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Review

The PARG frontier: mechanisms of PAR turnover and opportunities in precision oncology

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ABSTRACT

ADP-ribosylation is a versatile post-translational modification that governs fundamental processes, including DNA repair, transcription, and stress adaptation. Its homeostasis relies on the dynamic interplay between poly (ADP-ribose) polymerases (PARPs), which assemble mono- or poly-ADP-ribose (PAR) chains on target macromolecules, and ADP-ribosyl hydrolases, which dismantle them. Disruption of this balance leads to the accumulation of toxic PAR and cell death, revealing vulnerabilities that can be therapeutically exploited. PARP inhibitors (PARPis) have revolutionised the treatment of homologous recombination-deficient cancers via synthetic lethality. Yet, emerging resistance limits their long-term efficacy, underscoring the need for novel targets within ADP-ribose signalling. The poly(ADP-ribose) glycohydrolase (PARG), the principal enzyme involved in hydrolysing PAR, has emerged as a compelling candidate: its inhibition amplifies replication stress, drives mitotic catastrophe, and selectively kills cancer cells, particularly those reliant on PAR turnover for survival. Elevated PARG expression correlates with aggressive tumours and poor prognosis, positioning it as both a prognostic biomarker and therapeutic target. This review integrates recent structural and biochemical insights into PARG, highlighting the mechanisms of PAR reversal, regulatory control, and potential synthetic lethal interactions. We also discuss the discovery and development of selective PARG inhibitors, which promise to expand the therapeutic landscape, overcome PARPis resistance, and exploit vulnerabilities in replication-stressed cancers. By bridging mechanistic understanding with translational potential, targeting PARG represents a frontier in precision cancer therapy.

Abbreviations: PARPs, Poly(ADP-ribose) Polymerases; PAR, Poly-ADP-ribose; PARPis, PARP Inhibitors; PARG, Poly(ADP-ribose) Glycohydrolase; NAD^+, Nicotinamide Adenine Dinucleotide; MARylation, Mono-ADP-ribosylation; PARylation, Poly-ADP-ribose-ADP-ribosylation; DraG, ADP-ribosyl-(dinitrogen reductase) glycohydrolases; ARHs, ADP-ribosyl hydrolases; BER, Base-excision repair; SSBs, Single-strand breaks; DSBs, Double-strand break; NHEJ, Non-homologous end joining; HPF1, Histone PARylation Factor 1; YB-1, Y-box–binding protein 1; mono-ADPr, Mono-ADP-ribose; Glu/Asp-linked, Glutamate/Aspartate-linked; TARG1, Terminal ADP-ribose Glycohydrolase 1; MACROD2, Mono-ADP-ribosyl Hydrolase 2; ARH1, ADP-ribosyl Hydrolase 1; ARH3, ADP-ribosyl Hydrolase 3; Arg-linked, Arginine-linked; Ser-linked, Serine-linked; Af1521, Archaeoglobus fulgidus1521; SUDM, SARS-unique domain M; MacroH2A, MacroH2A.1 Histone; ALC1, Amplified in Liver Cancer 1; Nsp3, nonstructural protein 3; Mac1, MacroD-like macrodomain 1; SirTM, Macrodomain-linked sirtuins class M; DarTG2, DNA ADP-ribosyltransferase/DNA ADP-ribosyl glycohydrolase 2; dPARG, *Drosophila melanogaster* PARG; TcPARG, Thermomonospora curvata PARG; hPARG, Human PARG; hPARG111, Human PARG 111 kDa; NLS, nuclear localisation signal; PCNA, Proliferating cell nuclear antigen; PIP box, PCNA-binding motif; NES, nuclear export signal; RS/MTS, Regulatory segment/mitochondrial targeting sequence; hPARG-102, Human PARG 102 kDa; hPARG-99, Human PARG 99 kDa; hPARG-60, Human PARG 60 kDa; hPARG-55, Human PARG 55 kDa; NUDT16, Nucleoside Diphosphate Linked Moiety X-Type Motif 16; ENPP1, Ectonucleotide Pyrophosphatase/Phosphodiesterase 1; Tyr-linked, Tyrosine-linked; LLPS, liquid–liquid phase separation; NUDT5, Nucleoside Diphosphate Linked Moiety X-Type Motif 5; RAR, Retinoic Acid Receptor; ETs, Ellagitannins; GTs, Gallotannins; ADP-HPD, Adenosine 5′-diphosphate (hydroxymethyl)pyrrolidinediol; GPI16552, N-bis-(3-phenylpropyl)9-oxofluorene-2,7-diamide; RBPIs, Rhodanine-based PARG inhibitors; PDD0017273, 1-[(1,3-Dimethyl-1H-pyrazol-5-yl)methyl]-1,2,3,4-tetrahydro-N-(1-methylcyclopropyl)-3-[(2-methyl-5-thiazolyl)methyl]-2,4-dioxo-6-quinazolinesulfonamide; COH34, (E)-1-(((p-tolylthio)imino)methyl)naphthalen-2-ol; JA2131, 1,3-dimethyl-8-((2-morpholinoethyl)thio)-6-thioxo-1,3,6,9-tetrahydro-2H-purin-2-one; HR, Homologous Recombination; ER^+, Estrogen Receptor-positive.

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1. Introduction

The maintenance of genome integrity is fundamental to cellular survival and organismal health, yet the genome is constantly challenged by endogenous and exogenous stressors that can damage DNA. Cells have evolved a sophisticated network of signalling pathways to detect and repair these lesions, among which ADP-ribosylation plays a pivotal role. ADP-ribosylation is a reversible post-translational modification in which ADP-ribose dinucleotide units are covalently attached to proteins, nucleic acids, or other cellular macromolecules [1]. This modification is conserved across all domains of life [2–4] and regulates a broad array of cellular processes, including DNA damage repair [5–9], chromatin remodelling [10–12], transcription [6,11,13,14], ribosome biogenesis [15], cell death [9], stress responses [16–18], immune responses [19–24], and bacterial metabolism and infection [25–30].

Central to ADP-ribosylation signalling is the transfer of ADP-ribose moieties from nicotinamide adenine dinucleotide (NAD^+) to target molecules. In humans, this process is mediated by PARP enzymes, which catalyse the addition of mono- or poly-ADP-ribose chains (MARylation and PARylation, respectively), and reversed by ADP-ribosyl hydrolases, including macrodomain-containing enzymes and ADP-ribosyl-(dinitrogen reductase) glycohydrolases (DraG)-related ADP-ribosyl hydrolases (ARHs) [31]. The recognition and interpretation of PAR chains by specialised binding proteins establishes the so-called “PAR code”, which directs downstream signalling events critical for genome maintenance [32–41].

Among its diverse functions, ADP-ribosylation is best characterised for its role in safeguarding genomic integrity. Defective DNA damage response leads to genomic instability, increasing susceptibility to tumorigenesis, neurodegeneration, immune dysregulation, and age-related decline [42–45]. Nuclear PARPs, including the PARylating PARP1 and PARP2 and the MARylating PARP3, initiate the first wave of DNA damage response signalling [8,46–51]. PARP1 and PARP2 detect DNA lesions, coordinate base-excision repair (BER) at single-strand breaks (SSBs) [52,53], and participate in double-strand break (DSBs) repair through both homologous recombination at stalled replication forks [48,54,55] and non-homologous end joining (NHEJ) [56].

Upon engagement with SSBs and DSBs generated by genotoxic stress or during DNA replication [57–63], PARP1 rapidly undergoes automodification and ADP-ribosylates protein substrates in trans, including core histones [10,64–66]. Their activity is further modulated by regulatory cofactors such as Histone PARylation Factor 1 (HPF1) [67], Y-box–binding protein 1 (YB-1) [68], and even by intact DNA [69]. Depending on the structural context, PARP1/2 catalyse serine ADP-ribosylation (in cooperation with HPF1) [7,65,70–72], aspartate/glutamate ADP-ribosylation [73,74], and potentially tyrosine ADP-ribosylation [71,75], and can also install ADP-ribose directly onto DNA substrates [76–79]. In particular, assembly of the PARP1/2–HPF1 complex redirects PARP catalytic specificity, enabling efficient serine ADP-ribosylation on histones and thousands of additional substrates across the proteome [7,67,72,80–82]. The resulting accumulation of negatively charged PAR chains promotes chromatin relaxation, facilitates the recruitment of DNA damage response factors [41,83,84], and drives PAR-dependent biomolecular condensates that potentiate DNA repair [41,85–90].

Equally important, tight control of PAR synthesis and degradation is essential for maintaining cellular homeostasis. This regulation is executed by a diverse set of ADP-ribosyl hydrolases that collectively function as the central modulators of ADP-ribose turnover. PAR degradation is driven primarily by PARG, the major de-PARylating enzyme [91] and the only known hydrolase capable of resolving branched PAR structures [92]. This unique catalytic capacity establishes PARG as the principal regulator of PAR chain dynamics and a key determinant of ADP-ribosylation homeostasis.

Several other hydrolases instead act at the level of mono-ADP-ribose (mono-ADPr), specifically removing terminal ADP-ribose to terminate PARP-dependent chain elongation and signalling. These mono-ADP-ribosyl hydrolases exhibit pronounced residue specificity. For example, glutamate/aspartate-linked (Glu/Asp-linked) mono-ADPr is reversed by Terminal ADP-ribose Glycohydrolase 1 (TARG1) [93], Mono-ADP-ribosyl hydrolase 2 (MACROD2) [94], and the PARP14 macrodomain [95]. In contrast, ADP-ribosyl hydrolase 1 (ARH1) hydrolyses arginine-linked (Arg-linked) mono-ADPr [96,97]. ADP-ribosyl hydrolase 3 (ARH3) preferentially removes serine-linked (Ser-linked) mono-ADPr [98], but also degrades PAR chains—thereby suppressing parthanatos—and processes O-acetyl-ADP-ribose generated during sirtuin-mediated deacetylation [99,100], underscoring its notable structural versatility.

Collectively, the coordinated activities of these hydrolases give rise to a finely tuned, spatiotemporally regulated PAR-dependent signalling network that requires precise modulation to maintain genomic and cellular integrity.

The therapeutic targeting of ADP-ribosylation signalling poses a challenge to genomic stability by exploiting vulnerabilities in the DNA damage response pathway, which can be harnessed for anticancer therapy. The centrality of PARP1/2-mediated ADP-ribosylation in the DNA damage response has catalysed the development of PARP inhibitors (PARPis) as a major class of precision cancer therapeutics [101–103]. Clinically approved agents—including talazoparib, olaparib, niraparib, and rucaparib—exploit synthetic lethality by selectively targeting tumours harbouring defects in homologous recombination repair genes such as *BRCA1* and *BRCA2* [101,104,105]. Mechanistically, these inhibitors act by competing with NAD^+ for binding to the PARP catalytic site, thereby blocking PAR synthesis. Several PARPis additionally exert cytotoxicity by “trapping” PARP1/2 on chromatin at sites of DNA lesions, a process that stalls replication forks and exacerbates genome instability [105–108]. Their clinical efficacy has been firmly established across *BRCA*-mutated breast and ovarian cancers, and subsequently extended to pancreatic and prostate cancers [104,109–118].

Despite these successes, the therapeutic durability of PARPis is frequently undermined by acquired resistance. Mechanisms include restoration of homologous recombination, protection of stalled replication forks, and increased drug efflux, each of which enables tumour cells to evade PARPi-induced lethality [103,105,119]. These limitations have stimulated intense efforts to identify alternative or complementary nodes in the ADP-ribosylation cycle that might be therapeutically exploited.

Within this context, PARG has emerged as a compelling target. Pharmacological inhibition of PARG induces profound replication stress, particularly in tumour cells with pre-existing defects in the replication machinery, thereby promoting mitotic catastrophe and selective cancer cell killing [103,120–124]. Although a predictive genomic signature for PARG inhibitor sensitivity has not yet been defined, mounting evidence positions PARG as a mediator of oncogenic fitness. In breast cancer, elevated PARG activity has been shown to promote tumourigenesis by regulating SMAD signalling through enhanced PAR degradation, particularly in Human Epidermal Growth Factor Receptor 2 (HER2)-positive and triple-negative subtypes [125]. Genetic loss of PARG diminishes cellular transformation and invasive capacity, and facilitates sensitisation to DNA-damaging agents, thereby underscoring its dual utility as a therapeutic target and a prognostic marker.

Importantly, PARG inhibition not only offers a new therapeutic avenue but also provides a powerful tool for probing the mechanistic underpinnings of PAR turnover and the broader consequences of dysregulated ADP-ribosylation in cancer biology.

Reflecting growing translational interest, several clinical trials are now evaluating PARG inhibitors as monotherapies and in combination with other DNA-directed agents. Together, these efforts signal a broadening of the therapeutic landscape of ADP-ribosylation biology—one that extends beyond PARP inhibition to encompass the full dynamics of PAR metabolism.

2. Macrodomain: evolutionary conservation

PARG belongs to the family of macrodomain-containing ADP-ribosyl hydrolases, the largest group of macrodomain proteins [126]. All members share a conserved ADP-ribose-binding domain, known as the macrodomain, which mediates interactions with ADP-ribose, PAR, and O-acetyl-ADP-ribose—key metabolites of NAD^+ metabolism [40,127,128]. These binding properties have enabled the identification of ADP-ribosylated substrates *in vitro* using the *Archaeoglobus fulgidus*1521 (Af1521) macrodomain as a binder [129], improving the isolation and mass spectrometry-based characterisation of ADP-ribosylated proteins [130–134].

Macrodomain-containing proteins are evolutionarily conserved across all kingdoms of life, from viruses and bacteria to humans. They perform essential roles in inter- and intracellular signalling, transcriptional regulation, DNA repair, and maintenance of genomic stability [31,135]. Structurally, macrodomain proteins are classified into at least six phylogenetic groups: MacroD-type, MacroD2-type, SARS-unique domain M (SUDM)-type, MacroH2A Histone (MacroH2A)-type, Amplified in Liver Cancer 1 (ALC1)-type, and PARG-type [127].

Some macrodomains function as selective readers of ADP-ribosylation signalling. For example, MacroH2A1.1 and ALC1 (MacroH2A- and ALC1-type, respectively) bind PAR to facilitate chromatin compaction and DNA damage-induced chromatin remodelling [127]. By contrast, MacroD-like proteins (MacroD1, MacroD2, PARP9, PARP14) and TARG1 (ALC1-like) possess catalytic activity that hydrolyses mono-ADP-ribosylation (MARylation) from acidic amino acid residues, and they also act on O-acetyl-ADP-ribose and terminal phosphate esters of nucleic acids [77,95,127,136].

In viruses and bacteria, macrodomains often contribute to pathogenicity. For instance, SARS-CoV-2 nonstructural protein 3 (nsp3) contains three macrodomains, with MacroD-like macrodomain 1 (Mac1) reversing host anti-viral MARylation and promoting viral survival, while the SUD-M domain is involved in viral replication [137]. Certain bacteria employ a sirtuin-dependent reversible ADP-ribosylation system coupled to a Zn-dependent macrodomain (Macrodomain-linked sirtuins class M, SirTM), regulating virulence and stress responses via a zinc-dependent catalytic mechanism distinct from other macrodomains [138,139]. In the bacterial ALC1-group, the DNA ADP-ribosyl transferase/DNA ADP-ribosyl glycohydrolase 2 (DarT/G2) toxin-antitoxin system modulates stress and anti-phage responses through reversible MARylation of genomic DNA; overexpression of DarG removes MARylation, restoring growth, and represents a potential target for antimicrobial strategies [25,93,140–143].

PARG-type macrodomains are conserved across eukaryotes and bacteria, highlighting their fundamental role in PAR metabolism. In *Arabidopsis thaliana*, PARG1 regulates pattern-triggered immunity [144]. In *Caenorhabditis elegans*, nuclear and cytosolic PARGs modulate DNA damage responses and survival [145]. In *Drosophila melanogaster*, dPARG uniquely regulates PAR dynamics during DNA damage response and participates in transcriptional programmes linked to development and ageing [146–148]. Bacterial PARGs, such as *Thermomonospora curvata* PARG (TcPARG) and *Deinococcus radiodurans* PARG, were suggested to safeguard cells from genotoxic stress, including UV-induced DNA damage, by preventing toxic PAR accumulation [126,149].

The remarkable evolutionary conservation of PARG, combined with its multifaceted roles in DNA repair, replication, and stress response, underscores its central function in maintaining cellular homeostasis [126]. Human PARG (hPARG) acts as the principal gatekeeper of ADP-ribose dynamics, precisely sculpting PARylation signals to preserve genome integrity, regulate RNA metabolism, and support overall cellular resilience. Notably, hPARG is encoded by a single human gene, contrasting with the diversified families of other macrodomain hydrolases—highlighting the evolutionary pressure to maintain a dedicated, tightly regulated enzyme capable of coordinating diverse ADP-ribose turnover events.

2.1. hPARG splice variants and structural domain organisation

In mammals, a single gene encodes PARG, which undergoes alternative splicing to generate multiple isoforms with distinct molecular weights, subcellular localisations, and functional roles (Fig. 1A and Fig. 1B [150]. The full-length 111 kDa isoform, hPARG111, is organised into four structural subdomains:

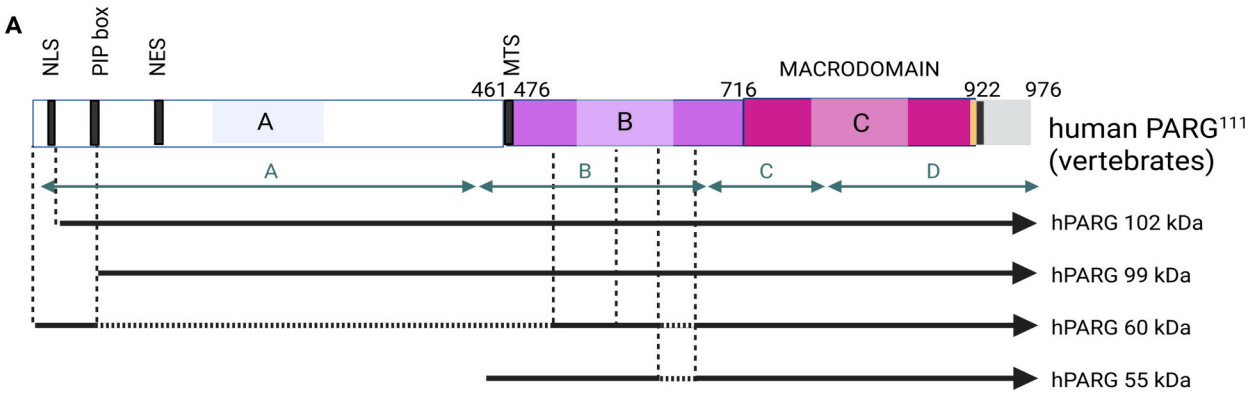
- A subdomain: Contains a nuclear localisation signal (NLS) [150], a Proliferating Cell Nuclear Antigen (PCNA)-binding motif (PIP box) [151], and a nuclear export signal (NES) [152], collectively regulating nuclear-cytoplasmic trafficking and facilitating interactions with replication-associated proteins.
- B subdomain: A highly structured and evolutionarily conserved region comprising a regulatory segment and a mitochondrial targeting sequence (RS/MTS), suggesting roles in subcellular targeting and functional regulation [153].
- C subdomain: Houses the catalytic core, with residues Asp737, Glu755, and Glu756 coordinating the hydrolysis of ribose–ribose glycosidic bonds in PAR chains [154,155].
- D subdomain: Mediates substrate recognition by interacting with ADP-ribose moieties, guiding the polymer into the catalytic site for cleavage [156].

The arrangement of the C and D subdomains forms the characteristic macrodomain fold, enabling precise recognition and efficient hydrolysis of PAR chains (Fig. 1A).

A variety of PARG splice and translation variants give rise to isoforms with distinct intracellular distributions and potentially specialised roles (Fig. 1A). The full-length hPARG-111 isoform is enriched in the nucleus due to two strong classical NLS sequences [150,157]. In contrast, the alternatively spliced hPARG-102 and hPARG-99 isoforms lack exon 1 and localise predominantly to the cytoplasm under unstimulated conditions [158]. Live-cell imaging of GFP-tagged constructs has shown that these patterns are not static: the cytoplasmic hPARG-102 isoform can translocate to the nucleus after γ-irradiation, whereas nuclear hPARG-111 partially redistributes to the cytoplasm [158]. Whether such shuttling occurs for endogenous PARG in a stimulus- or cell type-dependent manner remains to be clarified.

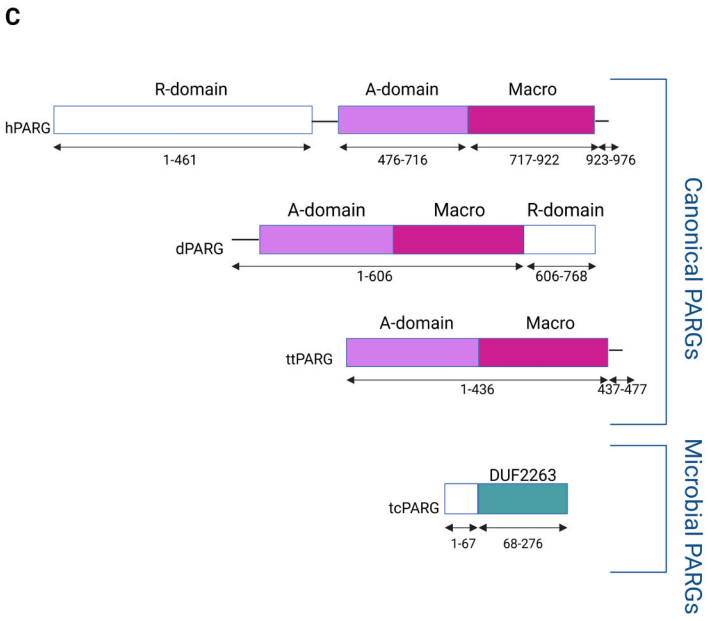
Additional isoforms arise via alternative translation initiation. hPARG-60 is detected in several cellular compartments. Initial work suggested nucleo-mitochondrial shuttling [150,157,159,160], but subsequent analyses indicate that hPARG-60 is predominantly nuclear, consistent with two putative NLS sequences mapped to amino acids 421–446 and 838–844 [161]. The shorter hPARG-55 isoform, produced from the same transcript, contains an accessible mitochondrial-targeting signal and is thus strictly mitochondrial [157]. Trafficking behaviour across the isoforms may be partly explained by embedded import and export motifs. Two putative NES sequences at amino acids 126–134 and 881–888 have been proposed to underlie the mainly cytoplasmic localisation of hPARG-102 and hPARG-99 [150,157].

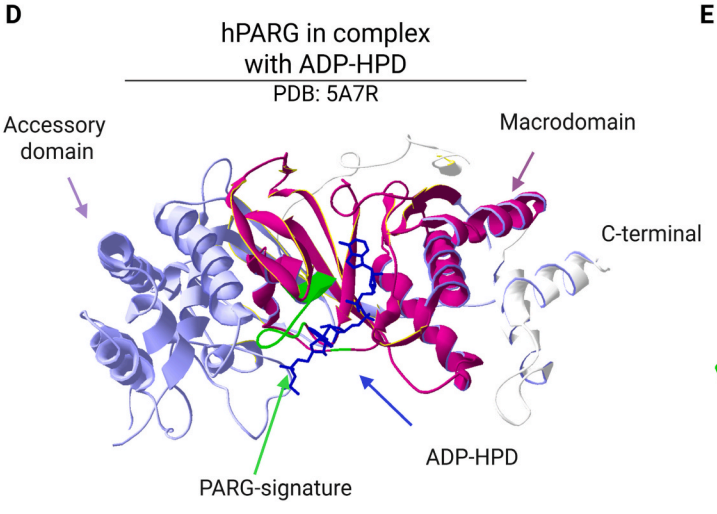
Importantly, functional evidence supports a role for mitochondrial ADP-ribose turnover mediated by hPARG-55 as well as by ARH3. Targeted expression of PARP1 in mitochondria, resulting in the constitutive presence of PAR within the organelle, demonstrated that the activity of the overexpressed PARG Δ1-460 construct (corresponding to the mitochondrial hPARG-55 isoform) was sufficient to significantly reduce mitochondrial PAR levels, similarly to ARH3, whereas a cytosolic PARG variant lacking the mitochondrial targeting signal left mitochondrial PAR unaffected [162]. This local PAR synthesis was shown to reduce mitochondrial NAD^+ levels and membrane potential, while concomitantly promoting a metabolic shift towards increased glycolysis. Moreover, PARP inhibition in this system revealed active mitochondrial PAR degradation, supporting the presence of an operative PAR-processing machinery within mitochondria and suggesting that mitochondrial PARG and ARH3 enzymes contribute to NAD^+-linked mitochondrial



B

PARG Isoforms	Subcellular Localisation
hPARG 111	Nucleus/ Cytoplasm
hPARG 102	Cytoplasm/ Nucleus
hPARG 99	Cytoplasm
hPARG 60	Nucleus
hPARG 55	Mitochondria





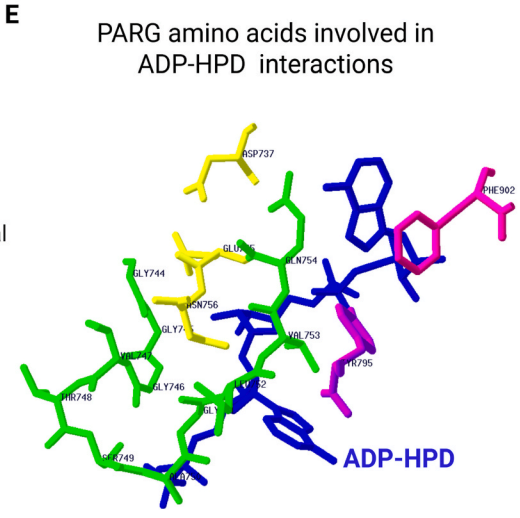


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Fig. 1. Structural organisation, isoforms, and catalytic features of human PARG. A. Schematic representation of the domain architecture of human PARG (hPARG). The full-length hPARG-111 isoform comprises an N-terminal regulatory domain (aa 1–461), an accessory domain (aa 476–716), and a C-terminal macrodomain (aa 717–922). hPARG-102 and hPARG-99 lack several conserved N-terminal motifs, whereas hPARG-60 contains an alternative 16-amino-acid N-terminus unique to this isoform. hPARG-55 lacks the regulatory domain entirely. hPARG can be subdivided into four functional regions: domain A (regulatory), domain B, and domains C and D, which together form the macrodomain fold. Domain A contains nuclear localisation signals (NLS), a PCNA-interacting protein (PIP) motif, and nuclear export signals (NES), whereas domain B harbours the regulatory segment/mitochondrial targeting sequence (RS/MTS). **B**. Intracellular localisation of the five hPARG isoforms. **C**. Comparison of domain organisation between canonical eukaryotic PARGs and microbial PARGs. Canonical PARGs from vertebrates, invertebrates, and lower eukaryotes contain both an accessory domain and a macrodomain. hPARG and *Drosophila melanogaster* PARG (dPARG) additionally possess a regulatory domain that varies in length and position. In contrast, microbial PARGs, exemplified by Thermomonospora curvata PARG (tcPARG), consist solely of the DUF2263 domain and lack accessory and regulatory regions; the function of DUF2263 remains unclear. **D**. Cartoon–stick representation of hPARG (PDB: 5A7R) bound to the ADP-HPD inhibitor. The accessory domain and macrodomain are shown with the PARG signature motif highlighted in green and the bound inhibitor in blue. **E**. Enlarged view of the catalytic pocket highlighting key residues involved in substrate binding and catalysis: Asp737, Glu755, and Glu756Asn (yellow); residues of the PARG signature motif GGG-$X_{6–8}$-QEE (Gly744, Gly746, Val747, Thr748, Ala750, Gly751; green); and aromatic residues Tyr795 (violet) and Phe902 (magenta).

regulatory pathways.

Mouse genetics further highlights functional differences among PARG isoforms. Deletion of exons 2 and 3, which removes the nuclear PARG-110 (the human hPARG-111 equivalent) and the cytoplasmic PARG-101/hPARG-102 and PARG-99 isoforms, results in viable mice that exhibit increased sensitivity to alkylating agents and ionising radiation [159,160]. In contrast, deletion of exons 3 and 4, which ablates all PARG isoforms, causes early embryonic lethality and profound hypersensitivity to DNA-damaging agents [163]. Notably, shorter isoforms such as hPARG-60 and hPARG-55 lack the N-terminal regulatory region proposed to modulate PARG activity, suggesting that they may be constitutively active [161] and responsible for degrading low-level PAR synthesised under basal conditions. Nevertheless, hPARG-55 and hPARG-60 were reported to be catalytically inactive *in vitro* due to the absence of exon 5-encoded amino acids [164], indicating that their biological relevance may instead rely on spatially restricted functions, protein–protein interactions, or cooperation with other mitochondrial ADP-ribosyl hydrolases, such as ARH3 [164]. Notably, these isoforms—hPARG-60 and the mitochondrial hPARG-55—appear to be essential for embryonic development [161].

Structurally, human PARG differs markedly from most bacterial PARG homologues, as it possesses an accessory domain and an N-terminal regulatory domain in addition to the conserved PARG-like macrodomain (Fig. 1C) [127,154,165]. These architectural differences have led to the classification of PARG enzymes into two broad groups: canonical PARGs, which include vertebrate and many eukaryotic enzymes, and bacterial PARGs, which generally lack these regulatory extensions [31,127]. Comparative analyses of the structural organisation of hPARG and dPARG within the canonical subgroup further highlight diversification in domain composition, suggesting that differences in these auxiliary elements may contribute to variations in substrate selectivity and catalytic behaviour between the two enzymes (Fig. 1C).

2.2. hPARG three-dimensional structure and substrate specificity

The canonical 111 kDa hPARG isoform is organised into three functional regions: an N-terminal putative regulatory domain, the PARG accessory domain, and the macrodomain—the latter two defining the characteristic architecture of canonical PARGs in higher organisms (Fig. 1A and Fig. 1C). The accessory domain adopts an α-helical fold and extends the core catalytic motif, which consists of a typically 10-stranded β-sheet. The precise functional role of the accessory domain remains to be fully elucidated [31].

Insights from the crystal structure of a catalytically inactive hPARG mutant (E756N) in complex with a synthetic dimeric ADP-ribose substrate (PDB: 5A7R) reveal that most substrate contacts are mediated by the macrodomain, with ADP-ribose positioned atop the β-sheet within the binding cleft [155] (Fig. 1D).

The hPARG macrodomain comprises a seven-stranded mixed β-sheet flanked by five α-helices and contains the PARG-specific GGGx(6–8)QEE catalytic motif within loop 1. The adenine moiety of ADP-ribose lies parallel to the protein surface, shielded from solvent via π–π stacking with the conserved Phe902 (Fig. 1D and Fig. 1E) [155]. Adenine binding is further stabilised by protein- and water-mediated interactions with ring nitrogens (N1, N7) and the C6 amino group, while Tyr795 coordinates O5′ and engages in edge-stacking with the adenosine moiety. Mutational studies, including adenine-to-hypoxanthine substitutions, confirm that these contacts confer ligand specificity, providing a structural basis for rational inhibitor design (Section 4).

The diphosphate-binding loop coordinates the diphosphate and distal ribose, imposing a strained conformation that positions C1″ and O1″ near Pα. A hydrophobic G[A,V][F,Y] motif within this loop directs the distal ribose toward the catalytic site. In canonical PARGs, a conserved glutamine preceding the GGGx(6–8)QEE motif interacts with the 3″OH group, positioning the 2′,1′-O-glycosidic bond adjacent to Glu756, which acts as a general base. Glu756 protonates the leaving group, forming an oxocarbenium intermediate, and subsequently activates a water molecule to complete hydrolysis, although the stereochemistry of the resulting ADP-ribose (α or β) remains unresolved [126,156,165–167].

The open substrate-binding cleft allows canonical PARGs to display both exo- and endo-activity [155,168]. In exoglycosidic mode, hPARG sequentially removes ADP-ribose units from the termini of PAR chains, hydrolysing α(1″-2′) O-glycosidic linkages—a critical step in the initial phase of de-PARylation (Fig. 2). Endoglycosidic cleavage enables hPARG to target internal ribose–ribose linkages, including branch points, generating shorter oligomers subsequently processed by other hydrolases [169,170] (Fig. 2). Structural analyses indicate that transitions between exo- and endo-binding modes depend on the PAR/PARG ratio [155,167,168]. This adaptive activity allows hPARG to modulate PAR degradation according to the extent of DNA damage: extensive PARylation under severe stress may promote apoptosis through the release of larger oligo-PAR fragments, amplifying the apoptotic signal [167]. Microbial PARGs, originally considered strict exohydrolases, also display endoglycosidic activity that can be exploited in mass spectrometry analyses of poly-ADP-ribose catabolism [126,168].

Substrate specificity is further reinforced by structural features stabilising PAR binding. Hydrogen bonds and electrostatic interactions within the macrodomain align the negatively charged PAR polymer, ensuring precise positioning for catalysis. This architecture underlies hPARG's high processivity and its ability to accommodate diverse PAR lengths and branching structures, essential for resolving extensive PARylation generated during severe genotoxic stress.

Unlike PARG, ARH3, and other macrodomain-containing hydrolases (Fig. 2), additional, structurally unrelated hydrolases have been reported to cleave PAR and MAR through distinct chemical mechanisms, namely by hydrolysing phosphodiester bonds. These include the phosphodiesterases Nucleoside Diphosphate–Linked Moiety X-Type Motif 16 (NUDT16) [171] and Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) [172]. In this context, the modification is converted into a protein-conjugated ribose-5′-phosphate, with the concomitant release of adenosine monophosphate (Fig. 2), thereby expanding the

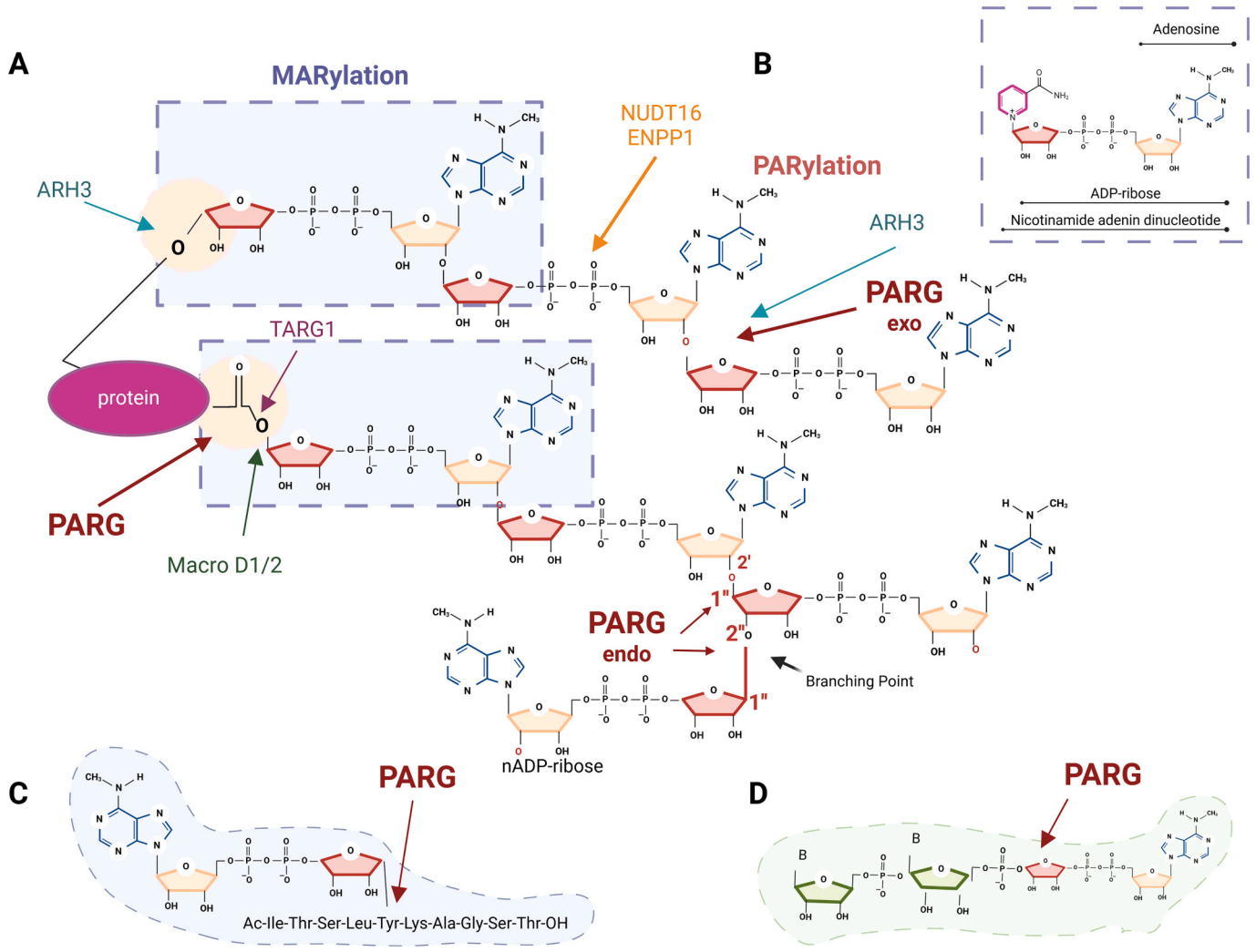

Fig. 2. Enzymatic activities and substrate specificity of hPARG. A. Reversal of mono-ADP-ribosylation (MARylation) on protein substrates. Serine-linked mono-ADP-ribosylation is hydrolysed by ARH3, whereas hPARG does not cleave the O-linked Ser-ADPr bond. Asp/Glu-linked mono-ADP-ribosylation is reversed by TARG1 and the macrodomain hydrolases MacroD1/2 and can also be processed by hPARG. **B**. hPARG activity on PARylated proteins. hPARG exhibits both exo- and endoglycosidic activities, hydrolysing ribose–ribose glycosidic bonds within PAR chains. Exoglycosidic cleavage releases free ADP-ribose, whereas endoglycosidic cleavage generates PAR oligomers of varying length and resolves PAR branching points. ARH3 degrades PAR chains exclusively via exoglycosidic activity. **C**. Non-canonical hPARG activity on Tyr-ADP-ribosylated synthetic peptides. Tyrosine ADP-ribosylation has been associated with ribosome biogenesis, although evidence is currently limited to *in vitro* assays. **D**. Emerging role of hPARG in RNA-associated ADP-ribosylation. hPARG regulates RNA-linked ADP-ribosylation pathways implicated in RNA metabolism, RNA damage surveillance, and potentially RNA structure and stability.

repertoire of cellular PAR-processing mechanisms.

2.3. *The dynamic process of ADPr signalling reversal in cells*

Historically, hPARG was believed to function almost exclusively as an exoglycosidase, removing distal ADP-ribose units from PAR chains (Fig. 2). Early methodological constraints—particularly the inability to detect labile ester-linked ADP-ribosylation—obscured the possibility that hPARG might also trim terminal ADP-ribosylation linkages *in vivo*. Recent technological advances, including mass spectrometry platforms that preserve ester-linked modifications, linkage-selective antibodies [173], and synthetic peptides containing site-specific ADP-ribosylation linkages [174], have significantly expanded our understanding of PARG substrate scope. Together with other recent achievements, these tools have prompted a reassessment of the mechanistic model of ADP-ribosylation turnover, revealing that hPARG is active not only toward PAR, including branches [92,175], but also toward mono(ADP-ribosyl) linkages, including Asp/Glu-ADP-ribosylation, Tyr-ADP-ribosylation, and even RNA-linked ADP-ribosylation (Fig. 2) [169,173,174,176,177].

During the DNA damage response—as well as in DNA damage-independent contexts such as transcription—initial PARP1 activation rapidly generates MARylation on glutamate and aspartate residues, including automodification of PARP1. These early events are comparatively minor, however, as serine-ADP-ribosylation becomes the predominant modification once the PARP1–HPF1 complex assembles in the presence of DNA damage [72,173]. PARG-mediated reversal of PARP1-dependent signalling proceeds through a stepwise, two-wave mechanism [100] (Fig. 3). In the first wave, hPARG exhibits high processivity toward PAR chains, cleaving the O-glycosidic ribose–ribose linkages and thereby releasing short PAR oligomers while leaving behind terminal mono-ADP-ribosylated residues on Asp/Glu and Ser. Although hPARG can remove a fraction of Glu/Asp-linked mono-ADPr [178,179], full resolution of these linkages primarily relies on TARG1 (Fig. 3A) [93,170]. Serine-linked mono-ADPr generated during the trimming process is then efficiently hydrolysed by the serine-specific ADP-ribosyl hydrolase ARH3 (Fig. 3B) [98]. PARG also cooperates with TARG1 to reverse DNA ADP-ribosylation at telomeres [79], further illustrating substrate- and context-specific coordination among ADP-ribosyl

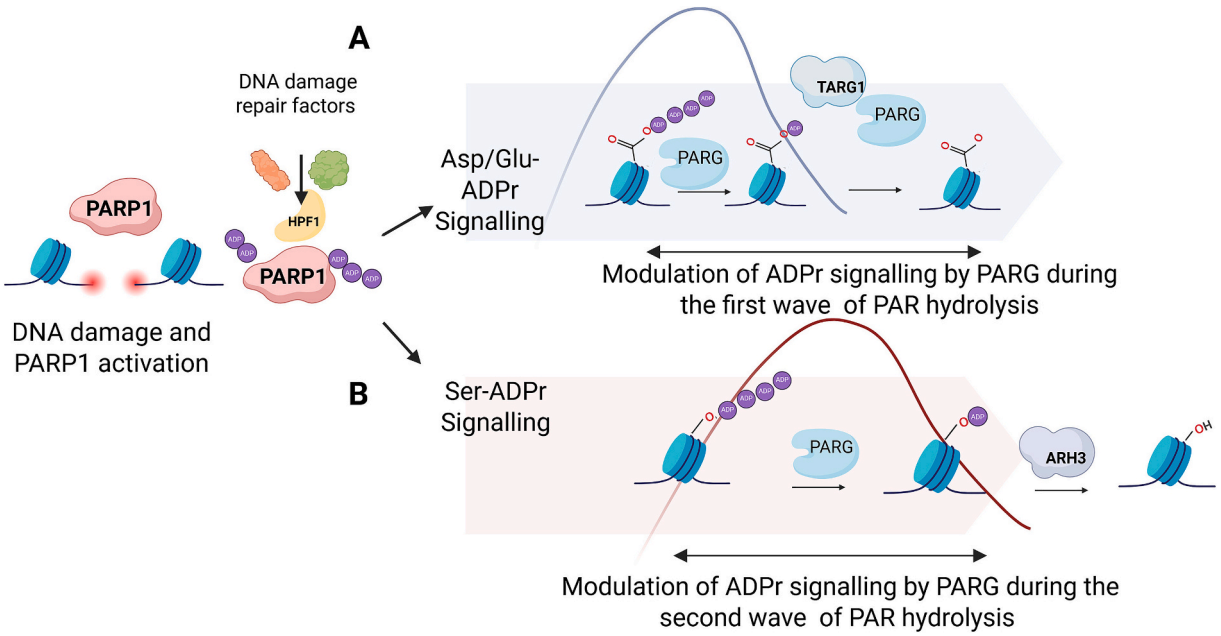

Fig. 3. Stepwise reversal of PARP1-dependent ADP-ribosylation signalling by hPARG. This figure illustrates a two-wave model of PARG-mediated reversal of PARP1 signalling. **A.** Following PARP1 activation (left side of the panel), hPARG preferentially hydrolyses PAR chains formed during early Asp/Glu-linked ADP-ribosylation signalling on DNA repair proteins. This releases PAR oligomers and mono-ADP-ribosylated substrates while leaving terminal Asp/Glu- and Ser-linked mono-ADPr. **B.** Upon formation of the PARP1–HPF1 complex, PARylation predominantly occurs on serine residues. hPARG processes serine-linked PAR chains through exo- and endoglycosidic cleavage, generating free ADP-ribose, short PAR oligomers, and Ser-mono-ADP-ribosylated substrates. hPARG does not hydrolyse the Ser-ADPr bond, which is subsequently removed by ARH3.

hydrolases. Importantly, hPARG does not cleave the ADP-ribose–amino acid glycosidic bond itself, underscoring its strict specialisation for degrading PAR chain architecture rather than removing the terminal modification.

A contrast emerges when comparing hPARG with its *Drosophila* homologue. dPARG displays broader substrate specificity, efficiently hydrolysing terminal serine- and tyrosine-linked (Tyr-linked) ADP-ribosylation. In *Drosophila*, which lacks the dedicated ARH3, dPARG serves as the primary enzyme reversing dPARP1–dHPF1-dependent ADP-ribosylation [146]. Structural analyses demonstrate that dPARG's catalytic core is highly conserved and closely resembles those of mammalian and protozoan PARGs. Its enhanced activity toward serine and tyrosine MAR arises not from a fundamentally distinct catalytic mechanism but rather from subtle structural variations near the active site that confer increased substrate flexibility. This evolutionary divergence illustrates how minor adjustments within the catalytic pocket can broaden PARG's biochemical repertoire in a lineage-specific manner.

Emerging evidence further indicates that removal of RNA-linked ADP-ribosylation may involve residues outside the canonical catalytic domain, suggesting a mechanistically distinct mode of substrate recognition and hydrolysis [176]. These findings broaden the conceptual framework of PARG activity beyond its classical definition as merely a PAR-degrading enzyme.

Collectively, structural, biochemical, and mechanistic insights highlight hPARG's surprising versatility in reversing ADP-ribosylation signalling. This expanded understanding of PARG activity provides the foundation for exploring its regulatory functions in cellular physiology and its therapeutic potential, as discussed in the following section.

3. ADP-ribosylation reversal and regulation of cellular processes by hPARG

Through its versatile catalytic activity, hPARG regulates the amplitude, duration, and spatial confinement of ADP-ribosylation signalling, positioning it at the centre of ADP-ribose metabolism, genome stability, and overall cellular homeostasis. Disruptions in this equilibrium result in toxic PAR accumulation, which compromises cell viability and can ultimately trigger cell death. This vulnerability has spurred interest in PARG inhibitors as components of synthetic lethality-based strategies aimed at exploiting replication-associated vulnerabilities in cancer cells [180]. Such approaches may expand therapeutic possibilities beyond those offered by PARPis, revealing new dependencies within ADP-ribosylation-regulated processes [180]. To date, few studies have comprehensively explored the interplay between PARP1 and PARG across cellular contexts. Identifying molecular pathways affected by chemical modulation of PARG can provide the rationale for alternative therapeutic strategies. The following sections summarise the principal cellular processes regulated by the PARP1–PARG axis that could be leveraged for anticancer interventions.

3.1. Nuclear functions regulated by hPARG

3.1.1. DNA repair and nuclear condensates

The PARP1–PARG axis is a central determinant of DNA damage response fidelity, modulating multiple steps of the repair cascade. PARP1 activation at single-strand DNA breaks initiates Asp/Glu-ADP-ribosylation and Ser-ADP-ribosylation signalling. hPARG is the principal enzyme responsible for removing or trimming these modifications in cells, thereby controlling both the magnitude and duration of PARP1-dependent signalling (Fig. 4A).

Maintenance of genome stability critically depends on PARG activity. Loss or inhibition of PARG leads to marked accumulation of Glu/Asp-ADP-ribosylation [173], disrupts DNA damage response pathways, and compromises replication stress tolerance [170]. Excess Asp/Glu-ADP-ribosylation induces replication fork slowing, DNA strand breaks, cell-cycle arrest, and cytotoxicity [170]. Cooperative activity with the hydrolase TARG1 further limits buildup of Asp/Glu-ADP-ribosylation: TARG1 loss enhances replication stress and sensitises cells to PARPis and Topoisomerase II poisons, while concurrent loss of TARG1 and PARG results in synthetic lethality due to uncontrolled ADP-ribosylation accumulation [170] (Fig. 4B).

As mentioned above, serine-linked ADP-ribosylation is similarly

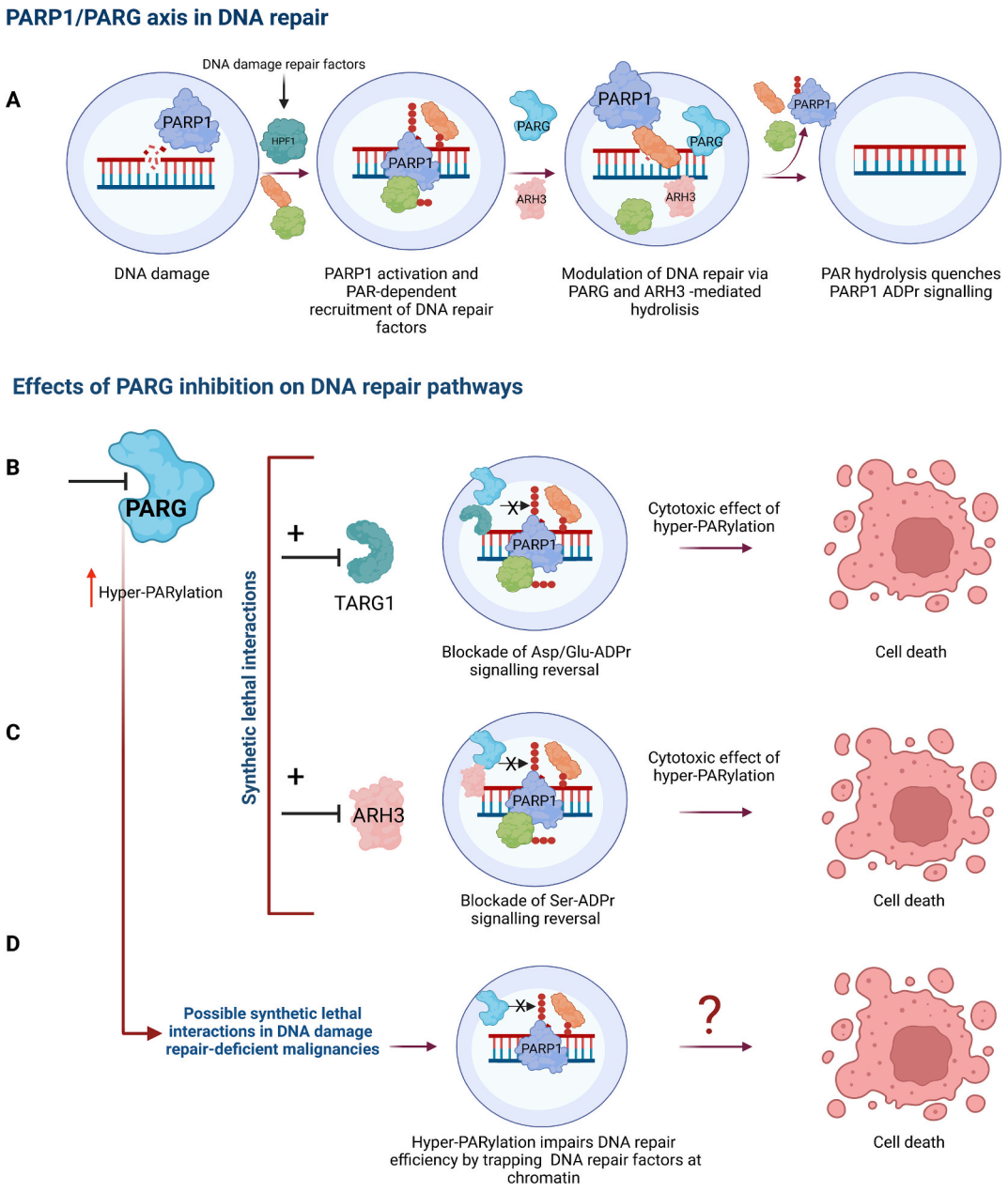

Fig. 4. Nuclear functions of hPARG in DNA repair. This figure highlights the role of hPARG in preserving genome stability by regulating PAR turnover. **A**. DNA damage activates PARP1 at lesion sites, leading to recruitment of HPF1 and DNA repair factors and induction of Asp/Glu- and Ser-linked ADP-ribosylation. hPARG limits PAR accumulation by controlling the magnitude and duration of PARP1-dependent signalling. **B**. Effects of PARG inhibition on DNA repair. Chemical inhibition of hPARG results in the accumulation of Asp/Glu-linked ADP-ribosylation, impairing DNA damage response pathways and replication stress tolerance. Hyper-PARylation induces replication fork slowing, DNA strand breaks, cell-cycle arrest, and cytotoxicity. TARG1 cooperates with hPARG to restrict Asp/Glu-ADPr accumulation, and the combined loss of both enzymes leads to synthetic lethality. **C**. Regulation of serine-linked ADP-ribosylation. hPARG trims serine-linked PAR chains to generate Ser-mono-ADP-ribosylated substrates, which are subsequently removed by ARH3. In ARH3-deficient cells, PARG inhibition causes excessive PAR accumulation, chromatin disorganisation, replication defects, telomere instability, and cell death. This synthetic lethal interaction is observed in both homologous recombination-deficient and proficient cancer models. **D**. Therapeutic implications. Impaired PAR removal following PARG inhibition compromises DNA repair efficiency, providing a rationale for targeting hPARG in cancers with defects in DNA damage response pathways.

governed by a two-step turnover mechanism in which PARG generates mono-Ser-ADP-ribosylation that is subsequently removed by ARH3 [169]. In *ARH3*-deficient cells, PARG inhibition produces hyper-PARylation, chromatin disorganisation, replication impairment, telomere defects, and cell death [100] (Fig. 4C). This synthetic lethal interaction is evident in both homologous recombination–deficient and proficient cancer models, where combined ARH3 and PARG suppression enhances cytotoxicity and potentiates alkylating agents [181].

PARG also participates in feedback regulation of PARP1 expression. In HeLa cells, PARG depletion lowers PARP1 transcript levels and reduces PAR accumulation, a compensatory mechanism that limits cytotoxic PAR buildup [182]. This reciprocal control provides a therapeutic opportunity, as PARG depletion increases sensitivity to staurosporine-induced apoptosis [182].

De-PARylation is further required for the timely recruitment and release of DNA repair factors. PARylated PARP1 recruits XRCC1 through non-covalent PAR binding; PARG-mediated PAR degradation promotes XRCC1 dissociation and progression of single-strand break repair.

Inhibition of PARG traps XRCC1 at chromatin and impairs repair efficiency [183]. Similarly, RECQL4 requires transient PARylation for recruitment to double-strand breaks, while PARG-mediated de-PARylation is necessary for the helicase to perform its end-joining and annealing activities [184]. These findings highlight the potential of PARG inhibitors to reveal new synthetic lethal interactions in DNA damage repair-deficient malignancies (Fig. 4D).

Recent advances in the DNA repair field have revealed that cells form membrane-less biomolecular condensates at sites of DNA damage to orchestrate the DNA damage response. PAR plays a central role in the nucleation, maturation, and dissolution of these condensates by promoting the reversible assembly of membrane-less structures that facilitate repair-factor recruitment (Fig. 5A) [86,87]. These condensates are selectively enriched in PARylated PARP1 and multiple DNA damage response components, enabling localised DNA repair [88–90,185]. Their formation is driven by liquid–liquid phase separation (LLPS), mediated by multivalent, non-covalent interactions between PAR and low-complexity protein domains in the presence of biogenic cations [86,185,186].

Among the PAR-responsive repair factors, the RNA-binding protein FUS is rapidly recruited to DNA lesions via non-covalent PAR binding (Fig. 5A). FUS is essential for the initiation of repair, as its loss abrogates the recruitment of 53BP1, NBS1, KU80, and SFPQ [187]. Recent evidence indicates that PAR promotes the initial condensation of FUS but is not required for its persistence; once assembled, FUS condensates adopt a prion-like, self-perpetuating architecture that remains stable even after PAR degradation at the damage site [188].

PARG-mediated PAR hydrolysis plays a key regulatory role in controlling the dynamics and turnover of these higher-order repair structures (Fig. 5B) [185]. Thus, chemical modulation of PARG offers a mechanistically novel approach for perturbing LLPS-driven DNA damage repair condensates, potentially sensitising cancer cells to replication stress and DNA-damaging therapies.

Emerging data further indicate that MARylation can also serve as a nucleating signal for biomolecular condensates, including stress granules, and may influence processes such as transcription, translation, starvation responses, and immune regulation [17,189]. Although the molecular determinants that drive MAR-dependent phase separation remain unclear, it is plausible that PARG inhibition—given its ability to remove MAR from Asp/Glu- and Tyr-ADP-ribosylated substrates [174,179]—could modulate these processes as well.

Finally, the recent discovery that PARP enzymes directly synthesise both protein-free and protein-linked PAR provides a new mechanistic framework for understanding DNA damage signalling, regulated cell death pathways such as parthanatos [190], and broader PAR-mediated intracellular communication [9]. These findings expand the functional landscape of PAR and underscore the importance of dissecting PARG's biochemical roles for future therapeutic innovation.

PARG also intersects with nuclear energy metabolism. Together with the Nucleoside Diphosphate Linked Moiety X-Type Motif 5 (NUDT5), PARG regenerates ATP from mono-ADP-ribose released during PAR degradation, a process required for efficient homologous recombination and RAD51 recombinase loading [191]. Perturbing this metabolic coupling—via PARG or NUDT5 inhibition—may therefore attenuate DNA

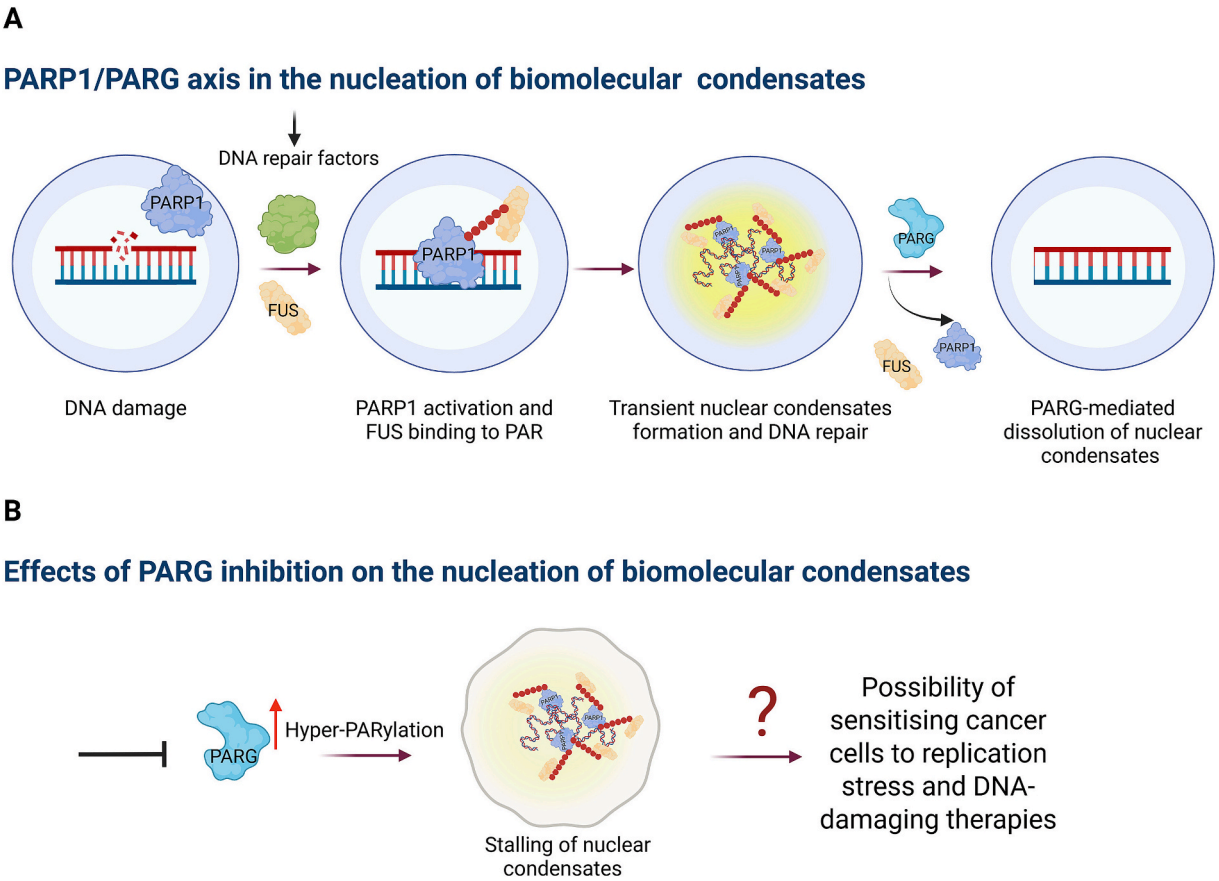

Fig. 5. hPARG **regulation of biomolecular condensates during dna repair.** This figure depicts the role of PAR metabolism in the assembly and dissolution of DNA damage-induced nuclear condensates. **A**. DNA damage-induced PARP1 auto-PARylation promotes the recruitment of repair factors, including the RNA-binding protein FUS, via non-covalent PAR interactions. These interactions drive the formation of transient, membrane-less nuclear condensates that coordinate DNA repair. hPARG-mediated PAR degradation facilitates condensate dissolution following repair completion. **B**. Effects of PARG inhibition. Inhibition of hPARG stabilises PARP1–repair factor assemblies, delaying condensate dissolution. Persistent condensates contribute to replication stress and can be exploited to sensitise cancer cells to DNA-damaging therapies.

repair capacity.

Regulation at the mRNA level further influences PARG function. In pancreatic ductal adenocarcinoma, the RNA-binding protein HuR stabilises PARG transcripts following PARP inhibition, supporting DNA repair and survival; HuR depletion reduces PARG expression and sensitises cells to PARPi [192].

Finally, PARG contributes to meiotic recombination. In *C. elegans*, PARG collaborates with meiotic chromosome-associated proteins to regulate double-strand break formation and homologous recombination, in part through scaffolding functions independent of its catalytic activity [193]. This suggests that both enzymatic and non-enzymatic roles of PARG may be therapeutically exploitable.

Collectively, these observations position hPARG as a central regulator of DNA damage repair fidelity—coordinating repair factor turnover, chromatin organisation, energy metabolism, and genome stability—and support therapeutic efforts to exploit PARG inhibition as a strategy to compromise DNA repair in cancer cells.

3.1.2. DNA replication

Excessive accumulation of PAR molecules is profoundly detrimental during DNA replication, where it can precipitate replication-fork collapse and the formation of DSBs (Fig. 6A and Fig. 6B). Under genotoxic or replicative stress, hPARG prevents the excessive accumulation of PAR that would otherwise obstruct the loading of RPA onto collapsed forks, thereby preserving the efficiency of homologous recombination–mediated repair [194]. Notably, this protective role is not restricted to stress conditions: given that most, if not all, endogenous poly(ADP-ribose) in proliferating cells is detected during normal S phase at sites of DNA replication [195], hPARG activity is likely to play a critical role during unperturbed S phase by suppressing aberrant replication-fork remodelling [196]. These observations collectively suggest that replication stress is an inherent and continuously mitigated feature of normal DNA synthesis, and that PARG inhibition has the potential to selectively exacerbate this intrinsic vulnerability in cancer cells.

A central component of hPARG's function in replication is the maintenance of replication-fork integrity. During Okazaki fragment maturation, transient PARylation of PCNA modulates its interaction with the Flap Endonuclease FEN1. hPARG removes PAR chains from PCNA, restoring productive PCNA–FEN1 binding and ensuring replication continuity [197]. Inhibition of PARG results in persistent PCNA PARylation, stalling of the replication fork, accumulation of SSBs, and ultimately catastrophic replication stress—an exploitable therapeutic outcome (Fig. 6C and Fig. 6D).

The pathogenic consequences of PAR accumulation during replication are further highlighted in preclinical ovarian cancer models. Pharmacological PARG inhibition induces marked sensitivity due to sustained fork stalling and replication catastrophe [121]. Mechanistically, PARG blockade is synthetically lethal with the checkpoint kinase CHK1: impaired PAR removal stabilises CHK1 at stalled forks, exacerbating replication arrest (Fig. 6E) [121]. Combined PARG/CHK1 inhibition markedly increases phosphorylation at Ser-139 of the histone variant H2AX, with γH2AX formation and apoptosis, while suppressing proliferation and clonogenic survival in both high- and low-grade serous ovarian cancer. Importantly, this combination does not confer sensitivity to PARPis, broadening therapeutic potential to tumour genotypes—including *BRCA*-wild-type cancers—that do not respond to classical PARPi therapy [121,122]. Moreover, this combined strategy offers a promising avenue to overcome both intrinsic and acquired PARPis resistance [122].

Beyond CHK1, the replication factor Timeless has emerged as another synthetic-lethal partner of PARG inhibition [121]. Loss or haploinsufficiency of Timeless phenocopies PARG-inhibitor sensitivity [198]. Integrative analyses using Timeless-manipulated models and intrinsically PARGi-sensitive ovarian cancer cells demonstrate that Timeless suppression induces replication catastrophe when combined with PARG inhibition [198] (Fig. 6F). Notably, nuclear PAR polymer levels increase in both resistant and sensitive contexts, indicating that PAR accumulation alone is insufficient to drive persistent replication stress. Instead, loss of Timeless or PARG reduces fork speed, and dual inhibition synergistically exacerbates fork asymmetry and instability [198]. ADP-ribosylome profiling further reveals that prolonged PARG inhibition in Timeless-deficient cells elevates ADP-ribosylation on chromatin-associated and RNA-processing factors, including Ki67, SAFB, and NOP2.

Importantly, nucleotide supplementation rescues PARG-inhibitor sensitivity in both engineered Timeless-deficient cells and intrinsically sensitive ovarian cancer lines, reversing all associated molecular and cell-cycle phenotypes except PAR polymer accumulation. Conversely, inhibition of thymidylate synthase—an enzyme central to deoxyribonucleoside triphosphate homeostasis—sensitises multiple ovarian cancer cell lines to PARG inhibition. Together, these findings demonstrate that PARG-inhibitor sensitivity reflects an impaired ability to regulate replisome velocity and to maintain helicase–polymerase coupling under nucleotide-limiting conditions [198]. These insights illuminate the molecular determinants that underpin PARG-inhibitor sensitivity and support the development of predictive biomarkers to prospectively identify tumours most likely to benefit from PARG-targeted therapies.

3.1.3. Transcription regulation

Over the past decade, several seminal studies have established the PARP1–PARG axis as a key regulator of chromatin architecture and transcriptional control [199–201] (Fig. 7A). Early biochemical work demonstrated that PARP1-dependent PARylation of polynucleosomes promotes chromatin decompaction, thereby enabling transcriptional activation [202]. PARP1 has been described to act as a transcriptional coregulator in cooperation with the basal transcription machinery, histone-modifying enzymes, and ATP-dependent chromatin remodellers. In addition, PARP1 modulates the activity of multiple sequence-specific transcription factors—including NF-κB, HES1, Elk1, Sox2, and nuclear hormone receptors—integrating environmental cues with transcriptional outputs [203]. Importantly, the recruitment of PARP1 to transcriptional loci implies localised enzymatic activation, establishing these sites as focal points for PARG-dependent signal termination.

Transcriptomic and chromatin studies demonstrate that PARG is selectively recruited to promoters of Retinoic Acid Receptor (RAR)–responsive genes, where its catalytic activity is required for ligand-dependent transcriptional activation [204]. In this setting, PARG functions as a coactivator-like factor: by rapidly removing promoter-proximal PAR chains, it promotes the local chromatin accessibility necessary for productive transcription initiation (Fig. 7B).

Recent chemical, genetic, and proteomic studies have substantially expanded the landscape of PARP1-dependent ADP-ribosylation, mapping the ADP-ribosylome across six human breast cancer cell lines, including both luminal (MCF-7, T-47D, ZR-75) and basal/triple-negative (HCC70, MDA-MB-231, MDA-MB-468) subtypes [205]. These analyses identified thousands of PARP1 substrates and revealed striking subtype-specific differences. Luminal breast cancer cells showed enrichment for ADP-ribosylation on chromatin regulators and transcriptional machinery. Conversely, basal/triple-negative cells displayed preferential modification of proteins involved in translation and RNA processing.

Importantly, extensive mapping of Asp/Glu-ADP-ribosylation sites indicates that PARP1-mediated MARylation at these residues regulates a wide array of cellular processes beyond canonical DNA repair pathways. This finding has significant therapeutic implications: because hPARG efficiently hydrolyses mono-Asp/Glu-ADP-ribosylation, its chemical modulation may provide a means to exploit non-DNA damage repair vulnerabilities in tumour subtypes driven by aberrant transcriptional, translational, or RNA-processing programmes (Fig. 7C).

More recently, PARG has been shown to exert tumour-suppressive transcriptional control in prostate cancer. In PC-3 cells, PARG

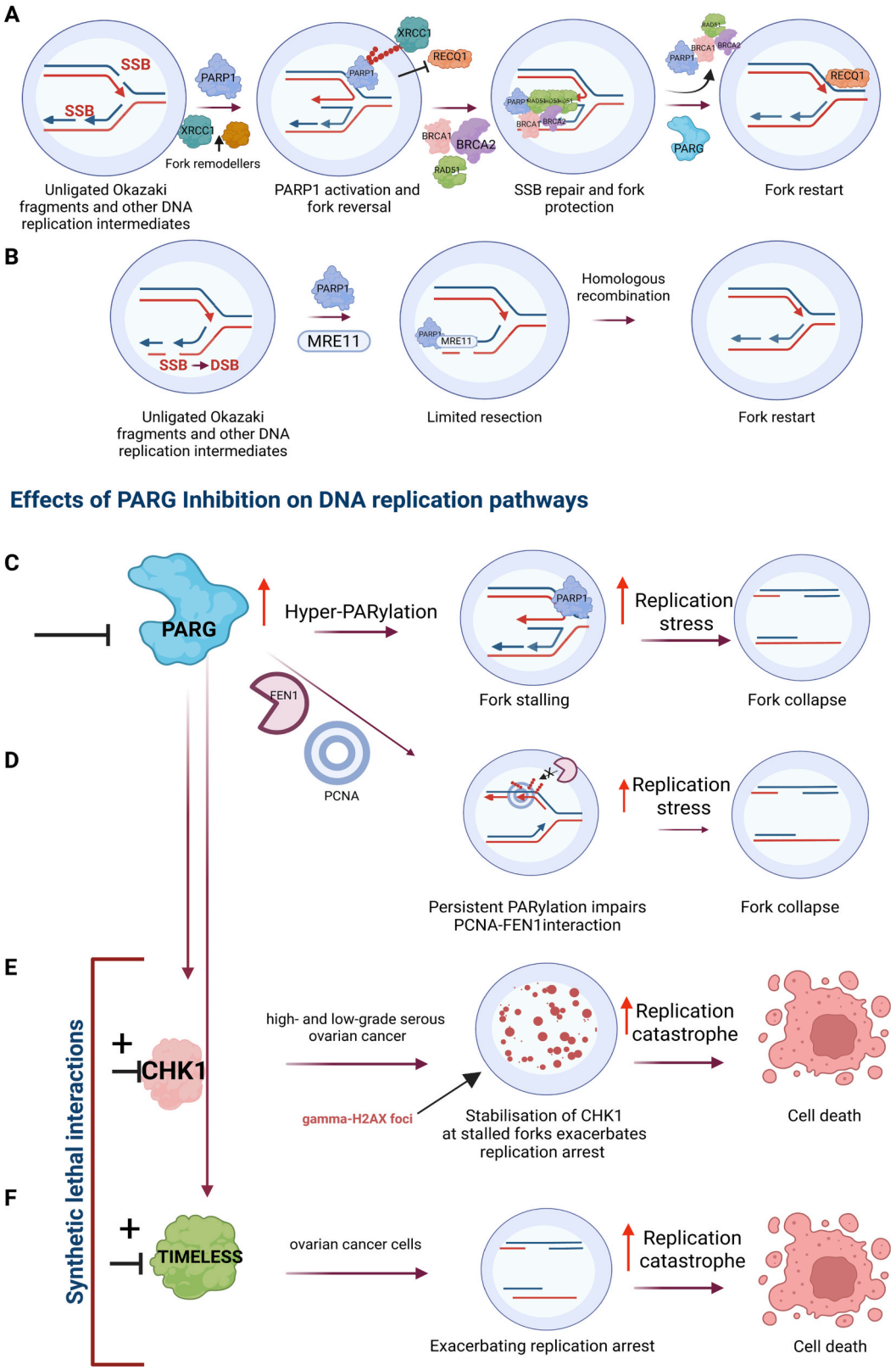

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Fig. 6. Nuclear functions of hPARG in DNA replication. This figure illustrates the role of hPARG in replication fork stability and replication stress responses. **A.** At single-strand breaks (SSBs), PARP1 activation recruits fork remodellers to stabilise replication forks and promote fork reversal, enabling repair and restart. This pathway is also engaged at unligated Okazaki fragments and replication intermediates. **B.** Conversion of SSBs into double-strand breaks (DSBs) during replication activates PARP1 and homologous recombination, facilitating lesion resolution and fork restart. **C.** Effects of PARG inhibition on replication. Chemical inhibition of hPARG induces hyper-PARylation, leading to fork stalling, replication stress, and fork collapse. This vulnerability can be exploited in replication-defective cancer cells. **D.** Regulation of Okazaki fragment processing. PARylation of PCNA disrupts its interaction with flap endonuclease 1 (FEN1). hPARG removes PAR from PCNA, restoring productive PCNA–FEN1 interactions. PARG inhibition results in persistent PCNA PARylation, fork stalling, accumulation of SSBs, and catastrophic replication stress. **E.** Synthetic lethality between PARG and CHK1 inhibition. Combined inhibition leads to PAR accumulation and stabilisation of CHK1 at stalled forks, exacerbating replication arrest, γH2AX formation, and apoptosis, offering a strategy to overcome intrinsic or acquired PARP inhibitor resistance. **F.** Timeless-dependent replication vulnerability. Timeless depletion or intrinsic PARG inhibitor sensitivity reduces fork speed, while combined Timeless suppression and PARG inhibition synergistically increase fork asymmetry and instability, culminating in replication catastrophe.

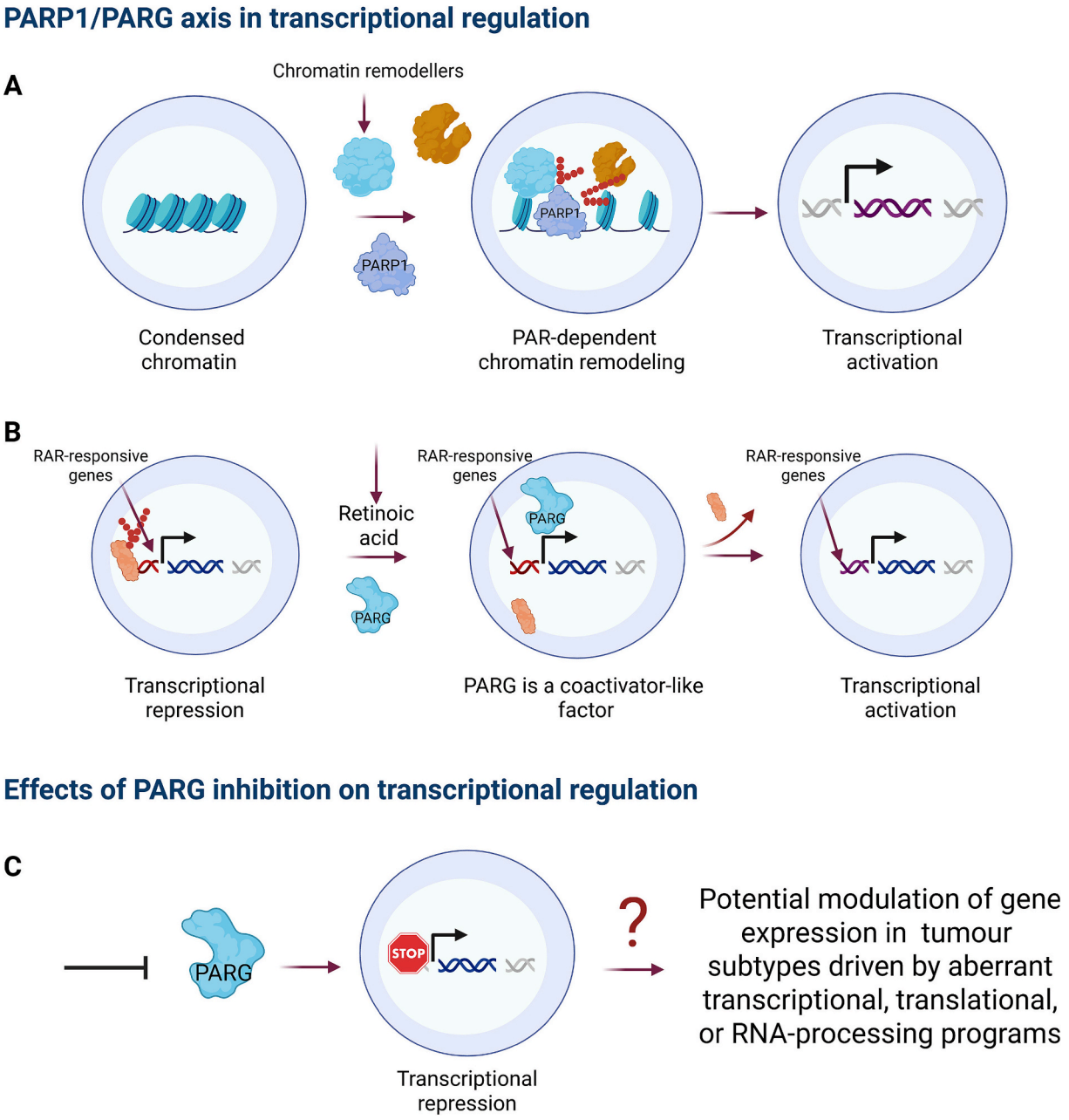

Fig. 7. Nuclear functions of hPARG in transcriptional regulation. A. PARylation-dependent chromatin remodelling. PARP1 activation promotes recruitment of chromatin-remodelling factors via non-covalent PAR interactions, driving chromatin decompaction and transcriptional activation. **B.** hPARG as a transcriptional coregulator. During transcriptional repression, PARylated factors restrict promoter accessibility, exemplified by retinoic acid receptor (RAR)-responsive genes. hPARG removes PAR, restoring chromatin accessibility and enabling transcription initiation. **C.** Effects of PARG inhibition on transcription. PARP1 regulates multiple sequence-specific transcription factors, including NF-κB, HES1, ELK1, SOX2, and nuclear hormone receptors. Modulation of hPARG activity may therefore influence aberrant transcriptional and RNA-processing programmes in specific tumour contexts.

overexpression leads to global PAR reduction and the coordinated downregulation of key oncogenic pathways—including TNFα/NF-κB, Interleukin-6/STAT3, MYC, and KRAS—resulting in decreased clonogenicity and reduced tumour growth *in vivo* [206]. These findings highlight a transcriptional dimension to PARG's tumour-modulating activity, complementing its established roles in genome stability.

Insights from *D. melanogaster* provide additional mechanistic clarity. dPARG protein stability is maintained through phosphorylation at two conserved sites (ph1 and ph2), modifications essential for protecting the enzyme from degradation and for sustaining the balance between germline stem cell renewal and normal development [147]. Disruption of either *D. melanogaster* PARP1 or PARG perturbs metabolic gene expression and results in developmental arrest before pupation [207], underscoring the importance of tightly controlled PAR turnover in organismal development. Furthermore, recent findings identify the C-terminal domain of dPARG as a critical regulatory module: loss of this domain accelerates age-related transcriptional dysregulation and shortens lifespan, demonstrating that PARG-dependent PAR dynamics influence transcriptional programmes linked to ageing [148]. Parallel observations in MCF7 human breast cancer cells reveal that PARP1 and PARG positively coregulate a shared set of stress-response and metabolic genes [208], suggesting a conserved regulatory logic across species.

Collectively, these studies expand the functional reach of ADP-ribosylation signalling into broad transcriptional governance, extending far beyond its classical roles in the DNA damage response or DNA replication.

The interplay between transcription and genome maintenance is intrinsically bidirectional. DNA lesions—arising from exogenous sources such as UV irradiation or from endogenous oxidative stress—can stall RNA polymerase II and impede transcription [209]. Conversely, transcription itself generates topological strain, R-loops, and DNA–RNA hybrid structures that can precipitate DNA damage. Thus, defects in the pathways that coordinate DNA repair and transcriptional stress responses lead to profound consequences for cellular homeostasis, contributing to cancer, neurodegeneration, and ageing.

In post-mitotic neurones, transcription–repair coupling takes on particular importance. DNA SSBs and unscheduled DNA synthesis occur predominantly at conserved neuronal enhancers—regulatory regions that function as "hotspots" for SSB repair [210]. Repair at these sites relies heavily on the PARP1–XRCC1 axis. Loss of XRCC1 results in accumulation of unresolved PARP1 activity, neuronal dysfunction, and neurodegenerative phenotypes, underscoring the essential role of short-patch SSB repair for neuronal viability. Failure to repair enhancer-associated lesions leads to enhancer mutagenesis, aberrant gene expression, and progressive neurological decline.

Given these interdependencies, deciphering the PARP–PARG interplay at the nexus of transcription and DNA repair will be critical for identifying therapeutic opportunities. A deeper understanding could inform strategies to mitigate transcription-associated genotoxicity in cancer therapy—particularly with agents such as platinum compounds—and to develop interventions targeting age-related disorders and neurodegenerative diseases driven by transcriptional stress.

3.2. Novel biological functions regulated by PARG

The recent discovery that PARG efficiently removes Tyr-linked ADP-ribosylation [174], a modification enriched on proteins involved in ribosome biogenesis and mRNA processing, further expands the functional landscape of PARG beyond canonical DNA damage repair (Fig. 4). Structural mapping of Tyr-ADP-ribosylation sites reveals that this modification frequently localises to surfaces critical for protein–protein interactions, suggesting that Tyr-ADP-ribosylation may impede the assembly or stability of ribonucleoprotein complexes. Such interference could attenuate ribosome maturation and disrupt co-transcriptional RNA processing. These mechanistic insights provide a clear rationale for exploring pharmacological hPARG inhibition as a strategy to stabilise Tyr-ADP-ribosylation, thereby perturbing ribosome biogenesis—a vulnerability frequently exploited in cancer cells with high biosynthetic demand.

The functional scope of PARG is further broadened by the identification of nucleic acids—both DNA and RNA—as direct ADP-ribosylation acceptors, demonstrating that ADP-ribosylation is not restricted to protein substrates. Notably, hPARG is the primary enzyme responsible for erasing RNA-linked ADP-ribosylation both *in vitro* and in Human Embryonic Kidney 293 cells [77,176], positioning it as a central regulator of RNA-associated ADP-ribosylation signalling. These findings imply that PARG modulates essential processes linked to RNA metabolism, RNA damage surveillance, and potentially RNA structure or stability.

These emerging roles expand therapeutic avenues: modulating Tyr-ADP-ribosylation or RNA ADP-ribosylation turnover via PARG inhibition may disrupt ribosome biogenesis, RNA processing, or nucleic-acid-associated stress responses, broadening the spectrum of tumours sensitive to ADP-ribosylation-targeted interventions. Development of selective, cell-permeable PARG inhibitors remains essential for probing these pathways and advancing therapeutic strategies.

4. Therapeutic potential of hPARG inhibitors

Growing recognition of PARG as a central regulator of ADP-ribosylation signalling, genome stability, and replication stress tolerance has catalysed intensive efforts to develop pharmacological inhibitors. To date, PARG inhibitors fall into two broad categories—natural product derivatives and synthetic small molecules—representing complementary strategies for targeting enzymatic activity (Table 1). Natural products, long valued for their anti-inflammatory, antioxidant, and anticancer properties [211–214], provided the earliest biochemical evidence that small molecules could modulate PARG. More recently, iterative medicinal chemistry and high-throughput screening have yielded increasingly selective, cell-permeable inhibitors with growing translational promise.

4.1. Natural PARG inhibitors

Hydrolysable tannins—glucogalloyl derivatives classified as ellagitannins (ETs) and gallotannins (GTs) [215]—represent the first natural products identified to inhibit PARG activity [216]. *In vitro* studies using purified human placental PARG revealed IC_{50} values of 8.3–12.5 μM for ETs and 16.8–28.9 μM for GTs [217], indicating that ETs are generally more potent. Mechanistically, ETs appear to inhibit PARG by competing with PAR for substrate binding in a manner dependent on the number of galloyl groups, whereas GTs display mixed inhibitory behaviour requiring higher concentrations.

Although these tannins served as the first proof-of-concept PARG inhibitors, their biological activity has also been demonstrated in cell-based systems. For example, pre-incubation of HaCaT cells with gallic acid prior to oxidative stress enhanced PAR accumulation and decreased PARP activity [218], and similar PAR-stabilising effects were observed in HeLa nuclear extracts [219]. Collectively, these findings highlight the potential of tannin derivatives to modulate PAR metabolism. Nevertheless, poor cell permeability and significant off-target effects limit their utility, preventing their progression as viable pharmacological tools.

4.2. Small-molecule PARG inhibitors

Efforts to develop more selective and potent inhibitors have focused on the unique adenine-binding pocket within the PARG catalytic macrodomain [220]. As illustrated in Fig. 1D, most synthetic PARG inhibitors occupy this conserved pocket, competing with ADP-ribose and thereby blocking PAR access to the catalytic site [103,120,221].

Table 1
Preclinical PARG inhibitors and their key pharmacological properties.

Drug chemotype	Drug name	IC_{50}	Properties	Activity and biological outcomes	Reference
Polyphenols	Tannin	16.8 μM	Low specific, low cell permeable	Impairment of PARG-mediated PAR hydrolysis	[217]
ADPr analogue	ADP-(hydroxymethyl)-Pyrrolidinediol (ADP-HPD)	120 nM	Specific, not cell-permeable	Impairment of PARG-mediated PAR hydrolysis	[223]
Fluorenone diamide	N-bis-(3-phenyl-propyl)9-oxofluorene-2,7-diamide (GPI16552)	1.7 μM	Low specific	Decrease of melanoma cell invasion and metastatic spreading in mice injected with B16 melanoma cells in combination with temozolomide, reduction of inflammatory response in spinal cord injury in mice	[260]
Rhodanine-based PARG inhibitors	RBPIs (RBPI1-RBP16)	1–6 μM	Low specific, not cell-permeable	Impairment of PARG-mediated PAR hydrolysis	[227]
Quinazolinesulfonamide	1-[(1,3-Dimethyl-1H-pyrazol-5-yl)methyl]-1,2,3,4-tetrahydro-N-(1-methylcyclopropyl)-3-[(2-methyl-5-thiazolyl)methyl]-2,4-dioxo-6-quinazolinesulfonamide (PDD0017273)	26 nM	Specific, potent, cell-permeable, low degree of bioavailability	Replication fork stalling and low DNA DSB repair in breast cancer cell lines with differing genetic backgrounds	[120]
Oxazole	(E)-1-(((p-tolylthio)imino)methyl)naphthalen-2-ol (COH34)	0.37 nM	Specific, potent, cell-permeable, effective *in vivo*	Lethality in cancer cells with DNA repair defects, antitumor activity in xenograft mouse cancer models, sensitisation of tumour cells with DNA repair defects to other DNA-damaging agents	[231]
Succinimide derivative	1,3-dimethyl-8-((2-morpholinoethyl)thio)-6-thioxo-1,3,6,9-tetrahydro-2H-purin-2-one (JA2131)	0.4 μM	Specific, cell-permeable	Sensitisation of cells to radiation-induced DNA damage, suppression of replication fork progression and impairment of cancer cell survival, killing of PARP inhibitor-resistant A172 glioblastoma cells	[221]

4.2.1. *First-generation synthetic PARG inhibitors*

The earliest synthetic inhibitor, Adenosine 5′-diphosphate (hydroxymethyl)pyrrolidinediol (ADP-HPD), is a nitrogen-in-the-ring analogue of ADP-ribose that potently inhibits PARG with an IC_{50} of 0.12 μM while showing no measurable inhibition of PARP1 or NAD^+ glycohydrolase [222]. Acting as a non-competitive inhibitor, ADP-HPD became an indispensable biochemical tool for dissecting the function of PARG in PAR turnover, DNA repair, and chromatin biology [223]. Despite its central role in mechanistic studies, its lack of cell permeability and high synthetic cost limit its utility *in vivo*.

Compounds such as N-bis-(3-phenyl-propyl)9-oxofluorene-2,7-diamide (GPI16552) and GPI18214 represent structurally distinct early PARG inhibitors. GPI16552 shows low potency (IC_{50} ~50 μM) and limited maximal inhibition but demonstrated synergy with temozolomide in melanoma, reducing tumour growth and metastasis in mouse models [224]. GPI18214, despite its undefined potency, has been shown to ameliorate zymosan-induced shock [225] and, in combination with GPI16552, to protect against experimental colitis [226]. However, poor potency and lack of cellular activity restrict their utility for mechanistic or clinical applications.

4.2.2. *Second-generation synthetic PARG inhibitors*

The limitations of first-generation compounds prompted the development of more potent, cell-permeable inhibitors. Rhodanine-based PARG inhibitors (RBPIs) emerged through structure-guided design and exhibit IC_{50} values of 1–6 μM with robust inhibition in biochemical and lysate assays [165,227]. Yet, concerns regarding cell permeability continue to limit their broader application.

A major breakthrough came with high-throughput screening campaigns that identified benzimidazolone and quinazolinone derivatives. PDD00017238 inhibits PARG with an IC_{50} of 40 nM and shows moderate cellular toxicity [120,228]. Its derivative, 1-[(1,3-Dimethyl-1H-pyrazol-5-yl)methyl]-1,2,3,4-tetrahydro-N-(1-methylcyclopropyl)-3-[(2-methyl-5-thiazolyl)methyl]-2,4-dioxo-6-quinazolinesulfonamide (PDD00017273), is even more potent (IC_{50} 26 nM) and, importantly, cell-permeable and non-toxic, producing dose-dependent PARG inhibition at concentrations as low as 0.3 μM [229]. Despite these advantages, rapid degradation and a short half-life hamper clinical translation [230].

A substantial advance in medicinal chemistry was achieved with (E)-1-(((p-tolylthio)imino)methyl)naphthalen-2-ol (COH34), identified using the Site-Moiety Map computational strategy [231]. COH34 displays exceptional potency (IC_{50} 0.37 nM), strong selectivity against other hydrolases (including TARG1 and ARH3), and robust cellular permeability. COH34 is synthetically lethal in *BRCA1/2*-deficient cancer cells and potentiates multiple DNA-damaging therapies. Remarkably, it also eliminates PARPi–resistant tumour cells. *In vivo* treatment with 20 mg/kg COH34 yielded potent antitumour activity without detectable toxicity, providing a compelling foundation for clinical development.

More recently, high-throughput screening efforts have identified thio-guanine analogues, including 1,3-dimethyl-8-((2-morpholinoethyl)thio)-6-thioxo-1,3,6,9-tetrahydro-2H-purin-2-one (JA2131), which inhibits PARG with an IC_{50} of 400 nM [221]. JA2131 is cell-permeable, induces PAR accumulation, elevates γH2AX upon irradiation, and reduces survival of HeLa cells to a degree comparable to olaparib—demonstrating the therapeutic potential of competitive PARG inhibition.

4.2.3. *Next-generation PARG inhibitors in clinical trials*

The first PARG inhibitors have now entered clinical evaluation (Table 2):

IDE161 exploits synthetic lethality in Homologous Recombination (HR)-deficient cancers and demonstrates potent activity in cell-line and patient-derived xenograft models, including PARPi-resistant ovarian and breast cancers [232]. Phase I trials (NCT05787587) are assessing safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy as monotherapy and with pembrolizumab.

ETX-19477 is a potent, cell-permeable inhibitor that induces robust intracellular PAR accumulation and exhibits antiproliferative activity across Estrogen Receptor-positive (ER^+)/$HER2^-$ breast cancer, ovarian, lung, and gastric cancers [233]. Oral bioavailability and favourable pharmacokinetics have supported its clinical testing (NCT06395519).

DAT-2645, developed by Danatlas Pharmaceuticals, is an orally available, selective PARG inhibitor that exhibits cytotoxicity in DNA damage repair-deficient tumour cells through synthetic lethality.

Table 2
PARG inhibitors currently under clinical investigation for the treatment of resistant solid tumours. Information derived from ClinicalTrials.gov (updated December 2025).

Drug	Activity (IC_{50})	Clinical Trials.gov identifier	Combinatorial Treatment	Phase	Cancer type	Results
XNW29016	Potent, selective (29 nM)	NCT06987500	No	Phase 1,2	Solid tumours *in vitro* anti-tumour effects in a set of PARPi-resistant cancer cell lines such as RMUG-S, KURAMOCHI and HCC1428. SNU601 and HCC1806 cells	ongoing
IDE-161	Potent, selective (n.r.)	NCT05787587	Pembrolizumab	Phase 1	Advanced or Metastatic Solid Tumours: Breast Cancer Ovarian Cancer Prostate Cancer Endometrial Cancer Colorectal Cancer Head and Neck CancersNSCLC	ongoing
DAT-2645	Potent, selective (n.r.)	NCT06614751	No	Phase 1	Solid cancers harbouring *BRCA1/2* loss of function alterations and/or other defects in the DNA damage repair pathway HRD Cancer Breast Cancer Prostate Cancer Colorectal Cancer Pancreatic Cancer Endometrial Cancer Gastric Cancer Advanced Cancer Metastatic Solid tumours	ongoing
ETX-19477	Potent, selective (n.r.)	NCT06395519	No	Phases 1, 2	Death and/or inhibition of the proliferation of multiple cancer cell types, including $ER^{+}HER2^{-}$ breast, serous and mucinous ovarian, lung, and gastric cancers and induces pan-nuclear γH2AX expression, a hallmark of replication catastrophe Advanced or Metastatic Solid Tumours Prostate Cancer Epithelial Ovarian Cancer harbouring *BRCA2* Mutation ER^{+} Breast Cancer Castrate Resistant Prostate Cancer *BRCA* Mutation Endometrial Cancer Colorectal CancerGastric Cancer	ongoing
SYN608	Potent, selective (n.d.)	NCT07088588	No	Phase 1	Advanced Solid Cancer Metastatic Solid Tumour Ovarian Cancer Breast Cancer *BRCA* MutationHRR Deficiency	Not recruiting

Following FDA IND approval in 2024, clinical trials (NCT06661475, CTR20243912) will evaluate safety and tolerability in patients with advanced solid tumours harbouring DNA damage response deficiencies.

XNW29016 is a selective PARG inhibitor that binds directly to the PARG catalytic domain, exhibiting an *in vitro* biochemical IC_{50} of 29 nM. It demonstrates robust antitumour activity *in vitro* across multiple PARP inhibitor–resistant cancer cell lines, including RMUG-S, KURAMOCHI, and HCC1428 [234]. An ongoing Phase I clinical trial (NCT06987500) is evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of XNW29016 in patients with advanced solid tumours.

SYN608 is a potent PARG chemical probe that induces cytotoxicity in DNA damage repair–deficient tumour cells through a synthetic lethality mechanism [235]. A Phase I clinical trial (NCT07088588) is currently assessing the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumour activity of SYN608 as a monotherapy in adult patients with advanced solid tumours.

These next-generation PARG inhibitors exemplify the rapid translation of mechanistic insights into therapeutic strategies, offering novel approaches to exploit replication stress and DNA repair vulnerabilities in cancer.

5. Discussion

The clinical success of PARPis has established ADP-ribosylation signalling as a tractable therapeutic vulnerability in cancers with DNA damage repair defects [85,101,103,118]. By exploiting synthetic lethality in HR–deficient tumours, PARP inhibition has transformed the management of breast, ovarian, pancreatic, and prostate cancers, providing a paradigm for precision oncology [104,109,116,117,236,237]. However, intrinsic and acquired resistance to PARPis remains a major limitation [105], underscoring the need to identify new nodes within the ADP-ribosylation network that are mechanistically distinct yet clinically actionable [103,180,238].

Genomic instability and replication stress are hallmarks of many cancers and arise from defective DNA repair, deregulated cell-cycle checkpoints, and oncogene-driven hyperproliferation. Replication stress generates stalled or collapsed forks that require timely repair to prevent catastrophic genomic damage [239–242]. Within this context, PARP1 and PARG act as reciprocal regulators of ADP-ribosylation dynamics, coordinating the detection, amplification, and resolution of DNA lesions [1]. While PARP1 rapidly synthesises poly-ADP-ribose to initiate chromatin remodelling and repair-factor recruitment, PARG is solely responsible for removing PAR chains, thereby controlling the duration and spatial confinement of the ADP-ribosylation signal [1,243,244].

Mechanistic studies have revealed that PARG inhibition disrupts this balance, resulting in persistent PAR accumulation, defective fork restart, and accumulation of toxic replication intermediates [120,122,123,196]. These biochemical consequences render PARG a compelling synthetic-lethal target in DNA damage response-deficient cancers. Preclinical models demonstrate that PARG-depleted or PARG-inhibited cells exhibit heightened sensitivity to replication stress–inducing agents and show

selective cytotoxicity in HR- or broader DNA damage repair-defective backgrounds [121,123,228,245]. This mechanistic rationale has driven rapid translational progress toward the development of PARG inhibitors.

Recent clinical translation of next-generation PARGis marks a major milestone. IDE161, the first PARG inhibitor to enter clinical trials, has shown potent preclinical activity in HR-deficient models and in PARP inhibitor–resistant ovarian and breast cancers, demonstrating that PARG targeting can overcome resistance mechanisms that limit PARPi efficacy [232]. Similarly, DAT-2645 exhibits selective lethality in DNA damage repair-deficient tumour cells, expanding the scope of PARG dependency across tumour types. Nevertheless, despite strong preclinical efficacy, the field currently lacks clinical data to define therapeutic windows, biomarkers of response, and mechanisms of acquired resistance. Ongoing trials will be essential to determine the translational potential of PARG inhibition as a standalone or combination strategy.

Future research must integrate structural biochemistry with functional genomics to fully elucidate the molecular determinants governing hPARG activity. Detailed structural analyses—such as co-crystallisation with synthetic ADP-ribosylated peptides—combined with biochemical interrogation of substrate specificity and protein–protein interactions [174] will provide essential insight into how PARG regulates distinct ADP-ribosylation architectures *in vivo*.

In addition, although insufficiently addressed in current literature, PARG likely represents the best candidate hydrolase reversing Tankyrase-1 and Tankyrase-2 activities—the only other PARP family members besides PARP1 and PARP2 capable of generating bona fide PAR chains [246]. Given the roles of Tankyrases in WNT signalling, telomere maintenance, spindle regulation, and other essential cellular processes [85,247–254], PARG inhibition may therefore exert biological effects that extend beyond impaired reversal of PARP1/2-dependent signalling. Understanding PARG-dependent mechanisms will not only refine drug design but also illuminate previously unrecognised ADP-ribosylation-regulated pathways that may represent new therapeutic vulnerabilities.

A further frontier lies in understanding the interplay between ADP-ribosylation and other post-translational modifications during the replication stress response. Emerging evidence highlights extensive crosstalk between ADP-ribosylation, phosphorylation, and ubiquitination at stalled replication forks [255]. Exploiting these combinatorial signalling networks may enable rational design of multi-target therapeutic strategies, particularly in cancers with complex DNA damage repair rewiring.

Beyond oncology, ADP-ribosylation-targeting therapeutics—including PARG inhibitors—may ultimately extend to non-cancer indications, as modulation of ADP-ribosylation signalling intersects with pathways regulating oxidative stress, inflammation and immune response, and neuronal survival [256–260]. Thus, deciphering the mechanistic biochemistry of PARG is likely to have broad clinical implications.

In summary, PARG has emerged as a mechanistically validated and clinically promising therapeutic target. Continued integration of biochemical mechanistic insight with translational research will be critical to advancing PARG inhibitors from experimental agents to effective therapies for DNA damage repair-deficient cancers and beyond.

CRediT authorship contribution statement

Giuliana Catara: Writing – review & editing, Writing – original draft, Investigation. **Gaetano Gerace:** Writing – review & editing, Investigation. **Raffaella Lauro:** Investigation. **Luca Palazzo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition.

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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.

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