HHS Public Access

Author manuscript

Free Radic Biol Med. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Free Radic Biol Med. 2017 June ; 107: 228–244. doi:10.1016/j.freeradbiomed.2016.11.039.

Coordination of DNA Single Strand Break Repair

Rachel Abbotts and **David M. Wilson III**[*]

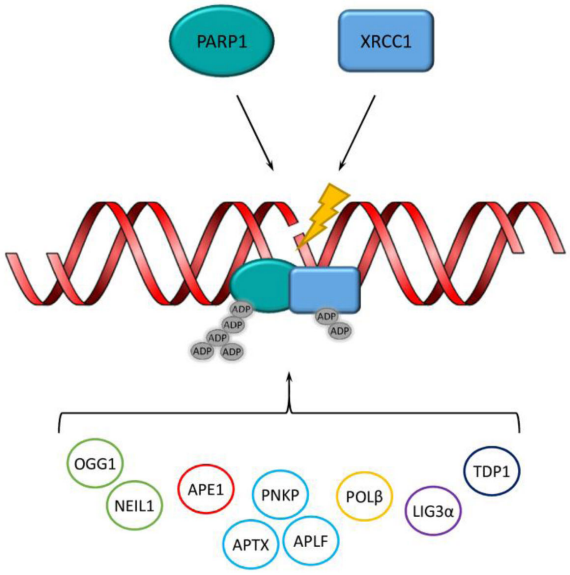
Laboratory of Molecular Gerontology, National Institute on Aging, Intramural Research Program, National Institutes of Health, Baltimore, MD 21224, USA

Abstract

The genetic material of all organisms is susceptible to modification. In some instances, these changes are programmed, such as the formation of DNA double strand breaks during meiotic recombination to generate gamete variety or class switch recombination to create antibody diversity. However, in most cases, genomic damage is potentially harmful to the health of the organism, contributing to disease and aging by promoting deleterious cellular outcomes. A proportion of DNA modifications are caused by exogenous agents, both physical (namely ultraviolet sunlight and ionizing radiation) and chemical (such as benzopyrene, alkylating agents, platinum compounds and psoralens), which can produce numerous forms of DNA damage, including a range of “simple” and helix-distorting base lesions, abasic sites, crosslinks and various types of phosphodiester strand breaks. More significant in terms of frequency are endogenous mechanisms of modification, which include hydrolytic disintegration of DNA chemical bonds, attack by reactive oxygen species and other byproducts of normal cellular metabolism, or incomplete or necessary enzymatic reactions (such as topoisomerases or repair nucleases). Both exogenous and endogenous mechanisms are associated with a high risk of single strand breakage, either produced directly or generated as intermediates of DNA repair. This review will focus upon the creation, consequences and resolution of single strand breaks, with a particular focus on two major coordinating repair proteins: poly(ADP-ribose) polymerase 1 (PARP1) and X-ray repair cross-complementing protein 1 (XRCC1).

Graphical abstract

[*]corresponding author: wilsonda@mail.nih.gov, (410) 558 8153 .



Keywords

oxidative DNA damage; PARP1; XRCC1; DNA repair; neurodegeneration; aging

The Endogenous DNA Damage Challenge

Since DNA is a chemical existing in an aqueous environment, it can undergo spontaneous hydrolysis, leading to the formation of abasic (or apurinic/apyrimidinic, AP) sites or inappropriate base entities [1]. It has been estimated that purines are lost at a rate of roughly 10,000 per human genome per day. AP sites, which are non-coding since they lack the instructional information provided by the base, have been shown to be potent blocks to replicating DNA polymerases and transcribing RNA polymerases, indicating that they can promote genomic instability or the activation of cell death responses. Moreover, spontaneous deamination of cytosine or 5-methylcytosine can result in uracil (U:G) or thymine (T:G) being present inappropriately in DNA. Based on the numerous deep-sequencing efforts in recent years, it has become clear that uracil and thymine arising via deamination are major driving forces behind the mutagenic events associated with the process of carcinogenesis [2].

In addition to spontaneous hydrolytic decay, endogenously generated intracellular metabolites are an important source of DNA modification [3]. For example, activity of the methyl group donor S-adenosylmethionine (SAM) generates ~4000 7-methylguanine residues per day in mammalian cells [4]. Although 7-methylguanine does not alter the coding specificity of the base and appears to be generally innocuous, it is at risk of converting to an AP site via glycosyl bond destabilization or conversion to a replication-blocking ring-opened derivative, 2,6-diamino-4-hydroxy-5N-methyl-formamidopyrimidine (mFaPy-G) [5]. Other base damages generated by SAM, such as 3-methyladenine, 3-methylthymine and 3-methylcytosine, are also potent blocks of DNA replication. Mutagenic O-alkylated adducts (such as O^6-methylguanine, O^4-methylthymine and O^4-ethylthymine),

which can cause GC→AT and TA→CG transitions during replication, are generated by N-nitroso compounds of both exogenous (nitrite/nitrate-containing food, cigarette smoke) and endogenous sources.

The intracellular generation of reactive oxygen species (ROS), such as superoxide anion radicals ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals (•OH), represents an additional, significant source of endogenous DNA damage. During mitochondrial oxidative phosphorylation, side reactions between the electron transport chain and molecular oxygen produce superoxide at a rate of 1-2% of the total oxygen consumption per day [6, 7]. To limit superoxide toxicity, superoxide dismutase (SOD) dismutates $O_2^{\bullet-}$ to H_2O_2. Another source of H_2O_2 is monoamine oxidase activity at the mitochondrial outer membrane, which is required for oxidative deamination of biogenic amines. The activities of catalase or glutathione peroxidase function as a detoxification mechanism by reducing H_2O_2 to water +/− oxygen. Spontaneous reduction of H_2O_2 catalyzed by Fe^{2+} (Fenton reaction) can also occur, yielding the highly reactive •OH, which can modify all cellular macromolecules, and DNA-bound Fe^{2+} is thought to be a major driver of oxidatively damaged DNA [8].

Numerous DNA backbone and base modifications generated by •OH (and other free radical) attack have been identified (reviewed in [9, 10]). Depending on the site of hydrogen abstraction from the 2-deoxyribose phosphate backbone by •OH, an oxidized abasic site, 2-deoxyribonolactone, or a single-strand break (SSB) harboring a 3′-phosphate or -phosphoglycolate can be generated [11]. •OH attack at the pi bonds of DNA bases, by •OH addition or hydrogen atom abstraction, generates a variety of base lesions. For example, the common base damage product 5,6-dihydroxy-5,6-dihydrothymine (thymine glycol) is generated when hydroxyl radical addition to the C5-position of thymine reacts with molecular oxygen to form a peroxyl radical that subsequently undergoes thiol-mediated reduction. Also common is hydroxyl addition to the C8-position of guanine, which can further undergo reduction to a ring-opened FaPy-G or oxidation to 8-oxo-7,8-dihydroguanine (8-oxo-G), a mutagenic base lesion often used as a marker of oxidative stress. Common forms of endogenous DNA damage and their consequences are summarized in Table 1 [4, 12-20].

Genomic damage may also be a consequence of necessary or failed enzymatic reactions. As will be discussed in greater detail later, a DNA SSB is an obligate intermediate of apurinic/apyrimidinic endonuclease 1 (APE1) activity during base excision repair (BER) of damaged bases [21]. Similarly, strand incision by RNase H2 is a critical step in the ribonucleotide excision repair (RER) pathway that resolves erroneous ribonucleotide incorporation into DNA [22]. DNA topoisomerase 1 (TOP1) creates a transient nicked DNA intermediate (‘cleavage complex’) to relax supercoiled DNA during transcription or replication. Nucleophilic attack from a tyrosine residue within the catalytic active site of TOP1 mediates a transesterification reaction that breaks the DNA phosphodiester bond, while forming a covalent enzyme-DNA intermediate. Religation occurs by reversal of this reaction, utilizing the DNA 5′-OH end as the leaving group [23]. Proximity of TOP1 cleavage complexes to transcription machinery, replication forks, or various DNA lesions (including strand breaks, abasic sites, and oxidized bases) can displace the cleaved 5′-OH, irreversibly preventing religation and leaving behind a covalent protein-DNA strand break intermediate [24].

Finally, members of the APOBEC (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide) family, which play a role in innate immunity via cytidine deamination in DNA/RNA viruses, have recently been demonstrated to deaminate cytosine and 5-methylcytosine in genomic DNA, potentially resulting in GC→AT transitions upon cell division at a rate of 4-6 per 1000 base pairs [25].

The Consequences of Persistent DNA Damage

Persistent, unrepaired DNA modifications are associated with a variety of cellular consequences. Replication is a particularly important mechanism by which a cell detects DNA damage [26]. On encountering a lesion, DNA polymerase progression can become stalled, resulting in an accumulation of exposed single-stranded DNA (ssDNA). This ssDNA becomes coated with the ssDNA binding protein replication protein A (RPA), which recruits and activates the ATR/CHK1 replication checkpoint [27]. Checkpoint activation promotes damage repair or bypass, maintains the stalled replisome, and suppresses firing of later origins until the blocking lesion is resolved.

One response to a stalled replication fork is a damage tolerance mechanism known as translesion synthesis (TLS), wherein the replicative polymerase is replaced with a specialized polymerase that is capable of replicating past the obstructive lesion. Compared to replicative polymerases, TLS polymerases exhibit low fidelity and are generally error-prone, representing a significant source of mutagenesis. However, the precise consequences of TLS are dependent upon the DNA lesion and polymerase choice; for example, POLζ can bypass and extend a variety of lesions (particularly bulky adducts or base distortions) with a high rate of mispairing and subsequent mutation, whereas POLη primarily inserts two adenines opposite UV-induced thymine dimers with an error-free result (reviewed in Lange [28] and Sale [29]). Whatever the replicative outcome, TLS is designed to permit bypass of the damage and restoration of normal chromosome duplication.

Alternatively, replisome stalling can persist, resulting in strand breakage, possibly due to topoisomerase cleavage [30, 31], and activation of the double strand break (DSB) repair (DSBR) endonuclease Artemis [32], or replication fork collapse following exhaustion of the RPA pool [33]. When the damage lesion is an SSB, fork collapse and one-ended DSB formation may occur directly upon interaction with the replisome [17, 34]. In most situations of persistent replicative polymerase arrest and failed resolution, the cell resorts to chromosome instability mechanisms (typically recombination) to permit survival or activates cell death outcomes. In addition, certain lesions (particularly crosslinks or bulky adducts) can stall RNA polymerase, blocking transcription. Prolonged transcriptional stress results in RPA- and ATR-mediated checkpoint activation, strand breakage, and cell death if transcription-coupled repair fails to remove the damage lesion [35, 36].

The Base Excision Repair Pathway

In light of the deleterious consequences of persistent, unrepaired DNA damage, organisms have developed a set of responses to: (i) remove lesions and restore the genome integrity to preserve normal functionality; (ii) “ignore” (TLS bypass) DNA modifications to permit

survival at the cost of increased genomic instability; (iii) halt cell cycle progression to provide time for adequate clearance of DNA lesions; or (iv) induce permanent cellular arrest (senescence) or execution (apoptosis) [37]. Of the pathways that fall into category (i) and carry out DNA repair, BER is considered the most critical for coping with many of the forms of DNA damage covered in the previous section. BER (Figure 1) is typically initiated by a DNA glycosylase, which recognizes specific types of base damage and excises them from the DNA backbone, leaving behind an AP site [38, 39]. Subsequent cleavage of the phosphodiester backbone by an AP site-specific endonuclease, such as APE1 in mammals, creates a SSB intermediate with a priming 3′-OH group and an abnormal 5′-deoxyribose phosphate (dRP) end [40, 41]. Following APE1 incision at a natural AP site, BER proceeds most commonly through removal of the 5′-dRP group and insertion of the missing nucleotide by DNA polymerase β (POLβ), in a process termed short-patch or single-nucleotide BER (Figure 1, left) [42]. The remaining nick would then be sealed by a DNA ligase, either DNA ligase 1 (LIG1) or ligase 3 (LIG3) in humans [43, 44].

Besides via the short-patch mechanism above, BER can be executed in an alternative procedure, termed long-patch BER (Figure 1, right). In this process, repair synthesis involves the incorporation of more than one nucleotide (possibly up to 13) in a strand-displacement reaction and the formation of a 5′-flap intermediate. The long-patch pathway is carried out through the coordinated activities of several replication-associated factors, such as replication factor C (RFC), proliferating cell nuclear antigen (PCNA), polymerases ε (POLε) and δ (POLδ), flap endonuclease 1 (FEN1), and LIG1 [45, 46]. While the factors that determine sub-pathway choice are still being resolved, studies have indicated that the initiating glycosylase, the nature of the 5′-terminus (i.e., whether it is a substrate for POLβ AP lyase activity), the cell cycle phase or replicative status of the cell, and the intracellular concentration of ATP can play a role in dictating the molecular steps of BER.

SSB repair (SSBR) is generally considered a specialized, sub-pathway of BER, since it often engages proteins dedicated to BER. As the name implies, SSBR copes with normal and abnormal strand breaks that arise either from reactions with DNA-damaging agents (endogenous or exogenous) or as intermediates in certain enzymatic events, as detailed earlier. In brief, SSBR consists of 1) strand break detection; 2) removal of 5′- or 3′-terminal blocking group; 3) gap-filling repair synthesis; and 4) nick-sealing by a DNA ligase [47]. As reviewed herein, two proteins key to orchestrating SSBR are poly(ADP-ribose) polymerase 1 (PARP1) and X-ray cross-complementing protein 1 (XRCC1). These factors serve critical roles as scaffolds for the assembly of many of the enzymatic components required to process abnormal strand break ends and ultimately restore the continuity of the phosphodiester backbone.

PARP1

Discovery

In 1963, Chambon et al. described the DNA-dependent synthesis of a polyadenylic acid-like compound [48], later identified as an ADP-ribose moiety generated from nicotinamide adenine dinucleotide (NAD^+) [49]. Nuclear fractions from a variety of eukaryotic cell types suggested the presence of a chromatin-bound enzyme capable of covalently linking

polymers of poly(ADP-ribose) (PAR) to histones and other nuclear proteins [[50, 51] and references therein]. Further studies indicated that this enzymatic activity was stimulated most effectively by the presence of duplex DNA containing a SSB or DSB [52]. In vitro observations of PARylation at sites of X-ray irradiation, followed by subsequent repair of associated DNA damage, established a role for this modification in the strand break repair response [53]. Initially named poly(ADP-ribose) synthetase, and now PARP1, the enzyme was purified and the encoding gene cloned by several independent groups in 1987 [54-57]. An additional sixteen members of the human PARP family have since been discovered, although PARP1 appears to be the major nuclear enzyme responsible for total cellular PARylation activity (reviewed in [58]). The PARP family has been implicated in performing specialized functions during numerous cellular processes, including DNA repair, translation, transcription, telomere maintenance, and chromatin remodeling.

Structure & biochemistry

The 23-exon, 43-kb human PARP1 gene is located on chromosome 1q41-42 [56, 59, 60]. Two pseudogenes have been identified on chromosomes 13 and 14 [56]. The human promoter region, in common with all cloned mammalian PARP1 promoters [61, 62], lacks typical regulatory elements, such as TATA or CAAT boxes [63]. A ~40-base-pair region surrounding the transcription start site contains a near-consensus initiator element that is capable of initiating RNA polymerase II transcription [64, 65]. Regulation of transcription has been shown to be mediated through binding sites for Sp1 [66], AP-2 [63], YY1 [67], Ets [68], and members of the nuclear factor I (NFI) family [69]. The human PARP1 transcript is 3042 nucleotides in length, harboring an open reading frame that encodes a 1014 amino acid protein of 113 kDa (Figure 2A) [54].

PARP1 catalytic activity involves the transfer of an ADP-ribose subunit from an NAD^+ molecule onto specific amino acid side chains of acceptor proteins, releasing one nicotinamide molecule. Three functional domains are involved in this process: an N-terminal DNA binding domain (DBD; residues 1-374); a central automodification domain (AD; residues 375-525), which accepts auto-poly(ADP-ribosyl)ation and permits the dimerization required for activity; and a highly-conserved ADP-ribosyl transferase catalytic domain located at the C-terminus (ART; residues 526-1014) that is required for ADP-ribose polymer generation [70].

Two homologous zinc finger motifs within the DBD are capable of recognizing and binding to a variety of damaged DNA structures (including SSBs and DSBs, cruciforms, crossovers and supercoils [71]) in a sequence-independent manner. Crystal structures of the DNA-bound zinc fingers indicates that a ‘phosphate backbone grip’ of each zinc finger domain binds in the DNA minor groove toward the 3′-end of the DNA strand without contacting the strand break terminus (Figure 2B). Concurrently, a base stacking loop contacts the exposed terminal base at the 3′-end of the break [72]. Deletion analysis suggests that the second zinc finger (ZnF2) is indispensable for strand break recognition [73], whereas the first (ZnF1) exhibits weaker DNA binding affinity, but is critical for DNA-dependent PARP1 activation [74, 75].

Subsequent to DNA binding, the enzymatic activity of PARP1 is stimulated 500 times above basal level [76, 77]. As part of the process, the ZnF1 base stacking loop undergoes a conformational shift that modulates a chain of interdomain interactions to permit transmission of the activation signal to the catalytic domain [72]. The first step in this chain of interactions is extensive contacts between ZnF1 and a third zinc-binding domain (ZnF3) in the DBD, which also has weak affinity for DNA [78]. X-ray crystallography indicates that extended loops of ZnF3 contact an 80-90 amino acid tryptophan-, glycine-, arginine-rich (WGR) domain distal to the AD. The WGR domain is also in contact with the DNA at the major groove, stacking a conserved tryptophan residue onto the terminal 5′-ribose, as well as bridging connections between ZnF1 and a PARP regulatory domain (PRD) in the C-terminal region of the protein [79]. The resultant conformational changes distort the PRD and destabilize the catalytic domain, enhancing NAD^+ binding within the catalytic fold [80]. A glutamate residue within the catalytic domain (Glu988) forms hydrogen bonds to the acceptor nucleophile and the nicotinamide ribose of the donor NAD^+, polarizing both molecules to favor ADP-ribose transfer. Furthermore, internal strain within the bound NAD^+ is relieved by breaking the N-glycosidic bond, driving the reaction forward [78, 81].

PARP1 is recognized to perform three distinct catalytic reactions. The initiating reaction attaches the first ADP-ribose unit to one of a group of acceptor proteins that includes histones, DNA repair proteins, transcription factors and chromatin modulators (Figure 2C). Most commonly, the initiation reaction targets the γ-carboxyl group of a glutamate residue, creating a labile glycosidic bond in keeping with the transient nature of the modification [82]. In PARP1 automodification, lysine and aspartate residues within the AD have also been implicated as targets for initiation of ADP-ribosylation [75, 83]. Following initiation, a second distinct elongation reaction is required to extend the ADP-ribose chain. During the elongation step, the acceptor nucleophile is the 2′-hydroxyl group of the existing adenine ribose, which is oriented for reaction by interactions with the catalytic Glu988 and Tyr907. As in initiation, Glu988 also polarizes the donor 2′-hydroxyl of the NAD^+ ribose to facilitate the reaction. The resulting polymer subunits are therefore linked by $1'' \rightarrow 2'$ ribose-ribose glycosidic (A-ribose) bonds. Thirdly, and lastly, PARP1 is capable of creating branched polymers that occur at a branching:elongation ratio of ~2% [84]. The active site cleft of PARP1 is sufficiently large to allow 180° rotation of the bound polymer, shifting the nicotinamide ribose into the acceptor position. ADP-ribose transfer utilizes the NAD^+ ribose as donor, creating a $1''' \rightarrow 2'$ ribose-ribose glycosidic (N-ribose) bond that places the following subunit in the elongation orientation (Figure 2D [85]).

Extensive evidence suggests that PARP1 requires protein dimerization for activation and catalytic function at sites of DNA damage [75, 86, 87]. How dimerization is mediated has not been fully elucidated, but may involve a leucine zipper motif in the AD [88] and/or intermolecular ZnF1-ZnF2 binding at a damage site [79]. In concert with the conformational intramolecular changes associated with DNA binding described above, dimerization permits access between each monomer's catalytic domain and PAR-acceptor sites, resulting in trans-ADP-ribosylation where each PARP1 subunit simultaneously acts as catalyst and acceptor molecule [79, 89]. Monomeric PARP1 is also capable of DNA binding (via ZnF2) and subsequent activation [77, 90], possibly to enable protein localization to undamaged chromatin [79].

Automodification is a major target of PARP1 activity [76, 91, 92], and plays an important role in self-limiting PARP1 catalytic activity. Automodification by negatively-charged PAR polymers can promote PARP1 dissociation from DNA, consequently suppressing its enzymatic function [93, 94]. Recent discovery of a 60-residue double-stranded DBD (DsDB), distinct from the N-terminal DBD (see above) and located in the AD between the BRCT and WGR domains, may play an important role in this process. In the basal state, this region (along with the WGR domain) may function as a suppressor of PAR synthesis. ZnF1/ZnF2 binding to a DNA break allows the DsDB to bind to double-stranded DNA, releasing this suppression. Automodification, including to the DsDB itself, displaces the bound duplex DNA (and ssDNA from ZnF2) resulting in protein dissociation and catalytic inhibition [95]. The rate of dissociation following automodification is unclear, but is probably dependent on the length of the PAR polymer and/or the affinity of PARP1 to the initial damage substrate [92].

In addition to PARylation of acceptor proteins, PARP1 is also able to directly interact with protein partners via a BRCT domain located at residues 389-487 within the central AD [96]. The PARP1 BRCT domain shares sequence homology with the highly conserved BRCA1 carboxyl-terminal (BRCT) domain superfamily that mediates protein interactions with a large number of DNA repair factors [97]. The best-characterized interaction of the PARP1 BRCT is with XRCC1, which constitutes a critical step in recruitment and coordination of repair factors to sites of DNA damage (see later). Other major SSBR factors have also been observed to interact with the PARP1 BRCT domain. A PARylation-independent interaction with the C-terminal region of POLβ does not seem to impact enzymatic activity, but may have an important role in POLβ recruitment, particularly within the long-patch BER pathway [98]. A direct interaction has been observed between automodified PARP1 and the N-terminal region of LIG3α as well, resulting in stimulation of ligase activity and recruitment to DNA damage sites [99]. Additionally, PARP1 physically interacts with the end-processing enzymes tyrosyl-DNA phosphodiesterase 1 (TDP1) and aprataxin (see later), mediating recruitment to damage sites, although not affecting functional activity [100, 101].

Interactions between specific BER/SSBR proteins and the PARP1 BRCT domain have recently been confirmed quantitatively by fluorescence-based approaches, which indicated similar binding affinities for PARP1 with XRCC1, POLβ and TDP1 [102, 103]. Of note, PARP1-XRCC1 and PARP1-POLβ binding affinities were not modulated by various BER intermediates, in contrast to the variable strength seen for the PARP1-APE1 interaction in the presence of different DNA substrates. Given that PARP1 concentration has been shown to regulate APE1 3′-exonuclease activity, this substrate-dependent modulation of the PARP1-APE1 interaction may reflect functional regulation dependent upon the damage lesion present [104]. The PARP1 BRCT domain has also been implicated in interactions with 8-oxo-G DNA glycosylase 1 (OGG1) [105] and endonuclease eight-like protein 1 (NEIL1) [106], leading to PARP1 stimulation (and subsequent PARylation of cellular proteins) and repression of glycosylase activity, suggesting a mechanism for coordination of the damage recognition and base excision step of BER. The physical association of PARP1 with these DNA glycosylases has been proposed to play a role in aging, given that the NEIL1-PARP1 interaction declines with age in a murine model [106]. Taken together, the data indicate an important role for PARP1 in initial DNA damage recognition and

subsequent coordination of the repair response, possibly in concert with XRCC1 (expanded upon in ‘XRCC1 Interactions in SSBR’, below).

Cell biology

First characterized for its role in the repair of DNA strand breaks, post-translational modification by PARylation is now recognized as a regulator of a broad range of biological functions, including cell death, transcriptional regulation, intracellular trafficking, coordination of cell division and energy metabolism [107, 108]. Although the precise contribution of individual PARP family members has yet to be fully elucidated, the various roles of the ubiquitously-expressed, nuclear PARP1 enzyme have been extensively studied.

Activation of PARP1 following the recognition of a DNA backbone interruption is a key mechanism for coordination of SSBR. Its primary role is likely in the autoribosylation-dependent recruitment of XRCC1, which functions as a scaffold protein to recruit and stimulate other SSBR proteins. Additionally, proteins involved in a wide range of DNA repair and damage response processes have been shown to either directly interact with PARP1, or possess ADP-ribose binding motifs that mediate their recruitment to sites of DNA damage following activation of PARP1 [109]. These include XRCC1, POLβ, LIG3, and the end-processing enzyme aprataxin (BER/SSBR); xeroderma pigmentosum complementing protein A (XPA; nucleotide excision repair [NER]); MSH6 (mismatch repair); DNA-PKcs and Ku70 (non-homologous end-joining [NHEJ]); DNA POLε (replication, long-patch BER, and NER) and its processivity factor PCNA; the replication-associated helicase/endonuclease WRN; the telomere maintenance protein telomerase; and several proteins involved in the DNA damage response and cell cycle progression (ataxia telangiectasia mutated kinase [ATM], p53 and its downstream checkpoint mediator p21), inflammatory and immune responses (NFκB and its downstream target inducible nitric oxide synthetase [iNOS]), and apoptosis (caspase-activated DNase) [98, 109-114].

PARP1 is often described as a BER enzyme, because of its many interactions with single-nucleotide and long-patch pathway members. Consistent with a role in SSBR, mouse embryonic fibroblasts (MEFs) derived from PARP1$^{-/-}$ mice exhibit delayed strand break resealing following alkylating agent exposure or gamma irradiation, accompanied with G2/M accumulation, chromosomal instability and cell death [115]. Similar results have been observed following siRNA downregulation of PARP1 [116], expression of a catalytically inactive mutant [117], or exposure to small molecule PARP inhibitors [118]. However, while the repair of strand interruptions (and hence SSBR) indisputably involves PARP1 activity [119], PARP1 appears to be dispensable for the repair of single strand damage initiated by DNA glycosylases [120, 121]. More recent studies using sparsely ionizing ultrasoft X-ray irradiation, however, suggest that SSBs and purine base damage are repaired via a PARP1-dependent mechanism, whereas pyrimidine base damage is not [122, 123]. Given these findings, PARP1 involvement in BER is seemingly dependent on the damage substrate and pathway choice.

In reconstituted BER assays and in vitro studies, functional PARP1 activity reduces repair kinetics, possibly by binding the nicked strand intermediate and delaying hand-off to downstream repair enzymes [124, 125]. The results to date have led to the hypothesis that

PARP1 is involved in BER primarily when an abasic site or nicked intermediate becomes uncoupled from the pathway, resulting in a substrate that both binds PARP1 [76] and ultimately activates PARylation for repair [125]. Notably, reconstituted BER studies have indicated that PARP1 binding may be particularly important in coordinating an APE1-independent repair response for AP sites that involves a complex of XRCC1, POLβ, LIG3α, polynucleotide kinase 3′-phosphatase (PNKP) and TDP1 [126]. Specifically, PARP1 has been shown to possess AP and 5′-dRP lyase activities, allowing it to cleave the abasic site in the absence of APE1, such that the presence of PNKP and TDP1 provide the end-processing capabilities required for completion of repair by POLβ and LIG3α [76, 127].

PARP1 also plays an important role in regulating chromatin structure during DNA repair. PARylation of histones (particularly H1 and H2B), protamines and high mobility group (HMG) proteins triggers chromatin decondensation to allow access to proteins involved in DNA synthesis, transcription or repair (reviewed in D'Amours et al. [107]). Following alkylation damage, 2-3% of histones are modified [128], opening the chromatin structure and rendering the DNA susceptible to nuclease attack [129]. This modulation is reversible following hydrolytic dissociation of the PAR polymers (mediated by poly(ADP-ribose) glycohydrase [PARG]; see below) [129]. Indeed, the kinetics of histone PAR modification and dissociation may play an important role in the coordination of repair. Following initial activation by a strand break, PARP1 modifies both itself and the localized histones, with a preference for automodification. In vitro turnover assays suggest that automodification soon reaches a steady state between PARylation and dissociation, at which point histone modification is favored, maintaining an open chromatin structure while repair occurs [130, 131]. Following completion of repair, PARP1 dissociates from the DNA and PARG activity hydrolyzes histone polymers to return the chromatin to its original state [107, 132]. Interestingly, a recent study indicates that PARP1 is recruited more efficiently to heterochromatin than euchromatin, which is instead highly enriched for FEN1 and PCNA, suggesting that transcriptional activity is an important determinant of BER pathway choice [133]. Damage-induced PARylation also co-localizes at foci containing XRCC1 complexed with SNF2H, a chromatin remodeling factor, suggesting a previously unrecognized role for XRCC1 in chromatin regulation possibly through PARP1 activity [134].

Tight control of cellular PAR is critical to prevent the detrimental effects of persistent PAR signaling, which include depletion of cellular NAD^+ levels and subsequent necrosis [135], and the PAR-specific parthanatos pathway, wherein excessive PAR levels induce translocation of apoptosis-inducing factor (AIF) from the mitochondria to the nucleus where it induces DNA fragmentation and cell death [136]. The major enzyme for removal of cellular PAR is PARG, which cleaves the O-glycosidic ribose-ribose bond between PAR molecules, releasing free ADP-ribose [137, 138]. A second enzyme, ADP-ribosylhydrolase 3 (ARH3), may also possess this activity [139]. The absence of a suitable O-glycosidic ribose-ribose bond means that neither enzyme is capable of cleaving the proximal PAR molecule from the modified protein. This role is instead performed by three enzymes possessing the ability to cleave mono(ADP-ribosyl)ated substrates (terminal ADP-ribose protein glycohydrase [TARG1], MacroD1, and MacroD2) [140-142]. This close control of PAR modification and catabolism results in high turnover of both enzyme and product (cellular PAR exhibits a half-life of 1 to 6 minutes [143]), and is likely critical in the

sequential handover of the damage site to downstream repair enzymes (reviewed in [144]). Accordingly, a murine PARG1$^{-/-}$ model exhibits early embryonic lethality [145], while cellular deficiency of the PAR-hydrolyzing enzymes results in an impairment of SSBR and DSBR that echoes the defect observed in PARP1 inhibition or depletion, suggesting the importance of PAR regulation in genomic stability [140, 145].

Animal model

Phenotypic characterization of PARP1$^{-/-}$ mouse models has been described by several groups. Homozygous animals are fertile with a normal lifespan. No overt phenotype has been described, although small litter size, reduced adult bodyweight (secondary to a reduction in cellular NAD^+ consumption that subsequently stimulates mitochondrial metabolism) [146, 147], and epidermal hyperplasia [148] have been reported. Animal-derived cells show an absence of basal ADP-ribose formation [148], but retain the capacity to synthesize ADP-ribose polymers following alkylating agent exposure [149]. This finding led to both the discovery of PARP2 and, given the embryonic lethality observed in a PARP1$^{-/-}$ PARP2$^{-/-}$ double mutant, established the essential role of PARylation in early development [150]. Splenocytes isolated from PARP1 knockout animals exhibit an elevated rate of spontaneous sister chromatid exchange (SCE), suggestive of genomic instability [151]. In keeping with this finding, PARP1$^{-/-}$ animals are hypersensitive to alkylating agents and to γ-irradiation (the latter manifested as acute small intestinal radiation toxicity [152]), associated with G2/M cell cycle arrest and severe genomic instability [146]. Animal-derived PARP1$^{-/-}$ cells also exhibit a dramatic increase in p53-Bax-mediated apoptosis in response to alkylation damage [153]. However, there is no evidence of an increased malignancy risk in these animals [151]. Taken together, these results demonstrate the important role that PARP1 plays in the repair of alkylation and radiation damage, and the maintenance of genomic stability, but also indicate the likelihood that additional PARPs (namely PARP2; see below) have the capacity to serve as compensatory enzymes.

XRCC1

Discovery

In the early 1980s, a number of Chinese hamster ovary (CHO) mutant cell lines were isolated on the basis of extreme hypersensitivity to various mutagens [154, 155]. A UV-sensitive subset was identified to be deficient in NER, the DNA repair pathway that resolves bulky adducts, such as UV photoproducts [156]. Also isolated was EM9, a mutant typified by sensitivity to alkylating agents, such as ethyl methanesulphonate (EMS), defective rejoining of DNA strand breaks after mutagen exposure, and an elevated baseline frequency of SCE [157, 158]. Correction of the EM9 defect was achieved by fusion hybridization with normal human fibroblasts or lymphocytes, producing clonal populations with SCE frequencies close to the parental cell baseline [159]. Complementation was confirmed via transfection of hybrid DNA, allowing localization of the EM9 defect (now designated as XRCC1) to chromosome 19q13.2 [160-162]. Subsequently, the complete XRCC1 sequence was isolated and determined [158].

Structure & biochemistry

The human XRCC1 gene is composed of 17 exons that span 32 kb on chromosome 19q13.2, in a region that also contains ERCC1 [163], ERCC2 [161] and LIG1 [164]. A likely transcription initiation site exists 105 bp upstream from the translation start site, preceded by a consensus TATA box sequence located at position −136 from the start codon. At the 3′ end, a prototypical polyadenylation consensus sequence has been described [158]. The human XRCC1 transcript is 2802 nucleotides in length. Translation of the 1899-nucleotide open reading frame from the ATG start codon produces a 633 amino acid protein of 69.5 kDa (Figure 3) [165-167].

The N-terminal domain (NTD), which spans residues 1-183 [122], is formed around a core β-sandwich consisting of a 5-stranded and a 3-stranded β-sheet connected by loops, three helices, and two short 2-stranded β-sheets, with disordered regions at residues 1-2 and 152-183 [166]. This region is critical for POLβ binding, both independently and in a ternary complex with a single-nucleotide gapped DNA substrate [168, 169]. The NTD may also be able to complex directly with DNA substrates, including gapped and nicked structures [166].

A central domain (BRCT-I), comprising residues 315-403, shares sequence homology with the highly conserved BRCT domain [97]. An essential role in XRCC1-PARP1 binding has been assigned to the BRCT-I domain [170]. A second BRCT domain at the C-terminus of the protein (BRCT-II; residues 538-633) is critical for interaction with DNA LIG3α [171, 172]. The intermediate linker regions between the various domains also mediate XRCC1-protein interactions. For example, deletion analyses suggest that the region between the NTD and the BRCT-I domain is required for APE1 [173], OGG1 [174] and PCNA [175] binding. This region also contains a NLS [158, 170]. Similarly, the area between the two BRCT domains is essential for binding to PNKP [176, 177], as well as housing a cluster of CK2 phosphorylation sites immediately downstream from the BRCT-I domain [178].

Unlike other members of the SSBR pathway, XRCC1 has no known enzymatic activity. Its cellular role is instead contingent upon its ability to interact with DNA and even more so a number of DNA repair proteins, with XRCC1-protein interactions having been described during each step of the BER process. While physical associations have been reported with a number of DNA glycosylases, the review here will focus on its interactions with enzymatic components that carry out SSB “clean-up”. Nevertheless, in brief, specific functional interactions of XRCC1 with OGG1 [179], NEIL1, NEIL2, endonuclease three-like homolog 1 (NTH1), methylpurine glycosylase (MPG) [180] and uracil N-glycosylase (UNG) [181, 182] have been argued to help promote base damage repair, although the major defect resulting from XRCC1-deficiency appears to be inefficient SSB processing and a consequent accumulation of SSBs. A more detailed overview of the interactome of XRCC1 is presented later.

Cell Biology

A hallmark of XRCC1 deficiency is a 3- to 6-fold elevation in the baseline frequency of SCE and chromosomal breakage [183-185]. 5-bromo-2′-deoxyuridine (BrdU) exposure, experimentally required in certain SCE assays for chromatid visualisation, enhances the rate

of SCE accumulation to 10- to 12-fold higher than wildtype [157, 186]. BrdU can itself influence the rate of crossover events, because incorporation is recognized and excised by uracil-DNA glycosylase [187, 188]. Impaired downstream repair of the resultant nicked intermediate would increase replication fork stalling, which has been observed in XRCC1-deficient cells [183, 189, 190]. RAD51-mediated homologous recombination (HR) to facilitate replication fork restart is a major mechanism of crossover events [191].

XRCC1-deficient EM9 cells are characterized by sensitivity to various genotoxic agents, including a 10-fold increase in cytotoxicity following exposure to the monofunctional alkylating agents EMS and MMS, moderate sensitivity to H_2O_2 and the topoisomerase inhibitor camptothecin, and weak sensitivity to ionizing and ultraviolet radiation, heavy metals and certain other alkylating agents (including ethyl nitrosourea, 1-methyl-3-nitro-1-nitrosoguanidine and mitomycin C) [157, 186, 192-194]. Following exposure to these agents, XRCC1-deficient cells exhibit a 2- to 3-fold reduced rate of rejoining of SSBs compared to wildtype cells, in keeping with a role in SSBR [157, 186, 193-195]. Accordingly, in biochemical assays, EM9 cell extracts exhibit a reduced rate of repair of plasmids containing a nicked abasic site substrate [122, 196]. Similar results have been observed following siRNA knockdown in human cancer (HeLa) and fibroblast cells, including sensitivity to MMS, hydrogen peroxide and ionizing radiation, and impaired strand break rejoining and SCE formation [197, 198].

The mild UV sensitivity of XRCC1-deficient cells may reflect a role for the protein in NER, the major mechanism by which cells remove helix-distorting lesions, including UV-induced photolesions, from DNA. Global genome NER (GG-NER), the sub-pathway that repairs lesions throughout the genome, consists of damage recognition, local DNA unwinding, dual 3′ and 5′ incision around the lesion, gap-filling and ligation. XRCC1 (in complex with its protein partner LIG3α) appears to be recruited to the site of damage following dual incision, where it functions in a post-incision complex that includes recognized GG-NER factors, such as PCNA, RPA, and POLδ, to carry out repair synthesis and ligation. Initial studies have indicated that recruitment to the NER site is mediated through interaction with PCNA, although a role for PARP1-mediated recruitment (as in SSBR) has not conclusively been excluded, given the evidence for PARP1 activation following UV damage [199-202]. The XRCC1-LIG3α-POLδ complex appears to be particularly important in quiescent and terminally-differentiated cells as the sole NER synthesis and ligation system, unlike in proliferating cells where a LIG1-POLε complex also operates [203].

Interestingly, a reduced rate of DSB rejoining has been observed in XRCC1-deficient cells [195, 204], a phenotype proposed to be a reflection of an accumulation of unrepaired SSBs being converted to one-ended DSBs on encountering the replication machinery [205, 206]. This may reflect a role for the XRCC1-LIG3α heterodimer in alternative NHEJ, a Ku-independent DSBR pathway wherein PARP1 strand break recognition drives the recruitment of repair proteins in a pathway that likely functions as a ‘backup’ to canonical NHEJ [207-212].

Animal model

Homozygous XRCC1 deletion is embryonically lethal in a murine model system, causing arrest of embryo development at embryonic day (E) 6.5 associated with morphological abnormalities in the visceral endoderm and epiblast cell loss [213]. This endoderm abnormality may account for the occasional organ rupture described in young heterozygous animals, which express ~50% of the wildtype level of XRCC1, are born at normal Mendelian ratios, and otherwise exhibit a normal lifespan without chromosomal instability or spontaneous neoplasms, suggesting that haploinsufficiency provides sufficient protein to maintain genomic integrity and animal health in the absence of genotoxin exposure [214]. Indeed, complementation with a transgene that expresses XRCC1 at <10% of normal (designated as XRCC1 hypomorph animals) rescues the embryonic lethality phenotype, generating normal litter sizes [215]. Though initially described as fertile and ostensibly normal, a later report described a ~25% reduction in body weight at weaning and into later life in the XRCC1 hypomorphs compared to wildtype littermates. No association with malignancy was observed in the hypomorph animals, suggesting that 10% of wildtype XRCC1 protein level is sufficient to maintain genomic stability [216].

Cells isolated from XRCC1$^{-/-}$ embryos exhibit a baseline accumulation of DNA strand breaks and are hypersensitive to EMS and X-ray irradiation [213]. When XRCC1 is present at a reduced level, observations of cellular sensitivity have been less consistent. Tebbs et al. did not observe an increase in MMS sensitivity in fibroblasts isolated from hypomorph animals [215]. Conversely, our group has reported increased strand break accumulation and cell death following menandione exposure in primary cerebellar granule cells derived from haploinsufficient XRCC1$^{+/-}$ animals [217], and liver toxicity and colonic premalignant lesions following in vivo exposure to the alkylating agent azoxymethane [214]. Haploinsufficient animals also exhibited increased brain damage, mortality and functional deficit following oxidative stress induced by ischemic stroke [218], perhaps indicating a cell type-specific dependence on XRCC1 function.

The XRCC1-PARP1 Ensemble

XRCC1 has been demonstrated to interact directly with DNA substrates, specifically duplexes containing single-nucleotide gaps (alone and in complex with POLβ; see above) and nicked duplex DNA [166, 219]. However, this is unlikely to represent a damage-sensing function, given that expression of an XRCC1 DNA-binding variant protein (Arg109Ala mutant) in XRCC1-deficient EM9 CHO cells fully corrects alkylation sensitivity and SSBR kinetics [220]. Recruitment of XRCC1 to DNA damage may instead be mediated mainly via interaction with PARP1, or one of its other binding partners.

A possible interaction between PARP1 and XRCC1 was first described by Caldecott et al. in 1996, following studies involving yeast two-hybrid and co-immunoprecipitation methods [221]. A BRCT sequence within the PARP1 AD interacts the XRCC1 BRCT-I domain [170]. Interaction is modulated by PARP1 automodification [221]; XRCC1 preferentially binds to oligo(ADP-ribosylated) PARP1 [170, 222], while interaction is abolished in the presence of the PARP inhibitor 3-aminobenzamide [223]. The physical interaction is complemented by PARP1 PARylation of XRCC1, either at a PAR-binding sequence motif

present in the BRCT-I domain [109] or at a BRCT-I phosphate binding pocket [224]. Temporally, PAR synthesis peaks almost immediately after induction of oxidatively damaged DNA, followed by rapid co-localization of XRCC1 foci that peak approximately ten minutes after damage. Confirmation that recruitment of XRCC1 to certain forms DNA damage involves its interaction with PARP1 was demonstrated by reduced co-localization: a) in PARP1-depleted MEFs; b) following PARP inhibitor exposure in human fibroblasts; and c) upon expression of an XRCC1 mutant that houses a modified BRCT-I domain that abolishes PARP1 complex formation [225, 226]. Functionally, XRCC1 binding negatively regulates PARP1 PARylation activity after oxidative stress, limiting the automodification that leads to PARP1 dissociation from DNA, thereby protecting the damaged DNA ends until repair can take place [170]. PARP1 is also able to interact with other BER proteins, including POLβ and LIG3α, probably enhanced by XRCC1-mediated recruitment. Accordingly, XRCC1 null cells exhibit elevated PAR levels following exposure to MMS, in addition to increased cellular sensitivity associated with impaired DNA repair [227].

PARP2, the second member of the PARP superfamily to be described, was discovered following the observation of residual PARylation in PARP1-deficient cells [149, 228]. PARP2 shares significant structural homology with the catalytic domain of PARP1, as well as possessing an NLS and DBD within its N-terminal region that are absent from PARP1 [228]. PARP1 and PARP2 share similar tissue expression patterns, although PARP2 induction is not observed in PARP1-deficient cells, suggestive of overlapping, but not redundant functions [229]. As with PARP1, PARP2 is recruited to sites of DNA damage, where it can interact with XRCC1, POLβ and LIG3α [223]. However, PARP2 accumulation occurs later and persists longer [230], and is associated with avid binding to DNA substrates containing gapped or flap structures, rather than the strand breaks observed to activate PARP1, suggestive of a role in the later stages of BER/SSBR [228, 231, 232]. As with PARP1, XRCC1 binding does exert a negative regulatory effect upon PARP2-mediated PAR synthesis activity; however, recruitment of XRCC1 to sites of DNA damage is not dependent upon PARP2 [230]. Despite having no significant impact upon SSBR rate, PARP2 depletion is associated with sensitivity to ionizing radiation and alkylating agents [233], possibly related to a role in DSBR [150, 223]. PARP2 has also been attributed roles in centromeric and telomeric stability, and lineage-dependent cellular development (including spermiogenesis, adipocyte differentiation and T cell development) (reviewed in [234, 235]).

XRCC1 interactions in SSBR

The primary role of XRCC1 is as a molecular scaffold to assemble SSBR proteins at sites of DNA damage to promote efficient repair. Under the control of the PARP1-XRCC1 scaffold, repair involves the transient assembly of multi-protein complexes, the composition of which depends upon the nature of the initiating lesion, chemistry of the repair intermediates, and post-translational modifications of the constituent pathway members (for a review of post-translational modifications in BER, see Svilar et al. [236])[237]. Accordingly, XRCC1 has been demonstrated to physically interact with and stimulate (or stabilize) the activity of a number of BER/SSBR factors.

APE1

APE1 is the major human AP endonuclease, catalyzing hydrolytic cleavage of the phosphodiester backbone 5′ to an abasic site during BER. The multifunctional conserved C-terminal domain of APE1 also contributes end-processing functions, such as 3′-phosphodiesterase and -phosphatase activities (Figure 4), while a separable redox regulatory function is present within its N-terminus (reviewed in [21]). Vidal et al. described a direct interaction between XRCC1 and the N-terminal region of APE1 (specifically, amino acids 1-35) that, although not essential, is able to stimulate its endonuclease or 3′-phosphodiesterase activity 5-fold. Accordingly, they found that XRCC1-deficient EM9 cells display a reduced ability to cleave AP sites, despite constitutively increased APE1 protein levels – a defect that could be reversed by re-expression of XRCC1 or exposure to recombinant XRCC1 protein in the extracts [173]. However, studies by La Belle et al. [238] and our group [239] revealed no difference in AP endonuclease activity in EM9 cells compared to a wildtype control line, nor a difference in the steady-state levels of AP sites within chromosomal DNA. Taken together, these results (in combination with evidence of non-essential interactions with several BER glycosylases, as described earlier) suggest that, while a role for XRCC1 in the pre-incision steps of BER cannot be ruled out, particularly in the context of chromatin, its predominant functions are performed at the site of DNA strand breaks. It would be interesting, therefore, to examine whether XRCC1 plays a role in directing the relatively inefficient 3′-repair activities of APE1 in cells.

POLβ

POLβ is an X-family DNA polymerase responsible for gap-filling during single-nucleotide BER and the repair of SSBs. The polymerase function is performed by three prototypical sub-domains within a 31kDa C-terminal domain: a nucleotidyl transferase sub-domain (‘palm’ domain; residues 152-262), flanked by a double-stranded DBD (‘thumb’ domain; residues 263-335) and a domain that binds the nascent base pairs (‘fingers’ domain; residues 88-151) [240]. An 8 kDa N-terminal domain binds ssDNA with high affinity and possesses AP- and 5′-dRP-lyase activities that contribute to AP site processing during BER (Figure 4) [241].

Two groups independently identified POLβ as a protein partner of XRCC1 [122, 221]. Subsequent chemical shift nuclear magnetic resonance (NMR) spectroscopy and site-directed mutagenesis studies initially mapped the interaction to the POLβ palm-thumb domains and the XRCC1 NTD (specifically, β-strands D and E of the five-stranded β-sheet, and the α2 helix), possibly forming a protective sandwiched structure around fragile gapped DNA intermediates [166, 169, 242, 243]. However, recent analysis has modified this model. Detailed structural characterization of the XRCC1-POLβ interface by Cuneo et al. indicated that redox modulation of the XRCC1 NTD enhances affinity for POLβ via interaction exclusively with the thumb domain [244]. Absence of the DNA-binding thumb domain from this interface likely excludes direct binding between the XRCC1 NTD and the DNA intermediate, in keeping with in vitro evidence that XRCC1 interaction with damaged DNA has limited biological relevance [220].

XRCC1 and POLβ co-localize at sites of laser-induced DNA damage, suggesting that XRCC1-POLβ complex formation facilitates POLβ recruitment and subsequent repair synthesis [245]. This hypothesis is supported by evidence that complementation of EM9 cells with XRCC1 mutants that exhibit a defective POLβ interaction (Glu69Lys or Val86Arg) are incomplete at correcting alkylation [220] or oxidative [168] sensitivity of the parental cell line. The biological significance of this interaction appears to relate to a role for POLβ in promoting full ligation activity of the XRCC1-LIG3α complex. Reconstitution of the core BER steps using a non-interacting XRCC1 NTD mutant (Val68Arg) found that ligation efficiency of the XRCC1-LIG3α complex is reduced in the absence of the POLβ interaction [168]. Efficient ligation in the context of the XRCC1-LIG3α-POLβ interaction prevents POLβ strand displacement and the formation of extended synthesis products, instead favoring single-nucleotide gap-filling; these results are substantiated by the presence of multiple-nucleotide patch synthesis products in XRCC1-deficient EM9 cells [122].

More recently, however, Fang and colleagues have reported that an XRCC1-POLβ interaction is not essential for either POLβ recruitment or DNA repair [246, 247]. A PARylation-independent physical interaction between the C-terminal region of POLβ and the PARP1 BRCT domain may instead provide an alternative mechanism for POLβ recruitment [98]. The main role of the interaction may therefore be in maintaining the stability of POLβ, since the polymerase is susceptible to C-terminal ubiquitylation and subsequent proteasome degradation when XRCC1 association is disrupted. Free XRCC1 is also susceptible to degradation, but is stabilized in the absence of POLβ binding by the chaperone protein HSP90, which regulates necroptosis by the CHIP (carboxyl terminus of Hsp70-interacting protein) pathway. The observation of differential patterns of XRCC1 partner choice (i.e. XRCC1-POLβ, XRCC1-HSP90 or free XRCC1) following exposure to various DNA-damaging agents supports the hypothesis that, in response to different lesions, the specific constituents of the repair complexes play an important role in regulating BER pathway choice [246]. It is likely that the XRCC1-POLβ interaction plays roles in both facilitating efficient SSB recognition and processing, and in regulating protein levels to optimize the repair response.

LIG3

The first XRCC1 protein partner to be identified was DNA LIG3 [171]. The LIG3 gene encodes multiple isoforms, including nuclear and mitochondrial versions of LIG3α, as well as LIG3β. Translation initiation at the first ATG codon of the LIG3 open reading frame generates the mitochondrial isoform of LIG3α, a protein that possesses an N-terminal mitochondrial leader sequence (MLS) that is cleaved off during entry into the mitochondria. An alternate internal start codon produces nuclear LIG3α, which lacks the MLS sequence [248]. Both nuclear and mitochondrial LIG3α isoforms contain a C-terminal BRCT domain that mediates both homodimer formation and interaction with the XRCC1 BRCT-II domain to form a more stable heterodimeric complex [167]. This heterodimer appears to represent the constitutive form of LIG3α, with XRCC1-deficient EM9 cells exhibiting reduced LIG3 levels and activity that can be corrected by transfection of wildtype XRCC1 [171]. Furthermore, interaction with XRCC1 is probably critical for cellular localization of the nuclear isoform given that LIG3α lacks a consensus NLS [249]. The LIG3β isoform, which

has been detected only in primary spermatocytes prior to meiosis I, is produced by alternate splicing that replaces the C-terminal BRCT domain with an NLS, and therefore does not interact with XRCC1 [250].

LIG3 is an ATP-dependent DNA ligase with roles in the final step of single-nucleotide BER, GG-NER, and a DNA-PK-independent alternate NHEJ pathway. Early studies indicated that XRCC1 mutation was associated with reduced nuclear LIG3α localization, a 6-fold decrease in LIG3α-adenylate intermediates, and impairment of the ligation step of single-nucleotide BER [196, 251]. However, despite being constitutively bound to XRCC1, LIG3α does not appear to play an essential role in nuclear DNA repair. Reduced expression of XRCC1 destabilizes LIG3, reducing protein levels 3-fold, without causing cellular hypersensitivity to MMS [215]. In a reconstituted BER system, pre-incubation of LIG3α with XRCC1 did not increase ligation efficiency compared to LIG3α alone [122]. In a murine model, absence of nuclear LIG3α did not replicate the genotoxin sensitivity observed in XRCC1 deficiency [252]. Furthermore, expression of an XRCC1 BRCT-II mutant that disrupts LIG3α binding was able to complement the repair defect of XRCC1-deficient cells [253], suggesting that XRCC1 can function independently of LIG3α. These results are probably accounted for by the high degree of functional redundancy between LIG3α and LIG1 in nuclear DNA repair (reviewed recently by Tomkinson and Sallmyr [249]). Conditional gene targeting studies have indicated that the essentiality of LIG3α is instead related to its mitochondrial function [252, 254, 255], while the absence of XRCC1 in mitochondria suggests that the XRCC1-LIG3α interaction is not involved in this role [252]. In this context, it appears the XRCC1-LIG3α interaction is primarily important in stabilizing the cellular LIG3α pool prior to its translocation to the mitochondria to participate in mitochondrial BER, while its role in nuclear repair appears to be less essential.

PNKP

PNKP plays an important role in end-processing at DNA strand breaks, resolving terminal 3′-phosphate and 5′-hydroxyl obstructive groups induced by ionizing radiation, •OH and the β,δ-AP lyase activity of certain DNA glycosylases [256, 257]. The enzyme is comprised of an N-terminal forkhead-associated (FHA) domain linked to a C-terminal domain that contains dual 5′-kinase and 3′-phosphatase active sites, as well as DNA and ATP binding sites that facilitate catalytic activity [258]. The PNK-FHA region has been demonstrated to bind to the ~150 base pair region linking the XRCC1 BRCT-I and -II domains. This interaction requires a bis-phosphorylated motif (pSer518/pThr519) that has previously been described as a consensus sequence for CK2 phosphorylation [178]. Presence of a third phosphorylated residue at an adjacent consensus sequence (Thr523) may recruit hierarchical binding of a second PNKP protein to form a 2:1 PNKP:XRCC1 complex [178, 259], although this has been disputed [260]. Additionally, nonphosphorylated XRCC1 may also bind to and stimulate PNKP, via a separate interaction involving the region surrounding XRCC1-Ala482 and the PNKP kinase/phosphatase catalytic portion [260].

PNKP may be able to independently initiate SSBR of damage substrates possessing 3′-phosphate and/or 5′-hydroxyl terminal groups (Figure 4), facilitating recruitment and binding of XRCC1 to generate a multiprotein complex with LIG3α (and possibly POLβ)

[261]. Other groups, however, have demonstrated that XRCC1-deficient EM9 cells do not form nuclear PNKP foci following DNA damage induction via hydrogen peroxide or laser microirradiation, suggesting that XRCC1 is important for PNKP recruitment to DNA lesions [177, 178, 245]. Reconstitution of the end-processing, gap-filling and ligation steps of SSBR using a DNA substrate containing 3′-phosphate and 5′-hydroxyl groups indicates that XRCC1 (but not POLβ or LIG3α) stimulates the enzymatic activities of PNKP, thereby accelerating repair. Accordingly, the reduced SSBR efficiency of a similar substrate by whole cell extracts from XRCC1-deficient cells was complemented by the addition of recombinant XRCC1 [176]. Ablation of the phosphorylation-mediated interaction via targeted XRCC1 mutation does not entirely eliminate SSBR stimulation, suggesting that the second binding mechanism involving non-phosphorylated XRCC1 is able to maintain a portion of the PNKP activation [260]. Thus, promotion of PNKP activity by XRCC1 appears to be mediated by two mechanisms: 1) enhanced discrimination capacity for terminal blocking groups and 2) increased PNKP turnover by displacement from the DNA product [262]. The interaction between PNKP and XRCC1 also appears important for stable retention of XRCC1 at the site of DNA damage [177, 263], possibly to prevent ubiquitin-mediated degradation and retain a cellular XRCC1 pool [264]. Taken together, it appears that the XRCC1-PNKP interaction has many important biological roles, including damage recognition, bilateral recruitment, repair stimulation and coordination, and XRCC1 protein stability.

APTX, APLF

XRCC1 is believed to interact with other end-processing repair enzymes (Figure 4). Aprataxin was initially identified as a putative DNA repair protein due to sequence homology with the FHA region of PNKP [265], and was later demonstrated to resolve the 5′-AMP intermediate formed when DNA ligase activity is aborted, typically as a result of non-ligatable DNA ends [266]. In its ‘long-form’ splicing variant, an NLS directs nuclear localization, where interaction with XRCC1 is observed [267-269]. As with PNKP, this interaction is mediated by binding between the aprataxin FHA domain and the CK2 phosphorylation sites in the XRCC1 inter-BRCT region [270, 271], and appears to play a role in maintaining steady-state levels of XRCC1 by an unknown mechanism [272]. Loss of aprataxin is characterized by an impaired SSBR response to DNA-damaging agents, including hydrogen peroxide, MMS, camptothecin and laser microirradiation [272-274], perhaps in part because it plays an important role in stabilization of a cellular pool of XRCC1.

XRCC1 interacts in a CK2-dependent manner with a third enzyme possessing an FHA domain, aprataxin- and PNKP-like factor (APLF), which is known to bind the NHEJ factors XRCC4 and XRCC5 (aka KU80) [275]. Although APLF has been assigned both single strand endonuclease and 3′-exonuclease/end resection activities [276-278], and appears to demonstrate recruitment and subsequent repair stimulation at both SSBs and DSBs, its exact cellular role has not been clearly defined. Recruitment to sites of DNA damage has also been attributed to a pair of PAR-binding zinc finger motifs located in the APLF C-terminus, accounting for the foci formation observed in XRCC1-deficient EM9 cells (at a reduced level in comparison to wildtype cells) following hydrogen peroxide exposure [275, 279].

More work is required to determine whether the XRCC1 interaction (and/or PARylation) has a role in enzymatic stimulation of APLF, in addition to its recruitment to sites of DNA damage.

TDP1

As previously discussed, TOP1 is essential to relax supercoiled DNA that forms ahead of replication forks and transcription complexes, creating a transient TOP1-linked SSB known as a cleavage complex that permits controlled rotation around the nicked strand [280]. Unresolved cleavage complexes (for example, when DNA modifications prevent realignment, or topoisomerase inhibitors prevent religation) can be converted to cytotoxic lesions by collision with replication forks [281] or, to a lesser degree, transcription complexes [282]. TDP1 limits this deleterious outcome by hydrolyzing the covalent bond between the TOP1 catalytic tyrosine residue and the 3′-DNA terminus (Figure 4) [283, 284]. This activity results in a SSB with a 3′-phosphate that can be first processed by PNKP to a 3′-hydroxyl group, and then extended and/or repaired by downstream BER enzymes. More recently, TDP1 has also been demonstrated to possess end-processing activity against additional 3′-blocking lesions, including 3′-phosphoglycolate groups induced by •OH, 3′-deoxyribose phosphates resulting from AP lyase processing of alkylation damage, and terminal nucleoside adducts following antiviral and anticancer nucleoside analog exposure (reviewed in [285]), as well as to cleave at AP sites to initiate a possible APE1-independent BER sub-pathway [286, 287].

The involvement of SSBR enzymes in TDP1-mediated repair, as well as the hypersensitivity of XRCC1-deficient cells to the TOP1 inhibitor camptothecin, suggests that XRCC1 plays a role in the repair of stabilized TOP1 cleavage complexes [288]. Accordingly, XRCC1 co-localizes with foci of TDP1 and the DSB-associated histone modification γH2AX following camptothecin exposure [289], and reconstitution assays indicate that XRCC1 enhances the activity of the TDP1/PNKP pathway in the repair of camptothecin-induced cleavage complexes [290]. Camptothecin-treated XRCC1-deficient cells exhibit only a partial response to aphidicolin, an inhibitor of polymerases α, δ and ε, which protects against camptothecin cytotoxicity by preventing the formation of replication-associated DSBs, suggesting a specific role in the repair of replication-independent (i.e. transcription-associated) damage [288, 290]. However, XRCC1 does not directly interact with TDP1. Instead, recruitment of TDP1 to cleavage complexes is mediated through its interaction with activated PARP1, both by PAR modification of TDP1, and by direct binding between the N-terminal domain of TDP1 and the catalytic domain of PARP1, which stabilizes TDP1 at the site of the cleavage complex. These TDP1-PARP1 complexes in turn recruit XRCC1 [101] (and hence LIG3α, which also physically interacts with TDP1 [291]), which presumably (though not yet proven definitively) functions as a repair scaffold as described above.

BER/SSBR Defects and Neurological Disease

Murine models have revealed that homozygous deletion of many of the core constituents of BER/SSBR (such as APE1, XRCC1, LIG3, POLβ) is incompatible with embryonic or postnatal survival, underscoring the importance of efficient and accurate resolution of

endogenous DNA damage [292]. Several groups have reported the characterization of heterozygous or conditional knockout animals, which has indicated that a frequent feature of defects in SSBR components is abnormalities in neurological development or maintenance [293]. For example, the postnatal lethality observed in mice carrying a homozygous POLβ deletion is associated with extensive cell death in newly generated post-mitotic neuronal cells in the central and peripheral nervous systems [294], and POLβ deletion may exacerbate the neurodegeneration phenotype of an Alzheimer disease mouse model [295]. Brain-specific conditional knockout of LIG3 in a murine model results in growth retardation and profound ataxia associated with cerebellar neurodegeneration [252]. Similarly, knockout of XRCC1 in the brain results in viable progeny that exhibit a rapidly progressive loss of cerebellar and hippocampal neurons during the postnatal period, associated with ataxia and death at approximately 4 months of age [296]. Mouse models have also provided evidence for a protective role of SSBR in the development of neuropathologies of aging, for example XRCC1 in ischemic stroke [218].

Notably, proteins with specialized roles specifically in SSBR have recognized neurological disease linkages in humans [297, 298]. Ataxia with ocular motor apraxia 1 (AOA1) is an autosomal recessive disorder caused by mutations in APTX that, in addition to the eponymous symptoms, is characterized by peripheral neuropathy, hypoalbuminemia, and, pathologically, loss of Purkinje cells and neurons from the anterior horn and dorsal root ganglia [265, 299]. A further AOA sub-type, AOA4, has been linked to a homozygous mutation in the PNKP gene (Gly375Trp) [300]. Compound heterozygote PNKP mutations have been implicated in the autosomal recessive developmental disorder MCSZ (microcephaly with early-onset, intractable seizures and development delay) [301] and in an unnamed disorder of neurodegeneration and cerebellar ataxia [302]. Accordingly, mice harboring a brain-specific PNKP knockout exhibit cortical and cerebellar neuron loss and early postnatal death, while an MCMZ mouse model expressing an intermediate level of PNKP protein demonstrates generalized neurodevelopmental and maintenance defects, including microcephaly [303]. Homozygous mutation in TDP1 (His493Arg), a gene that is normally highly expressed in neuronal cells, results in spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) [304]. A consistent feature of each of these disorders is selectivity for neurological tissue, likely a reflection of neuronal cell characteristics, including a post-mitotic status that is associated with inefficient compensatory DNA repair pathways (namely HR), and a high metabolic demand resulting in high levels of endogenous oxidative DNA damage [305]. Evidence that TDP1, aprataxin, and PNKP can each localize to the mitochondria, which is the overwhelming source of cellular ROS, and which is largely reliant on BER for mtDNA repair, suggests a significant mitochondrial component to these diseases as well that has not yet been fully explored (reviewed in Sykora et al. [306]).

Interestingly, the above human neurological disorders are devoid of a cancer phenotype, a finding not necessarily expected for diseases underpinned by mutations in DNA repair genes. The observation that HR is upregulated in SCAN1 lymphoblastoid cells [291] suggests that this compensatory repair mechanism may be sufficient to suppress malignant transformation in proliferating cells, whereas the low replicative potential of neurons favors activation of cell death upon transcription machinery arrest at accumulating SSB lesions.

Further study is required to fully understand how the SSBR defects manifest these phenotypes.

Closing Remarks

SSBR is a critical mechanism for resolving strand break forms of endogenous DNA damage, and our understanding of its key players and molecular coordination continues to evolve and become refined. Results regarding the activity and interactions of PARP1 suggest that the protein largely functions through its DNA binding-activated PARylation activity as a scaffold to recruit and coordinate the proteins that mediate repair, most notably XRCC1. XRCC1 shares this scaffold function, but has additional important roles that are mediated through its many direct interactions with its SSBR protein partners, including maintenance of repair factor stability, protein recruitment, and stimulation of enzymatic repair functions. Two of the most important XRCC1 associations appear to be with POLβ and PNKP, although its other interactions cannot be ignored. Despite the advances in our understanding of SSBR in the past thirty years, there remains much room for expanding our knowledge, as highlighted by the poorly understood basis for the phenotypes observed in defects of SSBR. We recognize, in particular, the need to better grasp the mechanics of sub-pathway choice (such as damage lesion specificity or post-translational modifications [237]), the role of cell type and replicative capacity in SSBR mechanics [305], the protein and organizational differences in nuclear and mitochondrial SSBR [306], and the role of polymorphic SSBR variants in aging and disease [307, 308].

Acknowledgements

We thank Drs. Evandro Fang and Beverly Baptiste for constructive comments on the article. This effort was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging.

References

[1]. Lindahl T. Instability and decay of the primary structure of DNA. Nature. 1993; 362(6422):709–15. [PubMed: 8469282]

[2]. Olinski R, Jurgowiak M, Zaremba T. Uracil in DNA--its biological significance. Mutat Res. 2010; 705(3):239–45. [PubMed: 20709185]

[3]. De Bont R, van Larebeke N. Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis. 2004; 19(3):169–85. [PubMed: 15123782]

[4]. Rydberg B, Lindahl T. Nonenzymatic methylation of DNA by the intracellular methyl group donor S-adenosyl-L-methionine is a potentially mutagenic reaction. EMBO J. 1982; 1(2):211–6. [PubMed: 7188181]

[5]. Gates KS, Nooner T, Dutta S. Biologically relevant chemical reactions of N7-alkylguanine residues in DNA. Chem Res Toxicol. 2004; 17(7):839–56. [PubMed: 15257608]

[6]. Turrens JF, Boveris A. Generation of superoxide anion by the NADH dehydrogenase of bovine heart mitochondria. Biochem J. 1980; 191(2):421–7. [PubMed: 6263247]

[7]. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009; 417(1):1–13. [PubMed: 19061483]

[8]. Wallace DC. Mitochondria and cancer. Nat Rev Cancer. 2012; 12(10):685–98. [PubMed: 23001348]

[9]. Dizdaroglu M, Jaruga P, Birincioglu M, Rodriguez H. Free radical-induced damage to DNA: mechanisms and measurement. Free Radic Biol Med. 2002; 32(11):1102–15. [PubMed: 12031895]

[10]. Gates KS. An overview of chemical processes that damage cellular DNA: spontaneous hydrolysis, alkylation, and reactions with radicals. Chem Res Toxicol. 2009; 22(11):1747–60. [PubMed: 19757819]

[11]. Pogozelski WK, Tullius TD. Oxidative Strand Scission of Nucleic Acids: Routes Initiated by Hydrogen Abstraction from the Sugar Moiety. Chem Rev. 1998; 98(3):1089–1108. [PubMed: 11848926]

[12]. Aguiar PH, Furtado C, Repoles BM, Ribeiro GA, Mendes IC, Peloso EF, Gadelha FR, Macedo AM, Franco GR, Pena SD, Teixeira SM, Vieira LQ, Guarneri AA, Andrade LO, Machado CR. Oxidative stress and DNA lesions: the role of 8-oxoguanine lesions in Trypanosoma cruzi cell viability. PLoS Negl Trop Dis. 2013; 7(6):e2279. [PubMed: 23785540]

[13]. Basu AK, Loechler EL, Leadon SA, Essigmann JM. Genetic effects of thymine glycol: site-specific mutagenesis and molecular modeling studies. Proc Natl Acad Sci U S A. 1989; 86(20): 7677–81. [PubMed: 2682618]

[14]. Duncan BK, Miller JH. Mutagenic deamination of cytosine residues in DNA. Nature. 1980; 287(5782):560–1. [PubMed: 6999365]

[15]. Engelward BP, Boosalis MS, Chen BJ, Deng Z, Siciliano MJ, Samson LD. Cloning and characterization of a mouse 3-methyladenine/7-methyl-guanine/3-methylguanine DNA glycosylase cDNA whose gene maps to chromosome 11. Carcinogenesis. 1993; 14(2):175–81. [PubMed: 8435858]

[16]. Hu J, de Souza-Pinto NC, Haraguchi K, Hogue BA, Jaruga P, Greenberg MM, Dizdaroglu M, Bohr VA. Repair of formamidopyrimidines in DNA involves different glycosylases: role of the OGG1, NTH1, and NEIL1 enzymes. J Biol Chem. 2005; 280(49):40544–51. [PubMed: 16221681]

[17]. Kuzminov A. Single-strand interruptions in replicating chromosomes cause double-strand breaks. Proc Natl Acad Sci U S A. 2001; 98(15):8241–6. [PubMed: 11459959]

[18]. Loeb LA, Preston BD. Mutagenesis by apurinic/apyrimidinic sites. Annu Rev Genet. 20(1986): 201–30.

[19]. Walsh CP, Xu GL. Cytosine methylation and DNA repair. Curr Top Microbiol Immunol. 301(2006):283–315.

[20]. Warren JJ, Forsberg LJ, Beese LS. The structural basis for the mutagenicity of O(6)-methylguanine lesions. Proc Natl Acad Sci U S A. 2006; 103(52):19701–6. [PubMed: 17179038]

[21]. Abbotts R, Madhusudan S. Human AP endonuclease 1 (APE1): from mechanistic insights to druggable target in cancer. Cancer Treat Rev. 2010; 36(5):425–35. [PubMed: 20056333]

[22]. Sparks JL, Chon H, Cerritelli SM, Kunkel TA, Johansson E, Crouch RJ, Burgers PM. RNase H2-initiated ribonucleotide excision repair. Mol Cell. 2012; 47(6):980–6. [PubMed: 22864116]

[23]. Wang JC. Cellular roles of DNA topoisomerases: a molecular perspective. Nat Rev Mol Cell Biol. 2002; 3(6):430–40. [PubMed: 12042765]

[24]. Pommier Y, Redon C, Rao VA, Seiler JA, Sordet O, Takemura H, Antony S, Meng L, Liao Z, Kohlhagen G, Zhang H, Kohn KW. Repair of and checkpoint response to topoisomerase I-mediated DNA damage. Mutat Res. 2003; 532(1-2):173–203. [PubMed: 14643436]

[25]. Shinohara M, Io K, Shindo K, Matsui M, Sakamoto T, Tada K, Kobayashi M, Kadowaki N, Takaori-Kondo A. APOBEC3B can impair genomic stability by inducing base substitutions in genomic DNA in human cells. Sci Rep. 2012; 2:806. [PubMed: 23150777]

[26]. Tercero JA, Longhese MP, Diffley JF. A central role for DNA replication forks in checkpoint activation and response. Mol Cell. 2003; 11(5):1323–36. [PubMed: 12769855]

[27]. Smits VA, Gillespie DA. DNA damage control: regulation and functions of checkpoint kinase 1. FEBS J. 2015; 282(19):3681–92. [PubMed: 26216057]

[28]. Lange SS, Takata K, Wood RD. DNA polymerases and cancer. Nat Rev Cancer. 2011; 11(2):96–110. [PubMed: 21258395]

[29]. Sale JE. Translesion DNA synthesis and mutagenesis in eukaryotes. Cold Spring Harb Perspect Biol. 2013; 5(3):a012708. [PubMed: 23457261]

[30]. Pourquier P, Ueng LM, Kohlhagen G, Mazumder A, Gupta M, Kohn KW, Pommier Y. Effects of uracil incorporation, DNA mismatches, and abasic sites on cleavage and religation activities of mammalian topoisomerase I. J Biol Chem. 1997; 272(12):7792–6. [PubMed: 9065442]

[31]. Wilstermann AM, Osheroff N. Base excision repair intermediates as topoisomerase II poisons. J Biol Chem. 2001; 276(49):46290–6. [PubMed: 11591703]

[32]. Riballo E, Kuhne M, Rief N, Doherty A, Smith GC, Recio MJ, Reis C, Dahm K, Fricke A, Krempler A, Parker AR, Jackson SP, Gennery A, Jeggo PA, Lobrich M. A pathway of double-strand break rejoining dependent upon ATM, Artemis, and proteins locating to gamma-H2AX foci. Mol Cell. 2004; 16(5):715–24. [PubMed: 15574327]

[33]. Toledo LI, Altmeyer M, Rask MB, Lukas C, Larsen DH, Povlsen LK, Bekker-Jensen S, Mailand N, Bartek J, Lukas J. ATR prohibits replication catastrophe by preventing global exhaustion of RPA. Cell. 2013; 155(5):1088–103. [PubMed: 24267891]

[34]. Strumberg D, Pilon AA, Smith M, Hickey R, Malkas L, Pommier Y. Conversion of topoisomerase I cleavage complexes on the leading strand of ribosomal DNA into 5'-phosphorylated DNA double-strand breaks by replication runoff. Mol Cell Biol. 2000; 20(11): 3977–87. [PubMed: 10805740]

[35]. Yamaizumi M, Sugano T. U.v.-induced nuclear accumulation of p53 is evoked through DNA damage of actively transcribed genes independent of the cell cycle. Oncogene. 1994; 9(10):2775–84. [PubMed: 8084582]

[36]. Derheimer FA, O'Hagan HM, Krueger HM, Hanasoge S, Paulsen MT, Ljungman M. RPA and ATR link transcriptional stress to p53. Proc Natl Acad Sci U S A. 2007; 104(31):12778–83. [PubMed: 17616578]

[37]. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature. 2001; 411(6835):366–74. [PubMed: 11357144]

[38]. Lindahl T. An N-glycosidase from Escherichia coli that releases free uracil from DNA containing deaminated cytosine residues. Proc Natl Acad Sci U S A. 1974; 71(9):3649–53. [PubMed: 4610583]

[39]. Jacobs AL, Schar P. DNA glycosylases: in DNA repair and beyond. Chromosoma. 2012; 121(1): 1–20. [PubMed: 22048164]

[40]. Mosbaugh DW, Linn S. Further characterization of human fibroblast apurinic/apyrimidinic DNA endonucleases. The definition of two mechanistic classes of enzyme. J Biol Chem. 1980; 255(24):11743–52. [PubMed: 6254980]

[41]. Li M, Wilson DM Iii. Major Human Apurinic/Apyrimidinic Endonuclease, APE1. Antioxid Redox Signal. 2013 Epub ahead of print.

[42]. Matsumoto Y, Kim K. Excision of deoxyribose phosphate residues by DNA polymerase beta during DNA repair. Science. 1995; 269(5224):699–702. [PubMed: 7624801]

[43]. Dianov G, Price A, Lindahl T. Generation of single-nucleotide repair patches following excision of uracil residues from DNA. Mol Cell Biol. 1992; 12(4):1605–12. [PubMed: 1549115]

[44]. Dianov G, Lindahl T. Reconstitution of the DNA base excision-repair pathway. Curr Biol. 1994; 4(12):1069–76. [PubMed: 7535646]

[45]. Klungland A, Lindahl T. Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1). Embo J. 1997; 16(11):3341–8. [PubMed: 9214649]

[46]. Matsumoto Y, Kim K, Bogenhagen DF. Proliferating cell nuclear antigen-dependent abasic site repair in Xenopus laevis oocytes: an alternative pathway of base excision DNA repair. Mol Cell Biol. 1994; 14(9):6187–97. [PubMed: 7915006]

[47]. Caldecott KW. DNA single-strand break repair. Exp Cell Res. 2014; 329(1):2–8. [PubMed: 25176342]

[48]. Chambon P, Weill JD, Mandel P. Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem Biophys Res Commun. 1963; 11:39–43. [PubMed: 14019961]

[49]. Nishizuka Y, Ueda K, Nakazawa K, Hayaishi O. Studies on the polymer of adenosine diphosphate ribose. I. Enzymic formation from nicotinamide adenine dinuclotide in mammalian nuclei. J Biol Chem. 1967; 242(13):3164–71. [PubMed: 4291072]

[50]. Okayama H, Edson CM, Fukushima M, Ueda K, Hayaishi O. Purification and properties of poly(adenosine diphosphate ribose) synthetase. J Biol Chem. 1977; 252(20):7000–5. [PubMed: 198398]

[51]. Hayaishi O, Ueda K. Poly(ADP-ribose) and ADP-ribosylation of proteins. Annu Rev Biochem. 46(1977):95–116. [PubMed: 197884]

[52]. Benjamin RC, Gill DM. Poly(ADP-ribose) synthesis in vitro programmed by damaged DNA. A comparison of DNA molecules containing different types of strand breaks. J Biol Chem. 1980; 255(21):10502–8. [PubMed: 6253477]

[53]. Benjamin RC, Gill DM. ADP-ribosylation in mammalian cell ghosts. Dependence of poly(ADP-ribose) synthesis on strand breakage in DNA. J Biol Chem. 1980; 255(21):10493–501. [PubMed: 7430132]

[54]. Kurosaki T, Ushiro H, Mitsuuchi Y, Suzuki S, Matsuda M, Matsuda Y, Katunuma N, Kangawa K, Matsuo H, Hirose T, et al. Primary structure of human poly(ADP-ribose) synthetase as deduced from cDNA sequence. J Biol Chem. 1987; 262(33):15990–7. [PubMed: 2824474]

[55]. Suzuki H, Uchida K, Shima H, Sato T, Okamoto T, Kimura T, Miwa M. Molecular cloning of cDNA for human poly(ADP-ribose) polymerase and expression of its gene during HL-60 cell differentiation. Biochem Biophys Res Commun. 1987; 146(2):403–9. [PubMed: 3113420]

[56]. Cherney BW, McBride OW, Chen DF, Alkhatib H, Bhatia K, Hensley P, Smulson ME. cDNA sequence, protein structure, and chromosomal location of the human gene for poly(ADP-ribose) polymerase. Proc Natl Acad Sci U S A. 1987; 84(23):8370–4. [PubMed: 2891139]

[57]. Alkhatib HM, Chen DF, Cherney B, Bhatia K, Notario V, Giri C, Stein G, Slattery E, Roeder RG, Smulson ME. Cloning and expression of cDNA for human poly(ADP-ribose) polymerase. Proc Natl Acad Sci U S A. 1987; 84(5):1224–8. [PubMed: 3029772]

[58]. Bock FJ, Chang P. New Directions in PARP Biology. FEBS J. 2016

[59]. Herzog H, Zabel BU, Schneider R, Auer B, Hirsch-Kauffmann M, Schweiger M. Human nuclear NAD+ ADP-ribosyltransferase: localization of the gene on chromosome 1q41-q42 and expression of an active human enzyme in Escherichia coli. Proc Natl Acad Sci U S A. 1989; 86(10):3514–8. [PubMed: 2498872]

[60]. Auer B, Nagl U, Herzog H, Schneider R, Schweiger M. Human nuclear NAD+ ADP-ribosyltransferase(polymerizing): organization of the gene. DNA. 1989; 8(8):575–80. [PubMed: 2513174]

[61]. Potvin F, Thibodeau J, Kirkland JB, Dandenault B, Duchaine C, Poirier GG. Structural analysis of the putative regulatory region of the rat gene encoding poly(ADP-ribose) polymerase. FEBS Lett. 1992; 302(3):269–73. [PubMed: 1601134]

[62]. Pacini A, Quattrone A, Denegri M, Fiorillo C, Nediani C, Cajal S. Ramon y, Nassi P. Transcriptional down-regulation of poly(ADP-ribose) polymerase gene expression by E1A binding to pRb proteins protects murine keratinocytes from radiation-induced apoptosis. J Biol Chem. 1999; 274(49):35107–12. [PubMed: 10574992]

[63]. Yokoyama Y, Kawamoto T, Mitsuuchi Y, Kurosaki T, Toda K, Ushiro H, Terashima M, Sumimoto H, Kuribayashi I, Yamamoto Y, et al. Human poly(ADP-ribose) polymerase gene. Cloning of the promoter region. Eur J Biochem. 1990; 194(2):521–6. [PubMed: 2125269]

[64]. Laniel MA, Poirier GG, Guerin SL. A conserved initiator element on the mammalian poly(ADP-ribose) polymerase-1 promoters, in combination with flanking core elements, is necessary to obtain high transcriptional activity. Biochim Biophys Acta. 2004; 1679(1):37–46. [PubMed: 15245915]

[65]. Smale ST. Transcription initiation from TATA-less promoters within eukaryotic protein-coding genes. Biochim Biophys Acta. 1997; 1351(1-2):73–88. [PubMed: 9116046]

[66]. Zaniolo K, Desnoyers S, Leclerc S, Guerin SL. Regulation of poly(ADP-ribose) polymerase-1 (PARP-1) gene expression through the post-translational modification of Sp1: a nuclear target protein of PARP-1. BMC Mol Biol. 2007; 8:96. [PubMed: 17961220]

[67]. Oei SL, Griesenbeck J, Schweiger M, Babich V, Kropotov A, Tomilin N. Interaction of the transcription factor YY1 with human poly(ADP-ribosyl) transferase. Biochem Biophys Res Commun. 1997; 240(1):108–11. [PubMed: 9367892]

[68]. Soldatenkov VA, Albor A, Patel BK, Dreszer R, Dritschilo A, Notario V. Regulation of the human poly(ADP-ribose) polymerase promoter by the ETS transcription factor. Oncogene. 1999; 18(27):3954–62. [PubMed: 10435618]

[69]. Laniel MA, Bergeron MJ, Poirier GG, Guerin SL. A nuclear factor other than Sp1 binds the GC-rich promoter of the gene encoding rat poly(ADP-ribose) polymerase in vitro. Biochem Cell Biol. 1997; 75(4):427–34. [PubMed: 9493965]

[70]. Kameshita I, Matsuda Z, Taniguchi T, Shizuta Y. Poly (ADP-Ribose) synthetase. Separation and identification of three proteolytic fragments as the substrate-binding domain, the DNA-binding domain, and the automodification domain. J Biol Chem. 1984; 259(8):4770–6. [PubMed: 6325408]

[71]. Kim MY, Zhang T, Kraus WL. Poly(ADP-ribosyl)ation by PARP-1: 'PAR-laying' NAD+ into a nuclear signal. Genes Dev. 2005; 19(17):1951–67. [PubMed: 16140981]

[72]. Langelier MF, Planck JL, Roy S, Pascal JM. Crystal structures of poly(ADP-ribose) polymerase-1 (PARP-1) zinc fingers bound to DNA: structural and functional insights into DNA-dependent PARP-1 activity. J Biol Chem. 2011; 286(12):10690–701. [PubMed: 21233213]

[73]. Gradwohl G, Menissier de Murcia JM, Molinete M, Simonin F, Koken M, Hoeijmakers JH, de Murcia G. The second zinc-finger domain of poly(ADP-ribose) polymerase determines specificity for single-stranded breaks in DNA. Proc Natl Acad Sci U S A. 1990; 87(8):2990–4. [PubMed: 2109322]

[74]. Ikejima M, Noguchi S, Yamashita R, Ogura T, Sugimura T, Gill DM, Miwa M. The zinc fingers of human poly(ADP-ribose) polymerase are differentially required for the recognition of DNA breaks and nicks and the consequent enzyme activation. Other structures recognize intact DNA. J Biol Chem. 1990; 265(35):21907–13. [PubMed: 2123876]

[75]. Altmeyer M, Messner S, Hassa PO, Fey M, Hottiger MO. Molecular mechanism of poly(ADP-ribosyl)ation by PARP1 and identification of lysine residues as ADP-ribose acceptor sites. Nucleic Acids Res. 2009; 37(11):3723–38. [PubMed: 19372272]

[76]. Khodyreva SN, Prasad R, Ilina ES, Sukhanova MV, Kutuzov MM, Liu Y, Hou EW, Wilson SH, Lavrik OI. Apurinic/apyrimidinic (AP) site recognition by the 5'-dRP/AP lyase in poly(ADP-ribose) polymerase-1 (PARP-1). Proc Natl Acad Sci U S A. 2010; 107(51):22090–5. [PubMed: 21127267]

[77]. Eustermann S, Videler H, Yang JC, Cole PT, Gruszka D, Veprintsev D, Neuhaus D. The DNA-binding domain of human PARP-1 interacts with DNA single-strand breaks as a monomer through its second zinc finger. J Mol Biol. 2011; 407(1):149–70. [PubMed: 21262234]

[78]. Langelier MF, Servent KM, Rogers EE, Pascal JM. A third zinc-binding domain of human poly(ADP-ribose) polymerase-1 coordinates DNA-dependent enzyme activation. J Biol Chem. 2008; 283(7):4105–14. [PubMed: 18055453]

[79]. Ali AA, Timinszky G, Arribas-Bosacoma R, Kozlowski M, Hassa PO, Hassler M, Ladurner AG, Pearl LH, Oliver AW. The zinc-finger domains of PARP1 cooperate to recognize DNA strand breaks. Nat Struct Mol Biol. 2012; 19(7):685–92. [PubMed: 22683995]

[80]. Langelier MF, Planck JL, Roy S, Pascal JM. Structural basis for DNA damage-dependent poly(ADP-ribosyl)ation by human PARP-1. Science. 2012; 336(6082):728–32. [PubMed: 22582261]

[81]. Hassler M, Ladurner AG. Towards a structural understanding of PARP1 activation and related signalling ADP-ribosyl-transferases. Curr Opin Struct Biol. 2012; 22(6):721–9. [PubMed: 22985748]

[82]. Ogata N, Ueda K, Kagamiyama H, Hayaishi O. ADP-ribosylation of histone H1. Identification of glutamic acid residues 2, 14, and the COOH-terminal lysine residue as modification sites. J Biol Chem. 1980; 255(16):7616–20. [PubMed: 6772638]

[83]. Tao Z, Gao P, Liu HW. Identification of the ADP-ribosylation sites in the PARP-1 automodification domain: analysis and implications. J Am Chem Soc. 2009; 131(40):14258–60. [PubMed: 19764761]

[84]. Keith G, Desgres J, de Murcia G. Use of two-dimensional thin-layer chromatography for the components study of poly(adenosine diphosphate ribose). Anal Biochem. 1990; 191(2):309–13. [PubMed: 2085177]

[85]. Ruf A, Rolli V, de Murcia G, Schulz GE. The mechanism of the elongation and branching reaction of poly(ADP-ribose) polymerase as derived from crystal structures and mutagenesis. J Mol Biol. 1998; 278(1):57–65. [PubMed: 9571033]

[86]. Panzeter PL, Althaus FR. DNA strand break-mediated partitioning of poly(ADP-ribose) polymerase function. Biochemistry. 1994; 33(32):9600–5. [PubMed: 8068636]

[87]. Pion E, Ullmann GM, Ame JC, Gerard D, de Murcia G, Bombarda E. DNA-induced dimerization of poly(ADP-ribose) polymerase-1 triggers its activation. Biochemistry. 2005; 44(44):14670–81. [PubMed: 16262266]

[88]. Kim JW, Kim K, Kang K, Joe CO. Inhibition of homodimerization of poly(ADP-ribose) polymerase by its C-terminal cleavage products produced during apoptosis. J Biol Chem. 2000; 275(11):8121–5. [PubMed: 10713134]

[89]. Mendoza-Alvarez H, Alvarez-Gonzalez R. Poly(ADP-ribose) polymerase is a catalytic dimer and the automodification reaction is intermolecular. J Biol Chem. 1993; 268(30):22575–80. [PubMed: 8226768]

[90]. Lilyestrom W, van der Woerd MJ, Clark N, Luger K. Structural and biophysical studies of human PARP-1 in complex with damaged DNA. J Mol Biol. 2010; 395(5):983–94. [PubMed: 19962992]

[91]. Lavrik OI, Prasad R, Sobol RW, Horton JK, Ackerman EJ, Wilson SH. Photoaffinity labeling of mouse fibroblast enzymes by a base excision repair intermediate. Evidence for the role of poly(ADP-ribose) polymerase-1 in DNA repair. J Biol Chem. 2001; 276(27):25541–8. [PubMed: 11340072]

[92]. Sukhanova MV, Abrakhi S, Joshi V, Pastre D, Kutuzov MM, Anarbaev RO, Curmi PA, Hamon L, Lavrik OI. Single molecule detection of PARP1 and PARP2 interaction with DNA strand breaks and their poly(ADP-ribosyl)ation using high-resolution AFM imaging. Nucleic Acids Res. 2016; 44(6):e60. [PubMed: 26673720]

[93]. Zahradka P, Ebisuzaki K. A shuttle mechanism for DNA-protein interactions. The regulation of poly(ADP-ribose) polymerase. Eur J Biochem. 1982; 127(3):579–85. [PubMed: 6293817]

[94]. Ferro AM, Olivera BM. Poly(ADP-ribosylation) in vitro. Reaction parameters and enzyme mechanism. J Biol Chem. 1982; 257(13):7808–13. [PubMed: 6282854]

[95]. Huambachano O, Herrera F, Rancourt A, Satoh MS. Double-stranded DNA binding domain of poly(ADP-ribose) polymerase-1 and molecular insight into the regulation of its activity. J Biol Chem. 2011; 286(9):7149–60. [PubMed: 21183686]

[96]. Loeffler PA, Cuneo MJ, Mueller GA, DeRose EF, Gabel SA, London RE. Structural studies of the PARP-1 BRCT domain. BMC Struct Biol. 2011; 11:37. [PubMed: 21967661]

[97]. Bork P, Hofmann K, Bucher P, Neuwald AF, Altschul SF, Koonin EV. A superfamily of conserved domains in DNA damage-responsive cell cycle checkpoint proteins. FASEB J. 1997; 11(1):68–76. [PubMed: 9034168]

[98]. Dantzer F, de La Rubia G, Menissier-De Murcia J, Hostomsky Z, de Murcia G, Schreiber V. Base excision repair is impaired in mammalian cells lacking Poly(ADP-ribose) polymerase-1. Biochemistry. 2000; 39(25):7559–69. [PubMed: 10858306]

[99]. Leppard JB, Dong Z, Mackey ZB, Tomkinson AE. Physical and functional interaction between DNA ligase IIIalpha and poly(ADP-Ribose) polymerase 1 in DNA single-strand break repair. Mol Cell Biol. 2003; 23(16):5919–27. [PubMed: 12897160]

[100]. Harris JL, Jakob B, Taucher-Scholz G, Dianov GL, Becherel OJ, Lavin MF. Aprataxin, poly-ADP ribose polymerase 1 (PARP-1) and apurinic endonuclease 1 (APE1) function together to protect the genome against oxidative damage. Hum Mol Genet. 2009; 18(21):4102–17. [PubMed: 19643912]

[101]. Das BB, Huang SY, Murai J, Rehman I, Ame JC, Sengupta S, Das SK, Majumdar P, Zhang H, Biard D, Majumder HK, Schreiber V, Pommier Y. PARP1-TDP1 coupling for the repair of topoisomerase I-induced DNA damage. Nucleic Acids Res. 2014; 42(7):4435–49. [PubMed: 24493735]

[102]. Moor NA, Vasil'eva IA, Anarbaev RO, Antson AA, Lavrik OI. Quantitative characterization of protein-protein complexes involved in base excision DNA repair. Nucleic Acids Res. 2015; 43(12):6009–22. [PubMed: 26013813]

[103]. Lebedeva NA, Anarbaev RO, Sukhanova M, Vasil'eva IA, Rechkunova NI, Lavrik OI. Poly(ADP-ribose)polymerase 1 stimulates the AP-site cleavage activity of tyrosyl-DNA phosphodiesterase 1. Biosci Rep. 2015; 35(4)

[104]. Sukhanova MV, Khodyreva SN, Lebedeva NA, Prasad R, Wilson SH, Lavrik OI. Human base excision repair enzymes apurinic/apyrimidinic endonuclease1 (APE1), DNA polymerase beta and poly(ADP-ribose) polymerase 1: interplay between strand-displacement DNA synthesis and proofreading exonuclease activity. Nucleic Acids Res. 2005; 33(4):1222–9. [PubMed: 15731342]

[105]. Noren Hooten N, Kompaniez K, Barnes J, Lohani A, Evans MK. Poly(ADP-ribose) polymerase 1 (PARP-1) binds to 8-oxoguanine-DNA glycosylase (OGG1). J Biol Chem. 2011; 286(52): 44679–90. [PubMed: 22057269]

[106]. Noren Hooten N, Fitzpatrick M, Kompaniez K, Jacob KD, Moore BR, Nagle J, Barnes J, Lohani A, Evans MK. Coordination of DNA repair by NEIL1 and PARP-1: a possible link to aging. Aging (Albany NY). 2012; 4(10):674–85. [PubMed: 23104860]

[107]. D'Amours D, Desnoyers S, D'Silva I, Poirier GG. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J. 1999; 342(2):249–68. [PubMed: 10455009]

[108]. Schreiber V, Dantzer F, Ame JC, de Murcia G. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006; 7(7):517–28. [PubMed: 16829982]

[109]. Pleschke JM, Kleczkowska HE, Strohm M, Althaus FR. Poly(ADP-ribose) binds to specific domains in DNA damage checkpoint proteins. J Biol Chem. 2000; 275(52):40974–80. [PubMed: 11016934]

[110]. Frouin I, Maga G, Denegri M, Riva F, Savio M, Spadari S, Prosperi E, Scovassi AI. Human proliferating cell nuclear antigen, poly(ADP-ribose) polymerase-1, and p21waf1/cip1. A dynamic exchange of partners. J Biol Chem. 2003; 278(41):39265–8. [PubMed: 12930846]

[111]. von Kobbe C, Harrigan JA, May A, Opresko PL, Dawut L, Cheng WH, Bohr VA. Central role for the Werner syndrome protein/poly(ADP-ribose) polymerase 1 complex in the poly(ADP-ribosyl)ation pathway after DNA damage. Mol Cell Biol. 2003; 23(23):8601–13. [PubMed: 14612404]

[112]. Lebel M, Lavoie J, Gaudreault I, Bronsard M, Drouin R. Genetic cooperation between the Werner syndrome protein and poly(ADP-ribose) polymerase-1 in preventing chromatid breaks, complex chromosomal rearrangements, and cancer in mice. Am J Pathol. 2003; 162(5):1559–69. [PubMed: 12707040]

[113]. Aguilar-Quesada R, Munoz-Gamez JA, Martin-Oliva D, Peralta A, Valenzuela MT, Matinez-Romero R, Quiles-Perez R, Menissier-de Murcia J, de Murcia G, Ruiz de Almodovar M, Oliver FJ. Interaction between ATM and PARP-1 in response to DNA damage and sensitization of ATM deficient cells through PARP inhibition. BMC Mol Biol. 2007; 8:29. [PubMed: 17459151]

[114]. Khoronenkova SV, Dianov GL. ATM prevents DSB formation by coordinating SSB repair and cell cycle progression. Proc Natl Acad Sci U S A. 2015; 112(13):3997–4002. [PubMed: 25775545]

[115]. Trucco C, Oliver FJ, de Murcia G, Menissier-de Murcia J. DNA repair defect in poly(ADP-ribose) polymerase-deficient cell lines. Nucleic Acids Res. 1998; 26(11):2644–9. [PubMed: 9592149]

[116]. Ding R, Pommier Y, Kang VH, Smulson M. Depletion of poly(ADP-ribose) polymerase by antisense RNA expression results in a delay in DNA strand break rejoining. J Biol Chem. 1992; 267(18):12804–12. [PubMed: 1618781]

[117]. Schreiber V, Hunting D, Trucco C, Gowans B, Grunwald D, De Murcia G, De Murcia JM. A dominant-negative mutant of human poly(ADP-ribose) polymerase affects cell recovery, apoptosis, and sister chromatid exchange following DNA damage. Proc Natl Acad Sci U S A. 1995; 92(11):4753–7. [PubMed: 7761396]

[118]. Boulton S, Kyle S, Durkacz BW. Interactive effects of inhibitors of poly(ADP-ribose) polymerase and DNA-dependent protein kinase on cellular responses to DNA damage. Carcinogenesis. 1999; 20(2):199–203. [PubMed: 10069454]

[119]. Satoh MS, Lindahl T. Role of poly(ADP-ribose) formation in DNA repair. Nature. 1992; 356(6367):356–8. [PubMed: 1549180]

[120]. Vodenicharov MD, Sallmann FR, Satoh MS, Poirier GG. Base excision repair is efficient in cells lacking poly(ADP-ribose) polymerase 1. Nucleic Acids Res. 2000; 28(20):3887–96. [PubMed: 11024167]

[121]. Strom CE, Johansson F, Uhlen M, Szigyarto CA, Erixon K, Helleday T. Poly (ADP-ribose) polymerase (PARP) is not involved in base excision repair but PARP inhibition traps a single-strand intermediate. Nucleic Acids Res. 2011; 39(8):3166–75. [PubMed: 21183466]

[122]. Kubota Y, Nash RA, Klungland A, Schar P, Barnes DE, Lindahl T. Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein. EMBO J. 1996; 15(23):6662–70. [PubMed: 8978692]

[123]. Reynolds P, Cooper S, Lomax M, O'Neill P. Disruption of PARP1 function inhibits base excision repair of a sub-set of DNA lesions. Nucleic Acids Res. 2015; 43(8):4028–38. [PubMed: 25813046]

[124]. Allinson SL, Dianova II, Dianov GL. Poly(ADP-ribose) polymerase in base excision repair: always engaged, but not essential for DNA damage processing. Acta Biochim Pol. 2003; 50(1): 169–79. [PubMed: 12673357]

[125]. Parsons JL, Dianova II, Allinson SL, Dianov GL. Poly(ADP-ribose) polymerase-1 protects excessive DNA strand breaks from deterioration during repair in human cell extracts. FEBS J. 2005; 272(8):2012–21. [PubMed: 15819892]

[126]. Prasad R, Williams JG, Hou EW, Wilson SH. Pol beta associated complex and base excision repair factors in mouse fibroblasts. Nucleic Acids Res. 2012; 40(22):11571–82. [PubMed: 23042675]

[127]. Prasad R, Dyrkheeva N, Williams J, Wilson SH. Mammalian Base Excision Repair: Functional Partnership between PARP-1 and APE1 in AP-Site Repair. PLoS One. 2015; 10(5):e0124269. [PubMed: 26020771]

[128]. Krupitza G, Cerutti P. Poly(ADP-ribosylation) of histones in intact human keratinocytes. Biochemistry. 1989; 28(9):4054–60. [PubMed: 2473778]

[129]. Realini CA, Althaus FR. Histone shuttling by poly(ADP-ribosylation). J Biol Chem. 1992; 267(26):18858–65. [PubMed: 1326536]

[130]. Thomassin H, Menard L, Hengartner C, Kirkland JB, Poirier GG. Poly(ADP-ribosyl)ation of chromatin in an in-vitro poly(ADP-ribose)-turnover system. Biochim Biophys Acta. 1992; 1137(2):171–81. [PubMed: 1420323]

[131]. Lagueux J, Shah GM, Menard L, Thomassin H, Duchaine C, Hengartner C, Poirier GG. Poly(ADP-ribose) catabolism in mammalian cells. Mol Cell Biochem. 1994; 138(1-2):45–52. [PubMed: 7898474]

[132]. Althaus FR. Poly ADP-ribosylation: a histone shuttle mechanism in DNA excision repair. J Cell Sci. 1992; 102(Pt 4):663–70. [PubMed: 1429884]

[133]. Lan L, Nakajima S, Wei L, Sun L, Hsieh CL, Sobol RW, Bruchez M, Van Houten B, Yasui A, Levine AS. Novel method for site-specific induction of oxidative DNA damage reveals differences in recruitment of repair proteins to heterochromatin and euchromatin. Nucleic Acids Res. 2014; 42(4):2330–45. [PubMed: 24293652]

[134]. Kubota Y, Shimizu S, Yasuhira S, Horiuchi S. SNF2H interacts with XRCC1 and is involved in repair of H2O2-induced DNA damage. DNA Repair (Amst). 2016; 43:69–77. [PubMed: 27268481]

[135]. Ha HC, Snyder SH. Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. Proc Natl Acad Sci U S A. 1999; 96(24):13978–82. [PubMed: 10570184]

[136]. Wang Y, Kim NS, Haince JF, Kang HC, David KK, Andrabi SA, Poirier GG, Dawson VL, Dawson TM. Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). Sci Signal. 2011; 4(167):ra20. [PubMed: 21467298]

[137]. Miwa M, Tanaka M, Matsushima T, Sugimura T. Purification and properties of glycohydrolase from calf thymus splitting ribose-ribose linkages of poly(adenosine diphosphate ribose). J Biol Chem. 1974; 249(11):3475–82. [PubMed: 4831224]

[138]. Slade D, Dunstan MS, Barkauskaite E, Weston R, Lafite P, Dixon N, Ahel M, Leys D, Ahel I. The structure and catalytic mechanism of a poly(ADP-ribose) glycohydrolase. Nature. 2011; 477(7366):616–20. [PubMed: 21892188]

[139]. Niere M, Mashimo M, Agledal L, Dolle C, Kasamatsu A, Kato J, Moss J, Ziegler M. ADP-ribosylhydrolase 3 (ARH3), not poly(ADP-ribose) glycohydrolase (PARG) isoforms, is

responsible for degradation of mitochondrial matrix-associated poly(ADP-ribose). J Biol Chem. 2012; 287(20):16088–102. [PubMed: 22433848]

[140]. Sharifi R, Morra R, Appel CD, Tallis M, Chioza B, Jankevicius G, Simpson MA, Matic I, Ozkan E, Golia B, Schellenberg MJ, Weston R, Williams JG, Rossi MN, Galehdari H, Krahn J, Wan A, Trembath RC, Crosby AH, Ahel D, Hay R, Ladurner AG, Timinszky G, Williams RS, Ahel I. Deficiency of terminal ADP-ribose protein glycohydrolase TARG1/C6orf130 in neurodegenerative disease. EMBO J. 2013; 32(9):1225–37. [PubMed: 23481255]

[141]. Jankevicius G, Hassler M, Golia B, Rybin V, Zacharias M, Timinszky G, Ladurner AG. A family of macrodomain proteins reverses cellular mono-ADP-ribosylation. Nat Struct Mol Biol. 2013; 20(4):508–14. [PubMed: 23474712]

[142]. Rosenthal F, Feijs KL, Frugier E, Bonalli M, Forst AH, Imhof R, Winkler HC, Fischer D, Caflisch A, Hassa PO, Luscher B, Hottiger MO. Macrodomain-containing proteins are new mono-ADP-ribosylhydrolases. Nat Struct Mol Biol. 2013; 20(4):502–7. [PubMed: 23474714]

[143]. Alvarez-Gonzalez R, Althaus FR. Poly(ADP-ribose) catabolism in mammalian cells exposed to DNA-damaging agents. Mutat Res. 1989; 218(2):67–74. [PubMed: 2770765]

[144]. Thomas C, Tulin AV. Poly-ADP-ribose polymerase: machinery for nuclear processes. Mol Aspects Med. 2013; 34(6):1124–37. [PubMed: 23624145]

[145]. Koh DW, Lawler AM, Poitras MF, Sasaki M, Wattler S, Nehls MC, Stoger T, Poirier GG, Dawson VL, Dawson TM. Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality. Proc Natl Acad Sci U S A. 2004; 101(51):17699–704. [PubMed: 15591342]

[146]. de Murcia JM, Niedergang C, Trucco C, Ricoul M, Dutrillaux B, Mark M, Oliver FJ, Masson M, Dierich A, LeMeur M, Walztinger C, Chambon P, de Murcia G. Requirement of poly(ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. Proc Natl Acad Sci U S A. 1997; 94(14):7303–7. [PubMed: 9207086]

[147]. Bai P, Canto C, Oudart H, Brunyanszki A, Cen Y, Thomas C, Yamamoto H, Huber A, Kiss B, Houtkooper RH, Schoonjans K, Schreiber V, Sauve AA, Menissier-de Murcia J, Auwerx J. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell Metab. 2011; 13(4):461–8. [PubMed: 21459330]

[148]. Wang ZQ, Auer B, Stingl L, Berghammer H, Haidacher D, Schweiger M, Wagner EF. Mice lacking ADPRT and poly(ADP-ribosyl)ation develop normally but are susceptible to skin disease. Genes Dev. 1995; 9(5):509–20. [PubMed: 7698643]

[149]. Shieh WM, Ame JC, Wilson MV, Wang ZQ, Koh DW, Jacobson MK, Jacobson EL. Poly(ADP-ribose) polymerase null mouse cells synthesize ADP-ribose polymers. J Biol Chem. 1998; 273(46):30069–72. [PubMed: 9804757]

[150]. Menissier de Murcia J, Ricoul M, Tartier L, Niedergang C, Huber A, Dantzer F, Schreiber V, Ame JC, Dierich A, LeMeur M, Sabatier L, Chambon P, de Murcia G. Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. EMBO J. 2003; 22(9):2255–63. [PubMed: 12727891]

[151]. Wang ZQ, Stingl L, Morrison C, Jantsch M, Los M, Schulze-Osthoff K, Wagner EF. PARP is important for genomic stability but dispensable in apoptosis. Genes Dev. 1997; 11(18):2347–58. [PubMed: 9308963]

[152]. Masutani M, Nozaki T, Nakamoto K, Nakagama H, Suzuki H, Kusuoka O, Tsutsumi M, Sugimura T. The response of Parp knockout mice against DNA damaging agents. Mutat Res. 2000; 462(2-3):159–66. [PubMed: 10767627]

[153]. Beneke R, Geisen C, Zevnik B, Bauch T, Muller WU, Kupper JH, Moroy T. DNA excision repair and DNA damage-induced apoptosis are linked to Poly(ADP-ribosyl)ation but have different requirements for p53. Mol Cell Biol. 2000; 20(18):6695–703. [PubMed: 10958667]

[154]. Thompson LH, Rubin JS, Cleaver JE, Whitmore GF, Brookman K. A screening method for isolating DNA repair-deficient mutants of CHO cells. Somatic Cell Genet. 1980; 6(3):391–405. [PubMed: 7404270]

[155]. Busch DB, Cleaver JE, Glaser DA. Large-scale isolation of UV-sensitive clones of CHO cells. Somatic Cell Genet. 1980; 6(3):407–18. [PubMed: 7404271]

[156]. Thompson LH, Busch DB, Brookman K, Mooney CL, Glaser DA. Genetic diversity of UV-sensitive DNA repair mutants of Chinese hamster ovary cells. Proc Natl Acad Sci U S A. 1981; 78(6):3734–7. [PubMed: 6943579]

[157]. Thompson LH, Brookman KW, Dillehay LE, Carrano AV, Mazrimas JA, Mooney CL, Minkler JL. A CHO-cell strain having hypersensitivity to mutagens, a defect in DNA strand-break repair, and an extraordinary baseline frequency of sister-chromatid exchange. Mutat Res. 1982; 95(2-3): 427–40. [PubMed: 6889677]

[158]. Thompson LH, Brookman KW, Jones NJ, Allen SA, Carrano AV. Molecular cloning of the human XRCC1 gene, which corrects defective DNA strand break repair and sister chromatid exchange. Mol Cell Biol. 1990; 10(12):6160–71. [PubMed: 2247054]

[159]. Thompson LH, Brookman KW, Minkler JL, Fuscoe JC, Henning KA, Carrano AV. DNA-mediated transfer of a human DNA repair gene that controls sister chromatid exchange. Mol Cell Biol. 1985; 5(4):881–4. [PubMed: 3990694]

[160]. Siciliano MJ, Carrano AV, Thompson LH. Assignment of a human DNA-repair gene associated with sister-chromatid exchange to chromosome 19. Mutat Res. 1986; 174(4):303–8. [PubMed: 3736579]

[161]. Mohrenweiser HW, Carrano AV, Fertitta A, Perry B, Thompson LH, Tucker JD, Weber CA. Refined mapping of the three DNA repair genes, ERCC1, ERCC2, and XRCC1, on human chromosome 19. Cytogenet Cell Genet. 1989; 52(1-2):11–4. [PubMed: 2558854]

[162]. Thompson LH, Bachinski LL, Stallings RL, Dolf G, Weber CA, Westerveld A, Siciliano MJ. Complementation of repair gene mutations on the hemizygous chromosome 9 in CHO: a third repair gene on human chromosome 19. Genomics. 1989; 5(4):670–9. [PubMed: 2591959]

[163]. Thompson LH, Mooney CL, Burkhart-Schultz K, Carrano AV, Siciliano MJ. Correction of a nucleotide-excision-repair mutation by human chromosome 19 in hamster-human hybrid cells. Somat Cell Mol Genet. 1985; 11(1):87–92. [PubMed: 3919454]

[164]. Barnes DE, Kodama K, Tynan K, Trask BJ, Christensen M, De Jong PJ, Spurr NK, Lindahl T, Mohrenweiser HW. Assignment of the gene encoding DNA ligase I to human chromosome 19q13.2-13.3. Genomics. 1992; 12(1):164–6. [PubMed: 1733856]

[165]. Zhang X, Morera S, Bates PA, Whitehead PC, Coffer AI, Hainbucher K, Nash RA, Sternberg MJ, Lindahl T, Freemont PS. Structure of an XRCC1 BRCT domain: a new protein-protein interaction module. EMBO J. 1998; 17(21):6404–11. [PubMed: 9799248]

[166]. Marintchev A, Mullen MA, Maciejewski MW, Pan B, Gryk MR, Mullen GP. Solution structure of the single-strand break repair protein XRCC1 N-terminal domain. Nat Struct Biol. 1999; 6(9): 884–93. [PubMed: 10467102]

[167]. Cuneo MJ, Gabel SA, Krahn JM, Ricker MA, London RE. The structural basis for partitioning of the XRCC1/DNA ligase III-alpha BRCT-mediated dimer complexes. Nucleic Acids Res. 2011; 39(17):7816–27. [PubMed: 21652643]

[168]. Dianova II, Sleeth KM, Allinson SL, Parsons JL, Breslin C, Caldecott KW, Dianov GL. XRCC1-DNA polymerase beta interaction is required for efficient base excision repair. Nucleic Acids Res. 2004; 32(8):2550–5. [PubMed: 15141024]

[169]. Marintchev A, Gryk MR, Mullen GP. Site-directed mutagenesis analysis of the structural interaction of the single-strand-break repair protein, X-ray cross-complementing group 1, with DNA polymerase beta. Nucleic Acids Res. 2003; 31(2):580–8. [PubMed: 12527765]

[170]. Masson M, Niedergang C, Schreiber V, Muller S, Menissier-de Murcia J, de Murcia G. XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol. 1998; 18(6):3563–71. [PubMed: 9584196]

[171]. Caldecott KW, McKeown CK, Tucker JD, Ljungquist S, Thompson LH. An interaction between the mammalian DNA repair protein XRCC1 and DNA ligase III. Mol Cell Biol. 1994; 14(1):68–76. [PubMed: 8264637]

[172]. Nash RA, Caldecott KW, Barnes DE, Lindahl T. XRCC1 protein interacts with one of two distinct forms of DNA ligase III. Biochemistry. 1997; 36(17):5207–11. [PubMed: 9136882]

[173]. Vidal AE, Boiteux S, Hickson ID, Radicella JP. XRCC1 coordinates the initial and late stages of DNA abasic site repair through protein-protein interactions. EMBO J. 2001; 20(22):6530–6539. [PubMed: 11707423]

[174]. Marsin S, Vidal AE, Sossou M, Menissier-de Murcia J, Page F. Le, Boiteux S, Murcia G. de, Radicella JP. Role of XRCC1 in the coordination and stimulation of oxidative DNA damage repair initiated by the DNA glycosylase hOGG1. J Biol Chem. 2003; 278(45):44068–74. [PubMed: 12933815]

[175]. Fan J, Otterlei M, Wong HK, Tomkinson AE, Wilson DM 3rd. XRCC1 co-localizes and physically interacts with PCNA. Nucleic Acids Res. 2004; 32(7):2193–201. [PubMed: 15107487]

[176]. Whitehouse CJ, Taylor RM, Thistlethwaite A, Zhang H, Karimi-Busheri F, Lasko DD, Weinfeld M, Caldecott KW. XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair. Cell. 2001; 104(1):107–17. [PubMed: 11163244]

[177]. Della-Maria J, Hegde ML, McNeill DR, Matsumoto Y, Tsai MS, Ellenberger T, Wilson DM 3rd, Mitra S, Tomkinson AE. The interaction between polynucleotide kinase phosphatase and the DNA repair protein XRCC1 is critical for repair of DNA alkylation damage and stable association at DNA damage sites. J Biol Chem. 2012; 287(46):39233–44. [PubMed: 22992732]

[178]. Loizou JI, El-Khamisy SF, Zlatanou A, Moore DJ, Chan DW, Qin J, Sarno S, Meggio F, Pinna LA, Caldecott KW. The protein kinase CK2 facilitates repair of chromosomal DNA single-strand breaks. Cell. 2004; 117(1):17–28. [PubMed: 15066279]

[179]. Campalans A, Moritz E, Kortulewski T, Biard D, Epe B, Radicella JP. Interaction with OGG1 is required for efficient recruitment of XRCC1 to base excision repair and maintenance of genetic stability after exposure to oxidative stress. Mol Cell Biol. 2015; 35(9):1648–58. [PubMed: 25733688]

[180]. Campalans A, Marsin S, Nakabeppu Y, O'Connor T R, Boiteux S, Radicella JP. XRCC1 interactions with multiple DNA glycosylases: a model for its recruitment to base excision repair. DNA Repair (Amst). 2005; 4(7):826–35. [PubMed: 15927541]

[181]. Otterlei M, Warbrick E, Nagelhus TA, Haug T, Slupphaug G, Akbari M, Aas PA, Steinsbekk K, Bakke O, Krokan HE. Post-replicative base excision repair in replication foci. EMBO J. 1999; 18(13):3834–44. [PubMed: 10393198]

[182]. Akbari M, Solvang-Garten K, Hanssen-Bauer A, Lieske NV, Pettersen HS, Pettersen GK, Wilson DM 3rd, Krokan HE, Otterlei M. Direct interaction between XRCC1 and UNG2 facilitates rapid repair of uracil in DNA by XRCC1 complexes. DNA Repair. 2010; 9(7):785–95. [PubMed: 20466601]

[183]. Carrano AV, Minkler JL, Dillehay LE, Thompson LH. Incorporated bromodeoxyuridine enhances the sister-chromatid exchange and chromosomal aberration frequencies in an EMS-sensitive Chinese hamster cell line. Mutat Res. 1986; 162(2):233–9. [PubMed: 3748051]

[184]. Dominguez I, Daza P, Natarajan AT, Cortes F. A high yield of translocations parallels the high yield of sister chromatid exchanges in the CHO mutant EM9. Mutat Res. 1998; 398(1-2):67–73. [PubMed: 9626966]

[185]. Pinkel D, Thompson LH, Gray JW, Vanderlaan M. Measurement of sister chromatid exchanges at very low bromodeoxyuridine substitution levels using a monoclonal antibody in Chinese hamster ovary cells. Cancer Res. 1985; 45(11 Pt 2):5795–8. [PubMed: 4053051]

[186]. Zdzienicka MZ, van der Schans GP, Natarajan AT, Thompson LH, Neuteboom I, Simons JW. A Chinese hamster ovary cell mutant (EM-C11) with sensitivity to simple alkylating agents and a very high level of sister chromatid exchanges. Mutagenesis. 1992; 7(4):265–9. [PubMed: 1518409]

[187]. Saffhill R, Ockey CH. Strand breaks arising from the repair of the 5-bromodeoxyuridine-substituted template and methyl methanesulphonate-induced lesions can explain the formation of sister chromatid exchanges. Chromosoma. 1985; 92(3):218–24. [PubMed: 4017746]

[188]. Maldonado A, Hernandez P, Gutierrez C. Inhibition of uracil-DNA glycosylase increases SCEs in BrdU-treated and visible light-irradiated cells. Exp Cell Res. 1985; 161(1):172–80. [PubMed: 4054229]

[189]. Dillehay LE, Thompson LH, Minkler JL, Carrano AV. The relationship between sister-chromatid exchange and perturbations in DNA replication in mutant EM9 and normal CHO cells. Mutat Res. 1983; 109(2):283–96. [PubMed: 6843572]

[190]. Ray JH, Louie E, German J. Different mutations are responsible for the elevated sister-chromatid exchange frequencies characteristic of Bloom's syndrome and hamster EM9 cells. Proc Natl Acad Sci U S A. 1987; 84(8):2368–71. [PubMed: 3470802]

[191]. Sonoda E, Sasaki MS, Morrison C, Yamaguchi-Iwai Y, Takata M, Takeda S. Sister chromatid exchanges are mediated by homologous recombination in vertebrate cells. Mol Cell Biol. 1999; 19(7):5166–9. [PubMed: 10373565]

[192]. Christie NT, Cantoni O, Evans RM, Meyn RE, Costa M. Use of mammalian DNA repair-deficient mutants to assess the effects of toxic metal compounds on DNA. Biochem Pharmacol. 1984; 33(10):1661–70. [PubMed: 6233980]

[193]. Cantoni O, Murray D, Meyn RE. Induction and repair of DNA single-strand breaks in EM9 mutant CHO cells treated with hydrogen peroxide. Chem Biol Interact. 1987; 63(1):29–38. [PubMed: 3115605]

[194]. Churchill ME, Peak JG, Peak MJ. Correlation between cell survival and DNA single-strand break repair proficiency in the Chinese hamster ovary cell lines AA8 and EM9 irradiated with 365-nm ultraviolet-A radiation. Photochem Photobiol. 1991; 53(2):229–36. [PubMed: 2011627]

[195]. Schwartz JL, Giovanazzi S, Weichselbaum RR. Recovery from sublethal and potentially lethal damage in an X-ray-sensitive CHO cell. Radiat Res. 1987; 111(1):58–67. [PubMed: 3602355]

[196]. Cappelli E, Taylor R, Cevasco M, Abbondandolo A, Caldecott K, Frosina G. Involvement of XRCC1 and DNA ligase III gene products in DNA base excision repair. J Biol Chem. 1997; 272(38):23970–5. [PubMed: 9295348]

[197]. Brem R, Hall J. XRCC1 is required for DNA single-strand break repair in human cells. Nucleic Acids Res. 2005; 33(8):2512–20. [PubMed: 15867196]

[198]. Fan J, Wilson PF, Wong HK, Urbin SS, Thompson LH, Wilson DM 3rd. XRCC1 down-regulation in human cells leads to DNA-damaging agent hypersensitivity, elevated sister chromatid exchange, and reduced survival of BRCA2 mutant cells. Environ Mol Mutagen. 2007; 48(6):491–500. [PubMed: 17603793]

[199]. Pines A, Vrouwe MG, Marteijn JA, Typas D, Luijsterburg MS, Cansoy M, Hensbergen P, Deelder A, de Groot A, Matsumoto S, Sugasawa K, Thoma N, Vermeulen W, Vrieling H, Mullenders L. PARP1 promotes nucleotide excision repair through DDB2 stabilization and recruitment of ALC1. J Cell Biol. 2012; 199(2):235–49. [PubMed: 23045548]

[200]. Robu M, Shah RG, Petitclerc N, Brind'Amour J, Kandan-Kulangara F, Shah GM. Role of poly(ADP-ribose) polymerase-1 in the removal of UV-induced DNA lesions by nucleotide excision repair. Proc Natl Acad Sci U S A. 2013; 110(5):1658–63. [PubMed: 23319653]

[201]. Fischer JM, Popp O, Gebhard D, Veith S, Fischbach A, Beneke S, Leitenstorfer A, Bergemann J, Scheffner M, Ferrando-May E, Mangerich A, Burkle A. Poly(ADP-ribose)-mediated interplay of XPA and PARP1 leads to reciprocal regulation of protein function. FEBS J. 2014; 281(16): 3625–41. [PubMed: 24953096]

[202]. Purohit NK, Robu M, Shah RG, Geacintov NE, Shah GM. Characterization of the interactions of PARP-1 with UV-damaged DNA in vivo and in vitro. Sci Rep. 6(2016):19020. [PubMed: 26753915]

[203]. Moser J, Kool H, Giakzidis I, Caldecott K, Mullenders LH, Fousteri MI. Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase III alpha in a cell-cycle-specific manner. Mol Cell. 2007; 27(2):311–23. [PubMed: 17643379]

[204]. vanAnkeren SC, Murray D, Meyn RE. Induction and rejoining of gamma-ray-induced DNA single- and double-strand breaks in Chinese hamster AA8 cells and in two radiosensitive clones. Radiat Res. 1988; 116(3):511–25. [PubMed: 3060896]

[205]. Thompson LH, West MG. XRCC1 keeps DNA from getting stranded. Mutat Res. 2000; 459(1): 1–18. [PubMed: 10677679]

[206]. Caldecott KW. XRCC1 and DNA strand break repair. DNA Repair (Amst). 2003; 2(9):955–69. [PubMed: 12967653]

[207]. Audebert M, Salles B, Calsou P. Involvement of poly(ADP-ribose) polymerase-1 and XRCC1/DNA ligase III in an alternative route for DNA double-strand breaks rejoining. J Biol Chem. 2004; 279(53):55117–26. [PubMed: 15498778]

[208]. Charbonnel C, Gallego ME, White CI. Xrcc1-dependent and Ku-dependent DNA double-strand break repair kinetics in Arabidopsis plants. Plant J. 2010; 64(2):280–90. [PubMed: 21070408]

[209]. Ahmed EA, de Boer P, Philippens ME, Kal HB, de Rooij DG. Parp1-XRCC1 and the repair of DNA double strand breaks in mouse round spermatids. Mutat Res. 2010; 683(1-2):84–90. [PubMed: 19887075]

[210]. Saribasak H, Maul RW, Cao Z, McClure RL, Yang W, McNeill DR, Wilson DM 3rd, Gearhart PJ. XRCC1 suppresses somatic hypermutation and promotes alternative nonhomologous end joining in Igh genes. J Exp Med. 2011; 208(11):2209–16. [PubMed: 21967769]

[211]. Della-Maria J, Zhou Y, Tsai MS, Kuhnlein J, Carney JP, Paull TT, Tomkinson AE. Human Mre11/human Rad50/Nbs1 and DNA ligase IIIalpha/XRCC1 protein complexes act together in an alternative nonhomologous end joining pathway. J Biol Chem. 2011; 286(39):33845–53. [PubMed: 21816818]

[212]. Sharma S, Javadekar SM, Pandey M, Srivastava M, Kumari R, Raghavan SC. Homology and enzymatic requirements of microhomology-dependent alternative end joining. Cell Death Dis. 2015; 6:e1697. [PubMed: 25789972]

[213]. Tebbs RS, Flannery ML, Meneses JJ, Hartmann A, Tucker JD, Thompson LH, Cleaver JE, Pedersen RA. Requirement for the Xrcc1 DNA base excision repair gene during early mouse development. Dev Biol. 1999; 208(2):513–29. [PubMed: 10191063]

[214]. McNeill DR, Lin PC, Miller MG, Pistell PJ, de Souza-Pinto NC, Fishbein KW, Spencer RG, Liu Y, Pettan-Brewer C, Ladiges WC, Wilson DM 3rd. XRCC1 haploinsufficiency in mice has little effect on aging, but adversely modifies exposure-dependent susceptibility. Nucleic Acids Res. 2011; 39(18):7992–8004. [PubMed: 21737425]

[215]. Tebbs RS, Thompson LH, Cleaver JE. Rescue of Xrcc1 knockout mouse embryo lethality by transgene-complementation. DNA Repair (Amst). 2003; 2(12):1405–17. [PubMed: 14642568]

[216]. Ladiges WC. Mouse models of XRCC1 DNA repair polymorphisms and cancer. Oncogene. 2006; 25(11):1612–9. [PubMed: 16550161]

[217]. Kulkarni A, McNeill DR, Gleichmann M, Mattson MP, Wilson DM 3rd. XRCC1 protects against the lethality of induced oxidative DNA damage in nondividing neural cells. Nucleic Acids Res. 2008; 36(15):5111–21. [PubMed: 18682529]

[218]. Ghosh S, Canugovi C, Yoon JS, Wilson DM 3rd, Croteau DL, Mattson MP, Bohr VA. Partial loss of the DNA repair scaffolding protein, Xrcc1, results in increased brain damage and reduced recovery from ischemic stroke in mice. Neurobiol Aging. 2015; 36(7):2319–30. [PubMed: 25971543]

[219]. Mani RS, Karimi-Busheri F, Fanta M, Caldecott KW, Cass CE, Weinfeld M. Biophysical characterization of human XRCC1 and its binding to damaged and undamaged DNA. Biochemistry. 2004; 43(51):16505–14. [PubMed: 15610045]

[220]. Wong HK, Wilson DM 3rd. XRCC1 and DNA polymerase beta interaction contributes to cellular alkylating-agent resistance and single-strand break repair. J Cell Biochem. 2005; 95(4): 794–804. [PubMed: 15838887]

[221]. Caldecott KW, Aoufouchi S, Johnson P, Shall S. XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular 'nick-sensor' in vitro. Nucleic Acids Res. 1996; 24(22):4387–94. [PubMed: 8948628]

[222]. Kim IK, Stegeman RA, Brosey CA, Ellenberger T. A quantitative assay reveals ligand specificity of the DNA scaffold repair protein XRCC1 and efficient disassembly of complexes of XRCC1 and the poly(ADP-ribose) polymerase 1 by poly(ADP-ribose) glycohydrolase. J Biol Chem. 2015; 290(6):3775–83. [PubMed: 25477519]

[223]. Schreiber V, Ame JC, Dolle P, Schultz I, Rinaldi B, Fraulob V, Menissier-de Murcia J, de Murcia G. Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. J Biol Chem. 2002; 277(25):23028–36. [PubMed: 11948190]

[224]. Breslin C, Hornyak P, Ridley A, Rulten SL, Hanzlikova H, Oliver AW, Caldecott KW. The XRCC1 phosphate-binding pocket binds poly (ADP-ribose) and is required for XRCC1 function. Nucleic Acids Res. 2015; 43(14):6934–44. [PubMed: 26130715]

[225]. El-Khamisy SF, Masutani M, Suzuki H, Caldecott KW. A requirement for PARP-1 for the assembly or stability of XRCC1 nuclear foci at sites of oxidative DNA damage. Nucleic Acids Res. 2003; 31(19):5526–33. [PubMed: 14500814]

[226]. Okano S, Lan L, Caldecott KW, Mori T, Yasui A. Spatial and temporal cellular responses to single-strand breaks in human cells. Mol Cell Biol. 2003; 23(11):3974–81. [PubMed: 12748298]

[227]. Horton JK, Stefanick DF, Gassman NR, Williams JG, Gabel SA, Cuneo MJ, Prasad R, Kedar PS, Derose EF, Hou EW, London RE, Wilson SH. Preventing oxidation of cellular XRCC1 affects PARP-mediated DNA damage responses. DNA Repair (Amst). 2013; 12(9):774–85. [PubMed: 23871146]

[228]. Ame JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, Muller S, Hoger T, Menissierde Murcia J, de Murcia G. PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. J Biol Chem. 1999; 274(25):17860–8. [PubMed: 10364231]

[229]. Berghammer H, Ebner M, Marksteiner R, Auer B. pADPRT-2: a novel mammalian polymerizing(ADP-ribosyl)transferase gene related to truncated pADPRT homologues in plants and Caenorhabditis elegans. FEBS Lett. 1999; 449(2-3):259–63. [PubMed: 10338144]

[230]. Mortusewicz O, Ame JC, Schreiber V, Leonhardt H. Feedback-regulated poly(ADP-ribosyl)ation by PARP-1 is required for rapid response to DNA damage in living cells. Nucleic Acids Res. 2007; 35(22):7665–75. [PubMed: 17982172]

[231]. Schreiber, V., M., R., Ame, JC., Dantzer, F., Meder, V., Spenlehauer, C., Stiegler, P., Nidergang, C., Sabatier, L., Favaudon, V., Menissier de Murcia, J., Murcia, G. de PARP-2, structure-function relationship. In: Burkle, A., editor. Poly(ADP-ribosyl)ation. Landes Bioscience; Austin, USA: 2004. p. 13-31.

[232]. Kutuzov MM, Khodyreva SN, Ame JC, Ilina ES, Sukhanova MV, Schreiber V, Lavrik OI. Interaction of PARP-2 with DNA structures mimicking DNA repair intermediates and consequences on activity of base excision repair proteins. Biochimie. 2013; 95(6):1208–15. [PubMed: 23357680]

[233]. Fisher AE, Hochegger H, Takeda S, Caldecott KW. Poly(ADP-ribose) polymerase 1 accelerates single-strand break repair in concert with poly(ADP-ribose) glycohydrolase. Mol Cell Biol. 2007; 27(15):5597–605. [PubMed: 17548475]

[234]. Yelamos J, Schreiber V, Dantzer F. Toward specific functions of poly(ADP-ribose) polymerase-2. Trends Mol Med. 2008; 14(4):169–78. [PubMed: 18353725]

[235]. Yelamos J, Farres J, Llacuna L, Ampurdanes C, Martin-Caballero J. PARP-1 and PARP-2: New players in tumour development. Am J Cancer Res. 2011; 1(3):328–346. [PubMed: 21968702]

[236]. Svilar D, Goellner EM, Almeida KH, Sobol RW. Base excision repair and lesion-dependent subpathways for repair of oxidative DNA damage. Antioxid Redox Signal. 2011; 14(12):2491–507. [PubMed: 20649466]

[237]. Almeida KH, Sobol RW. A unified view of base excision repair: lesion-dependent protein complexes regulated by post-translational modification. DNA Repair (Amst). 2007; 6(6):695–711. [PubMed: 17337257]

[238]. La Belle M, Linn S, Thompson LH. Apurinic/apyrimidinic endonuclease activities appear normal in the CHO-cell ethyl methanesulfonate-sensitive mutant, EM9. Mutat Res. 1984; 141(1): 41–4. [PubMed: 6482894]

[239]. Wong HK, Kim D, Hogue BA, McNeill DR, Wilson DM 3rd. DNA damage levels and biochemical repair capacities associated with XRCC1 deficiency. Biochemistry. 2005; 44(43): 14335–43. [PubMed: 16245950]

[240]. Sawaya MR, Pelletier H, Kumar A, Wilson SH, Kraut J. Crystal structure of rat DNA polymerase beta: evidence for a common polymerase mechanism. Science. 1994; 264(5167): 1930–5. [PubMed: 7516581]

[241]. Prasad R, Beard WA, Strauss PR, Wilson SH. Human DNA polymerase beta deoxyribose phosphate lyase. Substrate specificity and catalytic mechanism. J Biol Chem. 1998; 273(24): 15263–70. [PubMed: 9614142]

[242]. Marintchev A, Robertson A, Dimitriadis EK, Prasad R, Wilson SH, Mullen GP. Domain specific interaction in the XRCC1-DNA polymerase beta complex. Nucleic Acids Res. 2000; 28(10): 2049–59. [PubMed: 10773072]

[243]. Gryk MR, Marintchev A, Maciejewski MW, Robertson A, Wilson SH, Mullen GP. Mapping of the interaction interface of DNA polymerase beta with XRCC1. Structure. 2002; 10(12):1709–20. [PubMed: 12467578]

[244]. Cuneo MJ, London RE. Oxidation state of the XRCC1 N-terminal domain regulates DNA polymerase beta binding affinity. Proc Natl Acad Sci U S A. 2010; 107(15):6805–10. [PubMed: 20351257]

[245]. Hanssen-Bauer A, Solvang-Garten K, Sundheim O, Pena-Diaz J, Andersen S, Slupphaug G, Krokan HE, Wilson DM 3rd, Akbari M, Otterlei M. XRCC1 coordinates disparate responses and multiprotein repair complexes depending on the nature and context of the DNA damage. Environ Mol Mutagen. 2011; 52(8):623–35. [PubMed: 21786338]

[246]. Fang Q, Inanc B, Schamus S, Wang XH, Wei L, Brown AR, Svilar D, Sugrue KF, Goellner EM, Zeng X, Yates NA, Lan L, Vens C, Sobol RW. HSP90 regulates DNA repair via the interaction between XRCC1 and DNA polymerase beta. Nat Commun. 2014; 5:5513. [PubMed: 25423885]

[247]. Horton JK, Gassman NR, Dunigan BD, Stefanick DF, Wilson SH. DNA polymerase beta-dependent cell survival independent of XRCC1 expression. DNA Repair (Amst). 2015; 26:23–9. [PubMed: 25541391]

[248]. Lakshmipathy U, Campbell C. The human DNA ligase III gene encodes nuclear and mitochondrial proteins. Mol Cell Biol. 1999; 19(5):3869–76. [PubMed: 10207110]

[249]. Tomkinson AE, Sallmyr A. Structure and function of the DNA ligases encoded by the mammalian LIG3 gene. Gene. 2013; 531(2):150–7. [PubMed: 24013086]

[250]. Mackey ZB, Ramos W, Levin DS, Walter CA, McCarrey JR, Tomkinson AE. An alternative splicing event which occurs in mouse pachytene spermatocytes generates a form of DNA ligase III with distinct biochemical properties that may function in meiotic recombination. Mol Cell Biol. 1997; 17(2):989–98. [PubMed: 9001252]

[251]. Caldecott KW, Tucker JD, Stanker LH, Thompson LH. Characterization of the XRCC1-DNA ligase III complex in vitro and its absence from mutant hamster cells. Nucleic Acids Res. 1995; 23(23):4836–43. [PubMed: 8532526]

[252]. Gao Y, Katyal S, Lee Y, Zhao J, Rehg JE, Russell HR, McKinnon PJ. DNA ligase III is critical for mtDNA integrity but not Xrcc1-mediated nuclear DNA repair. Nature. 2011; 471(7337):240–4. [PubMed: 21390131]

[253]. Taylor RM, Moore DJ, Whitehouse J, Johnson P, Caldecott KW. A cell cycle-specific requirement for the XRCC1 BRCT II domain during mammalian DNA strand break repair. Mol Cell Biol. 2000; 20(2):735–40. [PubMed: 10611252]

[254]. Lakshmipathy U, Campbell C. Mitochondrial DNA ligase III function is independent of Xrcc1. Nucleic Acids Res. 2000; 28(20):3880–6. [PubMed: 11024166]

[255]. Simsek D, Furda A, Gao Y, Artus J, Brunet E, Hadjantonakis AK, Van Houten B, Shuman S, McKinnon PJ, Jasin M. Crucial role for DNA ligase III in mitochondria but not in Xrcc1-dependent repair. Nature. 2011; 471(7337):245–8. [PubMed: 21390132]

[256]. Wiederhold L, Leppard JB, Kedar P, Karimi-Busheri F, Rasouli-Nia A, Weinfeld M, Tomkinson AE, Izumi T, Prasad R, Wilson SH, Mitra S, Hazra TK. AP Endonuclease-Independent DNA Base Excision Repair in Human Cells. Mol Cell. 2004; 15(2):209–20. [PubMed: 15260972]

[257]. Cadet J, Loft S, Olinski R, Evans MD, Bialkowski K, Richard Wagner J, Dedon PC, Moller P, Greenberg MM, Cooke MS. Biologically relevant oxidants and terminology, classification and nomenclature of oxidatively generated damage to nucleobases and 2-deoxyribose in nucleic acids. Free Radic Res. 2012; 46(4):367–81. [PubMed: 22263561]

[258]. Weinfeld M, Mani RS, Abdou I, Aceytuno RD, Glover JN. Tidying up loose ends: the role of polynucleotide kinase/phosphatase in DNA strand break repair. Trends Biochem Sci. 2011; 36(5):262–71. [PubMed: 21353781]

[259]. Ali AA, Jukes RM, Pearl LH, Oliver AW. Specific recognition of a multiply phosphorylated motif in the DNA repair scaffold XRCC1 by the FHA domain of human PNK. Nucleic Acids Res. 2009; 37(5):1701–12. [PubMed: 19155274]

[260]. Lu M, Mani RS, Karimi-Busheri F, Fanta M, Wang H, Litchfeld DW, Weinfeld M. Independent mechanisms of stimulation of polynucleotide kinase/phosphatase by phosphorylated and nonphosphorylated XRCC1. Nucleic Acids Res. 2010; 38(2):510–21. [PubMed: 19910369]

[261]. Parsons JL, Dianova II, Boswell E, Weinfeld M, Dianov GL. End-damage-specific proteins facilitate recruitment or stability of X-ray cross-complementing protein 1 at the sites of DNA single-strand break repair. FEBS J. 2005; 272(22):5753–63. [PubMed: 16279940]

[262]. Mani RS, Fanta M, Karimi-Busheri F, Silver E, Virgen CA, Caldecott KW, Cass CE, Weinfeld M. XRCC1 stimulates polynucleotide kinase by enhancing its damage discrimination and displacement from DNA repair intermediates. J Biol Chem. 2007; 282(38):28004–13. [PubMed: 17650498]

[263]. Lan L, Nakajima S, Oohata Y, Takao M, Okano S, Masutani M, Wilson SH, Yasui A. In situ analysis of repair processes for oxidative DNA damage in mammalian cells. Proc Natl Acad Sci U S A. 2004; 101(38):13738–43. [PubMed: 15365186]

[264]. Parsons JL, Tait PS, Finch D, Dianova II, Allinson SL, Dianov GL. CHIP-mediated degradation and DNA damage-dependent stabilization regulate base excision repair proteins. Mol Cell. 2008; 29(4):477–87. [PubMed: 18313385]

[265]. Moreira MC, Barbot C, Tachi N, Kozuka N, Uchida E, Gibson T, Mendonca P, Costa M, Barros J, Yanagisawa T, Watanabe M, Ikeda Y, Aoki M, Nagata T, Coutinho P, Sequeiros J, Koenig M. The gene mutated in ataxia-ocular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. Nature Genetics. 2001; 29(2):189–93. [PubMed: 11586300]

[266]. Ahel I, Rass U, El-Khamisy SF, Katyal S, Clements PM, McKinnon PJ, Caldecott KW, West SC. The neurodegenerative disease protein aprataxin resolves abortive DNA ligation intermediates. Nature. 2006; 443(7112):713–6. [PubMed: 16964241]

[267]. Caldecott KW. DNA single-strand break repair and spinocerebellar ataxia. Cell. 2003; 112(1):7–10. [PubMed: 12526788]

[268]. Sano Y, Date H, Igarashi S, Onodera O, Oyake M, Takahashi T, Hayashi S, Morimatsu M, Takahashi H, Makifuchi T, Fukuhara N, Tsuji S. Aprataxin, the causative protein for EAOH is a nuclear protein with a potential role as a DNA repair protein. Annals of Neurology. 2004; 55(2): 241–9. [PubMed: 14755728]

[269]. Hirano M, Yamamoto A, Mori T, Lan L, Iwamoto TA, Aoki M, Shimada K, Furiya Y, Kariya S, Asai H, Yasui A, Nishiwaki T, Imoto K, Kobayashi N, Kiriyama T, Nagata T, Konishi N, Itoyama Y, Ueno S. DNA single-strand break repair is impaired in aprataxin-related ataxia. Annals of Neurology. 2007; 61(2):162–74. [PubMed: 17315206]

[270]. Clements PM, Breslin C, Deeks ED, Byrd PJ, Ju L, Bieganowski P, Brenner C, Moreira MC, Taylor AM, Caldecott KW. The ataxia-oculomotor apraxia 1 gene product has a role distinct from ATM and interacts with the DNA strand break repair proteins XRCC1 and XRCC4. DNA Repair (Amst). 2004; 3(11):1493–502. [PubMed: 15380105]

[271]. Date H, Igarashi S, Sano Y, Takahashi T, Takahashi T, Takano H, Tsuji S, Nishizawa M, Onodera O. The FHA domain of aprataxin interacts with the C-terminal region of XRCC1. Biochem Biophys Res Commun. 2004; 325(4):1279–85. [PubMed: 15555565]

[272]. Luo H, Chan DW, Yang T, Rodriguez M, Chen BP, Leng M, Mu JJ, Chen D, Songyang Z, Wang Y, Qin J. A new XRCC1-containing complex and its role in cellular survival of methyl methanesulfonate treatment. Mol Cell Biol. 2004; 24(19):8356–65. [PubMed: 15367657]

[273]. Gueven N, Becherel OJ, Kijas AW, Chen P, Howe O, Rudolph JH, Gatti R, Date H, Onodera O, Taucher-Scholz G, Lavin MF. Aprataxin, a novel protein that protects against genotoxic stress. Human Molecular Genetics. 2004; 13(10):1081–93. [PubMed: 15044383]

[274]. Mosesso P, Piane M, Palitti F, Pepe G, Penna S, Chessa L. The novel human gene aprataxin is directly involved in DNA single-strand-break repair. Cell Mol Life Sci. 2005; 62(4):485–91. [PubMed: 15719174]

[275]. Iles N, Rulten S, El-Khamisy SF, Caldecott KW. APLF (C2orf13) is a novel human protein involved in the cellular response to chromosomal DNA strand breaks. Mol Cell Biol. 2007; 27(10):3793–803. [PubMed: 17353262]

[276]. Kanno S, Kuzuoka H, Sasao S, Hong Z, Lan L, Nakajima S, Yasui A. A novel human AP endonuclease with conserved zinc-finger-like motifs involved in DNA strand break responses. EMBO J. 2007; 26(8):2094–103. [PubMed: 17396150]

[277]. Macrae CJ, McCulloch RD, Ylanko J, Durocher D, Koch CA. APLF (C2orf13) facilitates nonhomologous end-joining and undergoes ATM-dependent hyperphosphorylation following ionizing radiation. DNA Repair (Amst). 2008; 7(2):292–302. [PubMed: 18077224]

[278]. Li S, Kanno S, Watanabe R, Ogiwara H, Kohno T, Watanabe G, Yasui A, Lieber MR. Polynucleotide kinase and aprataxin-like forkhead-associated protein (PALF) acts as both a single-stranded DNA endonuclease and a single-stranded DNA 3' exonuclease and can participate in DNA end joining in a biochemical system. J Biol Chem. 2011; 286(42):36368–77. [PubMed: 21885877]

[279]. Ahel I, Ahel D, Matsusaka T, Clark AJ, Pines J, Boulton SJ, West SC. Poly(ADP-ribose)-binding zinc finger motifs in DNA repair/checkpoint proteins. Nature. 2008; 451(7174):81–5. [PubMed: 18172500]

[280]. Pommier Y. Topoisomerase I inhibitors: camptothecins and beyond. Nat Rev Cancer. 2006; 6(10):789–802. [PubMed: 16990856]

[281]. Hsiang YH, Lihou MG, Liu LF. Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. Cancer Res. 1989; 49(18):5077–82. [PubMed: 2548710]

[282]. Wu J, Liu LF. Processing of topoisomerase I cleavable complexes into DNA damage by transcription. Nucleic Acids Res. 1997; 25(21):4181–6. [PubMed: 9336444]

[283]. Yang SW, Burgin AB Jr. Huizenga BN, Robertson CA, Yao KC, Nash HA. A eukaryotic enzyme that can disjoin dead-end covalent complexes between DNA and type I topoisomerases. Proc Natl Acad Sci U S A. 1996; 93(21):11534–9. [PubMed: 8876170]

[284]. Davies DR, Interthal H, Champoux JJ, Hol WG. The crystal structure of human tyrosyl-DNA phosphodiesterase, Tdp1. Structure. 2002; 10(2):237–48. [PubMed: 11839309]

[285]. Pommier Y, Huang SY, Gao R, Das BB, Murai J, Marchand C. Tyrosyl-DNA-phosphodiesterases (TDP1 and TDP2). DNA Repair (Amst). 2014; 19:114–29. [PubMed: 24856239]

[286]. Lebedeva NA, Rechkunova NI, Lavrik OI. AP-site cleavage activity of tyrosyl-DNA phosphodiesterase 1. FEBS Lett. 2011; 585(4):683–6. [PubMed: 21276450]

[287]. Lebedeva NA, Rechkunova NI, Ishchenko AA, Saparbaev M, Lavrik OI. The mechanism of human tyrosyl-DNA phosphodiesterase 1 in the cleavage of AP site and its synthetic analogs. DNA Repair (Amst). 2013; 12(12):1037–42. [PubMed: 24183900]

[288]. Barrows LR, Holden JA, Anderson M, D'Arpa P. The CHO XRCC1 mutant, EM9, deficient in DNA ligase III activity, exhibits hypersensitivity to camptothecin independent of DNA replication. Mutat Res. 1998; 408(2):103–10. [PubMed: 9739812]

[289]. Das BB, Antony S, Gupta S, Dexheimer TS, Redon CE, Garfield S, Shiloh Y, Pommier Y. Optimal function of the DNA repair enzyme TDP1 requires its phosphorylation by ATM and/or DNA-PK. EMBO J. 2009; 28(23):3667–80. [PubMed: 19851285]

[290]. Plo I, Liao ZY, Barcelo JM, Kohlhagen G, Caldecott KW, Weinfeld M, Pommier Y. Association of XRCC1 and tyrosyl DNA phosphodiesterase (Tdp1) for the repair of topoisomerase I-mediated DNA lesions. DNA Repair (Amst). 2003; 2(10):1087–100. [PubMed: 13679147]

[291]. El-Khamisy SF, Saifi GM, Weinfeld M, Johansson F, Helleday T, Lupski JR, Caldecott KW. Defective DNA single-strand break repair in spinocerebellar ataxia with axonal neuropathy-1. Nature. 2005; 434(7029):108–13. [PubMed: 15744309]

[292]. Brenerman BM, Illuzzi JL, Wilson DM 3rd. Base excision repair capacity in informing healthspan. Carcinogenesis. 2014; 35(12):2643–52. [PubMed: 25355293]

[293]. Chow HM, Herrup K. Genomic integrity and the ageing brain. Nat Rev Neurosci. 2015; 16(11): 672–84. [PubMed: 26462757]

[294]. Sugo N, Aratani Y, Nagashima Y, Kubota Y, Koyama H. Neonatal lethality with abnormal neurogenesis in mice deficient in DNA polymerase beta. EMBO J. 2000; 19(6):1397–404. [PubMed: 10716939]

[295]. Sykora P, Misiak M, Wang Y, Ghosh S, Leandro GS, Liu D, Tian J, Baptiste BA, Cong WN, Brenerman BM, Fang E, Becker KG, Hamilton RJ, Chigurupati S, Zhang Y, Egan JM, Croteau DL, Wilson DM 3rd, Mattson MP, Bohr VA. DNA polymerase beta deficiency leads to

neurodegeneration and exacerbates Alzheimer disease phenotypes. Nucleic Acids Res. 2015; 43(2):943–59. [PubMed: 25552414]

[296]. Lee Y, Katyal S, Li Y, El-Khamisy SF, Russell HR, Caldecott KW, McKinnon PJ. The genesis of cerebellar interneurons and the prevention of neural DNA damage require XRCC1. Nat Neurosci. 2009; 12(8):973–80. [PubMed: 19633665]

[297]. McKinnon PJ. DNA repair deficiency and neurological disease. Nat Rev Neurosci. 2009; 10(2): 100–12. [PubMed: 19145234]

[298]. Rulten SL, Caldecott KW. DNA strand break repair and neurodegeneration. DNA Repair (Amst). 2013; 12(8):558–67. [PubMed: 23712058]

[299]. Date H, Onodera O, Tanaka H, Iwabuchi K, Uekawa K, Igarashi S, Koike R, Hiroi T, Yuasa T, Awaya Y, Sakai T, Takahashi T, Nagatomo H, Sekijima Y, Kawachi I, Takiyama Y, Nishizawa M, Fukuhara N, Saito K, Sugano S, Tsuji S. Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. Nature Genetics. 2001; 29(2):184–8. [PubMed: 11586299]

[300]. Bras J, Alonso I, Barbot C, Costa MM, Darwent L, Orme T, Sequeiros J, Hardy J, Coutinho P, Guerreiro R. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. Am J Hum Genet. 2015; 96(3):474–9. [PubMed: 25728773]

[301]. Shen J, Gilmore EC, Marshall CA, Haddadin M, Reynolds JJ, Eyaid W, Bodell A, Barry B, Gleason D, Allen K, Ganesh VS, Chang BS, Grix A, Hill RS, Topcu M, Caldecott KW, Barkovich AJ, Walsh CA. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. Nat Genet. 2010; 42(3):245–9. [PubMed: 20118933]

[302]. Poulton C, Oegema R, Heijsman D, Hoogeboom J, Schot R, Stroink H, Willemsen MA, Verheijen FW, van de Spek P, Kremer A, Mancini GM. Progressive cerebellar atrophy and polyneuropathy: expanding the spectrum of PNKP mutations. Neurogenetics. 2013; 14(1):43–51. [PubMed: 23224214]

[303]. Shimada M, Dumitrache LC, Russell HR, McKinnon PJ. Polynucleotide kinase-phosphatase enables neurogenesis via multiple DNA repair pathways to maintain genome stability. EMBO J. 2015; 34(19):2465–80. [PubMed: 26290337]

[304]. Takashima H, Boerkoel CF, John J, Saifi GM, Salih MA, Armstrong D, Mao Y, Quiocho FA, Roa BB, Nakagawa M, Stockton DW, Lupski JR. Mutation of TDP1, encoding a topoisomerase I-dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. Nat Genet. 2002; 32(2):267–72. [PubMed: 12244316]

[305]. Iyama T, Wilson DM 3rd. DNA repair mechanisms in dividing and non-dividing cells. DNA Repair (Amst). 2013; 12(8):620–36. [PubMed: 23684800]

[306]. Sykora P, Wilson DM 3rd, Bohr VA. Repair of persistent strand breaks in the mitochondrial genome. Mech Ageing Dev. 2012; 133(4):169–75. [PubMed: 22138376]

[307]. Canugovi C, Misiak M, Ferrarelli LK, Croteau DL, Bohr VA. The role of DNA repair in brain related disease pathology. DNA Repair (Amst). 2013; 12(8):578–87. [PubMed: 23721970]

[308]. Koberle B, Koch B, Fischer BM, Hartwig A. Single nucleotide polymorphisms in DNA repair genes and putative cancer risk. Arch Toxicol. 2016

Highlights

- Overview of the types and consequences of prominent forms of endogenous DNA damage
- Detailed description of the structure, biochemistry and biology of PARP1 and XRCC1
- Comprehensive summary of the molecular choreography of single strand break repair
- Introduction of the link between defects in single strand break repair and neurological disease

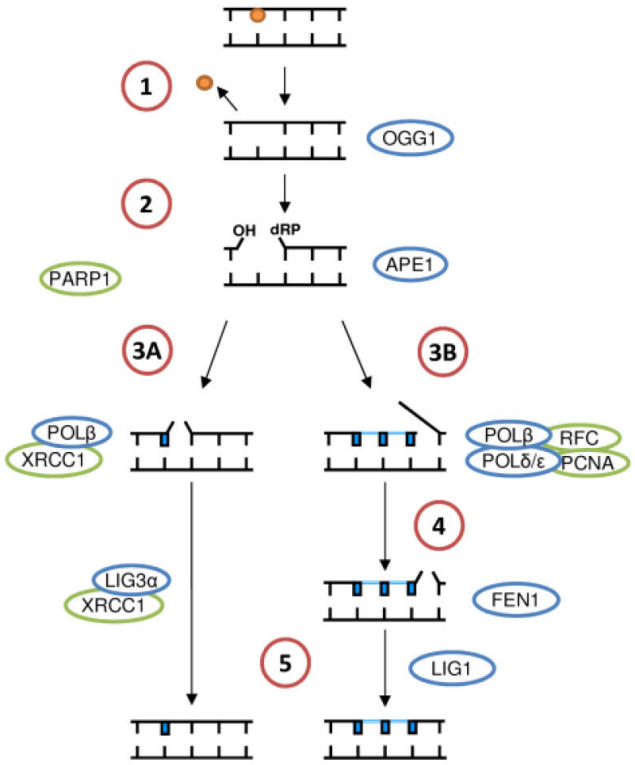


Figure 1.
Overview of BER.

1. BER is initiated by substrate-specific recognition and excision of a damaged base by a DNA glycosylase (e.g. OGG1), creating an abasic site. 2. APE1 incises the DNA backbone at the AP site, generating a strand break with 3′-hydroxyl and 5′-deoxyribosephosphate (dRP) flanking groups. Bifunctional glycosylases with AP lyase activity can also cleave the abasic site, generating a 3′-α,β-unsaturated aldehyde (or 3′-phosphate) and 5′-phosphate termini; blocking termini require additional processing (see text). 3. The excised nucleotide is replaced by DNA polymerase repair synthesis. A. Short-patch repair synthesis by POLβ involves the incorporation of a single nucleotide. B. In the long-patch pathway, a DNA polymerase (δ, ε or β) incorporates 2-12 nucleotides by strand displacement synthesis in conjunction with the sliding clamp PCNA, creating a flap intermediate that is removed by FEN1 (4). 5. The DNA nick is sealed by a ligase, namely DNA LIG3α (likely in complex with XRCC1) or LIG1. PARP1 preumably participates in the response when DNA damage or repair intermediates are not engaged by the classic BER machinery.

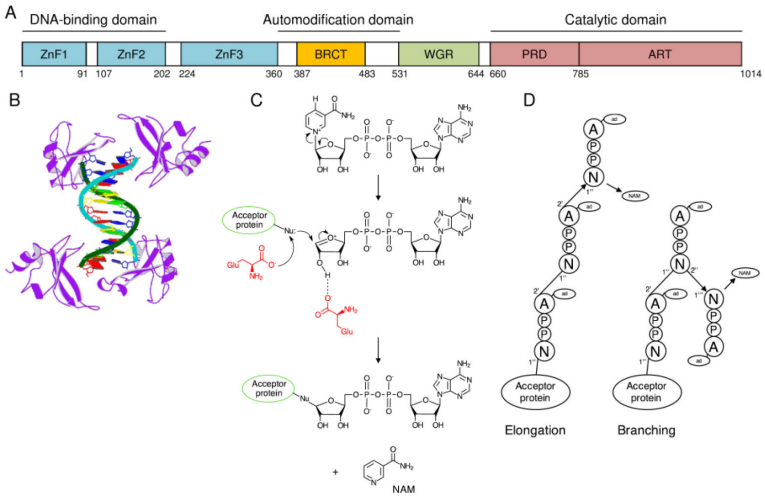


Figure 2.
PARP1.

A. PARP1 domain architecture. ZnF1-3: 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.

B. Crystal structure of PARP1 DBD in complex with DNA (PDB ID 4AV1) [79].

C. Schematic of ADP-ribosylation as catalyzed by PARP1, in which an ADP-ribose molecule is transferred from NAD^+ to an acceptor protein with the release of nicotinamide (NAM). Red structures represent critical residues of the PARP1 active site. Nu: acceptor protein nucleophile.

D. Elongation and branching reactions use the same chemistry, but vary in the orientation of the riboses. Elongation involves a $1'' \rightarrow 2'$ ribose-ribose (A-ribose) bond. Branching (every ~20 ADP-ribose units) involves a $1''' \rightarrow 2'$ ribose-ribose glycosidic (N-ribose) bond.

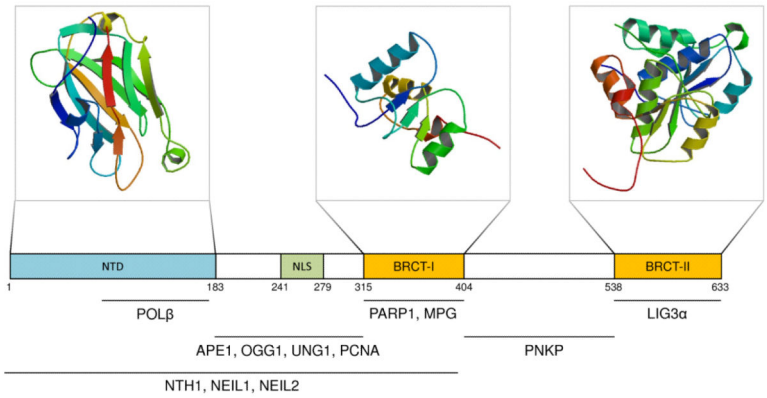


Figure 3.
XRCC1.

XRCC1 domain architecture with crystal structures of the N-terminal domain (NTD; PDB ID 1XNA [166]), BRCT-I (PDB ID 1CDZ [165]) and BRCT-II (PDB ID 3PC6 [167]). Also indicated are sites of interaction with other BER and SSBR proteins; see text for abbreviations. NLS = nuclear localization sequence.

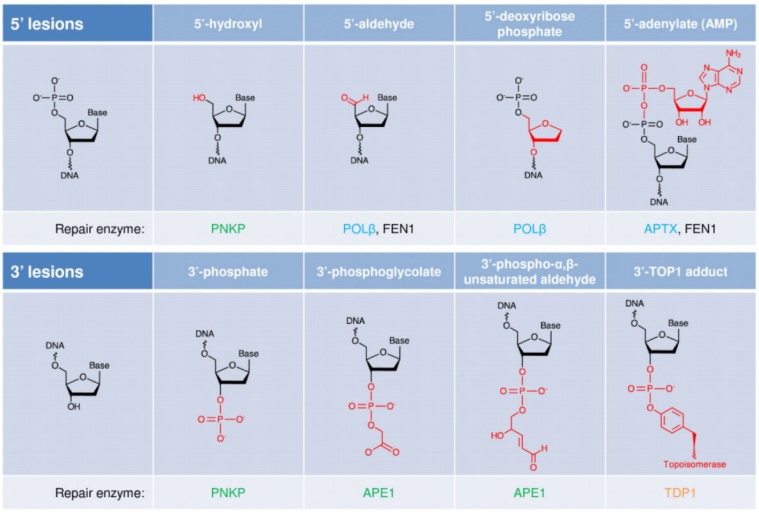


Figure 4.

Obstructive 5′ and 3′ strand break termini and the repair enzymes required for resolution. PARP1 and XRCC1 regulate the stability, complex assembly and coordination, and/or enzymatic activity of many of these repair factors as described in the text. Enzymes in green are known to interact with XRCC1, enzymes in orange are known to interact with both XRCC1 and PARP1, and enzymes in blue are known to interact with XRCC1 and possess a prototypical PAR binding site that may mediate an interaction with PARP1. PNKP: polynucleotide kinase 3′-phosphatase; POLβ: DNA polymerase β; FEN1: flap endonuclease 1; APTX: aprataxin; APE1: apurinic/apyrimidinic endonuclease 1; TDP1: tyrosyl DNA phosphodiesterase 1.

Table 1

Endogenous DNA damage types and associated lesions, their potential consequences, rates of formation, and major associated repair mechanism.

Damage type	Lesion	Potential consequences if unrepaired	Rate (per cell per day)	Major repair enzyme
Depurination/depyrimidation (spontaneous, glycosylase-mediated)	Abasic site	Mutagenic bypass, replication fork stalling, conversion to DSB	~10000	APE1
Cytosine deamination	Uracil (U:G)	Mutagenic base mispairing (C→T)	400	UNG, SMUG1, TDG
5-Methylcytosine deamination	Thymine (T:G)	Mutagenic base mispairing (C→T)	30	TDG, MBD4
Methylation	7-methylguanine	Tolerance, abasic site formation, ring-opening to FaPy-G	4000	MPG
	3-methyladenine	Replication stalling, chromosomal instability	600	MPG
Nitrosamine alkylation	O^6-methylguanine	Mutagenic base mispairing (G→A)	~200	MGMT
ROS attack, abortive TOP1 activity, etc.	SSB	Replication fork collapse, conversion to DSB	~10000	SSBR
Base oxidation	8-oxo-G	Mutagenic base mispairing (G→T)	~1000	OGG1
	Thymine glycol	Mutagenic base mispairing (T→C)	~500	NTH1

APE1: apurinic/apyrimidinic endonuclease 1; TDG: thymine-DNA glycosylase; UNG: uracil-DNA glycosylase; SMUG1: single strand selective monofunctional uracil DNA glycosylase 1; MBD4: methyl-CpG-binding domain protein 4, AAG: alkyladenine-DNA glycosylase; MPG: N-methylpurine-DNA glycosylase; MGMT: O^6-methylguanine-DNA methyltransferase; SSBR: single strand break repair; OGG1: oxoguanine glycosylase; 8-oxo-G: 8-oxo-7,8-dihydroguanosine; FaPy-G: 2,6-diamino-4-hydroxy-5-formamidopyrimidine; DSB: double strand break.