

high clearance rates, among others. Consequently, combination therapy has emerged to circumvent PARPi therapy drawbacks and to increase the efficiency of PARPi-mediated therapy. The combination of nano-delivery systems and irradiation appears as a solution to span the applicability of PARPi, as well as conduct to the design of personalized treatments for the patient.

However, much is still needed to be done to better understand how these therapies may be formulated. Solutions are needed to solve problems related to proper particle/formulation characterization, storage, manufacturing costs and consumer compliance.

In the near future, we believe that much will be uncovered regarding already-known PARP1 biological functions and how this protein may be involved in the intersection of several intracellular pathways. These assessments will pass through the analysis of PARP1 interactors and regulators, as we have seen with HPF1. This will also lead to a better understanding of how to evolve in PARP1 targeted therapy. It will possibly pass through new chemotherapeutic combination approaches, such as with inhibitors of proteins involved in the cell cycle, cell division, inflammatory processes, and energy metabolism among others. Every day new inhibitor compounds are being designed, and we believe that the next-generation compounds may be targeting alternative PARP1 domains, besides CAT. Moreover, we hypothesize that the evolution of PARP1 cancer therapy will pass through the combination of PARPi + nano-systems + irradiation therapy. In this way, nano-formulations, such as liposomes, may be designed to encapsulate PARPi with complementary chemotherapeutic compounds, and through liposome surface functionalization tumour target delivery may be achieved. Therefore, lower doses of irradiation therapy may be applied, thus reducing cytotoxic side-effects and increasing tumour elimination.

The next big stepping stone in PARP1 knowledge will be the determination of its complete structure by cryo-EM. Even though a putative molecular structure was determined with AI prediction software (Alphafold), several uncertainties are still to be verified. Through the structural determination of full-length PARP1, biological processes will be better understood, and newer and more specialized clinical compounds and therapies may be developed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by the Portuguese National Funding Agency (FCT-MCTES), through Radiation Biology and Biophysics Doctoral Training Programme (RaBBiT, PD/00193/2012), the Applied Molecular Biosciences Unit—UCIBIO (UIDB/04378/2020), the CEFITEC Unit (UIDB/00068/2020), UIDB/04559/2020 (LIBPhys) and UIDP/04559/2020 (LIBPhys), the FCT Scholarships grant number PD/BD/142765/2018 and COVID/BD/152660/2022, to C.J.F.C. from the RaBBiT Doctoral Training Programme.

Data availability

Data will be made available on request.

References

[1] N.E. Navin, J. Hicks, Tracing the tumor lineage, Mol. Oncol. 4 (2010) 267–283, https://doi.org/10.1016/j.molonc.2010.04.010.
[2] S. Bohunicky, B. Mousa, Biosensors: the new wave in cancer diagnosis, Nanotechnol. Sci. Appl. 4 (2010) 1–10, https://doi.org/10.2147/NSA.S13465.
[3] X. Meng, J. Zhong, S. Liu, M. Murray, A.M. Gonzalez-Angulo, A new hypothesis for the cancer mechanism, Cancer Metastasis Rev. 31 (2012) 247–268, https://doi.org/10.1007/s10555-011-9342-8.
[4] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013.
[5] A.M. Sonnenschein, C. Soto, The aging of the 2000 and 2011 Hallarks of cancer reviews: a critique, J. Biosci. 38 (2013) 651–663, https://doi.org/10.1007/s12038-013-9335-6.
[6] H.M. Shaw, M. Hall, Emerging treatment options for recurrent ovarian cancer: the potential role of olaparib, Onco Targets Ther 6 (2013) 1197–1206, https://doi.org/10.2147/OTT.S30748.
[7] W. Zhang, D.C. van Gent, L. Incrocci, W.M. van Weerden, J. Nonnekens, Role of the DNA damage response in prostate cancer formation, progression and treatment, Prostate Cancer Prostatic Dis. 23 (2020) 24–37, https://doi.org/10.1038/s41391-019-0153-2.

[8] A.M. Buckley, N. Lynam-Lennon, H. O'Neill, J. O'Sullivan, Targeting hallmarks of cancer to enhance radiosensitivity in gastrointestinal cancers, Nat. Rev. Gastroenterol. Hepatol. 17 (2020) 298–313, https://doi.org/10.1038/s41575-019-0247-2.

[9] S. Vyas, M. Chesarone-Cataldo, T. Todorova, Y. Huang, P. Chang, A systematic analysis of the PARP protein family identifies new functions critical for cell physiology, Nat. Commun. 4 (2013) 1–13, https://doi.org/10.1038/ncomms3240.

[10] J.-C. Amé, C. Spenlehauer, G. de Murcia, The PARP superfamily, BioEssays 26 (2004) 882–893, https://doi.org/10.1002/bies.20085.

[11] T. Jubin, A. Kadam, M. Jariwala, S. Bhatt, S. Sutariya, A.R. Gani, S. Gautam, R. Begum, The PARP family: insights into functional aspects of poly (ADP-ribose) polymerase-1 in cell growth and survival, Cell Prolif. 49 (2016) 421–437, https://doi.org/10.1111/cpr.12268.

[12] M.O. Hottiger, P.O. Hassa, B. Lüscher, H. Schüler, F. Koch-Nolte, Toward a unified nomenclature for mammalian ADP-ribosyltransferases, Trends Biochem. Sci. 35 (2010) 208–219, https://doi.org/10.1016/j.tibs.2009.12.003.

[13] G. Asher, H. Reinke, M. Altmeyer, M. Gutierrez-Arcelus, M.O. Hottiger, U. Schibler, Poly(ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding, Cell 142 (2010) 943–953, https://doi.org/10.1016/j.cell.2010.08.016.

[14] M. Mashimo, M. Kita, A. Nobeyama, A. Nomura, T. Fujii, PARP1 is activated by membrane damage and is involved in membrane repair through poly(ADP-ribosyl)ation, Genes Cells 27 (2022) 305–312, https://doi.org/10.1111/gtc.12926.

[15] F. Wang, M. Zhao, B. Chang, Y. Zhou, X. Wu, M. Ma, S. Liu, Y. Cao, M. Zheng, Y. Dang, J. Xu, L. Chen, T. Liu, F. Tang, Y. Ren, Z. Xu, Z. Mao, K. Huang, M. Luo, J. Li, H. Liu, B. Ge, Cytoplasmic PARP1 links the genome instability to the inhibition of antiviral immunity through PARylating cGAS, Mol. Cell 82 (2022) 2032–2049.e7, https://doi.org/10.1016/j.molcel.2022.03.034.

[16] H. Fu, R. Liu, Z. Jia, R. Li, F. Zhu, W. Zhu, Y. Shao, Y. Jin, Y. Xue, J. Huang, K. Luo, X. Gao, H. Lu, Q. Zhou, Poly(ADP-ribosylation) of P-TEFb by PARP1 disrupts phase separation to inhibit global transcription after DNA damage, Nat. Cell Biol. 24 (2022) 513–525, https://doi.org/10.1038/s41556-022-00872-5.

[17] S. Vyas, I. Matic, L. Uchima, J. Rood, R. Zaja, R.T. Hay, I. Ahel, P. Chang, Family-wide analysis of poly(ADP-ribose) polymerase activity, Nat. Commun. 5 (2014) 4426, https://doi.org/10.1038/ncomms5426.

[18] G.K. Herrmann, W.K. Russell, N.J. Garg, Y.W. Yin, Poly(ADP-ribose) polymerase 1 regulates mitochondrial DNA repair in an NAD-dependent manner, J. Biol. Chem. 296 (2021) 100309, https://doi.org/10.1016/J.JBC.2021.100309.

[19] T. Maruyama, K. Nara, H. Yoshikawa, N. Suzuki, Txk, a member of the non-receptor tyrosine kinase of the Tec family, forms a complex with poly(ADP-ribose) polymerase 1 and elongation factor 1α and regulates interferon-γ gene transcription in Th1 cells, Clin. Exp. Immunol. 147 (2006) 164–175, https://doi.org/10.1111/j.1365-2249.2006.03249.x.

[20] J. Reinemund, K. Seidel, U.M. Steckelings, D. Zaade, S. Klare, F. Rompe, M. Katerbaum, J. Schacherl, Y. Li, M. Menk, J.H. Schefe, P. Goldin-Lang, C. Szabo, G. Olah, T. Unger, H. Funke-Kaiser, Poly(ADP-ribose) polymerase-1 (PARP-1) transcriptionally regulates angiotensin AT2 receptor (AT2R) and AT2R binding protein (ATBP) genes, Biochem. Pharmacol. 77 (2009) 1795–1805, https://doi.org/10.1016/j.bcp.2009.02.025.

[21] M.Y. Kim, S. Mauro, N. Gévry, J.T. Lis, W.L. Kraus, NAD+-dependent modulation of chromatin structure and transcription by nucleosome binding properties of PARP-1, Cell 119 (2004) 803–814, https://doi.org/10.1016/j.cell.2004.11.002.

[22] B.A. Gibson, Y. Zhang, H. Jiang, K.M. Hussey, J.H. Shrimp, H. Lin, F. Schwede, Y. Yu, W.L. Kraus, Chemical genetic discovery of PARP targets reveals a role for PARP-1 in transcription elongation, Science 353 (2016) 45–50, https://doi.org/10.1126/science.aaf7865.

[23] C. Kim, X.-D. Wang, Y. Yu, PARP1 inhibitors trigger innate immunity via PARP1 trapping-induced DNA damage response, Elife 9 (2020), https://doi.org/10.7554/eLife.60637.

[24] S. Choudhuri, N.J. Garg, PARP1-cGAS-NF-κB pathway of proinflammatory macrophage activation by extracellular vesicles released during *Trypanosoma cruzi* infection and Chagas disease, PLoS Pathog. 16 (2020) e1008474, https://doi.org/10.1371/journal.ppat.1008474.

[25] I. Talhaoui, N.A. Lebedeva, G. Zarkovic, C. Saint-Pierre, M.M. Kutuzov, M. V. Sukhanova, B.T. Matkarimov, D. Gasparutto, M.K. Saparbaev, O.I. Lavrik, A. A. Ishchenko, Poly(ADP-ribose) polymerases covalently modify strand break termini in DNA fragments in vitro, Nucleic Acids Res. (2016) gkw675, https://doi.org/10.1093/nar/gkw675.

[26] G. Zarkovic, E.A. Belousova, I. Talhaoui, C. Saint-Pierre, M.M. Kutuzov, B. T. Matkarimov, D. Biard, D. Gasparutto, O.I. Lavrik, A.A. Ishchenko, Characterization of DNA ADP-ribosyltransferase activities of PARP2 and PARP3: new insights into DNA ADP-ribosylation, Nucleic Acids Res. 46 (2018) 2417–2431, https://doi.org/10.1093/nar/gkx1318.

[27] I.A. Richard, J.T. Burgess, K.J. O'Byrne, E. Bolderson, Beyond PARP1: the potential of other members of the poly (ADP-ribose) polymerase family in DNA repair and cancer therapeutics, Front. Cell Dev. Biol. 9 (2022), https://doi.org/10.3389/fcell.2021.801200.

[28] Q. Chen, M.A. Kassab, F. Dantzer, X. Yu, PARP2 mediates branched poly ADP-ribosylation in response to DNA damage, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-05588-5.

[29] M. Rouleau, D. McDonald, P. Gagné, M.-E. Ouellet, A. Droit, J.M. Hunter, S. Dutertre, C. Prigent, M.J. Hendzel, G.G. Poirier, PARP-3 associates with polycomb group bodies and with components of the DNA damage repair machinery, J. Cell. Biochem. 100 (2007) 385–401, https://doi.org/10.1002/jcb.21051.

[30] E.A. Belousova, A.A. Ishchenko, O.I. Lavrik, Dna is a new target of Parp3, Sci. Rep. 8 (2018) 4176, https://doi.org/10.1038/s41598-018-22673-3.

[31] S. Smith, I. Giriat, A. Schmitt, T. de Lange, Tankyrase, a poly(ADP-ribose) polymerase at human telomeres, Science 282 (1998) 1484–1487, https://doi.org/10.1126/science.282.5393.1484.

[32] B.D. Cook, J.N. Dynek, W. Chang, G. Shostak, S. Smith, Role for the related poly (ADP-ribose) polymerases Tankyrase 1 and 2 at human telomeres, Mol. Cell. Biol. 22 (2002) 332–342, https://doi.org/10.1128/MCB.22.1.332-342.2002.

[33] J.I. Sbodio, H.F. Lodish, N.-W. Chi, Tankyrase-2 oligomerizes with tankyrase-1 and binds to both TRF1 (telomere-repeat-binding factor 1) and IRAP (insulin-responsive aminopeptidase), Biochem. J. 361 (2002) 451, https://doi.org/10.1042/0264-6021:3610451.

[34] S.-M.A. Huang, Y.M. Mishina, S. Liu, A. Cheung, F. Stegmeier, G.A. Michaud, O. Charlat, E. Wiellette, Y. Zhang, S. Wiessner, M. Hild, X. Shi, C.J. Wilson, C. Mickanin, V. Myer, A. Fazal, R. Tomlinson, F. Serluca, W. Shao, H. Cheng, M. Shultz, C. Rau, M. Schirle, J. Schlegl, S. Ghidelli, S. Fawell, C. Lu, D. Curtis, M. W. Kirschner, C. Lengauer, P.M. Finan, J.A. Tallarico, T. Bouwmeester, J. A. Porter, A. Bauer, F. Cong, Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling, Nature 461 (2009) 614–620, https://doi.org/10.1038/nature08356.

[35] Y. Zhang, S. Liu, C. Mickanin, Y. Feng, O. Charlat, G.A. Michaud, M. Schirle, X. Shi, M. Hild, A. Bauer, V.E. Myer, P.M. Finan, J.A. Porter, S.-M.A. Huang, F. Cong, RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling, Nat. Cell Biol. 13 (2011) 623–629, https://doi.org/10.1038/ncb2222.

[36] P.F. Cho-Park, H. Steller, Proteasome regulation by ADP-Ribosylation, Cell 153 (2013) 614–627, https://doi.org/10.1016/j.cell.2013.03.040.

[37] R.C.T. Aguiar, K. Takeyama, C. He, K. Kreinbrink, M.A. Shipp, B-aggressive lymphoma family proteins have unique domains that modulate transcription and exhibit poly(ADP-ribose) polymerase activity, J. Biol. Chem. 280 (2005) 33756–33765, https://doi.org/10.1074/jbc.M505408200.

[38] T. Karlberg, M. Klepsch, A.-G. Thorsell, C.D. Andersson, A. Linusson, H. Schüler, Structural basis for lack of ADP-ribosyltransferase activity in poly(ADP-ribose) polymerase-13/zinc finger antiviral protein, J. Biol. Chem. 290 (2015) 7336–7344, https://doi.org/10.1074/jbc.M114.630160.

[39] W.L. Kraus, PARPs and ADP-Ribosylation: 50 years … and counting, Mol. Cell 58 (2015) 902–910, https://doi.org/10.1016/j.molcel.2015.06.006.

[40] M.-F. Langelier, T. Eisemann, A.A. Riccio, J.M. Pascal, PARP family enzymes: regulation and catalysis of the poly(ADP-ribose) posttranslational modification, Curr. Opin. Struct. Biol. 53 (2018) 187–198, https://doi.org/10.1016/j.sbi.2018.11.002.

[41] M.A. Demény, L. Virág, The PARP enzyme family and the hallmarks of cancer part 1. Cell intrinsic hallmarks, Cancers (Basel) 13 (2021) 2042. Doi: https://doi.org/10.3390/cancers13092042.

[42] C.V. Kuny, C.S. Sullivan, Virus–host interactions and the ARTD/PARP family of enzymes, PLoS Pathog. 12 (2016) e1005453, https://doi.org/10.1371/journal.ppat.1005453.

[43] A. Gomez, C. Bindesbøll, S.V. Satheesh, G. Grimaldi, D. Hutin, L. MacPherson, S. Ahmed, L. Tamblyn, T. Cho, H.I. Nebb, A. Moen, J.H. Anonsen, D.M. Grant, J. Matthews, Characterization of TCDD-inducible poly-ADP-ribose polymerase (TIPARP/ARTD14) catalytic activity, Biochem. J. 475 (2018) 3827–3846, https://doi.org/10.1042/BCJ20180347.

[44] I.A. Hendriks, S.C. Larsen, M.L. Nielsen, An advanced strategy for comprehensive profiling of ADP-ribosylation sites using mass spectrometry-based proteomics*, Mol. Cell. Proteomics 18 (2019) 1010–1026, https://doi.org/10.1074/mcp.TIR119.001315.

[45] S.C. Buch-Larsen, I.A. Hendriks, J.M. Lodge, M. Rykær, B. Furtwängler, E. Shishkova, M.S. Westphall, J.J. Coon, M.L. Nielsen, Mapping physiological ADP-Ribosylation using activated ion electron transfer dissociation, Cell Rep. 32 (2020) 108176, https://doi.org/10.1016/j.celrep.2020.108176.

[46] M.J. Suskiewicz, L. Palazzo, R. Hughes, I. Ahel, Progress and outlook in studying the substrate specificities of PARPs and related enzymes, FEBS J. 288 (2021) 2131–2142, https://doi.org/10.1111/febs.15518.

[47] Y. Tang, Y.-L. Wang, L. Yang, J.-X. Xu, W. Xiong, M. Xiao, M. Li, Inhibition of arginine ADP-ribosyltransferase 1 reduces the expression of poly(ADP-ribose) polymerase-1 in colon carcinoma, Int. J. Mol. Med. 32 (2013) 130–136, https://doi.org/10.3892/ijmm.2013.1370.

[48] D.M. Leslie Pedrioli, M. Leutert, V. Bilan, K. Nowak, K. Gunasekera, E. Ferrari, R. Imhof, L. Malmström, M.O. Hottiger, Comprehensive ADP-ribosylome analysis identifies tyrosine as an ADP-ribose acceptor site, EMBO Rep. 19 (2018), https://doi.org/10.15252/embr.201745310.

[49] F. Yan, C. Huang, X. Wang, J. Tan, S. Cheng, M. Wan, Z. Wang, S. Wang, S. Luo, A. Li, X. Guo, M. Feng, X. Liu, Y. Zhu, Y. Zhou, Threonine ADP-Ribosylation of ubiquitin by a bacterial effector family blocks host ubiquitination, Mol. Cell 78 (2020) 641–652.e9, https://doi.org/10.1016/j.molcel.2020.03.016.

[50] J. O'Sullivan, M. Tedim Ferreira, J.-P. Gagné, A.K. Sharma, M.J. Hendzel, J.-Y. Masson, G.G. Poirier, Emerging roles of eraser enzymes in the dynamic control of protein ADP-ribosylation, Nat. Commun. 10 (2019) 1182, https://doi.org/10.1038/s41467-019-08859-x.

[51] M.O. Hottiger, SnapShot : ADP-Ribosylation signaling SnapShot : ADP-Ribosylation signaling, Mol. Cell 58 (2015) 1134–1134.e1, https://doi.org/10.1016/j.molcel.2015.06.001.

[52] E. Barkauskaite, G. Jankevicius, A.G. Ladurner, I. Ahel, G. Timinszky, The recognition and removal of cellular poly(ADP-ribose) signals, FEBS J. 280 (2013) 3491–3507, https://doi.org/10.1111/febs.12358.
[53] F. Teloni, M. Altmeyer, Readers of poly(ADP-ribose): designed to be fit for purpose, Nucleic Acids Res. 44 (2016) 993–1006, https://doi.org/10.1093/nar/gkv1383.
[54] K. Crawford, J.J. Bonfiglio, A. Mikoč, I. Matic, I. Ahel, Specificity of reversible ADP-ribosylation and regulation of cellular processes, Crit. Rev. Biochem. Mol. Biol. 53 (2018) 64–82, https://doi.org/10.1080/10409238.2017.1394265.
[55] M.L. Meyer-Ficca, R.G. Meyer, D.L. Coyle, E.L. Jacobson, M.K. Jacobson, Human poly(ADP-ribose) glycohydrolase is expressed in alternative splice variants yielding isoforms that localize to different cell compartments, Exp. Cell Res. 297 (2004) 521–532, https://doi.org/10.1016/j.yexcr.2004.03.050.
[56] R.G. Meyer, M.L. Meyer-Ficca, C.J. Whatcott, E.L. Jacobson, M.K. Jacobson, Two small enzyme isoforms mediate mammalian mitochondrial poly(ADP-ribose) glycohydrolase (PARG) activity, Exp. Cell Res. 313 (2007) 2920–2936, https://doi.org/10.1016/j.yexcr.2007.03.043.
[57] G. Jankevicius, M. Hassler, B. Golia, V. Rybin, M. Zacharias, G. Timinszky, A. G. Ladurner, A family of macrodomain proteins reverses cellular mono-ADP-ribosylation, Nat. Struct. Mol. Biol. 20 (2013) 508–514, https://doi.org/10.1038/nsmb.2523.
[58] R. Žaja, G. Aydin, B.E. Lippok, R. Feederle, B. Lüscher, K.L.H. Feijs, Comparative analysis of MACROD1, MACROD2 and TARG1 expression, localisation and interactome, Sci. Rep. 10 (2020) 8286, https://doi.org/10.1038/s41598-020-64623-y.
[59] E. Prokhorova, T. Agnew, A.R. Wondisford, M. Tellier, N. Kaminski, D. Beijer, J. Holder, J. Groslambert, M.J. Suskiewicz, K. Zhu, J.M. Reber, S.C. Krassnig, L. Palazzo, S. Murphy, M.L. Nielsen, A. Mangerich, D. Ahel, J. Baets, R. J. O'Sullivan, I. Ahel, Unrestrained poly-ADP-ribosylation provides insights into chromatin regulation and human disease, Mol. Cell 81 (2021) 2640–2655.e8, https://doi.org/10.1016/j.molcel.2021.04.028.
[60] J.G.M. Rack, L. Palazzo, I. Ahel, (ADP-ribosyl)hydrolases: structure, function, and biology, Genes Dev. 34 (2020) 263–284, https://doi.org/10.1101/gad.334631.119.
[61] M. Mashimo, J. Kato, J. Moss, Structure and function of the ARH family of ADP-ribosyl-acceptor hydrolases, DNA Repair (Amst) 23 (2014) 88–94, https://doi.org/10.1016/j.dnarep.2014.03.005.
[62] A.-L. Perraud, B. Shen, C.A. Dunn, K. Rippe, M.K. Smith, M.J. Bessman, B. L. Stoddard, A.M. Scharenberg, NUDT9, a member of the Nudix hydrolase family, is an evolutionarily conserved mitochondrial ADP-ribose pyrophosphatase, J. Biol. Chem. 278 (2003) 1794–1801, https://doi.org/10.1074/jbc.M205601200.
[63] B.A. Peculis, K. Reynolds, M. Cleland, Metal determines efficiency and substrate specificity of the nuclear NUDIX decapping proteins X29 and H29K (Nudt16), J. Biol. Chem. 282 (2007) 24792–24805, https://doi.org/10.1074/jbc.M704179200.
[64] T. Iyama, N. Abolhassani, D. Tsuchimoto, M. Nonaka, Y. Nakabeppu, NUDT16 is a (deoxy)inosine diphosphatase, and its deficiency induces accumulation of single-strand breaks in nuclear DNA and growth arrest, Nucleic Acids Res. 38 (2010) 4834–4843, https://doi.org/10.1093/nar/gkq249.
[65] G. Lu, J. Zhang, Y. Li, Z. Li, N. Zhang, X. Xu, T. Wang, Z. Guan, G.F. Gao, J. Yan, hNUDT16: a universal decapping enzyme for small nucleolar RNA and cytoplasmic mRNA, protein, Cell 2 (2011) 64–73, https://doi.org/10.1007/s13238-011-1009-2.
[66] S.I. Belli, J.W. Goding, Biochemical characterization of human PC-1, an enzyme possessing alkaline phosphodiesterase I and nucleotide pyrophosphatase activities, Eur. J. Biochem. 226 (1994) 433–443, https://doi.org/10.1111/j.1432-1033.1994.tb20068.x.
[67] Y. Yano, Y. Hayashi, K. Sano, H. Nagano, M. Nakaji, Y. Seo, T. Ninomiya, S. Yoon, H. Yokozaki, M. Kasuga, Expression and localization of ecto-nucleotide pyrophosphatase/phosphodiesterase I-1 (E-NPP1/PC-1) and −3 (E-NPP3/CD203c/PD-Iβ/B10/gp130RB13-6) in inflammatory and neoplastic bile duct diseases, Cancer Lett. 207 (2004) 139–147, https://doi.org/10.1016/j.canlet.2003.11.002.
[68] L. Palazzo, C.M. Daniels, J.E. Nettleship, N. Rahman, R.L. McPherson, S. Ong, K. Kato, O. Nureki, A.K.L. Leung, I. Ahel, ENPP1 processes protein ADP-ribosylation in vitro, FEBS J. 283 (2016) 3371–3388, https://doi.org/10.1111/febs.13811.
[69] P. Chambon, J.D. Weill, P. Mandel, Nicotinamide mononucleotide activation of a new DNA-dependent polyadenylic acid synthesizing nuclear enzyme, Biochem. Biophys. Res. Commun. 11 (1963) 39–43, https://doi.org/10.1016/0006-291X(63)90024-X.
[70] P. Chambon, J.D. Weill, J. Doly, M.T. Strosser, P. Mandel, On the formation of a novel adenylic compound by enzymatic extracts of liver nuclei, Biochem. Biophys. Res. Commun. 25 (1966) 638–643, https://doi.org/10.1016/0006-291X(66)90502-X.
[71] L. van Beek, É. McClay, S. Patel, M. Schimpl, L. Spagnolo, T. Maia de Oliveira, Parp power: a structural perspective on parp1, parp2, and parp3 in dna damage repair and nucleosome remodelling, Int. J. Mol. Sci. 22 (2021) 1–23, https://doi.org/10.3390/ijms22105112.
[72] M.F. Langelier, L. Zandarashvili, P.M. Aguiar, B.E. Black, J.M. Pascal, NAD+ analog reveals PARP-1 substrate-blocking mechanism and allosteric communication from catalytic center to DNA-binding domains, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-03234-8.
[73] J.D. Steffen, M.M. McCauley, J.M. Pascal, Fluorescent sensors of PARP-1 structural dynamics and allosteric regulation in response to DNA damage, Nucleic Acids Res. 44 (2016) 9771–9783, https://doi.org/10.1093/nar/gkw710.
[74] J.M. Dawicki-McKenna, M.F. Langelier, J.E. DeNizio, A.A. Riccio, C.D. Cao, K. R. Karch, M. McCauley, J.D. Steffen, B.E. Black, J.M. Pascal, PARP-1 activation requires local unfolding of an autoinhibitory domain, Mol. Cell 60 (2015) 755–768, https://doi.org/10.1016/j.molcel.2015.10.013.
[75] M.F. Langelier, J.L. Planck, S. Roy, J.M. Pascal, Structural Basis for DNA Damage–Dependent Poly(ADP-ribosyl)ation by Human PARP-1, Science 336 (2012) 728–732, https://doi.org/10.1126/science.1216338.
[76] J.M. Dawicki-Mckenna, M. Langelier, J.E. Denizio, A. Riccio, C.D. Cao, K. R. Karch, M. Mccauley, J.D. Steffen, E. Ben, J.M. Pascal, PARP-1 activation requires local unfolding of an autoinhibitory domain, Mol. Cell 60 (2015) 755–768, https://doi.org/10.1016/j.molcel.2015.10.013.PARP-1.
[77] A.A. Riccio, G. Cingolani, J.M. Pascal, PARP-2 domain requirements for DNA damage-dependent activation and localization to sites of DNA damage, Nucleic Acids Res. 44 (2015) 1691–1702, https://doi.org/10.1093/nar/gkv1376.
[78] M.F. Langelier, A.A. Riccio, J.M. Pascal, PARP-2 and PARP-3 are selectively activated by 5′ phosphorylated DNA breaks through an allosteric regulatory mechanism shared with PARP-1, Nucleic Acids Res. 42 (2014) 7762–7775, https://doi.org/10.1093/nar/gku474.
[79] G.J. Grundy, L.M. Polo, Z. Zeng, S.L. Rulten, N.C. Hoch, P. Paomephan, Y. Xu, S. M. Sweet, A.W. Thorne, A.W. Oliver, S.J. Matthews, L.H. Pearl, K.W. Caldecott, PARP3 is a sensor of nicked nucleosomes and monoribosylates histone H2B (Glu2), Nat. Commun. 7 (2016) 12404, https://doi.org/10.1038/ncomms12404.
[80] E. Obaji, T. Haikarainen, L. Lehti, H. Artd, Structural basis for DNA break recognition by ARDT2/PARP2, Nucleic Acids Res. 46 (2018) 12154–12165, https://doi.org/10.1093/nar/gky927.
[81] E. Pion, G.M. Ullmann, J.C. Amé, D. Gérard, G. De Murcia, E. Bombarda, DNA-induced dimerization of poly(ADP-ribose) polymerase-1 triggers its activation, Biochemistry 44 (2005) 14670–14681, https://doi.org/10.1021/bi050755o.
[82] S. Eustermann, H. Videler, J.C. Yang, P.T. Cole, D. Gruszka, D. Veprintsev, D. Neuhaus, The DNA-binding domain of human PARP-1 interacts with DNA single-strand breaks as a monomer through its second zinc finger, J. Mol. Biol. 407 (2011) 149–170, https://doi.org/10.1016/j.jmb.2011.01.034.
[83] A.D. Edwards, K.D. Raney, J.C. Marecki, A.K. Byrd, G-Quadruplex Loops Regulate PARP-1 Enzymatic Activation 49, 2021, pp. 416–431, https://doi.org/10.1093/nar/gkaa1172.
[84] S.J. Baptista, M.M.C. Silva, E. Moroni, M. Meli, G. Colombo, T.C.P. Dinis, J.A. R. Salvador, Novel PARP-1 inhibitor scaffolds disclosed by a dynamic structure-based pharmacophore approach, PLoS ONE 12 (2017) 1–20, https://doi.org/10.1371/journal.pone.0170846.
[85] M.-C. Caron, A.K. Sharma, J. O'Sullivan, L.R. Myler, M.T. Ferreira, A. Rodrigue, Y. Coulombe, C. Ethier, J.-P. Gagné, M.-F. Langelier, J.M. Pascal, I.J. Finkelstein, M.J. Hendzel, G.G. Poirier, J.-Y. Masson, Poly(ADP-ribose) polymerase-1 antagonizes DNA resection at double-strand breaks, Nat. Commun. 10 (2019) 2954, https://doi.org/10.1038/s41467-019-10741-9.
[86] M.J. Suskiewicz, D. Munnur, Ø. Strømland, J.-C. Yang, L.E. Easton, C. Chatrin, K. Zhu, D. Baretić, S. Goffinont, M. Schuller, W.-F. Wu, J.M. Elkins, D. Ahel, S. Sanyal, D. Neuhaus, I. Ahel, Updated protein domain annotation of the PARP protein family sheds new light on biological function, Nucleic Acids Res. (2023), https://doi.org/10.1093/nar/gkad514.
[87] J.D. Steffen, R.M. Tholey, M. Langelier, J.L. Planck, J. Schiewer, S. Lal, N. A. Bildzukewicz, C.J. Yeo, K.E. Knudsen, J.R. Brody, J.M. Pascal, Targeting PARP-1 allosteric regulation offers therapeutic potential against cancer, Cancer Res. 74 (2015) 31–37, https://doi.org/10.1158/0008-5472.CAN-13-1701.
[88] D.V. Ferraris, Evolution of poly(ADP-ribose) Polymerase-1 (PARP-1) inhibitors. From concept to clinic, J. Med. Chem. 53 (2010) 4561–4584, https://doi.org/10.1021/jm100012m.
[89] R.J. Henning, M. Bourgeois, R.D. Harbison, Poly(ADP-ribose) polymerase (PARP) and PARP inhibitors: mechanisms of action and role in cardiovascular disorders, Cardiovasc. Toxicol. 18 (2018) 493–506, https://doi.org/10.1007/s12012-018-9462-2.
[90] C.M. Daniels, S.-E. Ong, A.K.L. Leung, The promise of proteomics for the study of ADP-Ribosylation, Mol. Cell 58 (2015) 911–924, https://doi.org/10.1016/j.molcel.2015.06.012.
[91] J.J. Bonfiglio, P. Fontana, Q. Zhang, T. Colby, I. Gibbs-Seymour, I. Atanassov, E. Bartlett, R. Zaja, I. Ahel, I. Matic, Serine ADP-Ribosylation depends on HPF1, Mol. Cell 65 (2017) 932–940.e6, https://doi.org/10.1016/j.molcel.2017.01.003.
[92] L. Palazzo, M.J. Suskiewicz, I. Ahel, Serine ADP-ribosylation in DNA-damage response regulation, Curr. Opin. Genet. Dev. 71 (2021) 106–113, https://doi.org/10.1016/j.gde.2021.07.005.
[93] N. Schultz, E. Lopez, N. Saleh-Gohari, T. Helleday, Poly(ADP-ribose) polymerase (PARP-1) has a controlling role in homologous recombination, Nucleic Acids Res. 31 (2003) 4959–4964, https://doi.org/10.1093/nar/gkg703.
[94] B.C. Woodhouse, I.I. Dianova, J.L. Parsons, G.L. Dianov, Poly (ADP-ribose) polymerase-1 modulates DNA repair capacity and prevents formation of DNA double strand breaks, DNA Repair (Amst) 7 (2008) 932–940, https://doi.org/10.1016/j.dnarep.2008.03.017.
[95] B.C. Woodhouse, G.L. Dianov, Poly ADP-ribose polymerase-1 : An international molecule of mystery, DNA Repair (Amst) 7 (2008) 1077–1086, https://doi.org/10.1016/j.dnarep.2008.03.009.
[96] B. Carney, S. Kossatz, T. Reiner, Molecular imaging of PARP, J. Nucl. Med. 58 (2017) 1025–1030, https://doi.org/10.2967/jnumed.117.189936.
[97] H. Thorsell, A. Ekblad, T. Karlberg, T. Low, M. Pinto, A.F. Trésaugues, L. Moche, M. Cohen, M.S. Schuler, Structural basis for potency and promiscuity in poly

(ADP-ribose) polymerase (PARP) and Tankyrase inhibitors, J. Med. Chem. 60 (2017) 1262–1271, https://doi.org/10.1021/acs.jmedchem.6b00990.
[98] T.E.H. Ogden, J.-C. Yang, M. Schimpl, L.E. Easton, E. Underwood, P.B. Rawlins, M.M. McCauley, M.-F. Langelier, J.M. Pascal, K.J. Embrey, D. Neuhaus, Dynamics of the HD regulatory subdomain of PARP-1; substrate access and allostery in PARP activation and inhibition, Nucleic Acids Res. 49 (2021) 2266–2288, https://doi.org/10.1093/nar/gkab020.
[99] K. Ryan, B. Bolaños, M. Smith, P.B. Palde, P.D. Cuenca, T.L. VanArsdale, S. Niessen, L. Zhang, D. Behenna, M.A. Ornelas, K.T. Tran, S. Kaiser, L. Lum, A. Stewart, K.S. Gajiwala, Dissecting the molecular determinants of clinical PARP1 inhibitor selectivity for tankyrase, J. Biol. Chem. 296 (2021) 1–13, https://doi.org/10.1074/JBC.RA120.016573.
[100] L. Zandarashvili, M. Langelier, U.K. Velagapudi, A. Mark, J.D. Steffen, R. Billur, Z. M. Hannan, A.J. Wicks, B. Krastev, S.J. Pettitt, C.J. Lord, T.T. Talele, J.M. Pascal, B.E. Black, Structural basis for allosteric PARP-1 retention on DNA breaks, Science 368 (2020) 1–24, https://doi.org/10.1126/science.aax6367.Structural.
[101] L. Fu, S. Wang, X. Wang, P. Wang, Y. Zheng, D. Yao, M. Guo, L. Zhang, L. Ouyang, Crystal structure-based discovery of a novel synthesized PARP1 inhibitor (OL-1) with apoptosis-inducing mechanisms in triple-negative breast cancer, Sci. Rep. 6 (2016) 1–14, https://doi.org/10.1038/s41598-016-0007-2.
[102] X. Chen, X. Huan, Q. Liu, Y. Wang, Q. He, C. Tan, Y. Chen, J. Ding, Y. Xu, Z. Miao, C. Yang, Design and synthesis of 2-(4,5,6,7-tetrahydrothienopyridin-2-yl)-benzoimidazole carboxamides as novel orally efficacious poly(ADP-ribose) polymerase (PARP) inhibitors, Eur. J. Med. Chem. 145 (2018) 389–403, https://doi.org/10.1016/j.ejmech.2018.01.018.
[103] A. Ruf, G. De Murcia, G.E. Schulz, Inhibitor and NAD+ binding to poly(ADP-ribose) polymerase as derived from crystal structures and homology modeling, Biochemistry 37 (1998) 3893–3900, https://doi.org/10.1021/bi972383s.
[104] T.D. Penning, G.D. Zhu, J. Gong, S. Thomas, V.B. Gandhi, X. Liu, Y. Shi, V. Klinghofer, E.F. Johnson, C.H. Park, E.H. Fry, C.K. Donawho, D.J. Frost, F. G. Buchanan, G.T. Bukofzer, L.E. Rodriguez, V. Bontcheva-Diaz, J.J. Bouska, D. J. Osterling, A.M. Olson, K.C. Marsh, Y. Luo, V.L. Giranda, Optimization of phenyl-substituted benzimidazole carboxamide poly(ADP-ribose) polymerase inhibitors: identification of (S)-2-(2-fluoro-4- (pyrrolidin-2-yl)phenyl)-1 H -benzimidazole-4-carboxamide (A-966492), a highly potent and efficacious inhibitor, J. Med. Chem. 53 (2010) 3142–3153, https://doi.org/10.1021/jm901775y.
[105] K. Hattori, Y. Kido, H. Yamamoto, J. Ishida, K. Kamijo, K. Murano, M. Ohkubo, T. Kinoshita, A. Iwashita, K. Mihara, S. Yamazaki, N. Matsuoka, Y. Teramura, H. Miyake, Rational approaches to discovery of orally active and brain-penetrable quinazolinone inhibitors of poly(ADP-ribose)polymerase, J. Med. Chem. 47 (2004) 4151–4154, https://doi.org/10.1021/jm0499256.
[106] T. Kinoshita, I. Nakanishi, M. Warizaya, A. Iwashita, Y. Kido, K. Hattori, T. Fujii, Inhibitor-induced structural change of the active site of human poly(ADP-ribose) polymerase, FEBS Lett. 556 (2004) 43–46, https://doi.org/10.1016/S0014-5793(03)01362-0.
[107] A. Iwashita, K. Hattori, H. Yamamoto, J. Ishida, Y. Kido, K. Kamijo, K. Murano, H. Miyake, T. Kinoshita, M. Warizaya, M. Ohkubo, N. Matsuoka, S. Mutoh, Discovery of quinazolinone and quinoxaline derivatives as potent and selective poly(ADP-ribose) polymerase-1/2 inhibitors, FEBS Lett. 579 (2005) 1389–1393, https://doi.org/10.1016/j.febslet.2005.01.036.
[108] A.R. Gangloff, J. Brown, R. De Jong, D.R. Dougan, C.E. Grimshaw, M. Hixon, A. Jennings, R. Kamran, A. Kiryanov, S. O'Connell, E. Taylor, P. Vu, Discovery of novel benzo[b][1,4]oxazin-3(4H)-ones as poly(ADP-ribose) polymerase inhibitors, bioorganic med, Chem. Lett. 23 (2013) 4501–4505, https://doi.org/10.1016/j.bmcl.2013.06.055.
[109] N. Ye, C.H. Chen, T. Chen, Z. Song, J.X. He, X.J. Huan, S.S. Song, Q. Liu, Y. Chen, J. Ding, Y. Xu, Z.H. Miao, A. Zhang, Design, synthesis, and biological evaluation of a series of benzo[de][1,7]naphthyridin-7(8 H)-ones bearing a functionalized longer chain appendage as novel PARP1 inhibitors, J. Med. Chem. 56 (2013) 2885–2903, https://doi.org/10.1021/jm301825t.
[110] S. Tomassi, J. Pfahler, N. Mautone, A. Rovere, C. Esposito, D. Passeri, R. Pellicciari, E. Novellino, M. Pannek, C. Steegborn, A. Paiardini, A. Mai, D. Rotili, From PARP1 to TNKS2 inhibition: a structure-based approach, ACS Med. Chem. Lett. 11 (2020) 862–868, https://doi.org/10.1021/acsmedchemlett.9b00654.
[111] G. Papeo, H. Posteri, D. Borghi, A.A. Busel, F. Caprera, E. Casale, M. Ciomei, A. Cirla, E. Corti, M. D'Anello, M. Fasolini, B. Forte, A. Galvani, A. Isacchi, A. Khvat, M.Y. Krasavin, R. Lupi, P. Orsini, R. Perego, E. Pesenti, D. Pezzetta, S. Rainoldi, F. Riccardi-Sirtori, A. Scolaro, F. Sola, F. Zuccotto, E.R. Felder, D. Donati, A. Montagnoli, Discovery of 2-[1-(4,4-Difluorocyclohexyl)piperidin-4-yl]-6-fluoro-3-oxo-2,3-dihydro-1H-isoindole-4-carboxamide (NMS-P118): a potent, orally available, and highly selective PARP-1 inhibitor for cancer therapy, J. Med. Chem. 58 (2015) 6875–6898, https://doi.org/10.1021/acs.jmedchem.5b00680.
[112] G. Papeo, P. Orsini, N.R. Avanzi, D. Borghi, E. Casale, M. Ciomei, A. Cirla, V. Desperati, D. Donati, E.R. Felder, A. Galvani, M. Guanci, A. Isacchi, H. Posteri, S. Rainoldi, F. Riccardi-Sirtori, A. Scolaro, A. Montagnoli, Discovery of stereospecific PARP-1 inhibitor Isoindolinone NMS-P515, ACS Med. Chem. Lett. 10 (2019) 534–538, https://doi.org/10.1021/acsmedchemlett.8b00569.
[113] H. Wang, B. Ren, Y. Liu, B. Jiang, Y. Guo, M. Wei, L. Luo, X. Kuang, M. Qiu, L. Lv, H. Xu, R. Qi, H. Yan, D. Xu, Z. Wang, C.-X. Huo, Y. Zhu, Y. Zhao, Y. Wu, Z. Qin, D. Su, T. Tang, F. Wang, X. Sun, Y. Feng, H. Peng, X. Wang, Y. Gao, Y. Liu, W. Gong, F. Yu, X. Liu, L. Wang, C. Zhou, Discovery of Pamiparib (BGB-290), a potent and selective poly (ADP-ribose) polymerase (PARP) inhibitor in clinical development, J. Med. Chem. 63 (2020) 15541–15563, https://doi.org/10.1021/acs.jmedchem.0c01346.
[114] M. Aoyagi-Scharber, A.S. Gardberg, B.K. Yip, B. Wang, Y. Shen, P.A. Fitzpatrick, Structural basis for the inhibition of poly(ADP-ribose) polymerases 1 and 2 by BMN 673, a potent inhibitor derived from dihydropyridophthalazinone, Acta Crystallogr. Sect. Struct. Biol. Commun. 70 (2014) 1143–1149, https://doi.org/10.1107/S2053230X14015088.
[115] A.E.G. Lindgren, T. Karlberg, A.G. Thorsell, M. Hesse, S. Spjut, T. Ekblad, C. D. Andersson, A.F. Pinto, J. Weigelt, M.O. Hottiger, A. Linusson, M. Elofsson, H. Schüler, PARP inhibitor with selectivity toward ADP-ribosyltransferase ARTD3/PARP3, ACS Chem. Biol. 8 (2013) 1698–1703, https://doi.org/10.1021/cb4002014.
[116] U.K. Velagapudi, M. Langelier, C. Delgado-martin, E. Morgan, S. Bakker, A. Ashworth, B.A. Patel, X. Shao, M. John, T.T. Talele, H. Sciences, U. States, H. Diller, F. Comprehensive, U. States, S. Francisco, U. States, Design and synthesis of poly(ADP-ribose) polymerase inhibitors: impact of adenosine pocket-binding motif appendage to the 3-Oxo-2,3-dihydrobenzofuran-7-carboxamide on potency and selectivity, J. Med. Chem. 62 (2019) 5330–5357, https://doi.org/10.1021/acs.jmedchem.8b01709.Design.
[117] M.F. Langelier, J.L. Planck, S. Roy, J.M. Pascal, Crystal structures of poly(ADP-ribose) polymerase-1 (PARP-1) zinc fingers bound to DNA: structural and functional insights into DNA-dependent PARP-1 activity, J. Biol. Chem. 286 (2011) 10690–10701, https://doi.org/10.1074/jbc.M110.202507.
[118] A.A.E. Ali, G. Timinszky, R. Arribas-bosacoma, M. Kozlowski, P.O. Hassa, M. Hassler, A.G. Ladurner, L.H. Pearl, A.W. Oliver, The zinc-finger domains of PARP1 cooperate to recognise DNA strand-breaks, Nat. Struct. Mol. Biol. 19 (2012) 685–692, https://doi.org/10.1038/nsmb.2335.The.
[119] M.R. Patel, A. Bhatt, J.D. Steffen, A. Chergui, J. Murai, Y. Pommier, J.M. Pascal, L. D. Trombetta, F.R. Fronczek, T.T. Talele, Discovery and structure–activity relationship of novel 2,3-dihydrobenzofuran-7-carboxamide and 2,3-dihydrobenzofuran-3(2*H*)-one-7-carboxamide derivatives as Poly(ADP-ribose) polymerase-1 Inhibitors, J. Med. Chem. 57 (2014) 5579–5601, https://doi.org/10.1021/jm5002502.
[120] S. Xie, O. Mortusewicz, H.T. Ma, P. Herr, R.R.Y. Poon, T. Helleday, C. Qian, Timeless interacts with PARP-1 to promote homologous recombination repair, Mol. Cell 60 (2015) 163–176, https://doi.org/10.1016/j.molcel.2015.07.031.
[121] F.H. Sun, P. Zhao, N. Zhang, L.L. Kong, C.C.L. Wong, C.H. Yun, HPF1 remodels the active site of PARP1 to enable the serine ADP-ribosylation of histones, Nat. Commun. 12 (2021) 1–10, https://doi.org/10.1038/s41467-021-21302-4.
[122] M.F. Langelier, K.M. Servent, E.E. Rogers, J.M. Pascal, A third zinc-binding domain of human poly(ADP-ribose) polymerase-1 coordinates DNA-dependent enzyme activation, J. Biol. Chem. 283 (2008) 4105–4114, https://doi.org/10.1074/jbc.M708558200.
[123] P.A. Loeffler, M.J. Cuneo, G.A. Mueller, E.F. Derose, S.A. Gabel, R.E. London, Structural studies of the PARP-1 BRCT domain, BMC Struct. Biol. 11 (2011) 37, https://doi.org/10.1186/1472-6807-11-37.
[124] T. Karlberg, M. Hammarstrom, P. Schutz, L. Svensson, H. Schuler, Crystal structure of the catalytic domain of human PARP2 in complex with PARP inhibitor ABT-888, Biochemistry 49 (2010) 1056–1058, https://doi.org/10.1021/bi902079y.
[125] L. Lehtiö, A.-S. Jemth, R. Collins, O. Loseva, A. Johansson, N. Markova, M. Hammarström, A. Flores, L. Holmberg-Schiavone, J. Weigelt, T. Helleday, H. Schüler, T. Karlberg, Structural basis for inhibitor specificity in human poly (ADP-ribose) polymerase-3, J. Med. Chem. 52 (2009) 3108–3111, https://doi.org/10.1021/jm900052j.
[126] S. Eustermann, W.-F. Wu, M.-F. Langelier, J.-C. Yang, L.E. Easton, A.A. Riccio, J. M. Pascal, D. Neuhaus, Structural basis of detection and signaling of DNA single-Strand breaks by human PARP-1, Mol. Cell 60 (2015) 742–754, https://doi.org/10.1016/j.molcel.2015.10.032.
[127] K. Kouyama, K. Mayanagi, S. Nakae, Y. Nishi, M. Miwa, T. Shirai, Single-particle analysis of full-length human poly(ADP-ribose) polymerase 1, Biophys. Physicobiol. 16 (2019) 59–67, https://doi.org/10.2142/biophysico.16.0_59.
[128] S. Bilokapic, M.J. Suskiewicz, I. Ahel, M. Halic, Bridging of DNA breaks activates PARP2–HPF1 to modify chromatin, Nature 585 (2020) 609–613, https://doi.org/10.1038/s41586-020-2725-7.
[129] J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, O. Ronneberger, K. Tunyasuvunakool, R. Bates, A. Žídek, A. Potapenko, A. Bridgland, C. Meyer, S. A.A. Kohl, A.J. Ballard, A. Cowie, B. Romera-Paredes, S. Nikolov, R. Jain, J. Adler, T. Back, S. Petersen, D. Reiman, E. Clancy, M. Zielinski, M. Steinegger, M. Pacholska, T. Berghammer, S. Bodenstein, D. Silver, O. Vinyals, A.W. Senior, K. Kavukcuoglu, P. Kohli, D. Hassabis, Highly accurate protein structure prediction with AlphaFold, Nature 596 (2021) 583–589, https://doi.org/10.1038/s41586-021-03819-2.
[130] M. Baek, F. DiMaio, I. Anishchenko, J. Dauparas, S. Ovchinnikov, G.R. Lee, J. Wang, Q. Cong, L.N. Kinch, R.D. Schaeffer, C. Millán, H. Park, C. Adams, C. R. Glassman, A. DeGiovanni, J.H. Pereira, A.V. Rodrigues, A.A. van Dijk, A. C. Ebrecht, D.J. Opperman, T. Sagmeister, C. Buhlheller, T. Pavkov-Keller, M. K. Rathinaswamy, U. Dalwadi, C.K. Yip, J.E. Burke, K.C. Garcia, N.V. Grishin, P. D. Adams, R.J. Read, D. Baker, Accurate prediction of protein structures and interactions using a three-track neural network, Science 373 (2021) 871–876, https://doi.org/10.1126/science.abj8754.
[131] N. Bouatta, P. Sorger, M. AlQuraishi, Protein structure prediction by AlphaFold 2: are attention and symmetries all you need? Acta Crystallogr. Sect. D Struct. Biol. 77 (2021) 982–991, https://doi.org/10.1107/S2059798321007531.
[132] M. Varadi, S. Anyango, M. Deshpande, S. Nair, C. Natassia, G. Yordanova, D. Yuan, O. Stroe, G. Wood, A. Laydon, A. Žídek, T. Green, K. Tunyasuvunakool,

S. Petersen, J. Jumper, E. Clancy, R. Green, A. Vora, M. Lutfi, M. Figurnov, A. Cowie, N. Hobbs, P. Kohli, G. Kleywegt, E. Birney, D. Hassabis, S. Velankar, AlphaFold protein structure database: massively expanding the structural coverage of protein-sequence space with high-accuracy models, Nucleic Acids Res. 50 (2022) D439–D444, https://doi.org/10.1093/nar/gkab1061.
[133] L.L. Schrodinger, The Pymol Molecular Graphics System, Version 2.0, 2017.
[134] H.L. Ko, E.C. Ren, Functional aspects of PARP1 in DNA repair and transcription, Biomolecules 2 (2012) 524–548, https://doi.org/10.3390/biom2040524.
[135] A. Swindall, J. Stanley, E. Yang, PARP-1: friend or foe of DNA damage and repair in tumorigenesis? Cancers (Basel) 5 (2013) 943–958, https://doi.org/10.3390/cancers5030943.
[136] D.W. Koh, A.M. Lawler, M.F. Poitras, M. Sasaki, S. Wattler, M.C. Nehls, T. Stöger, G.G. Poirier, V.L. Dawson, T.M. Dawson, Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality, Proc. Natl. Acad. Sci. 101 (2004) 17699–17704, https://doi.org/10.1073/pnas.0406182101.
[137] N.V. Malyuchenko, E.Y. Kotova, O.I. Kulaeva, M.P. Kirpichnikov, V.M. Studitskiy, PARP1 inhibitors: antitumor drug design, Acta Nat. 7 (2015) 27–37. http://www.ncbi.nlm.nih.gov/pubmed/26483957.
[138] J. Mateo, C.J. Lord, V. Serra, A. Tutt, J. Balmaña, M. Castroviejo-Bermejo, C. Cruz, A. Oaknin, S.B. Kaye, J.S. de Bono, A decade of clinical development of PARP inhibitors in perspective, Ann. Oncol. 30 (2019) 1437–1447, https://doi.org/10.1093/annonc/mdz192.
[139] P. Santofimia-Castaño, C. Huang, X. Liu, Y. Xia, S. Audebert, L. Camoin, L. Peng, G. Lomberk, R. Urrutia, P. Soubeyran, J.L. Neira, J. Iovanna, NUPR1 protects against hyperPARylation-dependent cell death, Commun. Biol. 5 (2022) 732, https://doi.org/10.1038/s42003-022-03705-1.
[140] H.-L. Ko, E.-C. Ren, Novel poly (ADP-ribose) polymerase 1 binding motif in hepatitis B virus core promoter impairs DNA damage repair, Hepatology 54 (2011) 1190–1198, https://doi.org/10.1002/hep.24502.
[141] D.-S. Kim, C.V. Camacho, A. Nagari, V.S. Malladi, S. Challa, W.L. Kraus, Activation of PARP-1 by snoRNAs controls ribosome biogenesis and cell growth via the RNA helicase DDX21, Mol. Cell 75 (2019) 1270–1285.e14, https://doi.org/10.1016/j.molcel.2019.06.020.
[142] C. Han, L.-Y. Sun, X.-Q. Luo, Q. Pan, Y.-M. Sun, Z.-C. Zeng, T.-Q. Chen, W. Huang, K. Fang, W.-T. Wang, Y.-Q. Chen, Chromatin-associated orphan snoRNA regulates DNA damage-mediated differentiation via a non-canonical complex, Cell Rep. 38 (2022) 110421, https://doi.org/10.1016/j.celrep.2022.110421.
[143] F. Berger, C. Lau, M. Ziegler, Regulation of poly(ADP-ribose) polymerase 1 activity by the phosphorylation state of the nuclear NAD biosynthetic enzyme NMN adenylyl transferase 1, Proc. Natl. Acad. Sci. 104 (2007) 3765–3770, https://doi.org/10.1073/pnas.0609211104.
[144] R. Midorikawa, Y. Takei, N. Hirokawa, KIF4 motor regulates activity-dependent neuronal survival by suppressing PARP-1 enzymatic activity, Cell 125 (2006) 371–383, https://doi.org/10.1016/j.cell.2006.02.039.
[145] K. Ouararhni, R. Hadj-Slimane, S. Ait-Si-Ali, P. Robin, F. Mietton, A. Harel-Bellan, S. Dimitrov, A. Hamiche, The histone variant mH2A1.1 interferes with transcription by down-regulating PARP-1 enzymatic activity, Genes Dev. 20 (2006) 3324–3336, https://doi.org/10.1101/gad.396106.
[146] A.B. Tufan, K. Lazarow, M. Kolesnichenko, A. Sporbert, J.P. von Kries, C. Scheidereit, TSG101 associates with PARP1 and is essential for PARylation and DNA damageinduced NF-κB activation, EMBO J. 41 (2022), https://doi.org/10.15252/embj.2021110372.
[147] C. Zhang, B. Zhou, F. Gu, H. Liu, H. Wu, F. Yao, H. Zheng, H. Fu, W. Chong, S. Cai, M. Huang, X. Ma, Z. Guo, T. Li, W. Deng, M. Zheng, Q. Ji, Y. Zhao, Y. Ma, Q.-E. Wang, T.-S. Tang, C. Guo, Micropeptide PACMP inhibition elicits synthetic lethal effects by decreasing CtIP and poly(ADP-ribosyl)ation, Mol. Cell 82 (2022) 1297–1312.e8, https://doi.org/10.1016/j.molcel.2022.01.020.
[148] H. Ma, G. Qi, F. Han, W. Lu, J. Peng, R. Li, S. Yan, C. Yuan, B. Kong, HMGB3 promotes PARP inhibitor resistance through interacting with PARP1 in ovarian cancer, Cell Death Dis. 13 (2022) 263, https://doi.org/10.1038/s41419-022-04670-7.
[149] F. Yang, J. Chen, B. Liu, G. Gao, M. Sebastian, C. Jeter, J. Shen, M.D. Person, M. T. Bedford, SPINDOC binds PARP1 to facilitate PARylation, Nat. Commun. 12 (2021) 6362, https://doi.org/10.1038/s41467-021-26588-y.
[150] R.J. Lake, R. Bilkis, H.-Y. Fan, Dynamic interplay between cockayne syndrome protein B and poly(ADP-ribose) polymerase 1 during oxidative DNA damage repair, Biomedicines 10 (2022) 361, https://doi.org/10.3390/biomedicines10020361.
[151] F. Wang, S. Zhu, L.A. Fisher, L. Wang, N.J. Eurek, J.K. Wahl, L. Lan, A. Peng, Phosphatase 1 nuclear targeting subunit mediates recruitment and function of poly (ADP-ribose) polymerase 1 in DNA repair, Cancer Res. 79 (2019) 2526–2535, https://doi.org/10.1158/0008-5472.CAN-18-1673.
[152] S. Lee, N. Kim, S. Kim, I.B. Park, H. Kim, S. Kim, B. Kim, J.M. Hwang, I. Baek, A. Gartner, J.H. Park, K. Myung, Ewing sarcoma protein promotes dissociation of poly(ADP-ribose) polymerase 1 from chromatin, EMBO Rep. 21 (2020), https://doi.org/10.15252/embr.201948676.
[153] E. Bolderson, J.T. Burgess, J. Li, N.S. Gandhi, D. Boucher, L.V. Croft, S. Beard, J. J. Plowman, A. Suraweera, M.N. Adams, A. Naqi, S.-D. Zhang, D.A. Sinclair, K. J. O'Byrne, D.J. Richard, Barrier-to-autointegration factor 1 (Banf1) regulates poly [ADP-ribose] polymerase 1 (PARP1) activity following oxidative DNA damage, Nat. Commun. 10 (2019) 5501, https://doi.org/10.1038/s41467-019-13167-5.
[154] M.J. Suskiewicz, F. Zobel, T.E.H. Ogden, P. Fontana, A. Ariza, J.-C. Yang, K. Zhu, L. Bracken, W.J. Hawthorne, D. Ahel, D. Neuhaus, I. Ahel, HPF1 completes the PARP active site for DNA damage-induced ADP-ribosylation, Nature 579 (2020) 598–602, https://doi.org/10.1038/s41586-020-2013-6.
[155] M.F. Langelier, R. Billur, A. Sverzhinsky, B.E. Black, J.M. Pascal, HPF1 dynamically controls the PARP1/2 balance between initiating and elongating ADP-ribose modifications, Nat. Commun. 12 (2021), https://doi.org/10.1038/s41467-021-27043-8.
[156] I. Gibbs-Seymour, P. Fontana, J.G.M. Rack, I. Ahel, HPF1/C4orf27 is a PARP-1-interacting protein that regulates PARP-1 ADP-Ribosylation activity, Mol. Cell 62 (2016) 432–442, https://doi.org/10.1016/j.molcel.2016.03.008.
[157] L. Piao, K. Fujioka, M. Nakakido, R. Hamamoto, Regulation of poly ADP-ribose polymerase 1 functions by post-translational modifications, Front. Biosci. 23 (2018) 4578, https://doi.org/10.2741/4578.
[158] M. Altmeyer, S. Messner, P.O. Hassa, M. Fey, M.O. Hottiger, Molecular mechanism of poly(ADP-ribosyl)ation by PARP1 and identification of lysine residues as ADP-ribose acceptor sites, Nucleic Acids Res. 37 (2009) 3723–3738, https://doi.org/10.1093/nar/gkp229.
[159] Z. Mao, C. Hine, X. Tian, M. Van Meter, M. Au, A. Vaidya, A. Seluanov, V. Gorbunova, SIRT6 promotes DNA repair under stress by activating PARP1, Science 332 (2011) 1443–1446, https://doi.org/10.1126/science.1202723.
[160] T.M. Kauppinen, W.Y. Chan, S.W. Suh, A.K. Wiggins, E.J. Huang, R.A. Swanson, Direct phosphorylation and regulation of poly(ADP-ribose) polymerase-1 by extracellular signal-regulated kinases 1/2, Proc. Natl. Acad. Sci. 103 (2006) 7136–7141, https://doi.org/10.1073/pnas.0508606103.
[161] R.H.G. Wright, G. Castellano, J. Bonet, F. Le Dily, J. Font-Mateu, C. Ballaré, A. S. Nacht, D. Soronellas, B. Oliva, M. Beato, CDK2-dependent activation of PARP-1 is required for hormonal gene regulation in breast cancer cells, Genes Dev. 26 (2012) 1972–1983, https://doi.org/10.1101/gad.193193.112.
[162] B.-G. Ju, D. Solum, E.J. Song, K.-J. Lee, D.W. Rose, C.K. Glass, M.G. Rosenfeld, Activating the PARP-1 sensor component of the Groucho/ TLE1 corepressor complex mediates a CaMKinase IIδ-dependent neurogenic gene activation pathway, Cell 119 (2004) 815–829, https://doi.org/10.1016/j.cell.2004.11.017.
[163] I. Kassner, A. Andersson, M. Fey, M. Tomas, E. Ferrando-May, M.O. Hottiger, SET7/9-dependent methylation of ARTD1 at K508 stimulates poly-ADP-ribose formation after oxidative stress, Open Biol. 3 (2013) 120173, https://doi.org/10.1098/rsob.120173.
[164] L. Piao, D. Kang, T. Suzuki, A. Masuda, N. Dohmae, Y. Nakamura, R. Hamamoto, The histone methyltransferase SMYD2 methylates PARP1 and promotes poly (ADP-ribosyl)ation activity in cancer cells, Neoplasia 16 (2014) 257–264.e2, https://doi.org/10.1016/j.neo.2014.03.002.
[165] P.O. Hassa, S.S. Haenni, C. Buerki, N.I. Meier, W.S. Lane, H. Owen, M. Gersbach, R. Imhof, M.O. Hottiger, Acetylation of poly(ADP-ribose) Polymerase-1 by p300/CREB-binding protein regulates coactivation of NF-κB-dependent transcription, J. Biol. Chem. 280 (2005) 40450–40464, https://doi.org/10.1074/jbc.M507553200.
[166] S.B. Rajamohan, V.B. Pillai, M. Gupta, N.R. Sundaresan, K.G. Birukov, S. Samant, M.O. Hottiger, M.P. Gupta, SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1, Mol. Cell. Biol. 29 (2009) 4116–4129, https://doi.org/10.1128/MCB.00121-09.
[167] S. Messner, D. Schuermann, M. Altmeyer, I. Kassner, D. Schmidt, P. Schär, S. Müller, M.O. Rottiger, Sumoylation of poly(ADP-ribose) polymerase 1 inhibits its acetylation and restrains transcriptional coactivator function, FASEB J. 23 (2009) 3978–3989, https://doi.org/10.1096/fj.09-137695.
[168] N. Martin, K. Schwamborn, V. Schreiber, A. Werner, C. Guillier, X.-D. Zhang, O. Bischof, J.-S. Seeler, A. Dejean, PARP-1 transcriptional activity is regulated by sumoylation upon heat shock, EMBO J. 28 (2009) 3534–3548, https://doi.org/10.1038/emboj.2009.279.
[169] N. Zhang, Y. Zhang, B. Wu, S. You, Y. Sun, Role of WW domain E3 ubiquitin protein ligase 2 in modulating ubiquitination and degradation of Septin4 in oxidative stress endothelial injury, Redox Biol. 30 (2020) 101419, https://doi.org/10.1016/j.redox.2019.101419.
[170] N. Zhang, Y. Zhang, H. Qian, S. Wu, L. Cao, Y. Sun, Selective targeting of ubiquitination and degradation of PARP1 by E3 ubiquitin ligase WWP2 regulates isoproterenol-induced cardiac remodeling, Cell Death Differ. 27 (2020) 2605–2619, https://doi.org/10.1038/s41418-020-0523-2.
[171] J. Groslambert, E. Prokhorova, I. Ahel, ADP-ribosylation of DNA and RNA, DNA Repair (Amst) 105 (2021) 103144, https://doi.org/10.1016/j.dnarep.2021.103144.
[172] A. Ray Chaudhuri, A. Nussenzweig, The multifaceted roles of PARP1 in DNA repair and chromatin remodelling, Nat. Rev. Mol. Cell Biol. 18 (2017) 610–621, https://doi.org/10.1038/nrm.2017.53.
[173] J.M. Pascal, The comings and goings of PARP-1 in response to DNA damage, DNA Repair (Amst) 71 (2018) 177–182, https://doi.org/10.1016/j.dnarep.2018.08.022.
[174] J.R. Chapman, M.R.G. Taylor, S.J. Boulton, Playing the end game : DNA double-Strand break repair pathway choice, Mol. Cell 47 (2012) 497–510, https://doi.org/10.1016/j.molcel.2012.07.029.
[175] B.D. Price, A.D.D. Andrea, Chromatin remodeling at DNA double-Strand breaks, Cell 152 (2013) 1344–1354, https://doi.org/10.1016/j.cell.2013.02.011.
[176] M.J. Smerdon, DNA repair and the role of chromatin structure, Curr. Opin. Cell Biol. 3 (1991) 422–428, https://doi.org/10.1016/0955-0674(91)90069.
[177] B.B. Das, S.N. Huang, J. Murai, I. Rehman, J.-C. Amé, S. Sengupta, S.K. Das, P. Majumdar, H. Zhang, D. Biard, H.K. Majumder, V. Schreiber, Y. Pommier, PARP1–TDP1 coupling for the repair of topoisomerase I–induced DNA damage, Nucleic Acids Res. 42 (2014) 4435–4449, https://doi.org/10.1093/nar/gku088.
[178] K.W. Caldecott, Single-strand break repair and genetic disease, Nat. Rev. Genet. 9 (2008) 619–631, https://doi.org/10.1038/nrg2380.

[179] P. Reynolds, S. Cooper, M. Lomax, P. O'Neill, Disruption of PARP1 function inhibits base excision repair of a sub-set of DNA lesions, Nucleic Acids Res. 43 (2015) 4028–4038, https://doi.org/10.1093/nar/gkv250.
[180] K. Martin-Hernandez, J.-M. Rodriguez-Vargas, V. Schreiber, F. Dantzer, Expanding functions of ADP-ribosylation in the maintenance of genome integrity, Semin. Cell Dev. Biol. 63 (2017) 92–101, https://doi.org/10.1016/j.semcdb.2016.09.009.
[181] A. Pines, M.G. Vrouwe, J.A. Marteijn, D. Typas, M.S. Luijsterburg, M. Cansoy, P. Hensbergen, A. Deelder, A. de Groot, S. Matsumoto, K. Sugasawa, N. Thoma, W. Vermeulen, H. Vrieling, L. Mullenders, PARP1 promotes nucleotide excision repair through DDB2 stabilization and recruitment of ALC1, J. Cell Biol. 199 (2012) 235–249, https://doi.org/10.1083/jcb.201112132.
[182] S.-K. Ooi, S. Sato, C. Tomomori-Sato, Y. Zhang, Z. Wen, C.A.S. Banks, M. P. Washburn, J.R. Unruh, L. Florens, R.C. Conaway, J.W. Conaway, Multiple roles for PARP1 in ALC1-dependent nucleosome remodeling, Proc. Natl. Acad. Sci. 118 (2021), https://doi.org/10.1073/pnas.2107277118.
[183] M. Robu, R.G. Shah, N. Petitclerc, J. Brind'Amour, F. Kandan-Kulangara, G. M. Shah, Role of poly(ADP-ribose) polymerase-1 in the removal of UV-induced DNA lesions by nucleotide excision repair, Proc. Natl. Acad. Sci. 110 (2013) 1658–1663, https://doi.org/10.1073/pnas.1209507110.
[184] O.D. Scharer, Nucleotide excision repair in eukaryotes, Cold Spring Harb. Perspect. Biol. 5 (2013) a012609, https://doi.org/10.1101/cshperspect.a012609.
[185] Y. Liu, F.A. Kadyrov, P. Modrich, PARP-1 enhances the mismatch-dependence of 5′-directed excision in human mismatch repair in vitro, DNA Repair (Amst) 10 (2011) 1145–1153, https://doi.org/10.1016/j.dnarep.2011.08.012.
[186] J.-P. Gagné, M. Isabelle, K.S. Lo, S. Bourassa, M.J. Hendzel, V.L. Dawson, T. M. Dawson, G.G. Poirier, Proteome-wide identification of poly(ADP-ribose) binding proteins and poly(ADP-ribose)-associated protein complexes, Nucleic Acids Res. 36 (2008) 6959–6976, https://doi.org/10.1093/nar/gkn771.
[187] Y. Sun, T.J. McCorvie, L.A. Yates, X. Zhang, Structural basis of homologous recombination, Cell. Mol. Life Sci. 77 (2020) 3–18, https://doi.org/10.1007/s00018-019-03365-1.
[188] M. Li, X. Yu, Function of BRCA1 in the DNA damage response is mediated by ADP-Ribosylation, Cancer Cell 23 (2013) 693–704, https://doi.org/10.1016/j.ccr.2013.03.025.
[189] F. Zhang, J. Shi, C. Bian, X. Yu, Poly(ADP-ribose) mediates the BRCA2-dependent early DNA damage response, Cell Rep. 13 (2015) 678–689, https://doi.org/10.1016/j.celrep.2015.09.040.
[190] S. Ying, Z. Chen, A.L. Medhurst, J.A. Neal, Z. Bao, O. Mortusewicz, J. McGouran, X. Song, H. Shen, F.C. Hamdy, B.M. Kessler, K. Meek, T. Helleday, DNA-PKcs and PARP1 bind to unresected stalled DNA replication forks where they recruit XRCC1 to mediate repair, Cancer Res. 76 (2016) 1078–1088, https://doi.org/10.1158/0008-5472.CAN-15-0608.
[191] R. Aguilar-Quesada, J.A. Muñoz-Gámez, D. Martín-Oliva, A. Peralta, M. T. Valenzuela, R. Matínez-Romero, R. Quiles-Pérez, J.M. Murcia, G. de Murcia, M. R. de Almodóvar, F.J. Oliver, Interaction between ATM and PARP-1 in response to DNA damage and sensitization of ATM deficient cells through PARP inhibition, BMC Mol. Biol. 8 (2007) 29, https://doi.org/10.1186/1471-2199-8-29.
[192] J.-F. Haince, S. Kozlov, V.L. Dawson, T.M. Dawson, M.J. Hendzel, M.F. Lavin, G. G. Poirier, Ataxia telangiectasia mutated (ATM) signaling network is modulated by a novel poly(ADP-ribose)-dependent pathway in the early response to DNA-damaging agents, J. Biol. Chem. 282 (2007) 16441–16453, https://doi.org/10.1074/jbc.M608406200.
[193] S. Gajewski, A. Hartwig, PARP1 is required for ATM-mediated p53 activation and p53-mediated gene expression after ionizing radiation, Chem. Res. Toxicol. 33 (2020) 1933–1940, https://doi.org/10.1021/acs.chemrestox.0c00130.
[194] M.S. Luijsterburg, I. de Krijger, W.W. Wiegant, R.G. Shah, G. Smeenk, A.J.L. de Groot, A. Pines, A.C.O. Vertegaal, J.J.L. Jacobs, G.M. Shah, H. van Attikum, PARP1 links CHD2-mediated chromatin expansion and H3.3 deposition to DNA repair by non-homologous end-joining, Mol. Cell 61 (2016) 547–562, https://doi.org/10.1016/j.molcel.2016.01.019.
[195] S. Sharma, S.M. Javadekar, M. Pandey, M. Srivastava, R. Kumari, S.C. Raghavan, Homology and enzymatic requirements of microhomology-dependent alternative end joining, Cell Death Dis. 6 (2015) e1697, https://doi.org/10.1038/cddis.2015.58.
[196] R. Ceccaldi, J.C. Liu, R. Amunugama, I. Hajdu, B. Primack, M.I.R. Petalcorin, K. W. O'Connor, P.A. Konstantinopoulos, S.J. Elledge, S.J. Boulton, T. Yusufzai, A. D. D'Andrea, Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair, Nature 518 (2015) 258–262, https://doi.org/10.1038/nature14184.
[197] P.A. Mateos-Gomez, F. Gong, N. Nair, K.M. Miller, E. Lazzerini-Denchi, A. Sfeir, Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination, Nature 518 (2015) 254–257, https://doi.org/10.1038/nature14157.
[198] M.E. Luedeman, S. Stroik, W. Feng, A.J. Luthman, G.P. Gupta, D.A. Ramsden, Poly (ADP) ribose polymerase promotes DNA polymerase theta-mediated end joining by activation of end resection, Nat. Commun. 13 (2022) 4547, https://doi.org/10.1038/s41467-022-32166-7.
[199] G.V. Chaitanya, J.S. Alexander, P.P. Babu, PARP-1 cleavage fragments: signatures of cell-death proteases in neurodegeneration, Cell Commun. Signal. 8 (2010) 31, https://doi.org/10.1186/1478-811X-8-31.
[200] Y. Zhou, L. Liu, S. Tao, Y. Yao, Y. Wang, Q. Wei, A. Shao, Y. Deng, Parthanatos and its associated components: promising therapeutic targets for cancer, Pharmacol. Res. 163 (2021) 105299, https://doi.org/10.1016/j.phrs.2020.105299.
[201] P. Huang, G. Chen, W. Jin, K. Mao, H. Wan, Y. He, Molecular mechanisms of Parthanatos and its role in diverse diseases, Int. J. Mol. Sci. 23 (2022) 7292, https://doi.org/10.3390/ijms23137292.
[202] L. Wang, C. Liang, F. Li, D. Guan, X. Wu, X. Fu, A. Lu, G. Zhang, PARP1 in carcinomas and PARP1 inhibitors as antineoplastic drugs, Int. J. Mol. Sci. 18 (2017) 2111, https://doi.org/10.3390/ijms18102111.
[203] V. Ossovskaya, I.C. Koo, E.P. Kaldjian, C. Alvares, B.M. Sherman, Upregulation of poly (ADP-ribose) polymerase-1 (PARP1) in triple-negative breast cancer and other primary human tumor types, genes, Cancer 1 (2010) 812–821, https://doi.org/10.1177/1947601910383418.
[204] A. Mazzotta, G. Partipilo, S. De Summa, F. Giotta, G. Simone, A. Mangia, Nuclear PARP1 expression and its prognostic significance in breast cancer patients, Tumour Biol. 37 (2016) 6143–6153, https://doi.org/10.1007/s13277-015-4465-0.
[205] L.A. Byers, J. Wang, M.B. Nilsson, J. Fujimoto, P. Saintigny, J. Yordy, U. Giri, M. Peyton, Y.H. Fan, L. Diao, F. Masrorpour, L. Shen, W. Liu, B. Duchemann, P. Tumula, V. Bhardwaj, J. Welsh, S. Weber, B.S. Glisson, N. Kalhor, I.I. Wistuba, L. Girard, S.M. Lippman, G.B. Mills, K.R. Coombes, J.N. Weinstein, J.D. Minna, J. V. Heymach, Proteomic profiling identifies dysregulated pathways in small cell lung Cancer and novel therapeutic targets including PARP1, Cancer Discov. 2 (2012) 798–811, https://doi.org/10.1158/2159-8290.CD-12-0112.
[206] J.C. Brenner, F.Y. Feng, S. Han, S. Patel, S.V. Goyal, L.M. Bou-Maroun, M. Liu, R. Lonigro, J.R. Prensner, S.A. Tomlins, A.M. Chinnaiyan, PARP-1 inhibition as a targeted strategy to treat Ewing's sarcoma, Cancer Res. 72 (2012) 1608–1613, https://doi.org/10.1158/0008-5472.CAN-11-3648.
[207] W.-W. Zuo, C.-F. Zhao, Y. Li, H.-Y. Sun, G.-M. Ma, Y.-P. Liu, S. Kang, High expression of PARP1 in tumor and stroma cells predicts different prognosis and platinum resistance in patients with advanced epithelial ovarian cancer, Front. Oncol. 12 (2022), https://doi.org/10.3389/fonc.2022.931445.
[208] J.D. Puentes-Pardo, S. Moreno-SanJuan, J. Casado, J. Escudero-Feliu, D. López-Pérez, P. Sánchez-Uceta, P. González-Novoa, J. Gálvez, Á. Carazo, J. León, PARP-1 expression influences cancer stem cell phenotype in colorectal cancer depending on p53, Int. J. Mol. Sci. 24 (2023) 4787, https://doi.org/10.3390/ijms24054787.
[209] M.A. Demény, L. Virág, The PARP enzyme family and the hallmarks of cancer part 2: hallmarks related to cancer host interactions, Cancers (Basel) 13 (2021) 2057, https://doi.org/10.3390/cancers13092057.
[210] M. Yi, B. Dong, S. Qin, Q. Chu, K. Wu, S. Luo, Advances and perspectives of PARP inhibitors, Exp. Hematol. Oncol. 8 (2019) 29, https://doi.org/10.1186/s40164-019-0154-9.
[211] E. Kotova, A.D. Pinnola, A.V. Tulin, Small-molecule collection and high-throughput colorimetric assay to identify PARP1 inhibitors, Methods Mol. Biol. 780 (2011) 491–516, https://doi.org/10.1007/978-1-61779-270-0_29.
[212] T. Zhu, J.-Y. Zheng, L.-L. Huang, Y.-H. Wang, D.-F. Yao, H.-B. Dai, Human PARP1 substrates and regulators of its catalytic activity: an updated overview, Front. Pharmacol. 14 (2023) 1137151, https://doi.org/10.3389/fphar.2023.1137151.
[213] G.F. Elmasry, E.E. Aly, F.M. Awadallah, S.M. El-Moghazy, Design and synthesis of novel PARP-1 inhibitors based on pyridopyridazinone scaffold, Bioorg. Chem. 87 (2019) 655–666, https://doi.org/10.1016/j.bioorg.2019.03.068.
[214] G. O'Sullivan Coyne, A. Chen, S. Kummar, Delivering on the promise: poly ADP ribose polymerase inhibition as targeted anticancer therapy, Curr. Opin. Oncol. 27 (2015) 475–481, https://doi.org/10.1097/CCO.0000000000000238.
[215] C.J. Lord, A. Ashworth, PARP inhibitors: the first synthetic lethal targeted therapy Europe PMC funders group, Science 355 (2017) 1152–1158, https://doi.org/10.1126/science.aam7344.PARP.
[216] K.E. McCann, S.A. Hurvitz, Advances in the use of PARP inhibitor therapy for breast cancer, Drugs Context 7 (2018) 1–30, https://doi.org/10.7573/dic.212540.
[217] J. Rudolph, G. Roberts, K. Luger, Histone Parylation factor 1 contributes to the inhibition of PARP1 by cancer drugs, Nat. Commun. 12 (2021) 736, https://doi.org/10.1038/s41467-021-20998-8.
[218] S. Boussios, P. Karihtala, M. Moschetta, A. Karathanasi, A. Sadauskaite, E. Rassy, N. Pavlidis, Combined strategies with poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer: a literature review, Diagnostics 9 (2019) 87, https://doi.org/10.3390/diagnostics9030087.
[219] H. Yang, P. Tang, B. Tang, Y. Huang, X. Xiong, H. Li, Novel poly(ADP-ribose) polymerase inhibitor veliparib: biophysical studies on its binding to calf thymus DNA, RSC Adv. 7 (2017) 10242–10251, https://doi.org/10.1039/C6RA28213J.
[220] H. Yang, Q. Zeng, Z. He, D. Wu, H. Li, Determination of the DNA binding properties of a novel PARP inhibitor MK-4827 with calf-thymus DNA by molecular simulations and detailed spectroscopic investigations, New J. Chem. 43 (2019) 6702–6711, https://doi.org/10.1039/C9NJ00667B.
[221] Y. Du, H. Yamaguchi, Y. Wei, J.L. Hsu, H.-L. Wang, Y.-H. Hsu, W.-C. Lin, W.-H. Yu, P.G. Leonard, G.R. Lee, M.-K. Chen, K. Nakai, M.-C. Hsu, C.-T. Chen, Y. Sun, Y. Wu, W.-C. Chang, W.-C. Huang, C.-L. Liu, Y.-C. Chang, C.-H. Chen, M. Park, P. Jones, G.N. Hortobagyi, M.-C. Hung, Blocking c-met–mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors, Nat. Med. 22 (2016) 194–201, https://doi.org/10.1038/nm.4032.
[222] Q. Dong, Y. Du, H. Li, C. Liu, Y. Wei, M.-K. Chen, X. Zhao, Y.-Y. Chu, Y. Qiu, L. Qin, H. Yamaguchi, M.-C. Hung, EGFR and c-MET cooperate to enhance resistance to PARP inhibitors in hepatocellular carcinoma, Cancer Res. 79 (2019) 819–829, https://doi.org/10.1158/0008-5472.CAN-18-1273.
[223] R. Abbotts, M.J. Topper, C. Biondi, D. Fontaine, R. Goswami, L. Stojanovic, E. Y. Choi, L. McLaughlin, A.A. Kogan, L. Xia, R. Lapidus, J. Mahmood, S.B. Baylin, F.V. Rassool, DNA methyltransferase inhibitors induce a BRCAness phenotype

that sensitizes NSCLC to PARP inhibitor and ionizing radiation, Proc. Natl. Acad. Sci. 116 (2019) 22609–22618, https://doi.org/10.1073/pnas.1903765116.
[224] C.E. Knezevic, G. Wright, L.L. Remsing Rix, W. Kim, B.M. Kuenzi, Y. Luo, J. M. Watters, J.M. Koomen, E.B. Haura, A.N. Monteiro, C. Radu, H.R. Lawrence, U. Rix, Proteome-wide profiling of clinical PARP inhibitors reveals compound-specific secondary targets, cell, Chem. Biol. 23 (2016) 1490–1503, https://doi.org/10.1016/j.chembiol.2016.10.011.
[225] N. Gan, Q. Sun, P. Tang, D. Wu, T. Xie, Y. Zhang, H. Li, Determination of interactions between human serum albumin and niraparib through multi-spectroscopic and computational methods, Spectrochim. Acta A Mol. Biomol. Spectrosc. 206 (2019) 126–134, https://doi.org/10.1016/j.saa.2018.07.100.
[226] L. Cai, X. Xu, W. Chen, The current state of the art in PARP inhibitor-based delivery Nanosystems, Pharmaceutics 14 (2022) 1647, https://doi.org/10.3390/pharmaceutics14081647.
[227] B. Singh, S. Yang, A. Krishna, S. Sridhar, Nanoparticle formulations of poly (ADP-ribose) polymerase inhibitors for cancer therapy, Front. Chem. 8 (2020), https://doi.org/10.3389/fchem.2020.594619.
[228] A.L. van de Ven, S. Tangutoori, P. Baldwin, J. Qiao, C. Gharagouzloo, N. Seitzer, J.G. Clohessy, G.M. Makrigiorgos, R. Cormack, P.P. Pandolfi, S. Sridhar, Nanoformulation of olaparib amplifies PARP inhibition and sensitizes PTEN/TP53- deficient prostate cancer to radiation, Mol. Cancer Ther. 16 (2017) 1279–1289, https://doi.org/10.1158/1535-7163.MCT-16-0740.
[229] J. Hao, Y. Liu, T. Zhang, J. He, H. Zhao, R. An, Y. Xue, Efficacy and safety of PARP inhibitors in the treatment of advanced ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials, Crit. Rev. Oncol. Hematol. 157 (2021) 103145, https://doi.org/10.1016/j.critrevonc.2020.103145.
[230] G. Valabrega, G. Scotto, V. Tuninetti, A. Pani, Differences in PARP inhibitors for the treatment of ovarian cancer: mechanisms of action, pharmacology, safety, and efficacy, Int. J. Mol. Sci. 22 (2021) 4203, https://doi.org/10.3390/ijms22084203.
[231] G. Sun, Y. Liu, Efficacy and safety of PARP inhibitor maintenance therapy for ovarian cancer: a meta-analysis and trial sequential analysis of randomized controlled trials, Front. Pharmacol. 15 (2024) 1460285, https://doi.org/10.3389/fphar.2024.1460285.
[232] J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K. E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, J.S. de Bono, DNA-repair defects and olaparib in metastatic prostate cancer, N. Engl. J. Med. 373 (2015) 1697–1708, https://doi.org/10.1056/NEJMoa1506859.
[233] T. Helleday, E. Petermann, C. Lundin, B. Hodgson, R.A. Sharma, DNA repair pathways as targets for cancer therapy, Nat. Rev. Cancer 8 (2008) 193–204, https://doi.org/10.1038/nrc2342.
[234] J. Li, Q. Sun, C. Lu, H. Xiao, Z. Guo, D. Duan, Z. Zhang, T. Liu, Z. Liu, Boron encapsulated in a liposome can be used for combinational neutron capture therapy, Nat. Commun. 13 (2022) 2143, https://doi.org/10.1038/s41467-022-29780-w.
[235] J.A. Perez-Fidalgo, A. Cortés, E. Guerra, Y. García, M. Iglesias, U. Bohn Sarmiento, E. Calvo García, L. Manso Sánchez, A. Santaballa, A. Oaknin, A. Redondo, M. J. Rubio, A. González-Martín, Olaparib in combination with pegylated liposomal doxorubicin for platinum-resistant ovarian cancer regardless of BRCA status: a GEICO phase II trial (ROLANDO study), ESMO Open 6 (2021) 100212, https://doi.org/10.1016/j.esmoop.2021.100212.
[236] J.A. Magalhães, D.C. Arruda, M.S. Baptista, D.B. Tada, Co-encapsulation of methylene blue and PARP-inhibitor into poly(lactic-co-glycolic acid) nanoparticles for enhanced PDT of cancer, Nanomaterials 11 (2021) 1514, https://doi.org/10.3390/nano11061514.
[237] C.J.F. Conceição, E. Moe, P.A. Ribeiro, M. Raposo, Liposome formulations for the strategic delivery of PARP1 inhibitors: development and optimization, Nanomaterials 13 (2023) 1613, https://doi.org/10.3390/nano13101613.
[238] Y. Cheng, P. Zhao, S. Wu, T. Yang, Y. Chen, X. Zhang, C. He, C. Zheng, K. Li, X. Ma, G. Xiang, Cisplatin and curcumin co-loaded nano-liposomes for the treatment of hepatocellular carcinoma, Int. J. Pharm. 545 (2018) 261–273, https://doi.org/10.1016/j.ijpharm.2018.05.007.
[239] C. Has, S.M. Phapal, P. Sunthar, Rapid single-step formation of liposomes by flow assisted stationary phase interdiffusion, Chem. Phys. Lipids 212 (2018) 144–151, https://doi.org/10.1016/j.chemphyslip.2018.01.007.
[240] G. Ioele, M. De Luca, A. Garofalo, G. Ragno, Photosensitive drugs: a review on their photoprotection by liposomes and cyclodextrins, Drug Deliv. 24 (2017) 33–44, https://doi.org/10.1080/10717544.2017.1386733.
[241] N. Dan, Core–shell drug carriers: Liposomes, polymersomes, and niosomes, in: E. Andronescu, A.M. Grumezescu (Eds.), Nanostructures Drug Deliv, Elsevier, Cambridge, USA, 2017, pp. 63–105, https://doi.org/10.1016/B978-0-323-46143-6.00002-6.
[242] F. Pires, J.F. Santos, D. Bitoque, G. Araujo, A. Marletta, V.A. Nunes, P.A. Ribeiro, J.C. Silva, M. Raposo, Polycaprolactone / gelatin Nano fi ber membranes containing EGCG- loaded liposomes and their potential use for skin regeneration, ACS Appl. Bio Mater. 2 (2019) 4790–4800, https://doi.org/10.1021/acsabm.9b00524.
[243] M. Ruano, A. Mateos-Maroto, F. Ortega, H. Ritacco, J.E.F. Rubio, E. Guzmán, R. G. Rubio, Fabrication of robust capsules by sequential assembly of polyelectrolytes onto charged liposomes, Langmuir 37 (2021) 6189–6200, https://doi.org/10.1021/acs.langmuir.1c00341.
[244] S. Hama, M. Sakai, S. Itakura, E. Majima, K. Kogure, Rapid modification of antibodies on the surface of liposomes composed of high-affinity protein A-conjugated phospholipid for selective drug delivery, Biochem. Biophys. Rep. 27 (2021), https://doi.org/10.1016/j.bbrep.2021.101067.
[245] M. Wu, J. Liu, C. Hu, D. Li, J. Yang, Z. Wu, L. Yang, Y. Chen, S. Fu, J. Wu, Olaparib nanoparticles potentiated radiosensitization effects on lung cancer, Int. J. Nanomedicine 13 (2018) 8461–8472, https://doi.org/10.2147/IJN.S181546.
[246] T. Hirai, S. Saito, H. Fujimori, K. Matsushita, T. Nishio, R. Okayasu, M. Masutani, Radiosensitization by PARP inhibition to proton beam irradiation in cancer cells, Biochem. Biophys. Res. Commun. 478 (2016) 234–240, https://doi.org/10.1016/j.bbrc.2016.07.062.
[247] S.A. Jannetti, B.M. Zeglis, M.R. Zalutsky, T. Reiner, Poly(ADP-ribose)polymerase (PARP) inhibitors and radiation therapy, Front. Pharmacol. 11 (2020) 170, https://doi.org/10.3389/fphar.2020.00170.
[248] S.J. Derby, A.J. Chalmers, R.D. Carruthers, Radiotherapy-poly(ADP-ribose) polymerase inhibitor combinations: progress to date, Semin. Radiat. Oncol. 32 (2022) 15–28, https://doi.org/10.1016/j.semradonc.2021.09.005.
[249] J.M.F. Fischer, O. Popp, D. Gebhard, S. Veith, A. Fischbach, M. Scheffner, E. Ferrando-may, S. Beneke, A. Leitenstorfer, Poly (ADP-ribose) -mediated interplay of XPA and PARP1 leads to reciprocal regulation of protein function, FEBS J. 281 (2014) 3625–3641, https://doi.org/10.1111/febs.12885.