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Transcriptional regulation mechanism of PARP1 and its application in disease treatment

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Abstract
Poly (ADP-ribose) polymerase 1 (PARP1) is a multifunctional nuclear enzyme that catalyzes poly-ADP ribosylation in eukaryotic cells. In addition to maintaining genomic integrity, this nuclear enzyme is also involved in transcriptional regulation. PARP1 can trigger and maintain changes in the chromatin structure and directly recruit transcription factors. PARP1 also prevents DNA methylation. However, most previous reviews on PARP1 have focused on its involvement in maintaining genome integrity, with less focus on its transcriptional regulatory function. This article comprehensively reviews the transcriptional regulatory function of PARP1 and its application in disease treatment, providing new ideas for targeting *PARP1* for the treatment of diseases other than cancer.

Keywords PARP1, PARylation, Transcriptional regulation, Disease treatment, PARP1 inhibitor

Introduction

The tightly condensed chromatin structure protects the integrity of the genetic information. During transcription, transcription factors are required to directly bind to DNA fragments by loosening chromatin structures to respond to cellular signals and environmental and DNA damage [1]. Poly (ADP-ribose) polymerase (PARP) is a family of multifunctional enzymes that mediate changes in chromatin structure. PARP1 is the most widely studied protein in this family and plays a well-defined role in the response to DNA damage, either by loosening chromatin at specific sites to promote DNA repair or by prompting cell death to maintain genomic integrity in the case of extensive damage [2]. Interestingly, PARP1 is also involved in the regulation of chromatin remodelling and gene transcription in multiple ways, including poly(ADP-ribosyl)ation (PARylation), and is a potentially important intervention target for the treatment of cardiac injury, Epstein-Barr virus (EBV) infection, hereditary hemochromatosis, pancreatic cancer, and other diseases [3–5]. Most reviews of PARP1 have focused on its DNA damage repair function, paying less attention to its transcriptional regulatory function. This review focuses on the mechanisms underlying PARP1 transcriptional regulation and its application in disease treatment.

PARP1 structure and activities

The PARP family has 18 subtypes, of which the most abundant and ubiquitous member is PARP1. PARP1 is a highly conserved protein composed of 1014 amino acids and has a relative molecular weight of approximately 113 kDa. It has a total length of approximately 47,399 bp and 25 exons. Its coding gene is in the q41-q42 region

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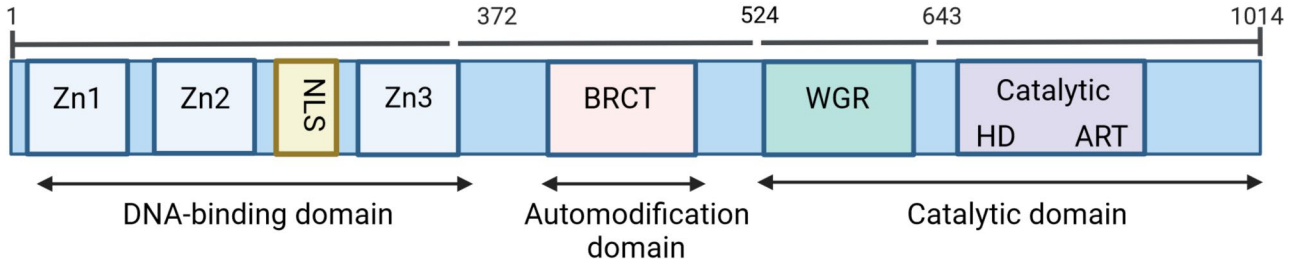

Fig. 1 The DNA-binding domain contains three zinc finger (Zn) motifs (Znl, Zn2, and Zn3) and a nuclear localization signal (NLS). The automodification domain contains specific glutamate and lysine residues serving as acceptors for ADP-ribose moieties. The catalytic domain contains WGR motif is defined by a conserved Trp, Gly, and Arg residue-rich domain and "PARP signature" made up of the highly conserved PAR signature subdomain. This figure was created using BioRender.com

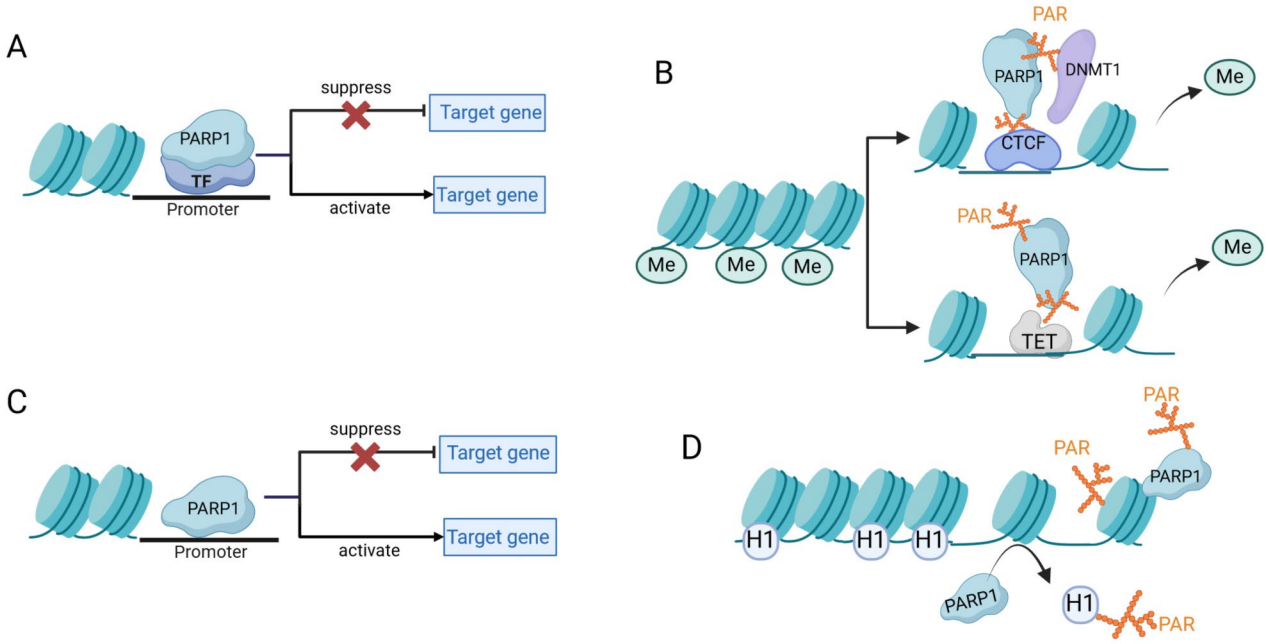

Fig. 2 PARP1 transcriptional regulation. (**A**) PARP1 is involved in transcriptional regulation as a transcriptional coregulator. (**B**) PARP1 is a DNA methylation factor involved in transcriptional regulation. (**C**) PARP1 acts as an activator/repressor transcription factor that directly binds to promoters to regulate transcription. (**D**) PARP1 competes with histone H1 for binding to the nucleosome and is involved in transcriptional regulation. This figure was created using BioRender.com

of the chromosome. PARP1 contains three functional domains: the N-terminal DNA-binding domain, the central automodification domain, and the C-terminal catalytic domain. The DNA-binding domain contains three zinc-finger (Zn) motifs (Znl, Zn2, and Zn3) and a nuclear localization signal (NLS) [6]. Zn1 and Zn2 are involved in the recognition of DSBs/SSBs and mediate the binding of PARP1 to DNA. Zn3 mediates the regulation of the DNA-binding domain (DBD) on the catalytic activity. The nuclear localization signal within the DBD is located between the Zn2 and Zn3 fingers. The automodification domain contains specific glutamate and lysine residues that serve as acceptors for ADP-ribose moieties, as well as a BRCT domain that interacts with many DNA damage response proteins. The catalytic domain, which is the most conserved domain across the PARP family, consists of a WGR motif and the "PARP signature." The WGR motif is defined by a conserved Trp, Gly, and Arg residue-rich domain, and the "PARP signature" sequence is required for the catalysis of PAR synthesis [7]. (Fig. 1)

PARP1 participates in transcriptional regulation as a transcriptional coregulator

PARP1, as a transcriptional co-regulator, plays a key role in several key biological processes, promoting the recruitment of transcriptional activators or the release of transcriptional repressors in the process of regulating transcriptional complexes, acting in synergistic activation or inhibition (Fig. 2A) [23]. It can regulate transcription initiation by directly recruiting transcription factors or

regulating the expression of downstream genes by modifying transcription factors via PARylation.

PARP1 can interact directly with transcription factors to enhance or inhibit their DNA-binding abilities. In this process, PARP1 acts as a co-activator or co-repressor depending on its binding partner. First, nuclear factor-κB (NF-κB) is a widely expressed transcription factor that plays an important role in regulating the immune system. Experiments with enzymatic inhibitors and complementation experiments revealed that PARP1 can bind to the p50 and p65 subunits of NF-κB and act as a transcriptional coactivator independent of its enzymatic activity. This suggests that PARP1 inhibitors protect against various NF-κB-dependent diseases, such as septic shock and epithelial dysfunction in type I diabetes [8]. Second, transgelin (TAGLN) increases the metastatic potential of colon cancer cells by remodelling the cytoskeleton and promoting the formation of metastatic phenotypes in tumor cells by altering the expression of metastasis-related genes [24]. Co-immunoprecipitation and subsequently high-performance liquid chromatography/tandem mass spectrometry were performed and identified that PARP1 binds to TAGLN translocating into the nucleus to regulate the expression of key genes closely related to colon cancer formation and metastasis (*CALM1*, *MYO1F*, *WIPF1*) [9]. Third, among the multiple mechanisms promoting immunosuppression in the tumor microenvironment, programmed death ligand 1 (PD-L1), an inhibitory member of the B7 family, plays a central role in immune system evasion in many cancer types [25]. PD-L1 expression is upregulated in various epithelial tumors, including ovarian and breast cancer [26, 27]. Luciferase reporter assays indicate that PARP1 binds to the signal transducer and activator of transcription 3 (STAT3) to inhibit the expression of downstream *PDL1* [10], providing novel ideas for improving the clinical treatment of various cancers. Extracellular signal-regulated kinases (ERKs) are key transmitters of signals mediated by phospholipase C (PLC) activation. These kinases operate within the intracellular signal transduction pathways of mitogen-activated protein kinases (MAPKs) and regulate various cellular functions, including proliferation, growth, and differentiation [28]. It has been reported that PARP1 can directly interact with extracellular regulated ERK2 to increase the phosphorylation of the transcriptional activator ELK1, thereby activating c-Fos gene transcription in neurons and cardiomyocytes [11]. Lastly, PARP1 reportedly acts as a corepressor of transcription together with methionine adenosyltransferase 2 A (MATIIα) to inhibit the target genes expression of v-maf musculoaponeurotic fibrosarcoma oncogene family, protein K (MafK) and BTB and CNC homology 1 (Bach1) [12].

PARP1 participates in the transcriptional regulation of many other genes and cellular processes by modifying transcription factors via PARylation. First, in terms of adipogenesis, immunoprecipitation and detection of PARylated proteins and HA-tagged CCAAT/enhancer-binding protein β (C/EBPβ) revealed that NAD+-dependent catalytic activity of PARP1 PARylates three amino acids (K133, E135, E139) of the key pro-adipogenic transcription factor C/EBPβ to reduce its transcriptional activity by inhibiting its binding to DNA, thereby attenuating the differentiation of adipocyte precursors at an early stage [13]. Second, in terms of cardiovascular protection, the Electrophoretic Mobility Shift Assay (EMSA) and chromatin Immunoprecipitation (ChIP) revealed that PARP1 can modify the DBD of estrogen receptor α (ERα) by PARylation and promote its binding to the estrogen response element (ERE) in the promoter region, thereby activating ERα-mediated gene transcription [14]. Third, the SRY-related HMG box-containing (Sox) family of transcription factors includes Sox2, which is a key gene for maintaining the multifunctional state of embryonic stem cells. PARP1 interacts with Sox2 and PARylates it, thereby enhancing the expression of fibroblast growth factor 4 (*FGF4*) by reducing the binding of Sox2 to the *FGF4* enhancer, which positively affects the survival of implanted embryos and multiple stages of development [15]. Moreover, DNA pull-down, chromatin immunoprecipitation–quantitative PCR (ChIP single bond qPCR), and luciferase reporter assays revealed that PARP1 modifies the transcription factor DEAD-box helicase 5 (DDX5) in pancreatic cancer cells through PARylation, thereby attenuating the transcription of *CD24*, a gene associated with cancer invasion, metastasis, and poor patient prognosis [16]. Phagocytosis assays and animal models of pancreatic cancer have been used to evaluate the synergistic antitumor effects of PARP inhibitors and *CD24* blockers, suggesting a potential strategy for pancreatic cancer treatment [5].

Furthermore, PARP1 regulates genomic DNA methylation via PARylation. PAR from auto-PARylated PARP1 binds to DNA methyltransferase 1 (DNMT1) and inhibits its enzymatic activity, which prevents DNMT1 access to DNA, abrogating the methylation of CpGs [29, 30]. The effect of PARP1 on DNA methylation is also regulated by CCCTC-binding factor (CTCF). This protein promotes the self-modification of PARP1 and regulates the interaction between PARP1 and DNMT1 [17, 31]. CTCF preferentially recognizes unmethylated DNA regions. Therefore, PARP1 can bind to CTCF to keep specific CpG islands unmethylated by inhibiting the activity of DNMT1 (Fig. 2B) [17–19]. The high affinity of DNMT1 for PAR polymers interferes with its binding to the DNA methylation sites, thereby inhibiting its methylation activity [32]. As a result, blocking PARylation using PARP

inhibitors directly induces hypermethylation of CpG islands in L929 mouse fibroblasts [33].

PARP1 is also involved in keeping other gene regulatory sequences unmethylated. The ten-eleven translocation (TET) family converts 5mC to 5-hydroxymethylcytosine (5hmC), which mediates DNA demethylation [34]. The DNA methylation patterns of 5hmC are established and maintained by DNMTs, whereas DNA demethylation is initiated by the TET proteins. Covalent PARylation stimulates TET1 activity. The in vitro PARylation and PAR blot assays revealed that covalent PARylated TET1 could limit the access of DNMT1 to DNA to prevent DNA methylation, and it can favor the binding of transcription factors that bind PARs noncovalently (Fig. 2B) [20–22]. PARP1 together with TET2 stimulates the conversion of 5mC to 5hmC, which is crucial for early stage epigenetic modification during somatic cell reprogramming [35].

In short, PARP1 can participate in transcriptional regulation as a transcriptional co-regulator through both its enzymatic activity and its function independent of enzymatic activity (Table 1).

PARP1 participates in transcriptional regulation through binding specific DNA sequences

Many studies have described the direct effects of PARP1 on the transcriptional regulation of target genes by focusing on the binding of PARP1 to specific DNA sequences in the regulatory regions of these genes. PARP1 can regulate the expression of downstream genes by modifying the transcription complex by directly binding to the gene sequence.

Moreover, PARP1 can act as an activator transcription factor that binds directly to promoters to regulate transcription (Fig. 2C). First, DNA pull-down and ChIP assays have shown that PARP1 binds to the 5′-GGG CTGTCCCCAGG-3′ sequence of the double homeobox 4 (*DUX4*) promoter, allowing PARP1 to enter into the genome more easily and promote *DUX4* expression [36]. Disinhibition of the *DUX4* gene is closely related to facioscapulohumeral muscular dystrophy (FSHD), for which there are currently no therapeutic drugs available. Therefore, the discovery of the mechanism by which PARP1 promotes the transcriptional expression of *DUX4* provides a novel approach for the development of specific drugs for FSHD [37]. Second, the binding of PARP1 to the cardiac troponin T (cTnT) gene promoter is necessary for cTnT-mediated differentiation-dependent activation, and mutations at this site alter the process of muscle differentiation [39]. Third, PARP1 binds to the promoter region of the cellular-myelocytomatosis viral oncogene (*c-Myc*) to regulate the transcription of immediate early response genes and plays an important role in cell cycle reactivation of resting cells [40]. Fourth, C-C motif chemokine ligand 2 (*CCL2*) expression is an important factor that promotes tumor cell invasiveness. PARP1 interacts with p65 to regulate the activity of the *CCL2* promoter, playing a crucial role in regulating tumor cell invasiveness by maintaining *CCL2* levels in breast cancer cells [41]. Moreover, hypoxia plays an important role in tumor development. During early hypoxia, PARP1 interacts with mainly 1 Kb around hypoxia-inducible factor 1α (*HIF-1α*) target TSS (5'-ATGCA-3'), directly and synergistically activating *HIF-1α*-dependent gene expression and increasing tumor adaption to hypoxia [38]. HIF1-dependent gene expression in the absence of PARP1 is impaired in all cases irrespective whether *HIF-1α* recruitment to chromatin is lost, or maintained, indicating that PARP1 plays a role in HIF-1-dependent transcriptional regulation beyond *HIF-1α* recruitment. As PARP inhibitors have already been approved for clinical use, the identification of tumors expressing elevated HIF1α might expand the use PARP inhibitors to target the tumor adaptation to hypoxia. Additionally, PARP1 and p65 together assist in the binding of Snail family zinc finger 1 (Snail1) to the promoter of fibronectin 1 (*FN1*), which promotes epithelial-to-mesenchymal transition through the expression of *FN1*, thereby contributing to early cancer metastasis [42]. Forkhead box transcription factor 1 (*FOXO1*) is a tumor suppressor that regulates the expression of multiple genes involved in various biological processes including tumorigenesis and ageing [43]. PARP1 specifically binds to the −813 to -826 bp (i.e., 5′-TCACTGTATTCTT-3′) and the −1805 to -1828 bp (i.e., 5′-TCTTGTGGTCTTCACGTTTAC-3′) regions of the *FOXO1* promoter, while PARP1 binding does not affect the basal expression of the *FoxO1* gene [44]. This study provides new ideas for the application of PARP1 inhibitors in tumor therapy.

PARP1 can also act as a repressor transcription factor, directly binding to promoters to regulate transcription. First, germline mutations in *BRCA* genes (i.e., *BRCA1/2*) are major risk factors for hereditary tumors, including

Table 1 Examples of PARP1-interacting factors

Functions	Binding factors	References
PARP1 interacts directly with transcription factors	NF-κB	[8]
	TAGLN	[9]
	PD-L1	[10]
	ERK	[11]
	MATIIα	[12]
PARP1 modifys the transcription factors by PARylation.	β (C/EBPβ)	[13]
	ERα	[14]
	Sox2	[15]
	DDX5	[16]
	DNMT1	[5]
	CTCF	[17–19]
	TET	[20–22]

breast and ovarian cancers. PARP1 binds to the 5′-GT TTCACAAT-3′ sequence of the *BRCA2* promoter to inhibit its expression [45]. Second, the basal transcriptional activity of T-cell immune regulator 1 (*TCIRG1*) is negatively regulated by the binding of PARP1 to the 5′-TTCCCACAGC-3′ sequence of its promoter. Enhanced *TCIRG1* transcription following PARP1 inhibition promotes osteoclastogenesis [46]. Third, most hereditary hemochromatosis cases are caused by mutations in the hereditary hemochromatosis gene (*HFE*) [51]. PARP1 binds to the 5′-ATGGTCTTACCTA-3′ sequence of the *HFE* promoter to inhibit the expression of *HFE*, providing a novel approach for the treatment of hereditary hemochromatosis [47]. Fourth, Snail family transcriptional repressor 2 (*SNAI2*) plays an important role in resisting apoptosis, thereby mediating drug resistance in tumor cells [52]. PARP1 binds to the *SNAI2* promoter and inhibits its expression Transcriptional repression of *SNAI2* by blocking the PARP1-*SNAI2* transcriptional axis with PARP inhibitors may contribute to the resistance of non-*BRCA*-mutated tumors to PARP inhibitor therapy [48]. Additionally, Chemokine (CXC motif) ligand 1 (*CXCL1*) is highly and constitutively expressed in malignant melanomas. PARP1 binds to the promoter sequence of *CXCL1* and may be involved in its transactivation [49]. PARP1 can also regulate downstream gene expression by affecting DNA methylation via binding to the promoter regions of these target genes. Specifically, PARP1 affects DNA methylation by regulating the expression and activity of the DNA methyltransferase, DNMT1. It binds to the DNMT1 promoter in a PAR-dependent manner to prevent DNA methylation-induced silencing and to enhance gene transcription [50].

These findings show that PARP1 participates in the dynamic exchange of transcription factors at gene promoters by promoting the recruitment and release of specific transcriptional regulators (Table 2).

Table 2 Examples of PARP1's binding DNA sequences

Functions	Binding Sequences	References
PARP1 bind to specific DNA sequences as an activator	DUX4	[36, 37]
	HIF 1α	[38]
	cTnT	[39]
	c-Myc	[40]
	CCL2	[41]
	FN1	[42]
	FOXO1	[43, 44]
PARP1 bind to specific DNA sequences as an repressor	*BRCA2*	[45]
	TCIRG1	[46]
	HFE	[47]
	SNAI2	[48]
	CXCL1	[49]
	DNMT1	[50]

PARP1 participates in transcriptional regulation as a modulator of chromatin

PARP1 participates in the regulation of chromatin structure at various epigenetic levels. It recognizes specific structures and binds directly to nucleosomes, whose core histones H2A, H2B, H3, and H4 and linker histone H1 are direct targets of PARP1 [80]. PARP1 orchestrates these changes in the chromatin architecture and in turn chromatin-related functions. Therefore, we focused on elucidating the function of PARP1 in the regulation of H1, core histones, histone variants, and histone- and chromatin-modifying enzymes.

PARP1 competes with histone H1 to bind to nucleosomes and participates in transcriptional regulation

PARP1 competes with histone H1 to bind to gene promoters. The higher the ratio of PARP1 to H1, the higher the promoter activity, suggesting that PARP1 may be a biomarker of transcriptional activity [33]. The competition between PARP1 and H1 for target gene promoters contributes to the dynamic regulation of the expression of these genes (Fig. 2D) [53]. PARP1 binds to the linker DNA for nucleosome recombination. It also replaces the histone H1 linker in transcriptionally active regions to depolymerize chromatin, thereby promoting gene transcription [54].

For instance, PARP1 and histone H1 competitively bind to GATA-binding protein-3 (*GATA3*) to maintain the transcriptional environment of cyclin D1 (*CCND1*) [55]. In addition, hormone-dependent phosphorylation of PARP1 by cyclin-dependent kinase 2 (CDK2) activates PARylation of PARP1 to H1, which induces H1 release from chromatin and accelerates progesterone-mediated breast cancer cell proliferation [56]. Furthermore, PARP1 is involved in the regulation of neuronal excitation through chromatin plasticity–mediated transcriptional regulation [57]. Neuronal stimulation results in the replacement of H1 on the promoters of immediate early genes by PARP1, which was verified by blocking this process with a PARP inhibitor. Moreover, PARP1 PARylates H1 to remove it from the *c-fos* promoter, thereby making DNA more readily available to transcription factors and promoting gene expression [58]. Finally, PARP1 PARylates H1 and replaces it, binding to DNA and forming a loose chromatin structure that facilitates the regulation of aromatase promoter I.3/II activity [59].

In short, PARP1 promotes gene expression by competing with H1 to bind target genes and loosen chromatin structure.

PARP1 participates in transcriptional regulation by regulating core histones and other histone variants

PARP1 is capable of PARylating all four core histones besides H1. Histones participate in transcriptional

regulation through the bidirectional regulation of PARP1. First, EMSA and ChIP analyses have confirmed that PARP1 interacts with the linker histone complex H1.2 in the proximal promoter region of epoxide hydrolase 1 (*EPHX1*), stimulating the transcription of *EPHX1* and promoting the formation of hypercholanemia [60]. Second, in Drosophila, histones H2A and H2B inhibit the catalytic activity of PARP1, whereas histones H3 and H4 bind to the catalytic domain of PARP1 to induce PARylation of H4 in vitro [81]. The C-terminal domain of PARP1 interacts with H4, resulting in the long-term activation of PARP1, which relaxes chromatin through sustained accumulation of PAR to facilitate the entry of transcription factors into DNA [71]. Third, PARP1 is functionally associated with histone variants. The phosphorylation of histone H2Av can enhance PARP1 activation, thereby triggering histone H2Av transcriptional activation [62]. Fourth, in vitro and cell-based studies have shown that the replacement of H2A with H2Av changes the structure of the core nucleosome, favors the binding of PARP1 to H3 and H4, and forms a loose chromatin domain at the binding site of PARP1 [69, 70]. Phosphorylation of histone H2Av, induced by developmental signals, heat shock, or genotoxic stress, further exposes the N-terminal tail of H4 and activates the catalytic activity of PARP1, thereby initiating downstream gene transcription [63]. PARP1 promotes the exchange of histone H2AZ with H2A in the ERK pathway, which forms a loose chromatin structure and promotes the transcriptional activation of embryonic fibroblasts [61]. Fifth, PARP1 evicts the histone variant from the nuclear factor-activated T-cell 1 (*NFATC1*) promoter by PARylating H2B, thereby inhibiting NFATC1 expression and osteoclastogenesis [68]. Sixth, MacroH2A1.1 and macroH2A1.2 are splice variants of the same gene, each with a unique exon11. Like most macrodomains, the macrodomain of macroH2A1.1 can interact with NAD+-derived ligands, such as PAR, whereas macrodomains of macroH2A1.2 and macroH2A2 cannot achieve this [64]. This distinction is functionally important in cancer. Indeed, macroH2A1.1 is mainly expressed in differentiated, non-proliferative tissues, whereas macroH2A1.2 expression exerts important effects on both the proliferation and metastatic potential of cancer cells [65, 82]. By inhibiting the activation of PARP1, MacroH2A1.1 can silence the expression of many genes. For example, the promoter of the heat-shock protein 70.1 gene is activated and PARylated after the release of MacroH2A1.1 induced by heat shock [66]. PARP1, together with macroH2A1.1, promotes CBP/p300-mediated histone H2B acetylation and regulates the transcription of macroH2A1 target genes [67].

PARP1 participates in transcriptional regulation by regulating histone- and chromatin-modifying enzymes

PARP1 may alter chromatin structure by regulating the activity and localization of histone- and chromatin-modifying enzymes. For example, the interaction between PARP1 and lysine demethylase 5B (KDM5B) regulates the chromatin state. PARylation of KDM5B inhibits its binding to chromatin and its demethylase activity at specific sites in the genome. Thus, there is increased trimethylation of histone H3 lysine 4 (H3K4me3) at PARP1-regulated gene promoters, which keeps the chromatin structure open and enhances gene expression [72]. Second, the enzymatic activity of PARP1 plays an important role in regulating the methylation status of histone H3 lysine 9 (H3K9). Lysine demethylase 4D (KDM4D) enables covalent PARylation of H3K9 demethylase at its N- and C-terminal domains. When PARylated in the N-terminal domain, it cannot bind to retinoic acid-dependent gene promoters, resulting in the derepression of the dimethylation of histone H3 lysine 9 (H3K9me2) and transcriptional derepression of retinoic acid–dependent genes [73, 74]. Third, the trimethylation of histone H3 lysine 27 (H3K27me3) is enriched in chromatin regions that contain silent genes. PARP1-dependent PARylation plays an important role in regulating the methylation status of H3K27me3. PARylation regulates enhancer of zeste homolog 2 (EZH2), the catalytic subunit of polycomb repressive complex 2 (PRC2). PARP1 inhibition enhances the expression of *EZH2*, which catalyzes H3K27me3, leading to chromatin condensation and transcriptional repression [75]. Additionally, H3K4me3 and H3K36me3 are associated with the activation of promoters and genes, while H3K27ac can distinguish between active and poised enhancers [76, 77]. H3K9me3 and H3K27me3 are involved in the formation of repressive chromatin domains and gene silencing [78]. PARP1 binds to H3K4me3 and H3K36me3-binding regions but does not bind to either H3K9me3 or H3K27me3 sites, suggesting that PARP1 participates in the activation of gene expression by opening the chromatin structure [79].

In summary, these studies demonstrate how PAPR1 interacts with histone components and chromatin-modifying enzymes to influence downstream gene expression (Table 3).

Targeting the transcriptional regulatory function of PARP1 for disease therapy

In addition to its DNA damage repair functions, PARP1 regulates tumor formation and progression through transcriptional regulation, suggesting another strategy for the use of PARP inhibitors.

PARP1 directly interacts with transcription factors to enhance their DNA-binding ability. In this process, loss of heterozygosity of the tumor suppressor gene *APC* is

Table 3 Examples of PARP1-interacting factors

Functions	Binding factors	References
PARP1 regulates core histones and other histone variants	H1	[33, 53–59]
	H1.2	[60]
	H2A	[61]
	H2Av	[62, 63]
	H2AZ	[61]
	MacroH2A1.1	[64–67]
	macroH2A1.2	[64, 65]
	H2B	[68]
	H3	[69, 70]
	H4	[69–71]
PARP1 regulates histone- and chromatin-modifying enzymes	KDM5B	[72]
	KDM4D	[73, 74]
	H3K4me3	[72]
	H3K9me2	[73, 74]
	H3K27me3	[75]
	H3K4me3	[76–79]
	H3K36me3	[76–79]

frequently associated with familial and sporadic colorectal cancer, resulting in accumulation of β-catenin and activation of the transcription factor TCF/LEF. PARP1 interacts with TCF4 and forms a TCF4/β-catenin complex in colorectal cancer, increasing the transcriptional activation of TCF/LEF by β-catenin [83]. Therefore, the transcriptional regulatory function of PARP1 merits further investigation as a target for colorectal cancer therapy. Both EWS-FLI1 and EWS-ERG fusion gene products interact and depend on PARP1 function. The expression of both fusion products enhances DNA damage and increases their invasive potential, and PARP inhibition reduces EWS-FLI1-dependent tumor growth and metastasis in vivo [84]. Knockout of *PARP1* leads to a reduction in the expression of EWS-FLI1 target genes, indicating that PARP1 may play a key role in the transcriptional function of the EWS-FLI1 fusion protein, providing a novel research idea for the treatment of Ewing's sarcoma [85]. PARP1 also maintains type 2 helper T-cell inflammation, particularly in allergic responses and asthma. In sensitized mice, PARP1 inhibition attenuates OVA-induced acute airway inflammation by modulating the IL-4/STAT-6/GATA-3/IL-5 axis, which reduces both inflammation and neutrophil infiltration and improves allergic airway responses, dyspnea, and asthma-related remodelling [86].

PARP1 participates in the transcriptional regulation of cancer genes by modifying transcription factors via PARylation. In prostate cancer, androgen receptors (AR) play a key role in cell proliferation and maintenance of prostate cancer–related phenotypes. AR inhibitors are first-line treatments for diffuse disease; however, when cancer recurs, AR become active again [84]. Drug options are limited for patients with castration-resistant prostate cancer (CRPC). Therefore, it is necessary to identify new ways to modulate AR. In prostate cancer, PARP1 is recruited to sites of AR transcriptional function. The enzymatic activity of PARP1 is required for AR-driven gene expression, subsequent hormone therapy sensitivity, and prostate cancer cell proliferation in CRPC [84]. PARP1 inhibition attenuates AR transcriptional activity and alters androgen stimulation–induced histone modifications and chromatin structure [87]. Therefore, research on the regulation of AR by PARP1 is currently being translated into clinical trials that will expand the choice of drugs for patients with CRPC. Aging is the most significant factor associated with neurodegenerative diseases. PARylated TDP-43, FUS, and α-synuclein in neurodegenerative diseases and aging leads to neuroinflammation, autophagy dysfunction, and mitochondrial dysfunction. Therefore, the treatment of neurodegenerative diseases and aging by targeting PARP1 has great potential [88, 89]. Signal transducer and activator of transcription 5 (STAT5) signaling plays a pathogenic role in both hematological malignancies and solid tumors. Loss of STAT5 PARylation not only decreases STAT5 signaling to downstream targets, but also induces cytotoxicity, suggesting that PARP1 may be a therapeutic target in STAT5-activated cancers [90]. Homebox7 (HOXB7) mRNA is overexpressed in breast and ovarian carcinomas and promotes metastasis by inducing epithelial-mesenchymal transition (EMT) [91]. PARylation of HOXB7 by PARP1 reduces HOXB7 affinity for DNA, and, subsequently, the transcriptional activity of HOXB7 [92]. PARP1 inhibitors have been designed as NAD^+mimetics. However, the ubiquity of NAD in cells makes it difficult to completely eliminate PARP1 activity using NAD competitors, which tends to produce certain off-target effects [93]. The mechanism of action of histone-dependent PARP1 inhibitors differs from that of the classical NAD-like PARP1 inhibitors. NAD-like inhibitors stabilize the binding of PARP1 to histone H4, leaving the chromatin in a loosened state [63]. Conversely, histone-dependent inhibitors disrupt the binding of PARP1 to histone H4, excluding PARP1 from the complex [94]. Histone-dependent PARP1 inhibitors inhibit PARP1-mediated transcription more potently than NAD-like PARP1 inhibitors and are therefore more effective in prostate and renal tumors in vitro and in vivo. In summary, histone-dependent PARP1 inhibitors have strong potential for the treatment of urological tumors [95].

Additionally, PARP1 competes with histone components to bind to cancer gene promoters. PARP1 also enhances stability and accumulation of HIF-1α and HIF-2α. HIF-1α and HIF-2α are molecules involved in the most common mechanism of renal cell carcinoma, so it may be possible to treat the root cause of this disease [96, 97]. PARP1 promotes the expression of *HSP70*

by PARylating histone H1, which promotes tumor cell survival and resistance to antitumor drugs [98]. In breast cancer, a similar chromatin-dependent mechanism is involved in the estrogen-dependent regulation of gene expression with the involvement of PARP1. PARP1 induces the transcriptional activation of *MITF*, suggesting a role in melanomagenesis [99]. Therefore, targeting PARP1 is a promising therapeutic strategy for the treatment of steatohepatitis.

Together, these studies demonstrate that PARP1 can regulate the transcriptional functions of pathogenic genes, suggesting that targeting PARP1 transcriptional regulatory functions may greatly improve disease treatment. A better understanding of the mechanisms underlying PARP1 function is important for expanding the application of PARP inhibitors in multiple disease therapies.

Conclusion

In this article, we elaborate on the molecular mechanisms of PARP1 in gene regulation and its potential applications in disease treatment. Previous studies have focused on the functions of PARP1 in DNA repair and maintenance of genome integrity. PARP inhibitors are widely used as DNA damage agents for the treatment of various types of tumors, including ovarian, breast, and prostate cancers. However, an increasing number of studies have revealed the pivotal role of PARP1 in transcriptional regulation through multiple mechanisms, suggesting this protein is a potential intervention target for the treatment of FSHD, hereditary hemochromatosis, and many other diseases [5, 37, 49]. However, the behavior of PARP1 is complex, making it difficult to elucidate the precise mechanism underlying its involvement in disease progression. Consequently, PARP inhibitors can affect many biological processes mediated by PARP1, making it difficult to elucidate the precise mechanism by which they exert their therapeutic effects, thereby limiting their clinical application based on novel transcriptional regulatory targets. Although numerous studies have shown that PARP1-mediated transcriptional regulation is a potential target for many diseases, the evidence is mainly provided at the cellular or animal level, and its diverse biological effects make it challenging to achieve clinical therapeutic effects. However, PARP inhibitors, as marketed drugs, are clinically proven to be sufficiently safe. Therefore, by implementing a drug repositioning strategy, PARP inhibitors can directly enter clinical phase II targeting new indications, which may accelerate their efficacy validation for new indications and prevent their wider clinical applications from being constrained by mechanistic exploration. Nevertheless, a better understanding of the mechanisms underlying PARP1 function, particularly its transcriptional regulatory functions, remains crucial for expanding the clinical application of PARP inhibitors.

Abbreviations

PARP1	Poly (ADP-ribose) polymerase 1
PARylation	Poly(ADP-ribosyl)ation
EBV	Epstein-Barr virus
HH	Hereditary haemochromatosis
NF	κB-Nuclear factor-κB
TAGLN	Transgelin
PDL1	Death ligand 1
STAT3	Transcription 3
ERKs	Extracellular signal-regulated kinases
PLC	Phospholipase C
MAPKs	Mitogen-activated protein kinases
MATIIα	Methionine adenosyltransferase 2 A
MafK	V-maf musculoaponeurotic fibrosarcoma oncogene family, protein K
Bach1	BTB and CNC homology 1
C/EBPβ	CCAAT/enhancer-binding proteinβ
EMSA	The Electrophoretic Mobility Shift Assay
ChIP	Chromatin Immunoprecipitation
ERα	Oestrogen receptorα
ERE	Oestrogen response element
FGF4	Fibroblast growth factor 4
ChIPsingle bondqPCR	Chromatin immunoprecipitation-quantitative PCR
DDX5	DEAD-box helicase 5
CTCF	CCCTC-binding factor
TET	Ten-eleven translocation
DNMT1	DNA methyltransferases 1
DUX4	Double homeobox 4
cTnT	Cardiac troponin T
c	Myc-Cellular-myelocytomatosis viral oncogene
CCL2	C-C motif chemokine ligand 2
TCIRG1	T-cell immune regulator 1
HFE	Hereditary haemochromatosis gene
SNAI2	Snail family transcriptional repressor 2
CXCL1	Chemokine (CXC motif) ligand 1
HIF 1α	Hypoxia-inducible factor 1α
Snail1	Snail family zinc finger 1
FN1	Fibronectin 1
FOXO1	Forkhead box transcription factor 1
GATA3	GATA-binding protein-3 gene
CCND1	The cyclin D1
CDK2	Cyclin-dependent kinase 2
EPHX1	Epoxide hydrolase 1
NFATC1	Nuclear factor-activated T-cell 1
KDM5B	Lysine demethylase 5B
KDM4D	Lysine demethylase 4D
EZH2	Zeste homolog 2
PRC2	Polycomb repressive complex 2
CRPC	Castration-resistant prostate cancer
STAT5	Transcription 5
HOXB7	Homebox7
EMT	Epithelial-mesenchymal transition

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Data availability

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Declarations

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