We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Coordination of DNA Base Excision Repair by Protein-Protein Interactions

Nina Moor and Olga Lavrik

Abstract

The system of base excision repair (BER) evolved to correct the most abundant DNA damages in mammalian cells is the most essential for maintaining the genome integrity. The multistep BER process involves several enzymes and protein factors functioning in a coordinated fashion that ensures the repair efficiency. The coordination is facilitated by the formation of protein complexes stabilized via either direct or indirect DNA-mediated interactions. This review focuses on direct interactions of proteins participating in BER with each other and with noncanonical factors found recently to modulate the efficiency of BER. All the known partners of main BER participants, the sites responsible for their interaction, and the characteristics of protein-protein affinity are summarized. Well-documented evidences of how DNA intermediates and posttranslational modifications of proteins modulate protein-protein interactions are presented. The available data allow to suggest that the multiprotein complexes are assembled with the involvement of a scaffold protein XRCC1 and poly(ADP-ribose) polymerase 1, a key regulator of the BER process, irrespective of the DNA damage; the composition and the structure of the complexes are dynamically changed depending on the DNA damage, its chromatin environment, and the step of BER process.

Keywords: base excision repair, protein-protein interactions, noncanonical factors, posttranslational modifications of proteins, coordination of DNA repair

1. Introduction

Many forms of DNA damage are generated due to permanent action of endogenous and exogenous factors. In order to maintain genome integrity, cells have evolved several specific pathways to repair DNA lesions. Base excision repair (BER), which ensures correction of the most abundant damages—modified nitrogenous bases and apurinic/apyrimidinic (AP) sites—is critically important for survival of human cells [1–3]. Enzyme and protein factors of BER also participate in the repair of DNA single-strand breaks (SSBs) considered as a separate pathway of the BER system [4, 5]. The other repair systems (**Figure 1**) deal with bulky nucleobase lesions (NER), DNA double-strand breaks (HR; NHEJ), and mismatched bases (MMR). Impaired DNA repair is associated with embryonic lethality, rapid aging, and a variety of severe human hereditary diseases as well as development of cancer [7, 8]. The balance of DNA damage and DNA repair is highly relevant to both

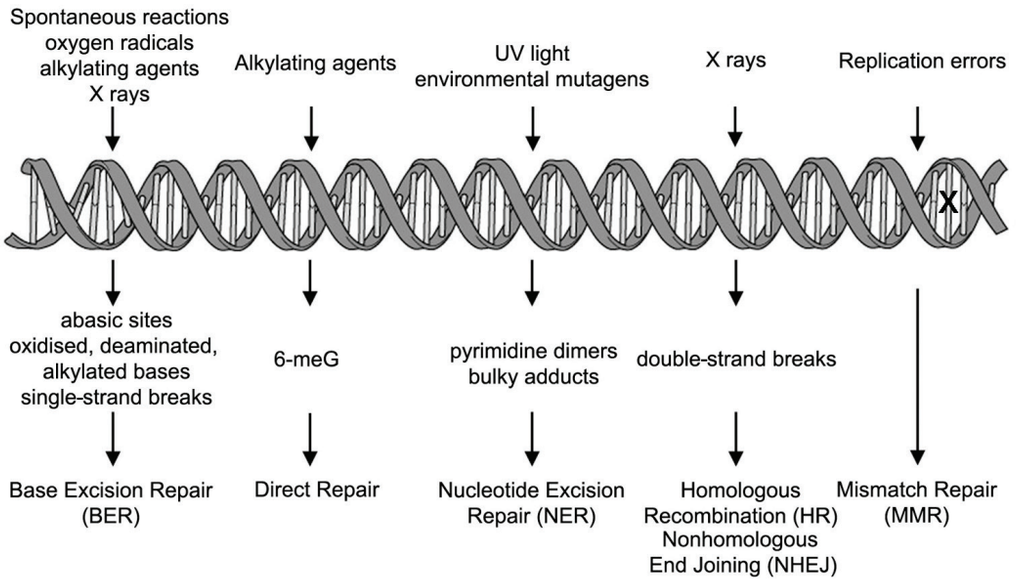


Figure 1.
DNA damages generated by endogenous and exogenous factors and specific systems of their repair. Letter X in DNA duplex marks mismatched base pair. Reproduced with modification from [6] with permission of Pleiades Publishing, Ltd.

cancerogenesis and effective anti-cancer therapy due to the ability of cancer cells to repair therapeutically induced DNA damage and impact therapeutic efficacy [9]. Hence, intensive investigation of DNA damage repair is essential to advance our understanding of molecular mechanisms maintaining genome integrity and to develop cancer therapy.

2. Main steps of BER and proteins involved

The widely accepted model for mammalian BER involves several sub-pathways presented schematically in **Figure 2**. The damaged bases are removed by DNA glycosylases specific to the certain type of damage; mono- and bifunctional DNA glycosylases form an intact or cleaved (via β- or β/δ-elimination mechanism) AP site, respectively [10]. The intact AP site is further processed by the main enzymatic activity of multifunctional AP endonuclease 1 (APE1) producing the one-nucleotide gap with 3′-hydroxyl and 5′-deoxyribose phosphate residue (5′-dRp) at the gap margins. Terminal blocking groups in the DNA intermediates produced by bifunctional DNA glycosylases are removed by the phosphatase activity of polynucleotide kinase/phosphatase (PNKP) or 3′-phosphodiesterase and 3′-phosphatase activities of APE1. At the next step, a bifunctional DNA polymerase β (Polβ) catalyzes the removal of the 5′-dRp residue by its dRp-lyase activity and one-nucleotide gap filling by the nucleotidyl transferase activity. The repair of DNA chain integrity via joining of the single-strand break is completed by DNA ligase IIIα (LigIIIα) acting in the complex with X-ray repair cross-complementing protein 1 (XRCC1). This main BER sub-pathway is known as a short-patch repair (SP BER). When the 5′-dRp residue is modified, it cannot be removed by the Polβ-lyase activity, and a long-patch sub-pathway of BER (LP BER) is realized. Polβ initiates the DNA strand displacement synthesis continued by replicative DNA polymerases δ and ε (Polδ and Polε) acting in the complexes with protein factors PCNA and RFC. The flap structure produced at this step is removed by the flap endonuclease 1 (FEN1). According to another model, FEN1 is capable of sequential removing nucleotides at the 5′-end of the break, and the produced gap is filled by the activities of Polβ or

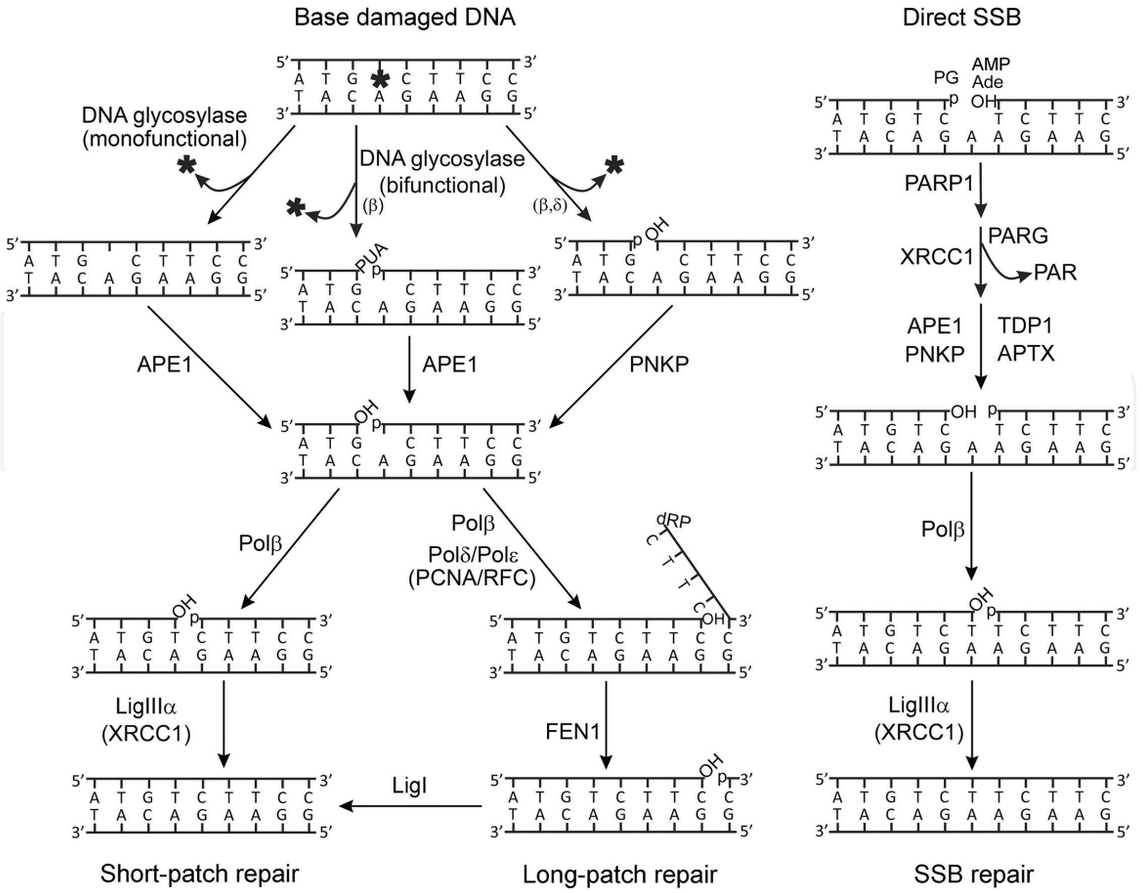


Figure 2.
BER sub-pathways for repair of damaged bases and DNA SSBs. Catalytic steps and proteins involved are schematically presented. The terminal groups in DNA intermediates and SSBs are designated as follows: PUA, 3′-phospho-α,β-unsaturated aldehyde; p, 3′−/5′-phosphate; OH, 3′−/5′-hydroxyl; dRP, 5′-deoxyribose phosphate; PG, 3′-phosphoglycolate; Ade, 5′-aldehyde group; and AMP, 5′-AMP. Reproduced with modification from [6] with permission of Pleiades Publishing, Ltd.

Polλ [11, 12]. Final ligation of the break is catalyzed by DNA ligase I (LigI). A new long-patch sub-pathway of BER that involves formation of a 9-nucleotide gap 5′ to the lesion has been recently discovered; it is mediated by DNA helicase RECQ1 and ERCC1-XPF endonuclease in cooperation with PARP1 and replication protein A (RPA) [13].

Repair of DNA SSBs arising directly via disintegration of the oxidized sugar and as a result of erroneous activity of DNA topoisomerase 1 involves the following steps: (1) detection of the break, (2) removal of blocking groups, (3) filling the gap, and (4) ligation of the break (**Figure 2**). The DNA breaks are detected primarily by poly(ADP-ribose) polymerase 1 (PARP1); the unblocking of 3′- and 5′-ends in breaks is catalyzed by specific activities of APE1, PNKP, aprataxin (APTX), and tyrosyl-DNA phosphodiesterase 1 (TDP1); gap filling and ligation are catalyzed by the same set of enzymes that participate in the respective steps of the short-patch repair of the damaged DNA bases (Polβ and LigIIIα). PARP1 is activated via the interaction with the damaged DNA; it catalyzes the synthesis of poly(ADP-ribose) (PAR) and covalent attachment of the PAR polymer to PARP1 itself and other proteins involved in the DNA repair [4, 5]. The XRCC1 protein is considered to be a main target of PARP1 catalyzed poly(ADP-ribosyl)ation. PARP1 has been suggested to play the main role in recruitment of the XRCC1 protein to the damages of chromosomal DNA [4, 5]. XRCC1 displays no enzymatic activity and is proposed to function as a scaffold protein of the BER process. PARP2 is another enzyme from the PARP family that is activated via binding with DNA SSB and catalyzes PAR

synthesis [14, 15]. The importance of both PARP1 and PARP2 for DNA repair is indicated by knockout studies revealed that knocking out the *parp1* gene activity increased the sensitivity of cells to DNA-damaging agents, while *parp1* and *parp2* double knockouts caused early embryonic lethality [16]. The role of PARP2 in BER processes and its possible synergism with PARP1 action are under intensive investigation [17, 18]. Poly(ADP-ribosyl)ation of proteins is a transient modification that turns over rapidly due to the enzymatic activity of poly(ADP-ribose) glycohydrolase (PARG) [19]. Another important function of PARP1 in DNA repair is remodeling of chromatin structure via poly(ADP-ribosyl)ation of histones and binding of the remodeling proteins with the synthesized PAR polymer [20].

Coordinated action of the enzymes catalyzing the sequential individual reactions of the multistep BER process is required for efficient repair of damaged DNA. One of the coordination mechanisms proposed previously is the "passing the baton," that implies the transfer of the DNA intermediate from the enzyme remaining bound to the product to the next enzyme [1, 21]. This model is supported by numerous data on mutual modulation of activities of the BER enzymes [2, 21]. The stimulating effect of APE1 on the catalytic activity of DNA glycosylase OGG1 explored in detail recently does not require direct interaction between the proteins and is adequately described by the "passing the baton" model [22]. Another mechanism of coordination implies the formation of multiprotein complexes (so-called repairosomes) composed of enzymes and scaffold proteins [2]. XRCC1 is a striking example of the scaffold protein involved in BER. The existence of "repairosomes" is evidenced by multiple interactions between enzymes and protein factors of BER detected even independent of the DNA damage. Most likely both mechanisms are relevant to coordination of the BER process.

3. Proteins involved in BER interact directly with each other

Many protein participants of BER have been shown to interact physically with each other. Data on their direct interactions and structural domains involved are summarized in **Table 1**. Interactions of the XRCC1 protein with multiple partners have been explored in the greatest detail. The structure of XRCC1 is composed of three domains linked with disordered fragments (linkers XL1 and XL2), one of which (XL1) contains a nuclear localization signal (**Figure 3**) [23]. The availability of two BRCT domains (BRCTa and BRCTb) mediating protein-protein interactions (for review, see [24]), in addition to the N-terminal domain (NTD) involved in DNA binding, favors the main function of XRCC1 as scaffold in structural organization of "repairosomes". Interestingly, the binding sites of four enzymes catalyzing sequential steps of BER—APE1, PNKP (N-terminal domain), Polβ, and LigIIIα—are localized in different structural modules of XRCC1 (**Figure 3**). A second PNKP interaction site localized recently in XRCC1 (linker XL1) binds PNKP (catalytic domain) with lower affinity; this interaction has been proposed to stimulate PNKP activity, in contrast to the high-affinity interaction responsible for PNKP recruitment to DNA damage [25]. At the same time, the binding sites of various DNA glycosylases in XRCC1 overlap with those for APE1, Polβ, and PARP1 (**Figure 3**). It is likely that the enzymes initiating the repair of damaged bases form dynamic contacts with XRCC1 and other constituents of "repairosome." Direct interactions of DNA glycosylases NEIL1, NEIL2, and MYH with other enzymes of SP and LP BER (APE1, PNKP, Polβ, LigIIIα, Polδ, FEN1, and LigI) have been shown (**Table 1**). The multiprotein complexes of XRCC1 detected in many studies to be formed by recombinant proteins and cell extracts contain Polβ, PNKP, and LigIIIα as stable partners, and their presence enhances the interaction of XRCC1 with

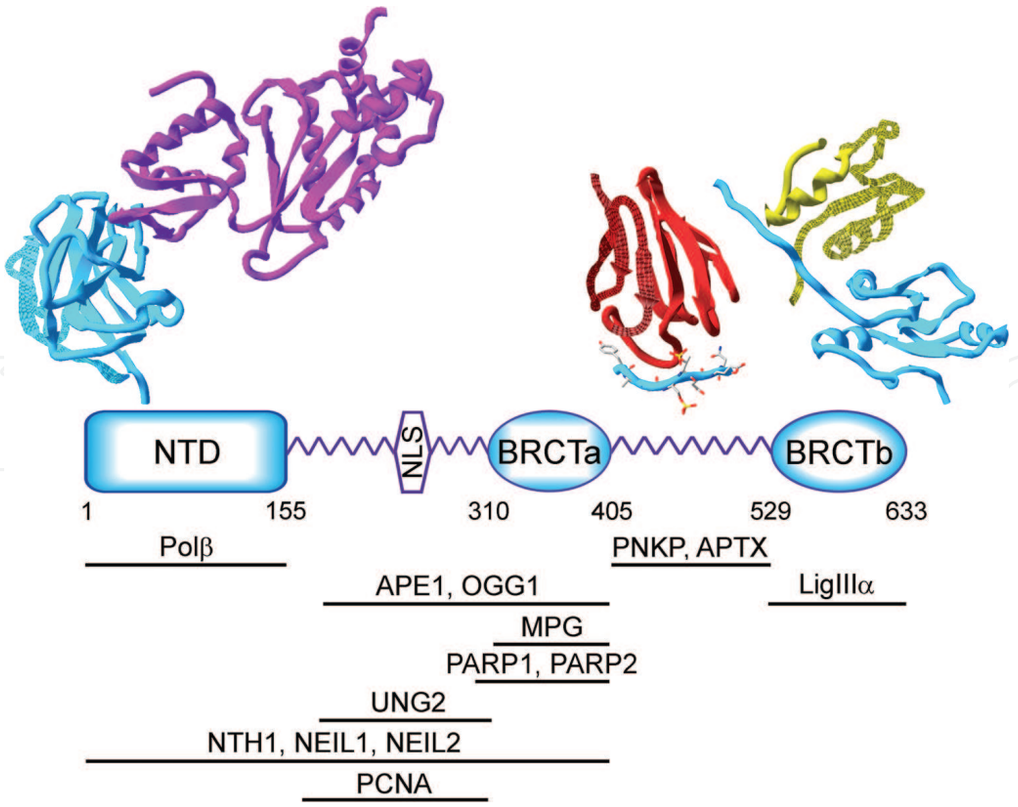


Figure 3.
The multidomain structure of XRCC1 and specific regions responsible for its scaffold function in BER. Protein partners and their binding sites in XRCC1 are shown schematically in the upper part of the figure. At the top, 3D structure models determined for the N-terminal domain, a fragment of XL2 linker, and the BRCTb domain crystallized as complexes with the respective domains of Polβ, PNKP, and LigIIIα (PDB codes: 3K75, 2W3O, and 3QVG) are presented. Reproduced with modification from [6] with permission of Pleiades Publishing, Ltd.

DNA glycosylases [30, 31, 33, 52]. PNKP and LigIIIα are the constituents of another multiprotein complex containing XRCC1 and TDP1 [53].

The PARP1 protein consists of multiple structural modules constituting an N-terminal DNA-binding domain and a C-terminal catalytic domain in addition to the central BRCT domain [55, 57]. The coordinating function of PARP1 in BER can be realized via direct interaction with some enzymes (PNKP, Polβ, LigIIIα, and TDP1) or indirect interaction mediated by the XRCC1 protein. The binding sites for main BER enzymes (Polβ and LigIIIα) and the scaffold XRCC1 protein are localized in the DNA binding and BRCT domains, while that for TDP1 is completed by the catalytic domain of PARP1 (**Table 1**). As a consequence, TDP1 is capable of the formation of a stable ternary complex with PARP1 and XRCC1 [53]. The overlapped binding sites for the majority of PARP1 partners create prerequisites for dynamic contacts in the preformed multiprotein assemblies, which can be stabilized in the complex with auto-modified PARP1 (PAR-PARP1). Many BER participants such as XRCC1, Polβ, PNKP, APTX, TDP1, LigIIIα, and LigI contain PAR-binding motifs, and some of them (XRCC1, LigIIIα, and TDP1) have been shown to interact with PAR-PARP1 more efficiently than with the unmodified PARP1 [46, 47, 58, 59]. The poly(ADP-ribose) acceptors have been identified in all the structural domains of PARP1; this expands significantly the platform for the formation of the "repairosomes" [60]. In contrast to PARP1, PARP2 does not have the BRCT domain and specialized zinc-fingers for DNA binding [15, 61]. The nonconserved WGR domain of PARP2 is responsible for the interaction with proteins (**Table 1**) as well as for DNA break detection [15]. The function of PARP2 (similar to that of PARP1) in coordination of the DNA repair process can be further mediated through its interaction with XRCC1 [17].

Protein (domain)[a]	Protein partner (domain)[a,b]
XRCC1 (NTD)	Polβ (CD) [23, 26–28]
XRCC1 (NTD + XL1)	NTH1 (CTD); NEIL1 (CTD); NEIL2 (NTD) [29–31]
XRCC1 (XL1)	PCNA [32]; UNG2 (CD) [33]; PNKP (CD) [25]
XRCC1 (XL1 + BRCTa)	APE1, OGG1 [34]
XRCC1 (BRCTa)	MPG, NTH1 (CTD), NEIL1 (CTD), NEIL2 (NTD) [29–31]; PARP1 (DBD, BRCT), PARP2 (WGR) [35, 36]
XRCC1 (XL2)	PNKP (NTD), APTX (FHA) [23, 37–39]
XRCC1 (BRCTb)	LigIIIα (BRCT) [40–42]
XRCC1	TDP1 [43]
PARP1 (DBD + BRCT)	Polβ (CD), PARP1, PARP2 (WGR) [36, 44, 45]; LigIIIα (55–122) [46]
PARP1 (CD)	TDP1 (NTD) [47]
APE1 (CTD)	MYH (293–351) [48]
NEIL1 (CTD)	PNKP, Polβ, FEN1, LigI [49]
Polβ (NTD)	NEIL1 (CTD), NEIL2 (NTD) [30, 31]; LigI (NTD) [50]
Polβ (CD)	PARP2 (WGR) [36]
Polβ	APE1 [51]; PNKP [52]
LigIIIα (BRCT)	NEIL1 (CTD), NEIL2 (NTD) [30, 31]; PARP2 (WGR) [36]; PNKP [52]; TDP1 (NTD) [53, 54]

[a]Protein domain(s) responsible for the interaction with protein partner(s) is shown in brackets. Structural composition of multidomain proteins: XRCC1: NTD 1–155, XL1 156–309, BRCTa 310–405, XL2 406–528, BRCTb 529–633; [23] PARP1: ZnF1 1–96, ZnF2 97–206, NLS 207–240, ZnF3 241–366, BRCT 381–484, WGR 518–661, CD 662–1014; [55] PARP2: NTD 1–63, WGR 64–198, CD 199–559; [36] LigIIIα: ZnF 1–100, linker 101–170, DBD 171–390, CD 391–836, BRCT 837–922 [56]. Designations: NTD/CTD, N-/C-terminal domain; CD, catalytic domain; DBD, DNA-binding domain; XL1/XL2, linker 1/2 in XRCC1 protein; NLS, nuclear localization signal; ZnF, zinc finger; FHA, forkhead-associated domain. The data for human and mouse (PARP2) recombinant proteins are presented.

[b]Techniques used in studies: affinity coprecipitation [25, 26, 29–36, 40, 41, 44–50], two-hybrid analysis [27, 30, 31, 35, 37, 46, 51–54], gel filtration [27, 28, 41, 42], ultracentrifugation [27, 50], coimmunoprecipitation [29, 31–33, 36–39, 41, 43, 46, 47, 52–54], fluorescence titration [38], fluorescence polarization [39], surface plasmon resonance [41], small-angle X-ray scattering [42], X-ray crystallography [23, 42, 45], and NMR [48].

Table 1.
Interactions between main proteins involved in BER.

Direct interactions between the enzymes catalyzing different, usually sequential, steps of the BER process have been demonstrated in several studies (**Table 1**). Interestingly, the enzyme of the final step of SP BER—LigIIIα has direct binding partners among the enzymes involved in both the initial and middle steps of the process (NEIL1, NEIL2, PNKP, and TDP1), utilizing the BRCT domain for the interaction. Data reported recently indicate the ability of this enzyme to control the assembly of multiprotein complexes on single-strand DNA damages similar to PARP1, thus suggesting a scaffolding function of LigIIIα in the coordination of BER [62].

Most interactions between proteins involved in BER have been detected using the affinity coprecipitation, two-hybrid analysis, and immunoprecipitation techniques (**Table 1**). These techniques provide no information on physicochemical, structural, and conformational parameters of the complexes, leaving open many questions on the mechanisms of their functioning, such as the relative contribution of the proteins to the formation of macromolecular associates and their stoichiometry, the roles of dynamic interactions, conformational changes, and DNA intermediates in the formation of functional assemblies. Information on the structural

organization of these complexes is very limited. The 3D structures determined by X-ray crystallography are known for the isolated domains/fragments of the XRCC1 protein in complexes with the respective domains of its stable partners Polβ, LigIIIα, and PNKP (**Figure 3**). It is interesting to note that the specific contact region of the XRCC1 protein with LigIIIα (not involved in XRCC1 homodimerization)—a polypeptide consisting of hydrophobic amino acid residues at the N-terminus of the BRCTb domain—was revealed in the X-ray study [42]. The binding sites localized in proteins by the traditional nonequilibrium techniques participate obviously in the most stable interactions. The available structural data are not sufficient to decipher the molecular mechanisms of BER coordination.

Using quantitative equilibrium techniques—fluorescence titration and fluorescence (Förster) resonance energy transfer (FRET)—we have characterized several homo- and hetero-oligomeric complexes of various BER proteins (**Figure 4**). *N*-hydroxysuccinimide esters of 5(6)-carboxyfluorescein (FAM) and 5(6)-carboxytetramethylrhodamine (TMR) were used for N-terminal fluorescent labeling of proteins. Direct (not mediated by DNA or other proteins) interactions of APE1 with Polβ, TDP1, and PARP1 and of Polβ with TDP1 as well as homo-oligomerization of APE1 have been detected for the first time. The apparent equilibrium dissociation constant (K_d) of the complexes is in the range of 23 to 270 nM. The XRCC1-PNKP complex characterized previously by using a similar approach has a K_d value in the same range [64]. The highest stability of the XRCC1 complex with Polβ was confirmed by the nonequilibrium approach, size exclusion chromatography coupled with multi-angle laser light-scattering (SEC-MALLS) [63]. Model DNAs imitating various DNA intermediates of BER have been shown to modulate the structure of protein complexes and their stability to different extents, depending on the type of DNA damage [63]. The DNA-dependent effects on the protein affinity for each other were most pronounced for the complexes of APE1 with different proteins (Polβ, XRCC1, and PARP1). Our findings advance understanding of the mechanisms underlying coordination and regulation of the BER process. The dependence of the efficiency of APE1 interaction with Polβ on the type of DNA intermediate indicates that functions of the two key enzymes are coordinated not only due to the differences in their affinity for DNAs as proposed previously in [65] but also due to the strength of their interaction with each other, which is controlled by DNA at different steps of repair. The higher affinity of APE1 for Polβ in the presence of AP-site containing DNA than in the complex with the incision product suggests that the efficient repair is facilitated by the transfer of the DNA intermediate to Polβ immediately during the incision step. The higher affinity of APE1 and Polβ for PARP1 than for each other in the presence of SSB containing DNA suggests that the regulation of functions of the BER participants via DNA-dependent modulation of their affinity for each other represents a common mechanism for various proteins. On the contrary, the stability of the XRCC1-Polβ complex does not depend on the presence of DNA intermediates, even though the most pronounced effect of different DNAs on the FRET signal, which reflects structural rearrangement of the complex, was detected for this complex. Our data indicate that this complex revealed in [66] to protect each protein from proteasome-mediated degradation may also serve as a stable component of the multiprotein assemblies, similar to the XRCC1-LigIIIα complex. Moreover, the XRCC1 binding sites with Polβ and LigIIIα do not overlap with regions mediating interactions with most other protein partners, thus enabling participation of the preformed ternary Polβ-XRCC1-LigIIIα complex in the entire Polβ- and XRCC1-dependent BER sub-pathway. Formation of the stable ternary complex *in vivo* is evidenced by synchronous accumulation of XRCC1, Polβ, and LigIIIα at the damage sites of DNA [67, 68].

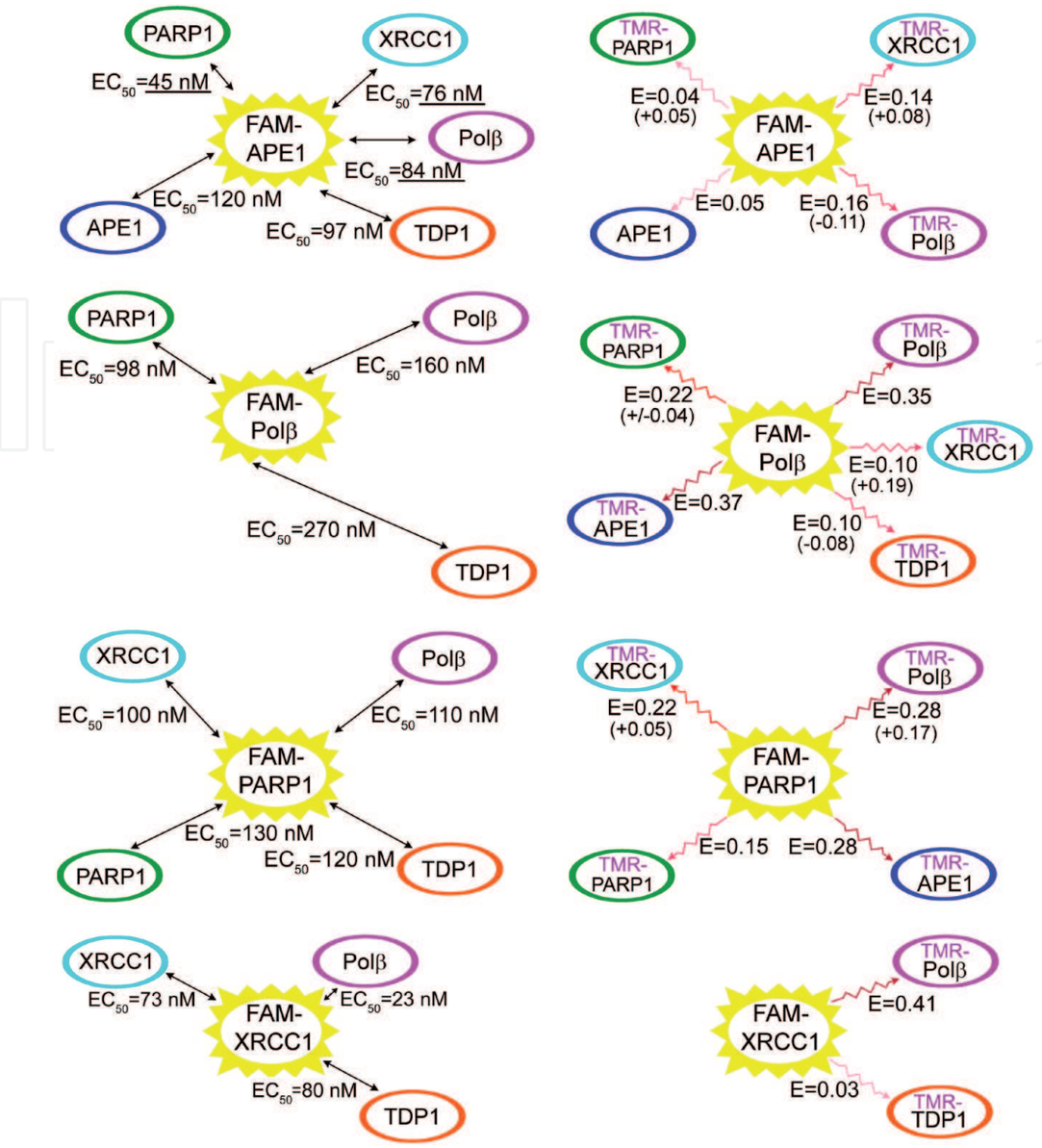


Figure 4.
Direct interactions between BER proteins detected by fluorescence titration and FRET [63]. The EC_{50} values represent apparent equilibrium dissociation constants of the complexes (determined as half-maximal effective concentrations of protein partners); the length of black arrows connecting the protein pairs is proportional to the binding affinity; the underlined EC_{50} values have changed remarkably in the presence of DNA intermediates. The interaction in each pair of FAM- (donor) and TMR-labeled (acceptor) proteins is characterized by FRET efficiency (E); the highest change of the E value induced by DNA intermediates (increase/decrease with +/− sign) is presented in brackets. Reproduced with modification from [6] with permission of Pleiades Publishing, Ltd.

Recently, the oligomeric states of BER proteins and their complexes have been estimated based on hydrodynamic sizes determined by using dynamic light scattering (DLS) technique [69]. All the proteins have been proposed to form homodimers upon their self-association. The most probable oligomerization state of the binary complexes formed by PARP1 with various proteins is a heterotetramer. The oligomerization state of the binary complexes formed by XRCC1 varies from heterodimer to heterotetramer, depending on the partner.

Interaction of PARP1 with Polβ and APE1 detected in our study [63] in both the absence and presence of DNA may contribute to regulation of the BER process. Cooperation between PARP1 and BER enzymes at different steps of DNA repair is evident from our previous studies. Interaction of PARP1, Polβ, and APE1 with the "central" DNA intermediate in BER established by photoaffinity labeling

of BER proteins in the cell extract suggests interplay between these proteins during repair synthesis catalyzed by Polβ [70]. The ability of PARP1 to compete with APE1 for the binding of an AP-site containing DNA indicates possible cooperation between the proteins upon the recognition and further incision of the AP site [71]. Following the incision of AP site, PARP1 can catalyze the synthesis of poly(ADP-ribose). According to the initially proposed mechanism of its action, PARP1 dissociates from the complex with DNA after covalent attachment of the negatively charged PAR polymer. Further studies of an active role of PAR in the formation of the repair complexes have modified this hypothesis. It was established that following poly(ADP-ribosyl)ation, PARP1 was capable of covalent binding to the photoreactive DNA intermediate; the lifetime of such complexes was shown to depend on both the size of covalently bound PAR and the initial affinity of PARP1 for the DNA damage [70]. Complexes of PAR-PARP1 with damaged DNA have been detected by atomic force microscopy [72]. Recently, kinetics of poly(ADP-ribosyl)ation and PAR homeostasis (but not the PARP1 protein) have been proposed to play a primary role in protection of cells from acute DNA damage [73]. Hence, the formation of BER complexes on the damaged DNA can be regulated via either poly(ADP-ribosyl)ation of proteins or their interactions with PAR polymer synthesized by PARP1 and PARP2. Poly(ADP-ribose) is the most important cell regulator of protein-protein and protein-nucleic acid interactions. [20, 74–78].

4. Interactions of BER proteins with noncanonical factors contribute to the regulation of DNA repair

Many proteins with various cellular functions, not considered previously to be involved in BER, have been shown to regulate this process via interactions with main participants. The HMGB1 protein—a chromatin architecture factor—interacts directly with three BER enzymes (APE1, Polβ, and FEN1), modulates their catalytic activity in the process of DNA repair, and, hence, ensures regulation of the process via the SP or LP BER sub-pathway [79–81]. Human DNA-binding proteins hSSB1 and SATB1 form complexes with DNA glycosylase OGG1, thus enhancing its efficiency in recognition of DNA damage and its repair [82, 83]. The human mitochondrial single-stranded DNA binding protein (mtSSB) interacts with NEIL1 in the presence and absence of a DNA substrate revealed to modulate the oligomerization state and stability of the NEIL1-mtSSB complex [84]. Protein factors of unknown nature that are not involved in chromatin structure remodeling form complex with DNA glycosylase NTH1 and stimulate its activity in BER initiation [85]. The SSRP1 protein entailed in chromatin disassembly as a histone H2A/H2B chaperone interacts with both PAR-PARP1 and XRCC1 and facilitates repair of SSBs [86]. In general, the mechanisms of BER functioning within chromatin are largely unexplored (for example, see [87]), remaining possibility to discover new noncanonical factors of BER.

In addition to multiple enzymatic functions in DNA repair, APE1 is known to play a regulatory role in the transcription processes, RNA processing, and ribosome biogenesis [76, 88]. The activities of the multifunctional enzyme, its expression level, and intracellular localization are regulated by its interaction with the multifunctional protein nucleophosmin (NPM1) [89]. Direct interactions of APE1 and several DNA glycosylases (TDG, NEIL2, NTH1, OGG1, and UNG2) with protein factors of nucleotide excision repair (XPC, XPG, CSB, and RPA) and homologous recombination (Rad52) have been shown to play a regulatory role in the overlapping repair pathways [90].

PARP1 forms stable complexes with Ku70/Ku80 proteins, and this interaction has been proposed to be an important regulator of the Ku70/80 heterodimer function in the repair of DNA double-strand breaks (DSBs) [91, 92]. Recent studies have demonstrated the involvement of Ku70 and Ku80 proteins in different steps of BER [93]. Septin4, a member of GTP binding protein family considered to be an essential component of the cytoskeleton, is a novel PARP1 interacting protein, and the interaction is enhanced under oxidative stress [94]. PARP1 interacts with NR1D1 protein, a nuclear receptor subfamily 1 group D member 1; the interaction is enhanced under oxidative stress and inhibits the catalytic activity of PARP1 [95]. Whether the interaction of these noncanonical factors with PARP1 may contribute to regulation of BER remains to be explored. The protein DBC1 (deleted in breast cancer 1), one of the most abundant yet enigmatic proteins in mammals containing a conserved domain similar to Nudix hydrolases (hydrolyzing nucleoside diphosphates) but lacking catalytic activity, interacts directly with the BRCT domain of PARP1; the strength of the interaction shown to inhibit the catalytic activity of PARP1 is modulated by NAD+ concentration [96]. Thus, a novel function of NAD+ to directly regulate protein-protein interactions, the modulation of which may protect against cancer, radiation, and aging, has been discovered.

The multifunctional Y-box-binding protein 1 (YB-1) is another noncanonical factor of BER. The proteolytic fragment of this positively charged intrinsically disordered protein localized in the nucleus is formed in response to DNA damage [97]. We have shown that YB-1 interacts with poly(ADP-ribose) and could be an acceptor for PARP1/PARP2 catalyzed poly(ADP-ribosyl)ation *in vitro* [98]. Several proteins essential for BER—APE1, Polβ, NEIL1, PARP1, and PARP2—directly interact with YB-1, although most complexes being less stable than the complexes of BER proteins with each other (the apparent K_d values are in the range of 340 to 810 nM as compared to those presented in **Figure 4**) [99]. A strong interaction detected between APE1 and YB-1 could be an important factor for the cooperative action of these multifunctional proteins in transcription regulation [100]. Interactions of YB-1 protein with BER enzymes could be responsible for the regulation of their activities: the AP-endonuclease activity of APE1 and 5′-dRp-lyase activity of Polβ are inhibited in the presence of YB-1, while the AP-lyase activity of NEIL1 is stimulated [99]. YB-1 was found to stimulate the catalytic activity of PARP1 via strong binding with poly(ADP-ribose) linked to PARP1, which increased the lifetime of this complex in DNA [99]. Acting as a cofactor of PARP1, YB-1 decreases the efficiency of PARP1 inhibitors [101].

5. Intersection of posttranslational modifications and protein-protein interactions in BER coordination

Posttranslational modifications (PTMs) of proteins involved in BER modulate catalytic and DNA-binding activities of individual proteins, their expression, intracellular localization, structure, and stability as well as protein-protein interactions and may therefore contribute to regulation of DNA repair either directly or indirectly. Numerous studies of PTMs and their functions in BER have been reviewed previously [90, 102–106]. As mentioned above, PARP1 modifies itself and binding partners with poly(ADP-ribose). Among the targets of PARP1 catalyzed ADP-ribosylation are two key BER proteins—XRCC1 and Polβ, and XRCC1 negatively regulates PARP1 activity [35, 107]. The automodification of PARP1 has been shown to enhance its interaction with XRCC1, LigIIIα, and TDP1; the length of

PAR polymer determines the efficiency of PAR-mediated accumulation of XRCC1 on DNA damage [46, 47, 108]. Recent studies have identified other PTMs, such as phosphorylation, acetylation, and methylation, to regulate the activity of PARP1 [104, 106]. Phosphorylation of PARP1 mediated by protein kinase CDK2 represents a novel DNA-independent mechanism of PARP1 activation [106]. Modifications of PARP1 mediated by AMP-activated protein kinase (AMPK) and lysine acetyltransferase 2B (PCAF) modulate both the activity of PARP1 and ADP-ribosylation of other proteins [106]. Polyubiquitination of PARP1 by E3 ubiquitin protein ligase is promoted by the automodification of PARP1 and targets PAR-PARP1 for proteasomal degradation [106]. It has to be noted that nonproteolytic roles of protein ubiquitination in regulation of DSBs repair and NER have been demonstrated [105]. PARP1 modification (at Lys486 residue) with small ubiquitin-like protein catalyzed by SUMO E3 ligase (SUMOylation) enhances p300-dependent acetylation of PARP1, while it has no effect on its activity [106].

The most abundant evidence on PTM-mediated regulation of protein-protein interactions is available for the XRCC1 protein. XRCC1 is an extensively phosphorylated protein with more than 45 phosphorylation sites localized in the linker regions and BRCTa domain [109]. Catalyzed by p38 MAPK kinase phosphorylation of the BRCTa domain (at T358 and T367 residues) has been shown to regulate PAR-mediated recruitment of XRCC1 to DNA damage [109]. The phosphorylation of XRCC1 by checkpoint kinase 2 (CHK2) at Thr284 residue *in vivo* and *in vitro* increases the affinity of XRCC1 for DNA glycosylase MPG, facilitating thereby initiation of BER [110]. As shown recently, the same kinase interacts with PARP1 and modifies the BRCT domain; the CHK2-dependent phosphorylation of PARP1 stimulates its catalytic activity and interaction with XRCC1 [111]. Seven sites of XRCC1 phosphorylation mediated by kinase CK2 (localized in the XL2 linker) are necessary to modulate the interaction of XRCC1 with end-processing enzymes—PNKP, APTX, and PNK-like factor APLF—and the efficiency of repair of chromosomal DNA SSBs [37–39, 112, 113]. Notably, the phosphorylated and unmodified forms of XRCC1 bind different structural domains of PNKP and modulate the kinase activity of PNKP or its accumulation on DNA damage, respectively [37, 38]. The oxidized form of XRCC1 stabilized by a disulfide bridge between Cys12 and Cys20 residues forms a more stable (in comparison with the reduced form) complex with Polβ; an increase in the number of intermolecular contacts in this complex has been confirmed by X-ray analysis of the complex [23]. The existence of oxidized form of XRCC1 *in vivo* is essential to protect cells against extreme oxidative stress [114]. XRCC1 is a substrate for SUMOylation promoted by DNA damage-induced PARylation; SUMOylation of XRCC1 contributes to regulation of BER via increasing its binding affinity for Polβ [115].

The most frequent PTMs discovered for the multifunctional protein APE1 include phosphorylation, acetylation, S-nitrosylation, S-glutathionylation, formation of disulfide bonds, and ubiquitination [90, 102]. Most modifications modulate redox activity of APE1 and its regulatory function in transcription. As Cys residues are targets of different modifications, it is essential to understand the competition between these PTMs and their roles in APE1 function. Numerous studies on APE1 phosphorylation by a variety of protein kinases provide contradictory data on modulation of the repair activity of APE1 [102]. Recently, it has been shown that acetylation of APE1 (at Lys residues in the mammalian-conserved N-terminal extension) enhances both the AP-endonuclease activity and the interaction with XRCC1 and XRCC1-LigIIIα complex, ensuring cell survival in response to genotoxic stress [116].

Acetylation of DNA glycosylase TDG weakens its interaction with APE1 and produces opposite effects on the excision activity of the enzyme toward various

types of base damages; repair of damage induced by the chemotherapeutic action of 5-fluorouracil is enhanced by the TDG acetylation [90]. Based on these data, the acetylation status of TDG within tumor cells was proposed to impact the chemotherapy efficacy. Phosphorylation of the flexible N-terminus of DNA glycosylase UNG2 (at Thr6 or Tyr8 residues) shown to disrupt interaction with the PCNA factor, without affecting the UNG2 catalytic activity or its RPA interaction, has been proposed to regulate the formation of the ternary PCNA-UNG2-RPA protein complex [117].

Various PTMs of Polβ (acetylation, phosphorylation, and methylation) modulate its 5′-dRp-lyase and nucleotidyl transferase activities; the only example of PTMs impacts on protein-protein interaction is inhibition of Polβ-PCNA interaction due to PRMT1-dependent methylation of Arg137 [102]. The enzymes completing BER—LigIIIα and LigI—undergo posttranslational modification *in vitro* and in *vivo*; however, the intersection of their PTMs with protein-protein interactions is yet unknown [102].

6. Conclusions

Intensive studies of DNA repair system ensuring repair of damaged bases and single-strand DNA breaks (BER) in recent decades have made impressive progress in establishing the participants of the repair process, main sub-pathways, and auxiliary mechanisms activated when the main BER sub-pathways are inefficient. In addition to the enzymes responsible for catalytic steps of BER, several proteins, such as XRCC1, PARP1, PARP2, and others, have been identified as BER participants essential for assembling and functioning of the dynamic multiprotein system. Multiprotein complexes of various compositions can be formed without the involvement of DNA, but their structure and stability are modulated by the damaged DNA and intermediates formed in different steps of BER. Interactions of individual BER enzymes with DNA substrates and products have been deciphered in detail by X-ray studies. This method is of little use to explore dynamic supramolecular structures operating in DNA repair. The next step is required to clarify how the BER system functions upon association of the multiprotein complexes with chromatin; novel methods in structural analysis, such as electron microscopy, and more complex models imitating DNA repair in chromatin structure might be helpful to apply. How protein-protein interactions and posttranslational modifications coordinate BER with other DNA repair systems requires future studies. Elucidation of molecular mechanisms underlying efficient BER and its dysregulation in pathological states will help broaden our understanding the origins of diseases and provide novel strategy of their treatment.

Acknowledgements

This work was financially supported partially under Russian State funded budget project (VI.57.1.2, 0309-2016-0001) and by the Russian Science Foundation (grant No. 14-24-00038).

Conflict of interest

The authors declare that there is no conflict of interest.

IntechOpen

IntechOpen

Author details

Nina Moor and Olga Lavrik*
Siberian Branch of the Russian Academy of Sciences, Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russia

*Address all correspondence to: lavrik@niboch.nsc.ru

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Kim Y-J, Wilson DM III. Overview of base excision repair biochemistry. Current Molecular Pharmacology. 2012;**5**:3-13. DOI: 10.2174/1874467211205010003

[2] Dutta A, Yang C, Sengupta S, Mitra S, Hegde ML. New paradigms in the repair of oxidative damage in human genome: Mechanisms ensuring repair of mutagenic base lesions during replication and involvement of accessory proteins. Cellular and Molecular Life Sciences. 2015;**7**:1679-1698. DOI: 10.1007/s00018-014-1820-z

[3] Whitaker AM, Schaich MA, Smith MR, Flynn TS, Freudenthal BD. Base excision repair of oxidative DNA damage: From mechanism to disease. Frontiers in Bioscience. 2017;**22**:1493-1522

[4] Caldecott KW. DNA single-strand break repair. Experimental Cell Research. 2014;**329**:2-8. DOI: 10.1016/j.yexcr.2014.08.027

[5] Abbotts R, Wilson DM III. Coordination of DNA single strand break repair. Free Radical Biology & Medicine. 2017;**107**:228-244. DOI: 10.1016/j.freeradbiomed.2016.11.039

[6] Moor NA, Lavrik OI. Protein-protein interactions in DNA base excision repair. Biochemistry (Mosc). 2018;**83**:411-422. DOI: 10.1134/S0006297918040120

[7] Hakem R. DNA-damage repair; the good, the bad, and the ugly. The EMBO Journal. 2008;**27**:589-605. DOI: 10.1038/emboj.2008.15

[8] Pan MR, Li K, Lin SY, Hung WC. Connecting the dots: From DNA damage and repair to aging. International Journal of Molecular Sciences. 2016;**17**:E685. DOI: 10.3390/ijms17050685

[9] Gavande NS, VanderVere-Carozza PS, Hinshaw HD, Jalal SI, Sears CR, Pawelczak KS, et al. DNA repair targeted therapy: The past or future of cancer treatment? Pharmacology & Therapeutics. 2016;**160**:65-83. DOI: 10.1016/j.pharmthera.2016.02.003

[10] Dizdaroglu M, Coskun E, Jaruga P. Repair of oxidatively induced DNA damage by DNA glycosylases: Mechanisms of action, substrate specificities and excision kinetics. Mutation Research. 2017;**771**:99-127. DOI: 10.1016/j.mrrev.2017.02.001

[11] Liu Y, Beard WA, Shock DD, Prasad R, Hou EW, Wilson SH. DNA polymerase beta and flap endonuclease 1 enzymatic specificities sustain DNA synthesis for long patch base excision repair. The Journal of Biological Chemistry. 2005;**280**:3665-3674. DOI: 10.1074/jbc.M412922200

[12] Lebedeva NA, Rechkunova NI, Dezhurov SV, Khodyreva SN, Favre A, Blanco L, et al. Comparison of functional properties of mammalian DNA polymerase lambda and DNA polymerase beta in reactions of DNA synthesis related to DNA repair. Biochimica et Biophysica Acta. 2005;**1751**:150-158. DOI: 10.1016/j.bbapap.2005.05.012

[13] Woodrick J, Gupta S, Camacho S, Parvathaneni S, Choudhury S, Cheema A, et al. A new sub-pathway of long-patch base excision repair involving 5′ gap formation. The EMBO Journal. 2017;**36**:1605-1622. DOI: 10.15252/embj.201694920

[14] Amé JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, et al. PARP-2, a novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. The Journal of Biological Chemistry. 1999;**274**:17860-17868. DOI: 10.1074/jbc.274.25.17860

[15] Obaji E, Haikarainen T, Lehtiö L. Structural basis for DNA break recognition by ARTD2/PARP2. Nucleic Acids Research. 2018. DOI: 10.1093/nar/gky927

[16] Ménissier-de Murcia J, Ricoul M, Tartier L, Niedergang C, Huber A, Dantzer F, et al. Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. The EMBO Journal. 2003;**22**:2255-2263. DOI: 10.1093/emboj/cdg206

[17] Hanzlikova H, Gittens W, Krejcikova K, Zeng Z, Caldecott KW. Overlapping roles for PARP1 and PARP2 in the recruitment of endogenous XRCC1 and PNKP into oxidized chromatin. Nucleic Acids Research. 2017;**45**:2546-2557. DOI: 10.1093/nar/gkw1246

[18] Ronson GE, Piberger AL, Higgs MR, Olsen AL, Stewart GS, McHugh PJ, et al. PARP1 and PARP2 stabilise replication forks at base excision repair intermediates through Fbh1-dependent Rad51 regulation. Nature Communications. 2018;**9**:746. DOI: 10.1038/s41467-018-03159-2

[19] Pascal JM, Ellenberger T. The rise and fall of poly(ADP-ribose): An enzymatic perspective. DNA Repair. 2015;**32**:10-16. DOI: 10.1016/j.dnarep.2015.04.008

[20] Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodeling. Nature Reviews. Molecular Cell Biology. 2017;**18**:610-621. DOI: 10.1038/nrm.2017.53

[21] Prasad R, Beard WA, Batra VK, Liu Y, Shock DD, Wilson SH. A review of recent experiments on step-to-step "hand-off" of the DNA intermediates in mammalian base excision repair pathways. Molecular Biology (Mosk). 2011;**45**:586-600

[22] Esadze A, Rodriguez G, Cravens SL, Stivers JT. AP-endonuclease 1 accelerates turnover of human 8-oxoguanine DNA glycosylase by preventing retrograde binding to the abasic-site product. Biochemistry. 2017;**56**:1974-1986. DOI: 10.1021/acs.biochem.7b00017

[23] London RE. The structural basis of XRCC1-mediated DNA repair. DNA Repair. 2015;**30**:90-103. DOI: 10.1016/j.dnarep.2015.02.005

[24] Gerloff DL, Woods NT, Farago AA, Monteiro AN. BRCT domains: A little more than kin, and less than kind. FEBS Letters. 2012;**586**:2711-2716. DOI: 10.1016/j.febslet.2012.05.005

[25] Breslin C, Mani RS, Fanta M, Hoch N, Weinfeld M, Caldecott KW. The Rev1 interacting region (RIR) motif in the scaffold protein XRCC1 mediates a low-affinity interaction with polynucleotide kinase/phosphatase (PNKP) during DNA single-strand break repair. The Journal of Biological Chemistry. 2017;**292**:16024-16031. DOI: 10.1074/jbc.M117.806638

[26] Kubota Y, Nash RA, Klungland A, Schär P, Barnes DE, Lindahl T. Reconstitution of DNA base excision-repair with purified human proteins: Interaction between DNA polymerase β and the XRCC1 protein. The EMBO Journal. 1996;**15**:6662-6670

[27] Marintchev A, Robertson A, Dimitriadis EK, Prasad R, Wilson SH, Mullen GP. Domain specific interaction in the XRCC1-DNA polymerase β complex. Nucleic Acids Research. 2000;**28**:2049-2059

[28] 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 β. Nucleic Acids Research. 2003;**31**:580-588

[29] Campalans A, Marsin S, Nakabeppu Y, O'Connor TR, Boiteux S, Radicella JP. XRCC1 interactions with multiple DNA glycosylases: A model for its recruitment to base excision repair. DNA Repair. 2005;**4**:826-835. DOI: 10.1016/j.dnarep.2005.04.014

[30] Wiederhold L, Leppard JB, Kedar P, Karimi-Busheri F, Rasouli-Nia A, Weinfeld M, et al. AP endonuclease-independent DNA base excision repair in human cells. Molecular Cell. 2004;**15**:209-220. DOI: 10.1016/j.molcel.2004.06.003

[31] Das A, Wiederhold L, Leppard JB, Kedar P, Prasad R, Wang H, et al. NEIL2-initiated, APE-independent repair of oxidized bases in DNA: Evidence for a repair complex in human cells. DNA Repair. 2006;**5**:1439-1448. DOI: 10.1016/j.dnarep.2006.07.003

[32] Fan J, Otterlei M, Wong HK, Tomkinson AE, Wilson DM III. XRCC1 co-localizes and physically interacts with PCNA. Nucleic Acids Research. 2004;**32**:2193-2201. DOI: 10.1093/nar/gkh556

[33] Akbari M, Solvang-Garten K, Hanssen-Bauer A, Lieske NV, Pettersen HS, Pettersen GK, et al. Direct interaction between XRCC1 and UNG2 facilitates rapid repair of uracil in DNA by XRCC1 complexes. DNA Repair. 2010;**9**:785-795. DOI: 10.1016/j.dnarep.2010.04.002

[34] Marsin S, Vidal AE, Sossou M, Ménissier-de Murcia J, Le Page F, Boiteux S, et al. Role of XRCC1 in the coordination and stimulation of oxidative DNA damage repair initiated by the DNA glycosylase hOGG1. The Journal of Biological Chemistry. 2003;**278**:44068-44074. DOI: 10.1074/jbc.M306160200

[35] Masson M, Niedergang C, Schreiber V, Muller S, Ménissier-de Murcia J, de Murcia G. XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Molecular and Cellular Biology. 1998;**18**:3563-3571

[36] Schreiber V, Amé JC, Dollé P, Schultz I, Rinaldi B, Fraulob V, et al. Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. The Journal of Biological Chemistry. 2002;**277**:23028-23036. DOI: 10.1074/jbc.M202390200

[37] Loizou JI, El-Khamisy SF, Zlatanou A, Moore DJ, Chan DW, Qin J, et al. The protein kinase CK2 facilitates repair of chromosomal DNA single-strand breaks. Cell. 2004;**117**:17-28

[38] Lu M, Mani RS, Karimi-Busheri F, Fanta M, Wang H, Litchfeld DW, et al. Independent mechanisms of stimulation of polynucleotide kinase/phosphatase by phosphorylated and non-phosphorylated XRCC1. Nucleic Acids Research. 2010;**38**:510-521. DOI: 10.1093/nar/gkp1023

[39] Luo H, Chan DW, Yang T, Rodriguez M, Chen BP, Leng M, et al. A new XRCC1-containing complex and its role in cellular survival of methyl methanesulfonate treatment. Molecular and Cellular Biology. 2004;**24**:8356-8365. DOI: 10.1128/MCB.24.19.8356-8365.2004

[40] Nash RA, Caldecott KW, Barnes DE, Lindahl T. XRCC1 protein interacts with one of two distinct forms of DNA ligase III. Biochemistry. 1997;**36**:5207-5211. DOI: 10.1021/bi962281m

[41] Beernink PT, Hwang M, Ramirez M, Murphy MB, Doyle SA, Thelen MP. Specificity of protein interactions mediated by BRCT domains of the XRCC1 DNA repair protein. The Journal of Biological Chemistry. 2005;**280**:30206-30213. DOI: 10.1074/jbc.M502155200

[42] Cuneo MJ, Gabel SA, Krahn JM, Ricker MA, London RE. The structural basis for partitioning of the XRCC1/DNA ligase III-α BRCT-mediated dimer complexes. Nucleic Acids Research. 2011;**39**:7816-7827. DOI: 10.1093/nar/gkr419

[43] Plo I, Liao ZY, Barceló JM, Kohlhagen G, Caldecott KW, Weinfeld M, et al. Association of XRCC1 and tyrosyl DNA phosphodiesterase (Tdp1) for the repair of topoisomerase I-mediated DNA lesions. DNA Repair. 2003;**2**:1087-1100

[44] Dantzer F, de La Rubia G, Ménissier-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**:7559-7569

[45] Ali AAE, Timinszky G, Arribas-Bosacoma R, Kozlowski M, Hassa PO, Hassler M, et al. The zinc-finger domains of PARP1 cooperate to recognize DNA strand breaks. Nature Structural & Molecular Biology. 2012;**19**:685-692. DOI: 10.1038/nsmb.2335

[46] Leppard JB, Dong Z, Mackey ZB, Tomkinson AE. Physical and functional interaction between DNA ligase IIIα and poly(ADP-ribose) polymerase 1 in DNA single-strand break repair. Molecular and Cellular Biology. 2003;**23**:5919-5927

[47] Das BB, Huang SY, Murai J, Rehman I, Amé JC, Sengupta S, et al. PARP1-TDP1 coupling for the repair of topoisomerase I-induced DNA damage. Nucleic Acids Research. 2014;**42**:4435-4449. DOI: 10.1093/nar/gku088

[48] Luncsford PJ, Manvilla BA, Patterson DN, Malik SS, Jin J, Hwang BJ, et al. Coordination of MYH DNA glycosylase and APE1 endonuclease activities via physical interactions. DNA Repair. 2013;**12**:1043-1052. DOI: 10.1016/j.dnarep.2013.09.007

[49] Hegde PM, Dutta A, Sengupta S, Mitra J, Adhikari S, Tomkinson AE, et al. The C-terminal domain (CTD) of human DNA glycosylase NEIL1 is required for forming BERosome repair complex with DNA replication proteins at the replicating genome: Dominant negative function of the CTD. The Journal of Biological Chemistry. 2015;**290**:20919-20933. DOI: 10.1074/jbc.M115.642918

[50] Dimitriadis EK, Prasad R, Vaske MK, Chen L, Tomkinson AE, Lewis MS, et al. Thermodynamics of human DNA ligase I trimerization and association with DNA polymerase β. The Journal of Biological Chemistry. 1998;**273**:20540-20550

[51] Bennett RA, Wilson DM III, Wong D, Demple B. Interaction of human apurinic endonuclease and DNA polymerase β in the base excision repair pathway. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:7166-7169

[52] Whitehouse CJ, Taylor RM, Thistlethwaite A, Zhang H, Karimi-Busheri F, Lasko DD, et al. XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair. Cell. 2001;**104**:107-117

[53] El-Khamisy SF, Saifi GM, Weinfeld M, Johansson F, Helleday T, Lupski JR, et al. Defective DNA single-strand break repair in spinocerebellar ataxia with axonalneuropathy-1. Nature. 2005;**434**:108-113. DOI: 10.1038/nature03314

[54] Chiang SC, Carroll J, El-Khamisy SF. TDP1 serine 81 promotes interaction with DNA ligase IIIα and facilitates cell survival following DNA damage. Cell Cycle. 2010;**9**:588-595. DOI: 10.4161/cc.9.3.10598

[55] 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**:728-732. DOI: 10.1126/science.1216338

[56] Cotner-Gohara E, Kim IK, Tomkinson AE, Ellenberger T. Two DNA-binding and nick recognition modules in human DNA ligase III. The Journal of Biological Chemistry. 2008;**283**:10764-10772. DOI: 10.1074/jbc.M708175200

[57] Eustermann S, Wu WF, Langelier MF, Yang JC, Easton LE, Riccio AA, et al. Structural basis of detection and signaling of DNA single-strand breaks by human PARP-1. Molecular Cell. 2015;**60**:742-754. DOI: 10.1016/j.molcel.2015

[58] Gagné JP, Isabelle M, Lo KS, Bourassa S, Hendzel MJ, Dawson VL, et al. Proteome-wide identification of poly(ADP-ribose) binding proteins and poly(ADP-ribose)-associated protein complexes. Nucleic Acids Research. 2008;**36**:6959-6976. DOI: 10.1093/nar/gkn771

[59] Teloni F, Altmeyer M. Readers of poly(ADP-ribose): Designed to be fit for purpose. Nucleic Acids Research. 2016;**44**:993-1006. DOI: 10.1093/nar/gkv1383

[60] Gagné JP, Ethier C, Defoy D, Bourassa S, Langelier MF, Riccio AA, et al. Quantitative site-specific ADP-ribosylation profiling of DNA-dependent PARPs. DNA Repair. 2015;**30**:68-79. DOI: 10.1016/j.dnarep.2015.02.004

[61] Bock FJ, Chang P. New directions in poly(ADP-ribose) polymerase biology. The FEBS Journal. 2016;**28**:4017-4031. DOI: 10.1111/febs.13737

[62] Abdou I, Poirier GG, Hendzel MJ, Weinfeld M. DNA ligase III acts as a DNA strand break sensor in the cellular orchestration of DNA strand break repair. Nucleic Acids Research. 2015;**43**:875-892. DOI: 10.1093/nar/gku1307

[63] 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 Research. 2015;**43**:6009-6022. DOI: 10.1093/nar/gkv569

[64] Mani RS, Fanta M, Karimi-Busheri F, Silver E, Virgen CA, Caldecott KW, et al. XRCC1 stimulates polynucleotide kinase by enhancing its damage discrimination and displacement from DNA repair intermediates. The Journal of Biological Chemistry. 2007;**282**:28004-28013. DOI: 10.1074/jbc.M704867200

[65] Liu Y, Prasad R, Beard WA, Kedar PS, Hou EW, Shock DD, et al. Coordination of steps in single-nucleotide base excision repair mediated by apurinic/apyrimidinic endonuclease 1 and DNA polymerase β. The Journal of Biological Chemistry. 2007;**282**:13532-13541. DOI: 10.1074/jbc.M611295200

[66] Fang Q, Inanc B, Schamus S, Wang XH, Wei L, Brown AR, et al. HSP90 regulates DNA repair via the interaction between XRCC1 and DNA polymerase β. Nature Communications. 2014;**5**:5513. DOI: 10.1038/ncomms6513

[67] Lan L, Nakajima S, Oohata Y, Takao M, Okano S, Masutani M, et al. *In situ* analysis of repair processes for oxidative DNA damage in mammalian cells. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**:13738-13743. DOI: 10.1073/pnas.0406048101

[68] Hanssen-Bauer A, Solvang-Garten K, Gilljam KM, Torseth K, Wilson DM III, Akbari M, et al. The region of XRCC1 which harbours the three most

common nonsynonymous polymorphic variants, is essential for the scaffolding function of XRCC1. DNA Repair. 2012;**11**:357-366. DOI: 10.1016/j.dnarep.2012.01.001

[69] Vasil'eva IA, Anarbaev RO, Moor NA, Lavrik OI. Dynamic light scattering study of base excision DNA repair proteins and their complexes. Biochimica et Biophysica Acta, Proteins and Proteomics. 2018. DOI: 10.1016/j.bbapap.2018.10.009

[70] 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. The Journal of Biological Chemistry. 2001;**276**:25541-25548. DOI: 10.1074/jbc.M102125200

[71] Khodyreva SN, Prasad R, Ilina ES, Sukhanova MV, Kutuzov MM, Liu Y, et al. Apurinic/apyrimidinic (AP) site recognition by the 5'-dRP/AP lyase in poly(ADP-ribose) polymerase-1 (PARP-1). Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**:22090-22095. DOI: 10.1073/pnas.1009182107

[72] Sukhanova MV, Abrakhi S, Joshi V, Pastre D, Kutuzov MM, Anarbaev RO, et al. 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 Research. 2016;**44**:e60. DOI: 10.1093/nar/gkv1476

[73] Schuhwerk H, Bruhn C, Siniuk K, Min W, Erener S, Grigaravicius P, et al. Kinetics of poly(ADP-ribosyl)ation, but not PARP1 itself, determines the cell fate in response to DNA damage *in vitro* and *in vivo*. Nucleic Acids Research. 2017;**45**:11174-11192. DOI: 10.1093/nar/gkx717

[74] Virág L, Robaszkiewicz A, Rodriguez-Vargas JM, Oliver FJ. Poly(ADP-ribose) signaling in cell death. Molecular Aspects of Medicine. 2013;**34**:1153-1167. DOI: 10.1016/j.mam.2013.01.007

[75] Altmeyer M, Neelsen KJ, Teloni F, Pozdnyakova I, Pellegrino S, Grøfte M, et al. Liquid demixing of intrinsically disordered proteins is seeded by poly(ADP-ribose). Nature Communications. 2015;**6**:8088. DOI: 10.1038/ncomms9088

[76] Vohhodina J, Harkin DP, Savage KI. Dual roles of DNA repair enzymes in RNA biology/post-transcriptional control. Wiley Interdisciplinary Reviews: RNA. 2016;**7**:604-619. DOI: 10.1002/wrna.1353

[77] Martin-Hernandez K, Rodriguez-Vargas JM, Schreiber V, Dantzer F. Expanding functions of ADP-ribosylation in the maintenance of genome integrity. Seminars in Cell & Developmental Biology. 2017;**63**:92-101. DOI: 10.1016/j.semcdb.2016.09.009

[78] Alemasova EE, Lavrik OI. At the interface of three nucleic acids: The role of RNA-binding proteins and poly(ADP-ribose) in DNA repair. Acta Naturae. 2017;**9**:4-16

[79] Prasad R, Liu Y, Deterding LJ, Poltoratsky VP, Kedar PS, Horton JK, et al. HMGB1 is a cofactor in mammalian base excision repair. Molecular Cell. 2007;**27**:829-841. DOI: 10.1016/j.molcel.2007.06.029

[80] Liu Y, Prasad R, Wilson SH. HMGB1: Roles in base excision repair and related function. Biochimica et Biophysica Acta. 2010;**1799**:119-130. DOI: 10.1016/j.bbagrm.2009.11.008

[81] Balliano A, Hao F, Njeri C, Balakrishnan L, Hayes JJ. HMGB1 stimulates activity of polymerase β on nucleosome substrates. Biochemistry.

2017;**56**:647-656. DOI: 10.1021/acs.biochem.6b00569

[82] Kaur S, Coulombe Y, Ramdzan ZM, Leduy L, Masson JY, Nepveu A. Special AT-rich sequence-binding protein 1 (SATB1) functions as an accessory factor in base excision repair. The Journal of Biological Chemistry. 2016;**291**:22769-22780. DOI: 10.1074/jbc.M116.735696

[83] Paquet N, Adams MN, Leong V, Ashton NW, Touma C, Gamsjaeger R, et al. hSSB1 (NABP2/ OBFC2B) is required for the repair of 8-oxo-guanine by the hOGG1-mediated base excision repair pathway. Nucleic Acids Research. 2015;**43**:8817-8829. DOI: 10.1093/nar/gkv790

[84] Sharma N, Chakravarthy S, Longley MJ, Copeland WC, Prakash A. The C-terminal tail of the NEIL1 DNA glycosylase interacts with the human mitochondrial single-stranded DNA binding protein. DNA Repair. 2018;**65**:11-19. DOI: 10.1016/j.dnarep.2018.02.012

[85] Maher RL, Marsden CG, Averill AM, Wallace SS, Sweasy JB, Pederson DS. Human cells contain a factor that facilitates the DNA glycosylase-mediated excision of oxidized bases from occluded sites in nucleosomes. DNA Repair (Amst). 2017;**57**:91-97. DOI: 10.1016/j.dnarep.2017.06.029

[86] Gao Y, Li C, Wei L, Teng Y, Nakajima S, Chen X, et al. SSRP1 cooperates with PARP and XRCC1 to facilitate single-strand DNA break repair by chromatin priming. Cancer Research. 2017;**77**:2674-2685. DOI: 10.1158/0008-5472.CAN-16-3128

[87] Menoni H, Di Mascio P, Cadet J, Dimitrov S, Angelov D. Chromatin associated mechanisms in base excision repair - nucleosome remodeling and DNA transcription, two key players. Free Radical Biology & Medicine. 2017;**107**:159-169. DOI: 10.1016/j.freeradbiomed.2016.12.026

[88] Tell G, Fantini D, Quadrifoglio F. Understanding different functions of mammalian AP endonuclease (APE1) as a promising tool for cancer treatment. Cellular and Molecular Life Sciences. 2010;**67**:3589-3608. DOI: 10.1007/s00018-010-0486-4

[89] Poletto M, Lirussi L, Wilson DM III, Tell G. Nucleophosmin modulates stability, activity, and nucleolar accumulation of base excision repair proteins. Molecular Biology of the Cell. 2014;**25**:1641-1652. DOI: 10.1091/mbc.E13-12-0717

[90] Limpose KL, Corbett AH, Doetsch PW. BERing the burden of damage: Pathway crosstalk and posttranslational modification of base excision repair proteins regulate DNA damage management. DNA Repair. 2017;**56**:51-64. DOI: 10.1016/j.dnarep.2017.06.007

[91] Connelly KE, Hedrick V, Sobreira TJP, Dykhuizen EC, Aryal UK. Analysis of human nuclear protein complexes by quantitative mass spectrometry profiling. Proteomics. 2018;**14**:e1700427. DOI: 10.1002/pmic.201700427

[92] Yang G, Liu C, Chen SH, Kassab MA, Hoff JD, Walter NG, et al. Super-resolution imaging identifies PARP1 and the Ku complex acting as DNA double-strand break sensors. Nucleic Acids Research. 2018;**46**(7):3446-3457. DOI: 10.1093/nar/gky088

[93] Kosova AA, Lavrik OI, Khodyreva SN. Ku antigen interaction with apurinic/apyrimidinic sites: Nonhomologous end joining vs base excision repair. MOJ Proteomics & Bioinformatics. 2014;**1**:00018. DOI: 10.15406/mojpb.2014.01.00018

[94] Zhang N, Zhang Y, Zhao S, Sun Y. Septin4 as a novel binding partner of PARP1 contributes to oxidative

stress induced human umbilical vein endothelial cells injure. Biochemical and Biophysical Research Communications. 2018;**496**:621-627. DOI: 10.1016/j.bbrc.2018.01.105

[95] Ka NL, Na TY, Lee MO. NR1D1 enhances oxidative DNA damage by inhibiting PARP1 activity. Molecular and Cellular Endocrinology. 2017;**454**:87-92. DOI: 10.1016/j.mce.2017.06.004

[96] Li J, Bonkowski MS, Moniot S, Zhang D, Hubbard BP, Ling AJ, et al. A conserved NAD+ binding pocket that regulates protein-protein interactions during aging. Science. 2017;**355**:1312-1317. DOI: 10.1126/science.aad8242

[97] Sorokin AV, Selyutina AA, Skabkin MA, Guryanov SG, Nazimov IV, Richard C, et al. Proteasome-mediated cleavage of the Y-box-binding protein 1 is linked to DNA-damage stress response. The EMBO Journal. 2005;**24**:3602-3612

[98] Alemasova EE, Pestryakov PE, Sukhanova MV, Kretov DA, Moor NA, Curmi PA, et al. Poly(ADP-ribosyl)ation as a new posttranslational modification of YB-1. Biochimie. 2015;**19**:36-44. DOI: 10.1016/j.biochi.2015.10.008

[99] Alemasova EE, Moor NA, Naumenko KN, Kutuzov MM, Sukhanova MV, Pestryakov PE, et al. Y-box-binding protein 1 as a non-canonical factor of base excision repair. Biochimica et Biophysica Acta. 2016;**1864**:1631-1640. DOI: 10.1016/j.bbapap.2016.08.012

[100] Sengupta S, Mantha AK, Mitra S, Bhakat KK. Human AP endonuclease (APE1/ref-1) and its acetylation regulate YB-1-p300 recruitment and RNA polymerase II loading in the drug-induced activation of multidrug resistance gene MDR1. Oncogene. 2011;**30**:4482-4493. DOI: 10.1038/onc.2010.435

[101] Alemasova EE, Naumenko KN, Kurgina TA, Anarbaev RO, Lavrik OI. The multifunctional protein YB-1 potentiates PARP1 activity and decreases the efficiency of PARP1 inhibitors. Oncotarget. 2018;**9**:23349-23365. DOI: 10.18632/oncotarget.25158

[102] Almeida KH, Sobol RW. A unified view of base excision repair: Lesion-dependent protein complexes regulated by post-translational modification. DNA Repair. 2007;**6**:695-711. DOI: 10.1016/j.dnarep.2007.01.009

[103] Choi S, Joo HK, Jeon BH. Dynamic Regulation of APE1/Ref-1 as a therapeutic target protein. Chonnam Medical Journal. 2016;**52**:75-80. DOI: 10.4068/cmj.2016.52.2.75

[104] Schuhwerk H, Atteya R, Siniuk K, Wang ZQ. PARPing for balance in the homeostasis of poly(ADP-ribosyl)ation. Seminars in Cell & Developmental Biology. 2017;**63**:81-91. DOI: 10.1016/j.semcdb.2016.09.011

[105] Natarajan C, Takeda K. Regulation of various DNA repair pathways by E3 ubiquitin ligases. Journal of Cancer Research and Therapeutics. 2017;**13**:157-169. DOI: 10.4103/0973-1482.204879

[106] Piao L, Fujioka K, Nakakido M, Hamamoto R. Regulation of poly(ADP-ribose) polymerase 1 functions by post-translational modifications. Frontiers in Bioscience. 2018;**23**:13-26

[107] Ohashi Y, Itaya A, Tanaka Y, Yoshihara K, Kamiya T, Matsukage A. Poly(ADP-ribosyl)ation of DNA polymerase β *in vitro*. Biochemical and Biophysical Research Communications. 1986;**140**:666-673

[108] 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. The Journal of Biological Chemistry. 2015;**290**:3775-3783. DOI: 10.1074/jbc.M114.624718

[109] de Sousa MML, Bjørås KØ, Hanssen-Bauer A, Solvang-Garten K, Otterlei M. p38 MAPK signaling and phosphorylations in the BRCT1 domain regulate XRCC1 recruitment to sites of DNA damage. Scientific Reports. 2017;**7**:6322. DOI: 10.1038/s41598-017-06770-3

[110] Chou WC, Wang HC, Wong FH, Ding SL, Wu PE, Shieh SY, et al. Chk2-dependent phosphorylation of XRCC1 in the DNA damage response promotes base excision repair. The EMBO Journal. 2008;**27**:3140-3150. DOI: 10.1038/emboj.2008.229

[111] Hsu PC, Gopinath RK, Hsueh YA, Shieh SY. CHK2-mediated regulation of PARP1 in oxidative DNA damage response. Oncogene. 2018. DOI: 10.1038/s41388-018-0506-7

[112] Kim K, Pedersen LC, Kirby TW, DeRose EF, London RE. Characterization of the APLF FHA-XRCC1 phosphopeptide interaction and its structural and functional implications. Nucleic Acids Research. 2017;**45**:12374-12387. DOI: 10.1093/nar/gkx941

[113] Horton JK, Stefanick DF, Çağlayan M, Zhao ML, Janoshazi AK, Prasad R, et al. XRCC1 phosphorylation affects aprataxin recruitment and DNA deadenylation activity. DNA Repair. 2018;**64**:26-33. DOI: 10.1016/j.dnarep.2018.02.004

[114] Horton JK, Seddon HJ, Zhao ML, Gassman NR, Janoshazi AK, Stefanick DF, et al. Role of the oxidized form of XRCC1 in protection against extreme oxidative stress. Free Radical Biology & Medicine. 2017;**107**:292-300. DOI: 10.1016/j.freeradbiomed.2017.02.005

[115] Hu LY, Chang CC, Huang YS, Chou WC, Lin YM, Ho CC, et al. SUMOylation of XRCC1 activated by poly (ADP-ribosyl)ation regulates DNA repair. Human Molecular Genetics. 2018;**27**:2306-2317. DOI: 10.1093/hmg/ddy135

[116] Roychoudhury S, Nath S, Song H, Hegde ML, Bellot LJ, Mantha AK, et al. Human apurinic/apyrimidinic endonuclease (APE1) is acetylated at DNA damage sites in chromatin, and acetylation modulates its DNA repair activity. Molecular and Cellular Biology. 2017;**37**:e00401-e00416. DOI: 10.1128/MCB.00401-16

[117] Weiser BP, Stivers JT, Cole PA. Investigation of N-terminal phospho-regulation of uracil DNA glycosylase using protein semisynthesis. Biophysical Journal. 2017;**113**:393-401. DOI: 10.1016/j.bpj.2017.06.016