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# Gene Section
Review

# PARP1 (poly(ADP-ribose) polymerase 1)

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## Abstract

PARP1 (poly(ADP-ribose) polymerase 1) is a nuclear protein involved in the regulation of various biological processes including apoptosis, DNA repair for the maintenance of genome integrity, epigenetic marking of chromatin, assembly of higher-order chromatin structures, transcriptional activation, differentiation, proliferation, and cell cycle. Particularly, due to its decisive role in several DNA repair pathways, the inhibition of PARP1 has emerged as a prominent therapeutic option in cancer treatment, by improving the efficiency of chemotherapeutics or radiation therapy.

**Keywords**
PARylation, DNA repair, cancer, inflammation, neurodegenerative diseases, viral infections

## Identity

**Other names**
PARP-1, ADPRT, ARTD1, PPOL, ADP-Ribosyltransferase NAD(+), Poly(ADP Ribosyl)Transferase, Poly(ADP-Ribose) Synthetase, EC 2.4.2., PADPRT-1, EC 2.4.2, ADPRT1, PARP

**HGNC (Hugo):** PARP1

**Location:** 1q42.12

**Local order**
Starts at 226360691 and ends at 226408093 (GRCh38.p13 Assembly) (Figure 1).

**Note**
PARP1 has been found to be related with almost all the biological events and signalling pathways.

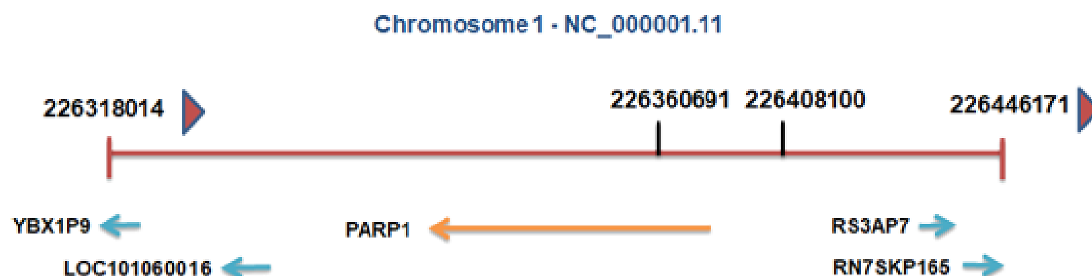


Figure 1. Genomic location of human PARP1 (Chromosome 1 - NC_000001.11, GRCh38.p13 Assembly)

# DNA/RNA

### Note

The poly (ADP-ribose) polymerase (PARP) proteins have been characterized as enzymes that catalyse the attachment of the ADP-ribose subunits to itself and to multiple target proteins by using $NAD^+$ as the substrate (Citarelli, Teotia, & Lamb, 2010; Ray Chaudhuri Nussenzweig, 2017). This post-transcriptional modification is called Poly(ADP-ribosyl)ation (PARylation) (Citarelli et al., 2010). PARylation is a reversible modification: it is accomplished by the concerted actions of poly(ADP-ribose) polymerase (PARP) enzymes and poly(ADP-ribose) (PAR) hydrolysing enzymes such as PAR glycohydrolase (PARG) and ADP-ribosyl hydrolase 3 (ADPRHL2) (Virág, Robaszkiewicz, Rodriguez-Vargas, Oliver, 2013). The removal of terminal ADP-ribose unit is achieved by the hydrolytic activity of macrodomain proteins (MACROD1, MACROD2, and OARD1) (Perina et al., 2014).

PARylation is a widely used process in eukaryotes. In eukaryotic species, the distribution of PARP proteins strictly follows the distribution of PARGs and at least one of the macrodomain proteins is also always present (Perina et al., 2014). On the other hand, PARP proteins are less common in bacteria and are thought to be acquired through horizontal gene transfer (Alemasova & Lavrik, 2019; Perina et al., 2014). In thermophilic archaeon Sulfolobus solfataricus, a protein with oligo(ADP-ribosyl) transferase activity was identified (Faraone-Mennella, Gambacorta, Nicolaus, Farina, 1998) and in a number of dsDNA viruses have also been found to possess PARP homologues (Perina et al., 2014).

Based on the sequence homology, humans are assumed to express 17 defined PARPs (Vyas, Chesarone-Cataldo, Todorova, Huang, Chang, 2013). PARP1, the first PARP purified and cloned from human, is a constitutive and the best studied member of the PARP family of proteins (Citarelli et al., 2010).

The PARP1 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, mosquito, C.elegans, A.thaliana, rice, and frog (Table 1).

| Gene Species | Gene Symbol | Identity (%) DNA |
|---|---|---|
| vs. P.troglodytes | PARP1 | 99,2 |
| vs. M.mulatta | PARP1 | 97,7 |
| vs. C.lupus | PARP1 | 88,4 |
| vs. B.taurus | PARP1 | 88,4 |
| vs. M.musculus | Parp1 | 86,5 |
| vs. R.norvegicus | Parp1 | 86,1 |
| vs. G.gallus | PARP1 | 75,2 |
| vs. X.tropicalis | parp1 | 72 |
| vs. D.rerio | parp1 | 69,5 |
| vs. D.melanogaster | Parp | 49,5 |
| vs. A.gambiae | AgaP_AGAP003230 | 53,1 |
| vs. C.elegans | pme-1 | 48,2 |
| vs. A.thaliana | PARP1 | 50,2 |
| vs. O.sativa | Os07g0413700 | 51,7 |

Table 1. Pairwise alignment of PARP1 gene (in distance from human) (HomoloGene:1222, NCBI).

## *Description*

The PARP1 gene is a protein-coding gene. It is located at 1q42.12 on the minus strand and consists of 23 exons spanning ~43 kb (starts at 226360691 and ends at 226408093; GRCh38.p13 Assembly, NCBI).

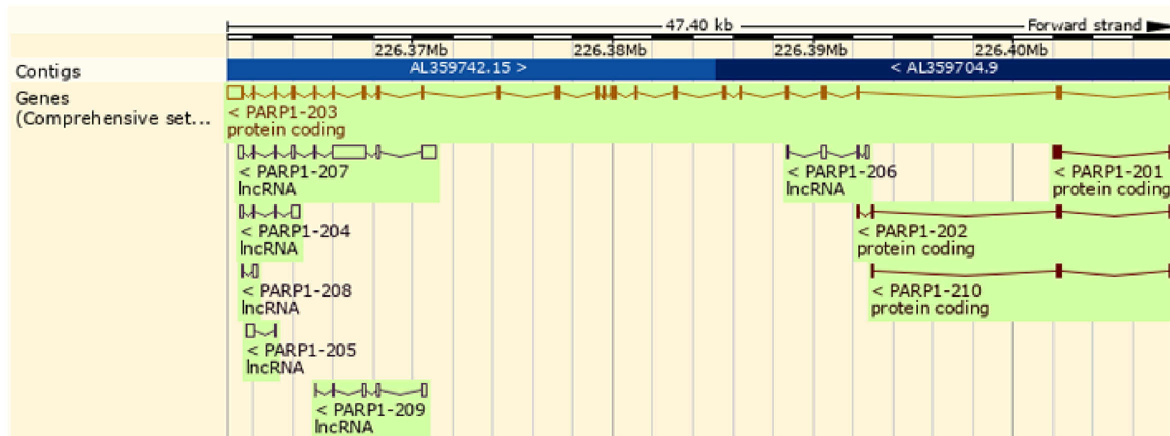


Figure 2. Display of human PARP1 gene transcript exons (Ensembl release 98 - September 2019)

| Name/Gene ID | Description | Location (bp) | Aliases |
|---|---|---|---|

| | | | |
|---|---|---|---|
| PARP1P2 (ID: 145) | poly(ADP-ribose) polymerase 1 pseudogene 2 | Chr 14, NC_000014.9 (63123001..63123935) | ADPRTP2, PPOLP2 |
| PARP1P1 (ID: 144) | poly(ADP-ribose) +B7:D7polymerase 1 pseudogene 1 | Chr 13, NC_000013.11 (110936624..110940232) | ADPRTP1, PPOLP1 |

Table 2. Transcripts of human PARP1 gene (Ensembl release 98 - September 2019)

## Transcription

This gene has 10 transcripts (splice variants) depending on Ensembl release 98 - September 2019 (Table 2 and Figure 2).

The human PARP1 promoter region does not contain typical regulatory elements, such as TATA or CAAT boxes.

A near 40-base-pair region surrounding the transcription start site described as containing a near-consensus initiator element capable of initiating RNA polymerase II transcription (Abbotts Wilson, 2017).

Detailed analyses of the promoter regions of PARP1 genes in humans, rats, and mice showed that PARP1 promoter sequences have binding sites for transcription factors SP1, AP-2, YY1, ETS1, and NF1.

In the distal promoter region of human PARP1 gene Candidate binding sites for several other factors including CDE, KLF4 (GKLF), BARB, RRM1 (MAZF), RREB1, HOX, GSX1 (GSH-1), CEBPB, NFIL3 (E4BP4), STAT6, cETSZ-1, PBX1, LEF1 (TCF), NF-kB, REL, ZNF148 (ZBP-89), KLF6 (CPBP), USF, CDF-1, EGR1, and IKZF1 (Ikaros 1) were also identified (Doetsch, Gluch, Poznanovic, Bode, & Vidakovic, 2012).

Additionally, at the post-transcriptional level, miR-124, MIR223, let-7a, miR-7-5p, and MIR125B2 were shown to regulate cellular PARP1 expression (Dash et al., 2017; J. Lai et al., 2019; Wielgos et al., 2017).

## Pseudogene

There are two known pseudogenes of PARP1: PARP1P1 and PARP1P2 located on chromosomes 13 and 14, respectively (Table 3). A germline, two-allele (A/B) polymorphism of PARP1P1 on chromosome 13q34-qter has been identified. In the B-allele, a 193 bp deletion was determined and this deletion has been shown to be associated with cancer predisposition to multiple myeloma, monoclonal gammopathies, prostate cancer, and lung cancers in African Americans. On the other hand, more recent studies do not support the earlier findings which suggest that the PARP1P1 genotype plays a critical role in cancer susceptibility (Lockett, Snowhite, Hu, 2005). Analyses, comprising a larger cohort that is selected based on case/control differences rather than racial/ethnic differences, are needed to clarify if there is any significant role of this pseudogene in cancer predisposition.

# Protein

**Note**

Encoded proteins by PARP1 gene in human are given in Table 4 and PARP1 protein similarity across species are given in Table 5.

| | | | | | |
|---|---|---|---|---|---|
| PARP1-201 | ENST00000366790.3 | 570 | - | - | Protein coding |
| PARP1-202 | ENST00000366792.3 | 553 | - | - | Protein coding |
| PARP1-203 | ENST00000366794.10 | 3978 | CCDS1554 | NM_001618.4 | Protein coding |
| PARP1-204 | ENST00000463968.5 | 830 | - | - | lncRNA |
| PARP1-205 | ENST00000468608.1 | 438 | - | - | lncRNA |
| PARP1-206 | ENST00000469663.1 | 542 | - | - | lncRNA |
| PARP1-207 | ENST00000490921.5 | 3165 | - | - | lncRNA |
| PARP1-208 | ENST00000491816.1 | 416 | - | - | lncRNA |
| PARP1-209 | ENST00000498787.1 | 628 | - | - | lncRNA |
| PARP1-210 | ENST00000629232.1 | 477 | - | - | Protein coding |

Table 3. Pseudogenes of human PARP1 gene (GRCh38 Assembly, NCBI)

| Name | Transcript ID | Protein | Charge | Isoelectric Point | Molecular Weight | CCDS | UniProt | RefSeq |
|---|---|---|---|---|---|---|---|---|
| PARP1-201 | ENST00000366790.3 | 155aa | 10,0 | 9,4862 | 17,324.99 g/mol | - | Q5VX85 | - |
| PARP1-202 | ENST00000366792.3 | 108aa | 3,0 | 7,7272 | 12,234.02 g/mol | - | Q5VX84 | - |
| PARP1-203 | ENST00000366794.10 | 1014aa | 31,5 | 9,3322 | 113,083.79 g/mol | CCDS1554 | A0A024R3T8 P09874 | NM_001618.4 |
| PARP1-210 | ENST00000629232.1 | 108aa | 3,0 | 7,7272 | 12,234.02 g/mol | - | Q5VX84 | - |

Table 4. Protein products of human PARP1 gene (Ensembl release 98 - September 2019

| Gene Species | Gene Symbol | Identity (%) PROTEIN |
|---|---|---|
| vs. P.troglodytes | PARP1 | 99 |
| vs. M.mulatta | PARP1 | 98,2 |
| vs. C.lupus | PARP1 | 94,1 |
| vs. B.taurus | PARP1 | 90,4 |
| vs. M.musculus | Parp1 | 92,2 |
| vs. R.norvegicus | Parp1 | 91,6 |
| vs. G.gallus | PARP1 | 79,5 |
| vs. X.tropicalis | parp1 | 75,7 |
| vs. D.rerio | parp1 | 72,1 |
| vs. D.melanogaster | Parp | 43,8 |
| vs. A.gambiae | AgaP_AGAP003230 | 46,5 |
| vs. C.elegans | pme-1 | 41,1 |
| vs. A.thaliana | PARP1 | 42,3 |
| vs. O.sativa | Os07g0413700 | 42,7 |

Table 5. Pairwise alignment of PARP1 protein sequences (in distance from human) (HomoloGene:1222, NCBI)

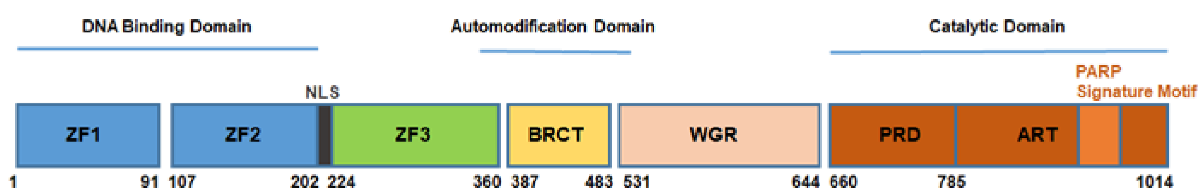

Figure 3. Domain organization of PARP1: ZF1-3: zinc finger domains 1-3; BRCT: BRCA1 C terminus domain; WGR: tryptophan-glycine-arginine rich domain; PRD: PARP regulatory domain; ART: catalytic domain, highly-conserved in other ADP-ribosyl transferases; NLS: Nuclear Localization Signal. The figure is modified from (Abbotts Wilson, 2017).

## Description

PARP1 encodes poly (ADP-ribosyl) transferase (EC 2.4.2.30) (NCBI Homo sapiens Annotation Release 109). Poly (ADP-ribose) polymerase1 (PARP1) is an isoform of the PARP enzyme family (Pacher Szabó, 2007). Full length PARP1 protein comprises three major functional domains: an amino-terminal DNA-binding domain, a carboxy-terminal catalytic domain (CD; also called as CAT), and a central auto modification domain (called as AMD or AD) (Altmeyer, Messner, Hassa, Fey, & Hottiger, 2009; Gross, Kotova, Maluchenko, Pascal, & Studitsky, 2016). DBD contains two zinc finger domains (ZFI/ZF1 and ZFII/ZF2; also known as Zn1 and Zn2). Langelier et al. reported that the ZF2 domain exhibits high binding affinity to DNA compared to the ZF1 domain and Gradwohl et al. showed that disruption of the metal-binding ability of the ZF2 dramatically reduces the binding to target DNA (Gradwohl et al., 1990). In addition, in both in vitro and in vivo, the ZF1 domain was found to be necessary for DNA-dependent PARP1 activity whereas the ZF2 domain was not required strictly (Langelier, Planck, Roy, & Pascal, 2011). An

additional zinc finger domain (ZFIII/ZF3; also known as Zn3) presents after DBD and it mediates inter-domain contacts, important for the PARP1 activation. (Langelier et al., 2011; Tao, Gao, Hoffman, Liu, 2008). A bipartite nuclear localization signal (NLS) also lies in DBD and contains a caspase cleavage site $DEVD_{214}$ (Castri et al., 2014). The AMD region is located in the central region of the enzyme and the region has acceptor amino acids for the covalent attachment of PAR. Moreover, a weak leucine-zipper motif has been described in the amino-terminal region of the AMD, which suggests that this motif may function in homo- and/or hetero-dimerization. The AMD of PARP1 also includes a breast cancer 1 protein (BRCA1) C-terminus (BRCT) domain as well as an unstructured loop that connects the AMD with the PARP homology domain (Altmeyer et al., 2009). The carboxy-terminal CD is the most conserved region across PARP family of proteins in different species. This domain has the 'PARP signature' characterized by NAD acceptor sites and critical residues involved in the initiation (the attachment of the first ADP-ribose moiety onto an acceptor amino acid), elongation (the addition of further ADP-ribose units onto already existing ones) and branching (the generation of branching points) of PAR (Altmeyer et al., 2009; Simonin et al., 1990). Followed by the CD, there is a WGR region, named after the identification of conserved amino acid sequence in the motif: Tryptophan-W, Glycine-G, Arginine-R. WGR region functions in DNA binding and inter-domain contacts essential for DNA damage-dependent activation (Altmeyer et al., 2009; Dawicki-McKenna et al., 2015; Langelier, Planck, Roy, Pascal, 2012). The domain organization of PARP1 is shown in Figure 3.

PARP1 is known to be activated by mono-ADP-ribosylation, acetylation, increased cellular calcium concentration, or by binding to tyrosyl tRNA synthase. On the other hand, self-PARylation and sumoylation were shown to inhibit PARP1 activity. PARP1 can also be phosphorylated in a reversible manner and the phosphorylation can activate (e.g., AMP-activated protein kinase [AMPK]) or inhibit (e.g., protein kinase C) PARP-1 activity (Bai, 2015). In addition, physical interactions with other proteins, including histones, HPF1, HMGN1, XPA, NEIL1, OGG1, DDB2, TP53, and MAPK1 (ERK2) found to regulate PARP1 activity (Alemasova Lavrik, 2019). It was also reported that dimerization of PARP1 enhances its enzymatic activity while further multimerization or dissociation to single PARP1 molecules leads to decreased enzymatic activity (Alemasova Lavrik, 2019).

## Expression

PARP1 is an abundantly and ubiquitously expressed protein in most tissues (Schiewer & Knudsen, 2014). Compared to normal counterparts, enhanced PARP1 expression is found in various types of tumors, but the most striking differences in PARP1 expression have been found in breast, ovarian, endometrial, lung, skin cancers and non-Hodgkin's lymphoma (Galia et al., 2012; Ossovskaya, Koo, Kaldjian, Alvares, Sherman, 2010).

## Localisation

PARP1 is primarily localized to the nucleus, but a distinct fraction was also detected in the mitochondria. Unlike nuclear PARP1, mitochondrial PARP1 has been shown to affect mitochondrial DNA repair negatively (Szczesny, Brunyanszki, Olah, Mitra, Szabo, 2014).

PARP1 is one of several known cellular substrates of CASP3 and CASP7 (caspase 3 and caspase 7) and cleavage of PARP1 by these caspases is considered to be a hallmark of apoptosis. Upon cleavage, two specific fragments of PARP1 are generated: an 89 kDa fragment containing AMD and the catalytic domain of the enzyme and a 24 kDa containing DBD. The 89 kDa fragment has a greatly reduced DNA binding capacity and is liberated from the nucleus into the cytosol. On the other hand, the 24 kDa cleaved fragment with 2 zinc-finger motifs does not leave the nucleus where it binds to nicked DNA irreversibly and therefore acts as a trans-dominant inhibitor of active PARP1 (Chaitanya, Alexander, Babu, 2010).

## Function

ADP-ribosylation is a posttranslational modification. By using the oxidized form of $NAD^+$ as a substrate, PARP enzymes bind and cleave $NAD^+$ to nicotinamide (NAM) and ADP-ribose (ADPR) and catalyze the covalent binding of ADPR units onto glutamate, aspartate, tyrosine, lysine, and serine residues of target proteins (Rodrèguez-Vargas, Oliver-Pozo, & Dantzer, 2019). PARP1, PARP2, tankyrase 1 (TNKS), and tankyrase 2 (TNKS2) synthesize branched PAR polymers and the remaining PARP enzymes are either mono or oligo ADPR-transferases. No enzymatic activity has been identified for ZC3HAV1 (PARP13) (Bai, 2015). PARP1 is the prototype member of the PARP family of enzymes and more than 80% of stimulated and basal cellular PARP activity are exerted by PARP1 (Bai, 2015; Rajamohan et al., 2009).

Although PARP1 has been long defined as a DNA-damage response protein, recent investigations highlight multiple functions of PARP1 including transcription, replication, aging, viral protection, cell cycle regulation, modification of chromosome structure, differentiation, inflammation, metabolic regulation, proteasomal degradation, and RNA processing (Bai, 2015; Rodrèguez-Vargas et al., 2019) (Figure 4).

**PARP1 functions in DNA repair**

Genotoxic stress results in various types of DNA lesions, including DNA single-strand breaks (SSBs) and double-strand breaks (DSBs). If not repaired, accumulated damage can disrupt genomic integrity. Fortunately, cells have evolved different DNA-damage repair responses that repair these DNA lesions to insure genomic stability (C. Liu, Vyas, Kassab, Singh, Yu, 2017).

PARP1 recognizes both SSBs and DSBs and transfers the ADP-ribose moiety of $NAD^+$ to the side chains of asparagine, aspartic acid, glutamic acid, arginine, lysine, serine and cysteine residues on its target proteins. Through their PAR-binding domains, these PAR chains form a platform and recruit DNA repair proteins. Therefore, PARP1 is an important DNA damage sensor for both SSBs and DSBs (Ray Chaudhuri Nussenzweig, 2017).

**PARP1 modulates chromatin structure and transcription**

PARP1 functions in chromatin compaction, decondensation and it modulates epigenetic marks via PARylating histones and chromatin remodeling enzymes (Quénet, El Ramy, Schreiber, Dantzer, 2009). Being as a component of enhancer/promoter-binding complexes, besides its effects on chromatin structure, PARP1 can bind to most of the RNA polymerase II transcribed genes and mediate around 3.5% of all transcribed RNAs covering a broad range of functions from inflammation to metabolism (Ke, Zhang, Lv, Zeng, & Ba, 2019; Kraus, 2008). PARP1 can also enhance the accessibility of promoters via histone and nucleosome replacements and can enhance transcription by replacing negative transcriptional cofactors with positive ones (Kraus & Hottiger, 2013; Muthurajan et al., 2014).

Recent findings described new roles of PARP1 in the regulation of RNA binding proteins, rRNA synthesis, ribosome biogenesis, and mRNA regulation (Ke et al., 2019; Ryu, Kim, Kraus, 2015). Accordingly, PARP1 can regulate gene expression at the post-transcriptional level.

**Cell death and PARP1**

As mentioned before, PARP1 is known to be cleaved and inactivated by active caspases 3 and 7 and this cleavage is accepted as a 'hallmark of apoptosis' (Castri et al., 2014; Desroches & Denault, 2019). The cleavage causes the formation of 24 kDa and 89 kDa fragments. Depending on the intensity and type of stimuli resulting in the cleavage, two main consequences have been reported: (1) reduced PARylation during DNA repair processes; (2) the modification of PARP1 transcriptional activity (Castri et al., 2014).

Recent studies indicate that PARP1 hyperactivation, ie. excessive PARylation by PARP1, can lead 'parthanatos', a form of necrotic cell death which PAR induces the nuclear translocation of apoptosis-inducing factor ( AIFM1) from mitochondria to initiate chromatinolysis and cell death independently of caspase activation. For a long time, it has been thought that the cell death caused by excessive activation of PARP occurs via the catalytic consumption of $NAD^+$ followed by ATP reduction and bioenergetic collapse. However, Andrabi et al. showed that not the decreased $NAD^+$, but PAR-dependent inhibition of hexokinase activity leads to defects in glycolysis and therefore causes the bioenergetic collapse. On the other hand, PARP1 activity is kept at much lower levels during normal unstressed cellular conditions (Andrabi et al., 2014; Dawicki-McKenna et al., 2015; Gupte, Liu, Kraus, 2017).

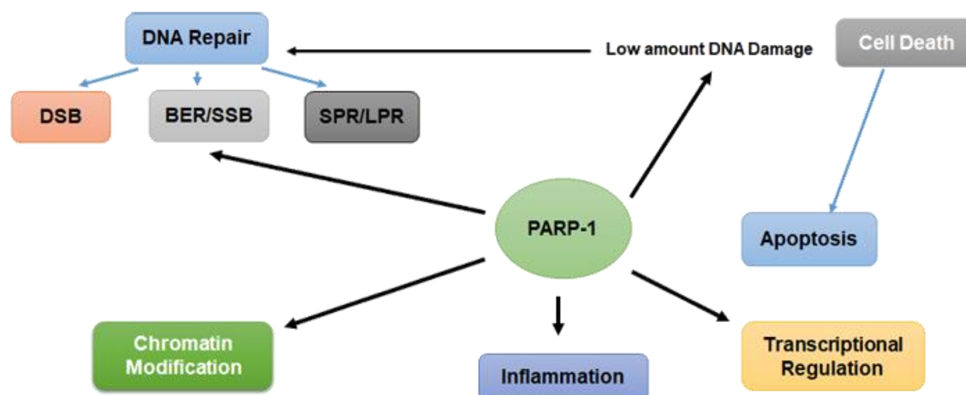


Figure 4. Multifaceted nature of PARP-1: PARP1 functions in DNA repair, chromatin modification, inflammation, transcriptional regulation, and cell death. DBS: Double Strand Break; BER: Base Excision Repair; SSB: Single Strand Break; SPR: Short-Patch Repair; LPR: Long-Patch Repair. The figure is modified from (Swindall, Stanley, Yang, 2013).

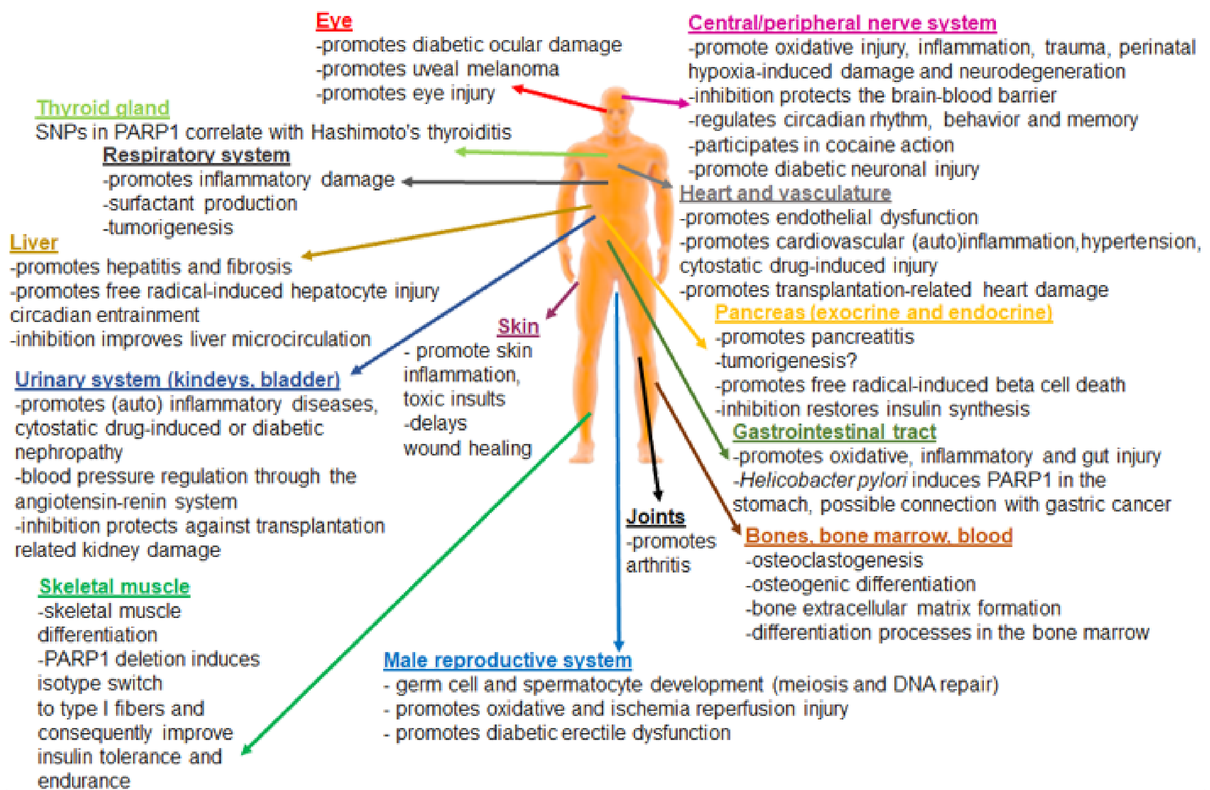


Figure 5. The Role of PARP1 in human organs. The figure is modified from (Bai, 2015).

# Mutations

**Note**

A list of PARP1 mutations in cancer can be found in: COSMIC, the Catalogue of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln =PARP1

## Germinal

Parp1$^{-/-}$ mice are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities (Tha Jackson Laboratory; www.jax.org/strain/002779).

## Somatic

Lys933Asn and Lys945Asn mutations were found to be significantly correlated with colorectal cancer (CRC) in the Saudi population. Since these mutations were identified to be localized in PARP1 catalytic domain (CD), mutations of these lysine residues were suggested to affect the PARP1 catalytic activity (Alshammari, Shalaby, Alanazi, Saeed, 2014).

In addition, Val762Ala polymorphism in the CD has been reported as the most common variant of PARP1 associated with an increased risk of many tumors (Toss Laura, 2013).

Using genome-wide and high-density CRISPR-Cas9 'tag-mutate-enrich' mutagenesis screens, Pettitt et al. identified PARP1 mutant alleles that cause in vitro and in vivo PARP inhibitor resistance. The results reveal that point mutations in the ZnF domains were sufficient for the inhibitor resistance (Pettitt et al., 2018).

**Polymorphisms:** In addition to mutations, through modulation of PARP1 expression level and enzyme activity, PARP1 gene polymorphisms can affect the outcome and response to therapy of cancer. For example, PARP1 SNP rs1805407, found in perfect linkage disequilibrium with two PARP1 promoter SNPs (rs2077197 and rs6665208), was shown to be associated with higher PARP1 expression (Abecassis et al., 2019). In another study, expression quantitative trait locus (eQTL) analysis in melanocytic cell types revealed that presence of the 1q42.1 melanoma risk allele (rs3219090[G]) is correlated with higher PARP1 levels. Furthermore, a proteomic screen identified that RECQL helicase binds to the insertion allele of PARP1 (indel SNP rs144361550) in melanoma cells and primary human melanocytes (J. Choi et al., 2017). In another study, using a new data integrative approach applied on multi-modal -omics, and clinical data, Abecassis et al. demonstrated that response to chemotherapy is directly linked to the gene expression, four methylation variables and PARP1 SNP rs1805407 in a cohort of metastatic melanoma patients (Abecassis et al., 2019). According to the results of another genotyping study, Val762Ala, Asp81Asp, and Lys352Lys polymorphisms and the haplotype-ACAAC in PARP1 are associated with reduced risk

of non-Hodgkin lymphoma in Korean males (Jin et al., 2010). In a case-control study conducted in the Hexi area of China, PARP1 2819G allele was shown to be associated with an increased risk of gastric cancer (He, Liu, Shan, Zhu, Li, 2012).

In addition, PAR metabolism is also involved in malignancies. For instance, PARylation of proteins in peripheral blood leukocytes was shown to be reduced by more than 50% in head, neck, breast and cervical cancers (Lakadong, Kataki, Sharan, 2010).

# Implicated in

PARP1 has been implicated in several human pathologies (Figure 5). Defects in PARP1 function have been shown to be associated with several diseases, such as conditions or diseases related with chronic inflammation, neurodegenerative disorders, cardiovascular diseases, and cancer.

## *Cardiovascular diseases*

Myocardial infarction (MI) is a common cardiovascular disease characterized by the induction of inflammation and apoptosis of cardiomyocytes because of the diminished levels of oxygen and nutrients in the myocardial tissue. In a rat model of MI, Wang et al. suggested that oxidative DNA damage caused by the generation of reactive species during the onset of MI can cause excessive activation of PARP1 followed by an imbalance of cell survival mechanisms that contribute to the death of cardiomyocytes. The authors showed that inhibition of iNOS (Inducible nitric oxide synthase), an important member of inflammatory cytokines regulated by PARP1 via the NF- kB pathway, or inhibition of PARP1 was able to reduce the level of apoptosis caused by the ischemic myocardial damage (J. Wang et al., 2015).

More recently, it has been shown that PARP1 can affect cardiac functions also via autophagy activation. Therefore, inhibition of PARP1 was suggested to be protective against cardiac ischemia injury by repressing autophagy (C. Wang, Xu, Zhang, Zhang, Huang, 2018).

## *Diabetes and Obesity*

PARP1 has been suggested to play an important role in adipogenesis and cellular metabolism (Erener, Hesse, Kostadinova, & Hottiger, 2011; Jokinen, Pirnes-Karhu, Pietiläinen, & Pirinen, 2017; Luo et al., 2017). In their in vivo study, Devalaraja-Narashimha and Padanilam showed that knock out of Parp reversed resistance to diet-induced obesity by decreasing energy expenditure in mice (Devalaraja-Narashimha Padanilam, 2010).

## *Central Nervous System Disorders*

PARP1 activation is known to be associated with the pathogenesis of several central nervous system disorders, including ischemia, neuroinflammation, and neurodegenerative diseases such as Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) (Martire, Mosca, & d'Erme, 2015; Palazzo, Mikolcevic, Mikoc, Ahel, 2019). Neurological disorders can be characterized by aggregation of cytotoxic proteins, enhanced levels of oxidative stress followed by DNA damage, PARP1 activation, and excess of cellular levels of PAR (Palazzo et al., 2019). For instance, in PD, intracellular monomericSNCA (alpha-synuclein) forms higher-ordered protein aggregates which can spread from cell to cell. These α-synuclein aggregates can activate nitric oxide synthase which enhances the production of NOS. NOS can cause DNA damage and activation of PARP1 and nuclear production of PAR. PAR is transported into the cytosol where it interacts with α-synuclein and further accelerates fibrillization and misfolding of this cytotoxic protein α-synuclein in a pathogenic loop. Ultimately, accumulation of pathologic α-synuclein results in cell death via parthanatos and neuronal dysfunction (Kam et al., 2018).

A growing number of evidence shows that mitochondrial function is strictly controlled by PARP1 which is responsible for about more than 90% of PARylation in the brain (Pieper et al., 2000). In addition to oxidative stress which is able to activate PARP1, recent studies claim that PARP1 is a critical component of a molecular interactions network responsible in the nervous system disorders related to mitochondrial function. It was suggested that deleterious consequences of PARP1 activation on mitochondrial function are caused by its interaction with SIRT1 (Sirtuin 1). In addition, the interaction of PARP1 with promoters of nuclear genes encoding for mitochondrial transcription factors and mtDNA repair proteins were identified (Czapski et al., 2018).

## *Viral Infections*

A broad range of DNA and RNA viruses are known to activate DNA repair pathways in the absence of host DNA damage. PARP1 is known to be recruited to the Kaposi's sarcoma-associated herpesvirus and Epstein-Barr virus genomes and it prevents viral replication by modifying viral proteins involved in genome replication and partitioning. On the other hand, hepatitis B virus was found to require PARP1 for efficient transcription. Additionally, PARP1 inhibits the expression of retrotransposons in Drosophila and retroviruses in avian cells (Gutierrez, Valdes, Serguera, & Llano, 2016). It has been reported that efficient HIV-1 (Human Immunodeficiency Virus-1) integration and transcriptional activation also require PARP1 activity (Ha et al., 2001; Yu, Liu, Yang, & Zhou, 2018). Recently, PARP1 was shown as a cofactor in the activity of the influenza A virus polymerase (Westera et al., 2019). In another study, Shou et al.

showed that PARP1 functions as a regulator of NF-kB by promoting its nuclear translocation and by facilitating its binding to the NF-kB response sequences in macrophages upon vaccinia virus infection; therefore PARP1 can provide viral control through natural killer (NK) cell recruitment to the site of infection (Shou, Fu, Huang, Yang, 2019)

## Gastric cancer

Depending on the survival analysis, upregulation of PARP1 expression was shown to be correlated with poor overall survival rates of gastric cancer patients (Afzal et al., 2019). Enhanced PARP1 expression was found to be significantly associated with Helicobacter pylori infection, decreased differentiation, increased depth of invasion, presence of lymphatic invasion and lymph node metastasis, and advanced tumor-node-metastasis stage (Y. Liu et al., 2016).

## Lung cancer

In lung adenocarcinoma patients, PARP1 was claimed to enhance tumor metastasis through supporting several metastatic features, including anoikis resistance, invasion, extravasation and self-renewal (E. B. Choi et al., 2016).

## Ovarian cancer and Breast cancer

Breast Cancer Susceptibility Genes BRCA1 and BRCA2 are tumor suppressors that function in the repair DSBs via the homologous recombination (HR) repair pathway. In BRCA mutant tumor cells, PARP inhibition was shown to induce 'synthetic lethality' resulting in profound tumor cell cytotoxicity without harming normal cells (Jiang, Li, Li, Bai, Zhang, 2019).

In addition to malignant tissues of BRCA-mutant, triple-negative, and receptor-positive breast carcinoma, PARP1 is overexpressed significantly in uterine carcinoma and ovarian carcinoma. As in breast carcinoma, ovarian cancer cells show high sensitivity to drugs designed for PARP1 inhibition (Iqbal et al., 2012; Thompson & Easton, 2003; L. Wang et al., 2017).

## Pancreatic cancer

BRCA2 mutation carriers have a more than 3 fold risk of developing pancreatic cancer and women with BRCA 1/2 mutation were shown to have an approximate 2.5 fold increase in the incidence of pancreatic cancer (Breast Cancer Linkage Consortium, 1999; Iqbal et al., 2012; Thompson Easton, 2003). In the context of familial pancreatic cancer, studies have shown that pedigrees with germline mutations in BRCA1 and BRCA2 have an increased lifetime risk of pancreatic cancer. A germline mutation in one of these genes represents the earliest risk factor in many familial pancreatic cancer kindreds. In patients with sporadic pancreatic cancer, BRCA1/2 were also found to be mutated in the most advanced pancreatic intraepithelial neoplasia lesions (Greer & Whitcomb, 2007). In BRCA1/2 mutated tumors, which homologous recombination ca not be utilized to repair DSBs, inhibitors of PARP are suggested to target tumor cells to terminate their BER rescue pathway thus leading to accumulation of DNA damage, genomic instability and eventually cell death (Fogelman et al., 2011; Yuan, Liao, Hsueh, Mirshahidi, 2011).

## Non-Hodgkin's lymphoma

PARP1 expression is known to be enhanced in non-Hodgkin's lymphoma (Ossovskaya et al., 2010). Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. Expression of LIM-domain only 2 (LMO2) is one of the best prognostic markers of longer survival following therapy. Very recently, LMO2 expression was found to lead dysfunction in homolog recombination (HR) and tumor cell sensitization to genotoxic agents and PARP1/2 inhibitors were shown to enhance this effect further. Therefore, Parvin et al. suggested that the utilization of PARP inhibitors in combination with immunochemotherapy in LMO2-expressing tumors such as DLBCL, follicular lymphoma, and T-ALL (Parvin et al., 2019).

BCL6 is one of the therapeutic targets in lymphoma. As a transcription factor, BCL6 is expressed in germinal centre B cells and it is fundamental for the formation of germinal centres and the production of high-affinity antibodies. On the other hand, during terminal differentiation to plasma cells, BCL6 has to be transcriptionally downregulated. BCL6 is known to be highly expressed in B cell non-Hodgkin's lymphoma and in a subset of cases of diffuse large cell lymphoma. PARP1 was shown to bind in a sequence-specific manner at the BCL6 locus and contributes to the regulation of BCL6 transcription (Ambrose, Papadopoulou, Beswick, Wagner, 2007).

## Melanoma

Melanoma is characterized by defects in repair and cell cycle regulation. Malfunctioning in nucleotide excision repair is thought to play an important role in melanoma. Since BRCA2 mutations are known to be associated with melanoma, PARP inhibitors were introduced into melanoma therapy. However, use of PARP inhibitors in melanoma therapy ended with controversial clinical observations. In an in vitro melanoma model, Cseh et al. showed that pharmacologic PARP inhibition triggers mitochondrial events known to be associated with cell survival, but also enhances the cytotoxic effects of cytostatic compounds (Cseh et al., 2019). These findings may explain the controversial results about the use of PARP inhibitors in the treatment of malignancies.

### Colorectal cancer

Colitis is the inflammation of the inner lining of the colon caused by several inflammatory factors like infection, ischaemia, and allergic reactions. Chronic inflammatory disorders, including inflammatory bowel diseases, Crohn's disease (CD) and ulcerative colitis (UC), are thought to result from a dysregulated mucosal immune response to commensal gut microbiota in genetically susceptible individuals. Colorectal cancer (CRC) is well known to be associated with long-standing and extensive colitis (Palazzo et al., 2019). PARP1 is overexpressed in human CRC and elevated PARP1 expression is correlated with disease progression. Although PARP1 has been reported to support the focal inflammation during the tumor progression, protective effects of PARP1 against DNA alkylation and oxidation damage during the initial steps of CRC have also been shown. Mechanistically, the pro-inflammatory functions of PARP1 were shown to be related with the modulation of NF-kB activity and stimulation of IL6-STAT3-cyclin D1 axis (Dörsam et al., 2018).

### Prostate cancer

n vivo and in vitro studies showed that PARP1 can modulate androgen receptor ( AR) functions by recruiting to the AR function sites, and therefore by promoting AR occupancy and AR functions (Schiewer et al., 2012).

Silencing of PARP1 was reported to downregulate epithelial-mesenchymal transition (EMT) markers, inhibit PI3K, suppress the expression of EGFR and p-GSK3B (Ser9) in in vivo and in vitro prostate cancer models (Y. Lai et al., 2018).

## To be noted

The design of PARP1 inhibitors and clinical trials of PARP1 inhibitors in cancer have been receiving considerable attention.

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