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Review Article

Modulatory Potential of Poly (ADP-Ribose) Polymerase 1 (PARP1) in BRCA-Mutated Tumors

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Poly (ADP-ribose) polymerase 1 is a versatile enzyme that is deeply involved in diverse cellular processes. It exerts influence on pivotal activities such as DNA repair, transcriptional regulation, and cell death. PARP1 is crucial due to its susceptibility to posttranslational modifications, each of which has distinct roles in shaping its functionality and interactions with other proteins. Among these modifications, the addition of ADP-ribose polymerase 1 and the addition of an acetyl group to lysine residues enhance PARP1 engagement in DNA repair, while ubiquitination and cleavage are involved in the degradation of PARP1. PARP1 modification has been exploited in cancer treatment, particularly in the context of breast and ovarian cancers marked by BRCA1 and BRCA2 mutations. However, resistance to PARP1 inhibitors and selective posttranslational modifications, which confer cellular functions remain elusive. The present review endeavors to detail the extent of PARP1 modifications, shedding light on their profound implications at the cellular remains a challenge, which often drives treatment failure. The effectiveness of PARP1 inhibitors relies on specific level. This trial is registered with NCT04550104, NCT06120491, NCT05367440, NCT05797168, NCT04644068, NCT05573724, NCT05489211, NCT05938270, and NCT02264678.

1. Introduction

Poly (ADP-ribose) polymerase 1 (PARP1) is an important enzyme that is maintained in eukaryotic cells. Its major role in DNA repair pathways has been identified as base excision [1, 2]. The ability of PARP1 to prevent DNA damage and binding is stunning, which results in the addition of ADP-ribose units combined with NAD + to target DNA repair proteins [2]. The ability to bind to the target site of damaged DNA triggers PARP to undergo a conformational change,

thereby resulting in PARylation (the catalyzing effect of proteins by poly (ADP-ribose) polymerase (PARP) enzymes) by the addition of adenosine phosphate (ADP-ribose) units from nicotinamide adenine dinucleotide (NAD+) for the polymerization of chains of ADP-ribose [3, 4]. The molecular basis of PARP1, which plays an important role in regulating both receptor and DNA damage detection and repair processes, is still under investigation. However, both PARP1, i.e., its N-terminal half containing different DNA damage and substrates have been reported to require the C-terminal half of PARP1 together with its selective component [5]. Furthermore, research has established that PARP1 synergizes with gene expression to promote chromatin formation by detecting DNA damage to catalyze the cleavage of its substrate NAD+ to form nicotinamide and ADP ribose, which thereby polymerize into long ADP-ribose chains and core histones [6–10].

Moreover, during DNA damage, posttranslational modifications of PARP1 play crucial roles in recruiting other DNA repair proteins to the damaged site of DNA and catalyzing repair mechanisms. The accumulation of PAR polymers on PARP1 proteins, known as PARylation, creates a scaffold that facilitates the recruitment and assembly of DNA repair factors such as XRCC1 and DNA ligases to initiate the repair process and regulate PARP enzymatic activity [11]. Conformational changes in PARP1 lead to modulation of enzymatic activity, which causes dissociation from DNA and self-regulatory mechanisms that stop PARP1 from building up excessively and enable timely DNA repair processes to proceed. These specific activities are linked to the modification, while cleavage results in apoptosis [12, 13].

Furthermore, the development of therapeutics to treat cancer using PARP1 inhibitors has attracted increased interest, especially for cancer caused by BRCA1 and BRCA2 mutations in breast cancer and ovarian cancer involving the synthetic lethality. However, cancer resistance to PARP1 inhibitors, as reported by different researchers, has been confirmed during treatment, and new strategies are needed to mitigate this resistance [14, 15]. Therefore, the present review discusses the different posttranslational modifications of PARP1, together with the associated activities, thereby highlighting the potential substrates involved both at the activating and inhibitory levels as a strategy to overcome cancer resistance.

2. The Artificial Death (Synthetic Lethality) Caused by Inhibitors of PARP

Synthetic lethal interactions embody a form of contextual necessity where a genetic alteration, such as a defect in a tumor suppressor gene, makes another gene vital for cell survival. By specifically inhibiting the product of this secondary, synthetically lethal gene, tumor cells can potentially be targeted while sparing noncancerous cells. This strategy offers a chance to eliminate tumor cells with precision while minimizing harm to healthy tissue [16].

Furthermore, the concept of synthetic lethality provides avenues to precisely target specific subsets of cancers characterized by distinct molecular changes, such as driver mutations [16, 17]. Alongside synthetic lethality, related genetic concepts like synthetic dosage lethality have emerged, where increased activity of one gene renders another gene essential, contrasting with the traditional loss-of-function scenario [16]. The enzymes PARP1 and PARP2 play crucial roles as DNA damage sensors, binding to various forms of DNA damage and initiating the DNA damage response pathway. Through a process called poly (ADP-ribosyl)ation (PARylation), PARP enzymes modify substrate proteins upon DNA binding. Extensive research has been dedicated to discovering and developing small-molecule PARP inhibitors, some of which have advanced to clinical use [18]. The discovery in 2005 of a synthetic lethal interaction between PARP inhibition and mutations in BRCA1 or BRCA2 represented a significant breakthrough. BRCA1 and BRCA2 are tumor suppressor genes linked to elevated cancer risk when mutated. These genes are essential for repairing double-stranded DNA breaks through homologous recombination. Tumors in individuals with germline BRCA mutations often display somatic loss-of-function mutations in the wild-type BRCA allele, leading to faulty homologous recombination. The synthetic lethal interaction between PARP inhibition and BRCA loss-of-function is thought to exacerbate double-stranded DNA breaks or collapsed replication forks caused by PARP inhibition or PARP trapping on DNA. Encouragingly, preclinical models of BRCA-mutant cancers have demonstrated significant synthetic lethal effects, prompting the translation of this approach into clinical trials [16, 19].

The efficacy of PARP inhibitors in patients with BRCA-mutant breast or ovarian cancer has been substantial enough to merit FDA approval for these treatments. Nevertheless, resistance to PARP inhibitors, whether interposed or acquired over time, poses a common challenge. Various mechanisms have been proposed to elucidate both types of resistance, with many focusing on the restoration of homologous recombination (HR) in cancer cells. This restoration can happen directly through reversion mutations in BRCA1 or BRCA2 or indirectly through alterations in other components of the DNA damage response (DDR) pathway. Like experiences with other targeted therapies, the use of PARP inhibitors seems to drive natural selection, favoring the survival and proliferation of tumor cell clones carrying BRCA reversion mutations over those that do not. Current efforts are concentrated on enhancing responses to PARP inhibitors, either through combination therapies or by targeting alternative pathways within BRCA-mutant tumor cells [20].

3. Catalytic Effect of Poly (ADP-Ribose) Polymerase on Proteins

Automodification endows PARP1 with low affinity for intact chromatin but increased affinity for nucleosomes with exposed DNA ends. This allows PARP to target damaged DNA in a selective manner. The molecular basis for the functional trigger from chromatin architectural proteins to transcription and the DNA damage response has not been determined; however, some authors suggest PARylation [21–25].

The PARP1 structure contains two ribose moieties and two phosphate groups per unit of polymer. Its conventional long structure contains a DNA binding domain, an automodification domain, a catalytic domain, and a PARP signature motif [11, 26]. Its modification involves the enzymatic activity of the PARP protein, NAD+, and histone PARylation factor 1 as substrates, leading to the covalent attachment of ADP-ribose units to these proteins. Automodifications play crucial roles in DNA damage repair, chromatin remodeling, and gene expression regulation [27, 28]. PARP automodification is a dynamic process that is tightly regulated and essential for efficient DNA damage repair. Impaired PARylation dysregulates PARP1 activity and may have implications for genome stability, DNA repair capacity, and disease development, including cancer and underlying mechanisms [15, 29, 30].

PARP1 and PARylation play crucial roles in DNA repair processes. When DNA damage is detected by PARP1, it binds to the damaged site and catalyzes the transfer of ADP-ribose units from NAD+ molecules to target proteins; this process is known as MARylation or PARylation. It is a posttranslational modification that can modify the activity and function of target proteins involved in DNA repair. PARylation regulates the recruitment and assembly of DNA repair proteins at the site of damaged DNA, where they create DNA repair complexes [31–35]. PARP1 plays a critical role in base excision repair (BER), which is a pathway that repairs DNA damage caused by the removal of damaged bases or small DNA lesions. PARP1 recognizes and binds to damaged DNA sites. Both PARylates itself and other proteins are involved in BER, such as X-ray repair cross complementing protein 1 (XRCC1). Furthermore, PARylation enhances effective single-stranded DNA repair by facilitating and coordinating the recruitment of BER protein to the spot [36–38]. PARP1 also contributes to the regulation of homologous recombination (HR). PARP1 facilitates the recruitment of TOPBP1, which is involved in a highly conserved DNA damage response (DDR) that includes DNA breaks in BRCA1 and BRCA2. PARylation of these proteins promotes their accumulation at the damaged site and enhances the efficiency of HR-mediated repair [39] (Figure 1).

4. Chemical Characteristics and Enzymatic Effect of Poly (ADP-Ribose) Polymerase 1

PARP1 is known to play an important role in DNA repair and various cellular processes, mainly in DNA damage repair and single-strand break repair, where it detects DNA damage and recruits other contributing factors. Phosphorylation is a posttranslational modification that involves the addition of a phosphate group to specific amino acid residues and therefore controls protein interaction, subcellular localization, enzymatic activity, and stability. PARP can undergo phosphorylation at several specific sites within its protein structure (Table 1). The exact mechanism of PARP1 phosphorylation might depend on the specific phosphorylation site and the cellular context. Serine 499 (S499) has been found to phosphorylate PARP. The phosphorylation of this site affects its catalytic activity and interaction with other proteins involved in DNA repair processes, while the loss of phosphatase confers sensitivity to PARP1 inhibitors in PTEN-deficient endometrial carcinoma. PARP phosphorylation at Ser400, Ser782, Ser785, and Ser786 has been observed in response to DNA damage. Phosphorylation at one or more of these sites modulates the localization of PARP1 and its interaction with other DNA repair factors, thus activating the repair system [45–49]. Ser903 phosphorylation has been implicated in the regulation of PARP1 activity. It has been reported that it modulates the DNA binding and catalytic activity of PARP1. Kauppinem et al. reported the sustained activation of PARP1 by phosphorylation at Ser372 and T373 mediated by extracellular signalling regulated kinase 1/2 (ERK 1/2). Phosphorylation at Y907 increases PARP1 enzymatic activity and reduces binding to a PARP inhibitor in breast cancer and lung cancer. Y992 mediates resistance to PARP1 inhibition in hepatocellular carcinoma, and Y829 is required for RelA/p65 PARylation and NF-kB-dependent expression of proinflammatory genes. Phosphorylation of the zinc finger protein MYND on PARP1 resulted in a decrease in DNA repair capacity in the nucleus, thus increasing the effectiveness of PARP1 inhibitors [40–44, 50]. The phosphorylation of PARP1 is specific and context dependent. It is regulated by various cellular signalling pathways and DNA damage response mechanisms and may have inhibitory or activating effects depending on the site (Figure 2).

5. Small Ubiquitin-Like Modifier Activity on PARP1

SUMOylation is a posttranslational modification that involves covalent attachment of the small ubiquitin-like modifier (SUMO) protein. SUMOylation of PARP1 influences its localization, activity, and interactions in heart cells [51]. SUMOylation is a reversible process that involves an enzymatic cascade similar to ubiquitination. These proteins include SUMO-activating enzymes (E1), SUMO-conjugating enzymes (E2), and SUMO ligases (E3), which work together to transfer SUMO to target proteins. Unlike ubiquitination, SUMOylation often leads to nondegradative changes in the properties of target proteins [52, 53].

The SUMOylation of PARP1 has been described in the context of DNA damage and repair processes. It regulates the enzymatic activity, DNA binding capacity, and interactions of DNA with other proteins in the cascade. SUMOylation of PARP1 regulates its recruitment to sites of DNA damage, where it can facilitate repair processes. It may also influence protein stability, subcellular localization, and protein binding, thereby affecting overall protein function within cells. Depending on the precise lysine residues that are altered, the kind of SUMO isoform attached, and the cellular environment, the effects of SUMOylation on PARP1 can differ. There are several SUMO isoforms, including SUMO1, SUMO2, SUMO3, and SUMO4.

Moreover, SUMOylation can target multiple lysine residues, including lysine 486 (K486), lysine 508 (K508), and lysine 521 (K521), in PARP1. These lysine residues within the PARP1 protein structure serve as acceptor sites for the

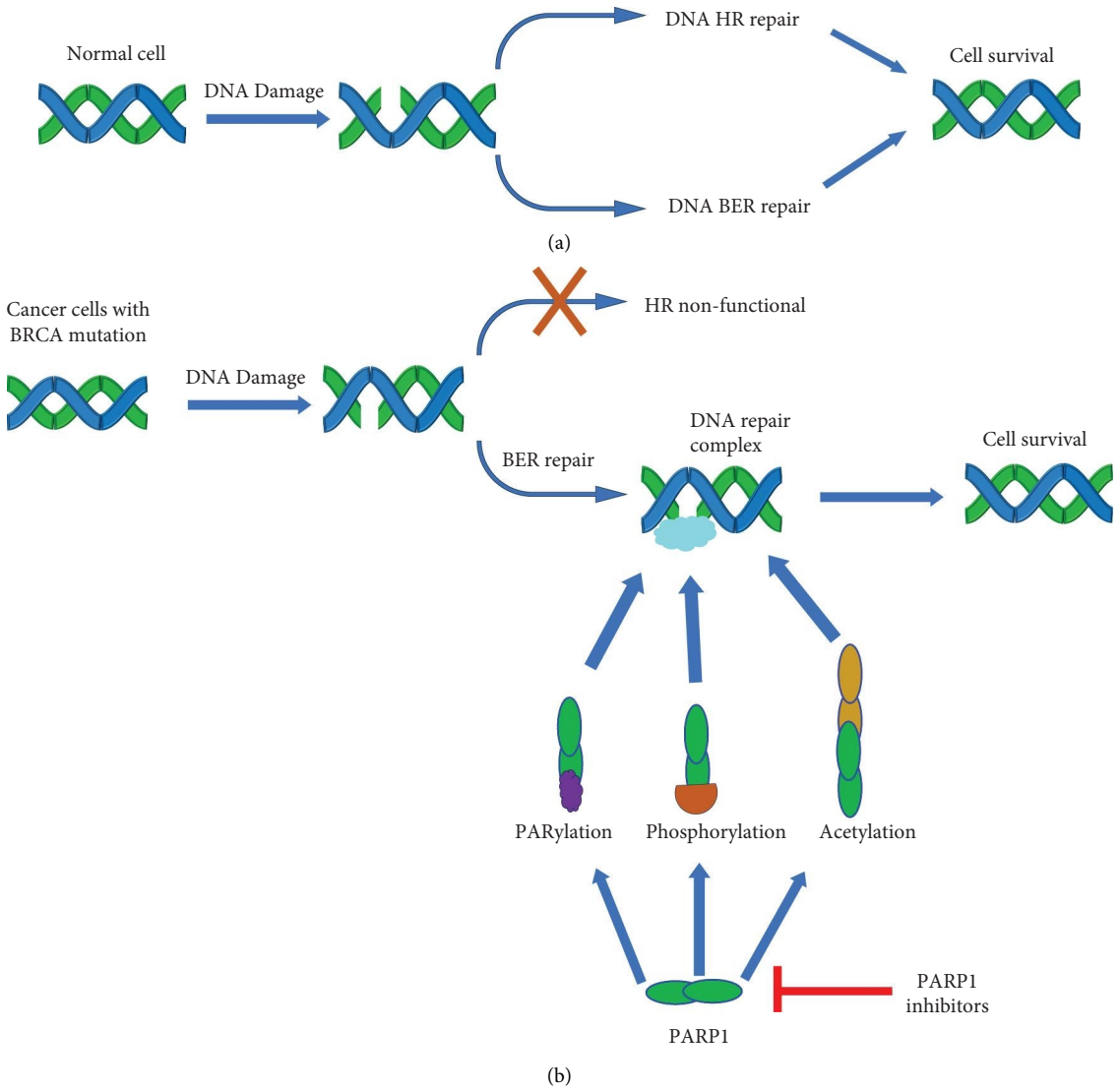

Figure 1: PARP1 modification is associated with the activation of DNA repair processes. The DNA repair process in normal cells is either homologous recombinant or base excision repair (a) and in mutated BRCA, DNA repair relies on BER, which is inhibited by PARP1 inhibitors (b).

Table 1: Common phosphorylation sites of PARP1.

Kinase	Sites	Effects	Reference
ERK1/2	S372, T373	Phosphorylation increases PARP1 activity	[40]
c-Met	Y907	pY907 increases PARP1 enzymatic activity and reduces binding to a PARP inhibitor in breast cancer and lung cancer	[41]
c-Abl	Y829	pY829 is required for PARylation of RelA/p65 and NF-kb-dependent expression of proinflammatory genes	[42]
SRC	Y992	pY992 mediates resistance to PARP1 inhibition in hepatocellular carcinoma	[43]
DNA-PK	T594	DNA-PK phosphorylates PARP1 on Thr594 and instructs its cytosolic translocation	[44]

covalent attachment of SUMO moieties. SUMOylation of PARP1 can modulate its activity and function, which affects its catalytic activity [54, 55]. It has been reported that altering the catalytic activity of PARP1 leads to a change in PARylation activity. It has been suggested that SUMOylation inhibits PARP1 enzymatic activity, potentially by interfering with its DNA binding ability or altering its interactions with other proteins [56].

Furthermore, The SUMOylation of PARP1 has also been implicated in the regulation of its cellular localization. It influences the subcellular distribution of PARP1, promoting its accumulation in specific nuclear bodies, such as

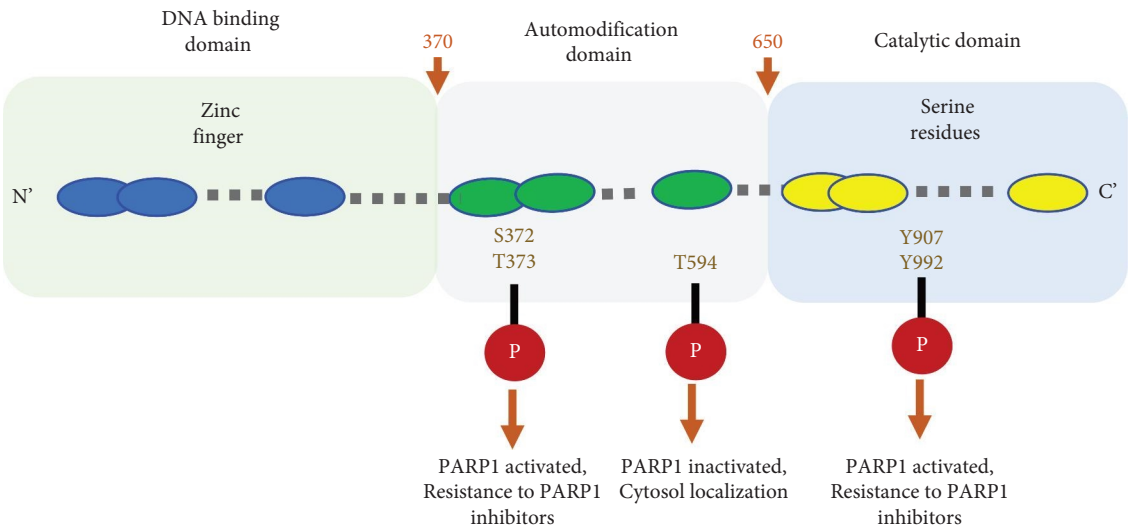

Figure 2: Phosphorylation of PARP1. The activity of PARP1 depends on the site of phosphorylation, where the activation is associated with resistance to PARP1 inhibitors, while cytosol localization is associated with lower activity.

promyelocytic leukaemia (PML) nuclear bodies. These nuclear bodies are involved in various cellular processes, including DNA repair and transcriptional regulation. SUMOylation of PARP1 modulates its interactions with other proteins involved in DNA repair and other cellular processes. It enhances the interaction between PARP1 and XRCC1, a crucial protein involved in base excision repair. This interaction promotes the assembly of DNA repair complexes at the site of DNA damage [56, 57].

Furthermore, SUMOylation occurs through crosstalk with other posttranslational modifications, including PARylation, on the same lysine residues of PARP1, thus leading to competitive modification. The interplay between SUMOylation and PARylation may have implications for the regulation of PARP1 activity and its involvement in DNA repair processes. SUMOylation is thus a dynamic, context-dependent, and regulatory process of PARP1 that impacts its localization, stability, and interactions with other proteins [43].

6. Structural Modification of PARP1 by Ubiquitin

Ubiquitination is a posttranslational modification involving the covalent attachment of ubiquitin molecules to lysine residues on target proteins, depending on the type and length of the ubiquitin chain and the attachment sites, which have various effects. The most reported type of protein is the protein used for proteasomal degradation, although it can also influence protein interactions, subcellular localization, and activity [58]. Through ubiquitination, PARP1 controls its equilibrium and functionality. When the ubiquitin chain is added to PARP1, the proteasome will recognize it and degrade it as a result. Different triggers cause PARP1 to become ubiquitinated. During DNA damage, the activity and stability of PARP1 are tightly regulated to prevent excessive activation or insufficient activation and allow proper termination once repair is completed [59].

Ubiquitination is a reversible process, and deubiquitinating enzymes (DUBs) remove ubiquitin moieties from PARP1, providing another level of regulation. This allows cells to finely tune the levels and activity of PARP1 in response to changing cellular conditions and requirements [60]. Ubiquitinated PARP1 is recognized by the proteasome, the cellular machinery responsible for protein degradation, leading to proteolytic cleavage and removal of ubiquitinated PARP1. This ubiquitin-proteasome system-mediated degradation regulates the abundance and turnover of PARP1 [61]. Ubiquitination regulates the stability of PARP1. Increased ubiquitination promotes the degradation of PARP1 and decreases its protein level; conversely, diubiquitinates (DUB), an enzyme that removes ubiquitin moieties, stabilizes PARP1 by counteracting ubiquitination [62].

Moreover, ubiquitination of PARP1 involves the activity of E3 ligases, which facilitate the transfer of ubiquitin molecules to target proteins. Different E3 ligases are involved in the ubiquitination of PARP1 under different cellular conditions or in response to specific stimuli. The E3 ligase RNF146 has been implicated in the ubiquitination of PARP1 in certain cellular contexts. Ubiquitination in combination with other posttranslational modifications of PARP1, such as phosphorylation and SUMOylation, provides an additional layer of DNA repair regulation [63] (Figure 3).

7. The Addition of an Acetyl Group to Lysine Residues

The addition of an acetyl group to lysine residues on proteins is one of the key and reversible posttranslational modifications of PARP1. This process is catalyzed by histone acetyltransferases (HATs), which add acetyl groups, while histone deacetylases (HDACs) remove acetyl groups. Acetylation of PARP1 influences its functions and interactions with other molecules. Some studies suggest that

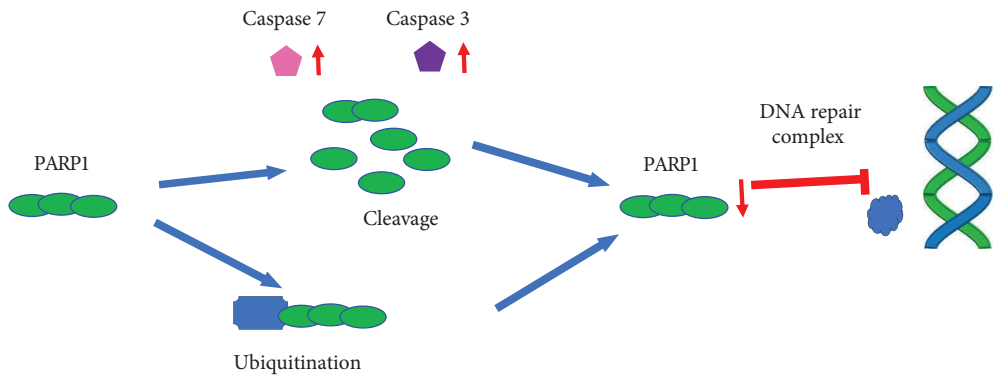

Figure 3: PARP1 stability is associated with its activity. The increased caspase 7 and caspase 3 cleave PARP1 and result in a reduced concentration of nuclear PARP, thus inhibiting its activity. Ubiquitination also contributes to the low concentration of PARP1.

acetylation of PARP1 positively regulates its enzymatic activity, mainly automodification and poly (ADP-ribosylation) activity. Moreover, acetylation of PARP1 affects its interactions with other proteins, modulating the formation of protein complexes involved in different cellular pathways [64]. Deacetylation of PARP1 also regulates and leads to a decrease in its enzymatic activity, particularly its ability to perform poly (ADP-ribose) polymerization, a crucial step in DNA repair. When PARP1 is acetylated, it may become more active, promoting its PARylation activity; on the other hand, diacetylation by HDACs or sirtuins might reduce PARP1 activity. The balance between the acetylation and deacetylation of PARP1 determines its function [65].

The acetylation or deacetylation of PARP1 may occur at various residues within its structure, thus affecting the final role of PARP1 [55]. The specific lysine residues affected by acetylation differ and depend on the cellular context and the acetyltransferase involved. The acetylation of PARP1 modulates its catalytic activity, potentially by altering its interaction with DNA and other proteins involved in DNA repair processes. Acetylation inhibits or enhances PARP1 activity through a mechanism dependent on the specific lysine acetylated [66].

Acetylation of PARP1 affects how it interacts with other protein molecules, including Ku70, XRCC1, and DNA repair proteins. This mechanism influences how these interactions occur, which in turn affects how DNA repair complexes assemble and function. The NAD+-dependent deacetylase sirtuin 1 (SIRT1) is primarily responsible for controlling the deacetylation of PARP1. SIRT1, which leads to the deacetylation of specific lysine residues, has been associated with the modulation of PARP1 activity and involvement in DNA repair processes [67, 68]. The acetylation and deacetylation of PARP1 are dynamic processes regulated by acetyltransferase and deacetylase activity. These modifications profoundly affect the activity of PARP1, ultimately impacting its role in DNA repair and other cellular processes [69].

8. Proteolytic Cleavage of PARP1

Proteolytic cleavage of the PARP1 protein into small fragments is a posttranslational modification that occurs in response to specific cellular signals, including severe DNA damage, such as double strand breaks. When the damage is extensive, PARP1 is proteolytically cleaved by caspases, which are a family of proteases involved in apoptosis. This cleavage results in the generation of a truncated PARP1 fragment, which is implicated in the regulation of cell death pathways, is considered a hallmark of apoptosis, and serves as a marker of caspase activation. The cleavage of PARP1 has a negative functional effect on DNA repair processes; by removing the full-length PARP1 protein, the repair response is compromised, and the cell may shift its focus to apoptotic pathways [70, 71].

During apoptosis, Caspase-3 and Caspase-7 are activated and cleave PARP1 at specific sites. Caspase-mediated cleavage of PARP1 leads to its inactivation and generation of C-terminal fragments, blocking the automodification domain of PARP1. The cleavage of PARP1 by caspase results in the loss of DNA-binding sites, compromising its ability to recognize and bind to DNA lesions. This cleavage-induced inactivation of PARP1 prevents its participation in DNA repair processes. The cleavage of PARP1 by caspase is a marker of apoptotic DNA fragmentation. The C-terminal fragment of PARP1 generated by caspase cleavage is subsequently released from the nucleus, where it contributes to the condensation and fragmentation of DNA in apoptotic cells [72, 73].

During apoptosis, caspase-mediated proteolysis of PARP1 plays intricate roles in determining the fate of cells undergoing programmed cell death. The activation of PARP1 by caspase promotes its participation in DNA repair and cellular processes associated with PARylation, while the cleavage-induced loss of the DNA-binding domain inhibits its DNA repair function. These processes collectively contribute to the execution of apoptosis and the clearance of apoptotic cells [13, 74] (Figure 3).

9. Substrates of PARP1

The modifications of PARP1 and its substrates define the outcomes. PARP1 utilizes NAD+ as its primary substrate to synthesize PAR chains as acceptor proteins, modulating their function. In addition to NAD+, PARP1 can use other nucleotides, such as nicotinamide adenine dinucleotide phosphate (NADP+), as substrates for PARylation [12].

Table 2: FDA-approved PARP inhibitors.

Drug	Cancer type	Indications	Ref
Olaparib	Ovarian cancer Breast cancer Pancreatic cancer Prostate cancer	Olaparib is approved for maintenance therapy in advanced ovarian cancer patients who responded to platinum-based chemotherapy, regardless of BRCA mutation status. It is also indicated for HER2-negative metastatic breast cancer with germline BRCA mutations and metastatic pancreatic cancer with germline BRCA mutations post platinum-based chemotherapy. Additionally, it is approved for castration resistant prostate cancer.	[86–88]
Niraparib	Ovarian cancer	Approved for ovarian cancer which has resisted to chemotherapy	[89]
Rucaparib	Ovarian cancer Prostate cancer	It is approved in castration-resistant prostate cancer and ovarian metastatic cancer	[90]
Talazoparib	Breast cancer	Talazoparib is approved for treating HER2-negative advanced or metastatic breast cancer in patients with germline BRCA mutations who have had previous chemotherapy	[91]

NAD+ is a coenzyme and essential molecule involved in energy metabolism and redox reactions at the cellular level. It acts as an electron carrier in cellular respiration and plays key roles in cellular energy production. During DNA repair, PARP1 consumes NAD+ as it catalyzes the addition of ADP-ribose units to proteins involved in repair processes. In the case of severe DNA damage, prolonged activation of PARP1 is associated with excessive consumption of NAD+, which leads to energy depletion and cell death. Thereby show the concept exploited in synthetic lethality [14].

PARP1 modifies various acceptors by adding a PAR chain to them. The acceptor proteins themselves can include PARP1 itself as well as other proteins involved in DNA repair, such as XRCC1, DNA ligase II, and histones. PARylation of these acceptor proteins plays crucial roles in processes such as DNA repair, chromatin remodeling, transcriptional regulation, and cell signalling [38, 75].

10. Modulation of PARP1 and Its Therapeutic Potential

Proteins play a vital role in regulating PARP1 to maintain genomic integrity and cellular balance. This enzyme is crucial for DNA repair and stability, and its activity, location, and interactions are finely tuned by various proteins in the cell. Understanding how these proteins function in cellular processes and their disruption in cancer can offer valuable insights into disease mechanisms and potential precision medicine strategies [76].

Moreover, dysregulation of proteins that regulate PARP1 can serve as biomarkers for cancer diagnosis, prognosis, and treatment response. Changes in the expression or function of these proteins may indicate underlying molecular changes driving the development and progression of cancer. PARP1 interacts with multiple proteins involved in DNA repair pathways, such as base excision repair (BER), homologous recombination (HR), and non-homologous end joining (NHEJ). Proteins like XRCC1, a key player in the BER pathway, and Ku70/Ku80, essential components of the NHEJ pathway, can impact PARP1 activity by facilitating its recruitment to DNA damage sites and modulating its enzymatic function [20, 77].

The concept of posttranslational modification of PARP1 has led to the development of PARP inhibitors as targeted cancer therapies. These inhibitors work by blocking the enzymatic activity of PARP1, preventing DNA damage repair and exacerbating DNA breaks. PARP inhibition is a targeted therapeutic strategy used in cancer treatment. The goal is to selectively block the enzymatic activity of PARP1, which is involved mainly in repair processes. In cancer cells with underlying defects in other DNA repair pathways, such as BRCA1 and BRCA2 gene mutations, PARP1 becomes crucial for survival. These mutations impair the ability of cells to repair DNA damage through homologous recombination. In such cases, PARP1 plays a compensatory role in DNA repair, helping cells to survive and proliferate. PARP1 inhibition can lead to synthetic lethality, where cancer cells are selectively killed while preserving normal cells [78].

PARP inhibitors are designed to block the activity of PARP1; thus, PARP1 may be translated through the combination of BRCA mutation and PARP1 inhibition, which cause the accumulation of DNA damage and lead to cell death, while normal cells compensate for homologous recombination and maintain genomic stability. Several cancer types such as breast and ovarian cancer with BRCA mutations, are shown promising treatments using the combined strategies of BRCA mutation and PARP1 inhibition [79].

Despite progress in PARP1 inhibitors, resistance to these agents is a significant challenge in treatment. Several mechanisms have been reported to contribute to this resistance. These include the restoration of homologous recombination pathways and the mutation of BRCA proteins, which depend heavily on PARP1 for DNA repair, to restore the functionality of HR pathways and reduce susceptibility to PARP1 inhibition. The second mechanism involves cells undergoing genetic changes that alter the activity or expression of PARP1. Increased drug efflux is a mechanism by which PARP1 inhibitors are actively released from within cells, reducing their intracellular concentration and effectiveness. To survive and proliferate despite the presence of DNA damage, epigenetic alterations in cancer cells might lead to changes in gene expression, affecting cellular responses to PARP inhibitors [80–85].

Table 3: Small molecules and their stages in clinical trials.

Molecule	Conditions	Phases	NCT number
Saruparib (AZD5305)	Non-small-cell lung cancer	PHASE1	NCT04550104
	Metastatic castration-sensitive prostate cancer	PHASE3	NCT06120491
	Metastatic prostate cancer	PHASE1|PHASE2	NCT05367440
	Ovarian cancer, lung adenocarcinoma	PHASE1|PHASE2	NCT05797168
	Ovarian cancer, breast cancer, pancreatic cancer, prostate cancer additional indications below for module 4 and 5 |Non-small-cell lung cancer, colorectal cancer, bladder cancer, gastric cancer, biliary cancer, cervical cancer, endometrial cancer, small-cell lung cancer only in module 5	PHASE1|PHASE2	NCT04644068
	Advanced solid malignancies	PHASE1	NCT05573724
	Endometrial cancer, gastric cancer, metastatic castration-resistant prostate cancer, ovarian cancer, colorectal cancer, urothelial cancer, biliary tract cancer	PHASE2	NCT05489211
	Prostate cancer	PHASE1	NCT05938270
	Adv solid malig-H&N SCC, ATM pro/Def NSCLC, gastric, breast, and ovarian cancer	PHASE1|PHASE2	NCT02264678

11. PARP Inhibitors in Treatment for Cancer

PARP inhibitors are a key treatment option for cancer, especially for tumors with DNA repair pathway deficiencies like BRCA mutations. They work by exploiting synthetic lethality, offering a targeted approach to cancer therapy with promising results. The success of PARP inhibitors is most notable in treating tumors with BRCA1 or BRCA2 mutations, which makes cancer cells highly sensitive to PARP inhibition-induced synthetic lethality. Clinical trials have shown significant responses and improved outcomes in patients with BRCA-mutated breast, ovarian, and other cancers treated with PARP inhibitors, leading to regulatory approval (Table 2).

Furthermore, saruparib is currently in clinical trials for various cancer types, showing low toxicity and increased specificity [92, 93]. Table 3 reveals several molecules and their present stages in clinical trial.

12. Conclusion

It is important to note that while PARP inhibitors have shown remarkable clinical outcomes, their use is limited to specific cancer types and has specific genetic characteristics, mainly breast cancer and ovarian cancer with BRCA mutation. The choice of treatment is based on individual patient factors and genetic profiling of the cancer type [14]. When PARP is inhibited, alternative pathways are altered, leading to the accumulation of unrepaired DNA breaks and cell death during replication. Recent study reports the interaction between long non-coding RNAs which interact with PARP1 and increase the BER repair activity [94]. The concept of PARP1 inhibition is essential in treatment and in understanding the mechanism of resistance. We highlighted different modifications that may be beneficial to treatment and open for further evaluation of clinical application, as PARP1 modifications hold the potential to be critical components of targeted cancer therapy, improving patient outcomes and quality of life.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Valens Munyembaraga and Delphine Cyuzuzo designed and conducted the review study. Sunday Amos Onikanni wrote the manuscript. Tran Nhat Phong Dao and Babatunji Emmanuel Oyinloye helped with the literature review. Hen-Hong Chang supervised and revised the review. All the authors have read and approved the final version of the manuscript.

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