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REVIEW

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

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Abstract Oxidized bases in the mammalian genome, which are invariably mutagenic due to their mispairing property, are continuously induced by endogenous reactive oxygen species and more abundantly after oxidative stress. Unlike bulky base adducts induced by UV and other environmental mutagens in the genome that block replicative DNA polymerases, oxidatively damaged bases such as 5-hydroxyuracil, produced by oxidative deamination of cytosine in the template strand, do not block replicative polymerases and thus need to be repaired prior to replication to prevent mutation. Following up our earlier studies, which showed that the Nei endonuclease VIII like 1 (NEIL1) DNA glycosylase, one of the five base excision repair (BER)-initiating enzymes in mammalian cells, has enhanced expression during the S-phase and higher affinity for replication fork-mimicking single-stranded (ss) DNA substrates, we recently provided direct experimental evidence for NEIL1's role in replicating template strand repair. The key requirement for this event, which we named as the 'cow-catcher' mechanism of pre-replicative BER, is NEIL1's non-productive binding (substrate binding without product formation) to the lesion base in ss DNA template to stall DNA synthesis, causing fork regression. Repair of the lesion in reannealed duplex is then carried out by NEIL1 in association with the DNA replication proteins. NEIL1 (and other BER-initiating enzymes) also interact with several accessory and non-canonical proteins including the heterogeneous nuclear ribonucleoprotein U and Y-box-binding protein 1 as well as high mobility group box 1 protein, whose precise roles in BER are still obscure. In this review, we have discussed the recent advances in our understanding of oxidative genome damage repair pathways with particular focus on the pre-replicative template strand repair and the role of scaffold factors like X-ray repairs cross-complementing protein 1 and poly (ADP-ribose) polymerase 1 and other accessory proteins guiding distinct BER sub-pathways.

Keywords Base excision repair · Single strand break repair · DNA glycosylase · Reactive oxygen species · Oxidized DNA bases · Pre-replicative repair of oxidized bases · NEIL1 · Non-canonical proteins

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Introduction

The human cell genome is continuously exposed to oxidative damage by reactive oxygen species (ROS), generated both endogenously during metabolic processes, and by exogenous agents including environmental carcinogens and ionizing radiation (IR). Reactive nitrogen species (RNS) NO· generated by NO synthase (NOS) reacts with superoxide anion ($O_2^{\cdot-}$) to produce peroxynitrite (ONOO−) and other reactive species [1]. In addition, localized unfolding of chromatin during DNA transactions,

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particularly replication and transcription, makes DNA more vulnerable to genotoxic agents. This necessitates continuous surveillance of the genome via DNA repair and other DNA damage response proteins by their dynamic interaction not only with the DNA but also with replication and transcription machineries as well as histones, and other cellular components. During the past few decades, repair of oxidative/alkylated base lesions and single-strand breaks (SSBs) via base excision repair (BER) and single-strand break repair (SSBR) pathways, respectively, has been extensively studied. More recently, complexities and cross-talks among various repair pathways with replication/transcription machineries and non-canonical proteins are being recognized. In this review, we have focused on the unique BER sub-pathways associated with DNA replication, which is critical for preventing mutations and the roles of some accessory proteins therein. These proteins via their unique ability to involve in specific multiprotein interactions not only enhance BER/SSBR activity but can also regulate cross-talk among repair sub-pathways.

An overview of oxidative genomic insults in aerobic cells

Oxidizing radicals and other compounds, broadly categorized as ROS and RNS, are generated as by-products of respiration and other cellular activities, and also as a result of exposure to chemical pollutants, drugs, tobacco smoke, xenobiotics and IR. ROS include superoxide ($O_2^{\cdot-}$), hydroxyl (OH·), peroxyl (RO_2·), and alkoxyl (RO·) radicals and non-radical species like peroxynitrite, singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2) [2]. NADPH oxidases (NOX), a group of membrane bound enzymes are major producers of endogenous ROS, and are often activated by multiple cellular stress factors including nutritional deficiency and inflammation [3]. $O_2^{\cdot-}$ is also produced in the inner mitochondrial membrane due to incomplete reduction of O_2 at Complex I (NADH dehydrogenase) and Complex III (cytochrome bc1 complex) in the electron transport chain. OH·, the most potent oxidizing agent is generated from $O_2^{\cdot-}$ and H_2O_2 via Haber–Weiss reaction, and also from H_2O_2 by Fenton reaction catalyzed by iron (Fe) and copper (Cu) ions. These essential transition metals are usually sequestered by storage proteins (e.g. ferritin/transferrin for Fe and ceruloplasmin for Cu); however, pathological conditions or cellular stress augments their accumulation in the nucleus in the free ionic form resulting in enhanced ROS production [4]. These reactive molecules damage genomic DNA by oxidizing bases as well as the deoxyribose backbone, leading to various base modifications, formation of apurinic/apyrimidinic (AP) sites and strand breaks. The oxidized DNA base lesions induced by ROS include 8-oxo-7,8 dihydroguanine (8-oxo-G), FapyG, thymine glycol, 5-hydroxymethyluracil, 5-formyluracil, 5-methylcytosine, etc. (Fig. 1a) [5]. In addition to base oxidation, OH· also reacts with DNA by H abstraction leading to sugar modifications, with or without cleavage of the pentose ring. Such chemical modifications often generate AP sites or strand breaks with blocked termini that need processing by specific end-processing enzymes prior to repair. Common 3′ terminal blocking groups are phosphate, phosphoglycolaldehyde, and phosphoglycerate, while non-ligatable 5′ termini include OH and phosphodeoxyribose derivatives [6]. RNS include peroxynitrite (ONOO−), nitrogen dioxide radical (NO_2·), nitroxyl anion (NO^-), nitrosonium cation (NO^+), etc. [1] and cause nitration, nitrosation and deamination of DNA bases. NO· also indirectly generates exocyclic DNA adducts like 1, N^6-ethenoadenine (εA) and N^2,3-ethenoguanine by reaction of secondary lipid peroxidation products with DNA [7].

BER/SSBR pathways are crucial for the repair of oxidative genome damage

It is commonly postulated that approximately 10^4 oxidative lesions are produced in the mammalian genome per day, which are efficiently repaired via BER/SSBR proteins, with overlapping reaction steps [8]. Unrepaired base lesions and AP sites could be replicated by DNA translesion synthesis (TLS) polymerases whose replication infidelity could cause point mutations. Spontaneous deamination of C to U, or ROS mediated generation of 5-hydroxyuracil (5-OHU) leads to GC → AT transition mutation during replication via misincorporation of A opposite 5-OHU, albeit at a low frequency [9]. 8-oxo-G generated by oxidation of G mispairs with A, resulting in GC → TA transversion mutation [10]. Accumulation of such spontaneous mutations likely generated single nucleotide polymorphism (SNPs) observed in the mammalian genome and also could lead to carcinogenic mutations. Furthermore, accumulation of unrepaired SSBs in replicating genome would lead to lethal double-strand breaks (DSBs) [11]. Thus BER/SSBR is an essential process for constant surveillance of the chromatin to prevent mutations from oxidative damage [12].

Initial characterization of minimal BER reactions

Early enzymes of BER were first discovered in *E. coli*—excision of uracil from DNA by a monofunctional DNA glycosylase (later named as uracil-DNA glycosylase or UDG) [13] and demonstration of AP endonuclease activity of endonuclease II [14–16]. Other monofunctional DNA

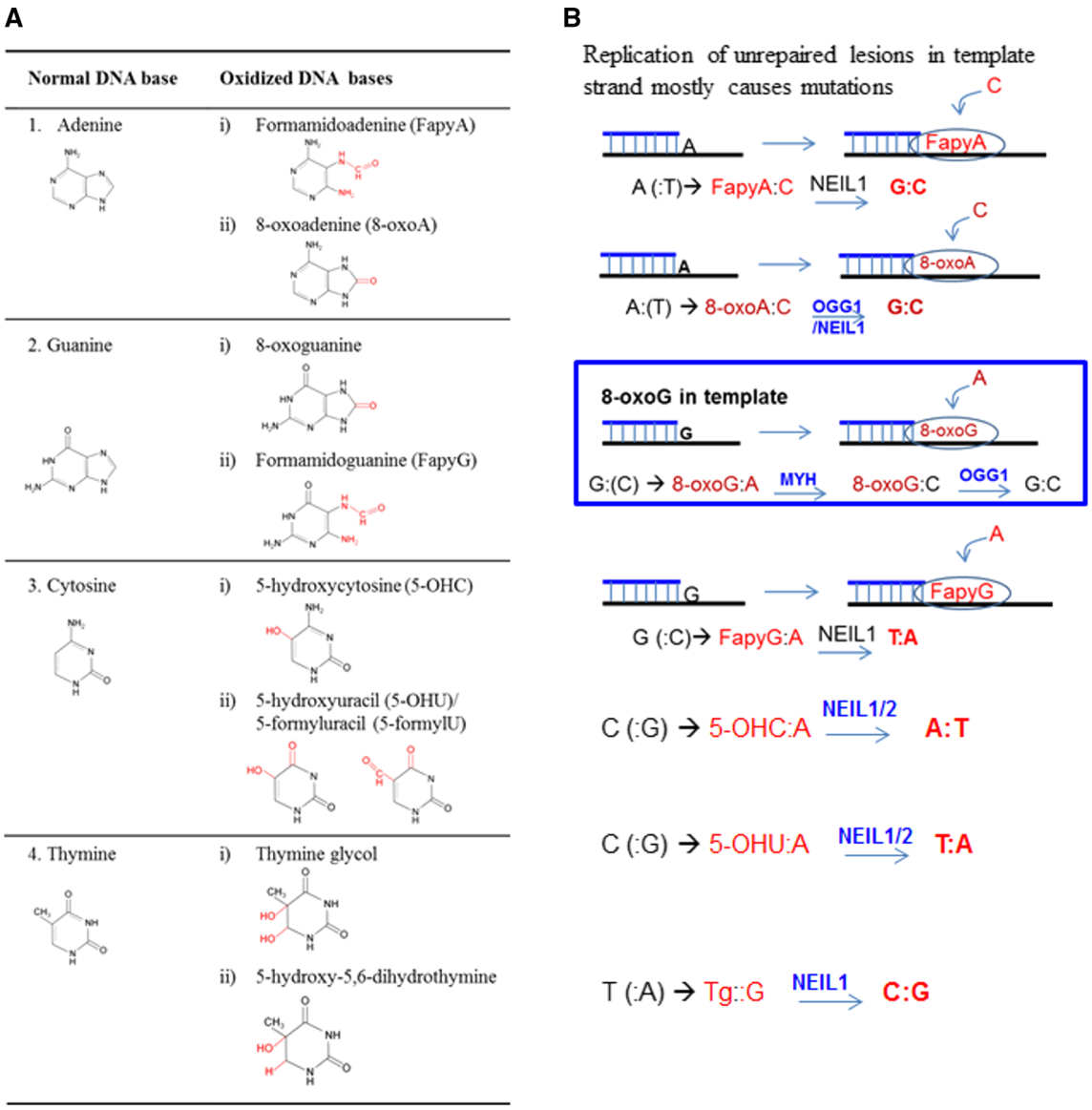


Fig. 1 Schematic illustration of how unrepaired replication of majority of oxidized DNA base lesions causes irreversible mutations. **a** Common oxidized base modifications. **b** Illustration of replication of various base lesions in template strand, which cause mutations except for 8-oxo-G, where a misincorporated A, is reversed by MYH, followed by OGG1-mediated removal of 8-oxo-G

glycosylases, for example, SMUG1 remove U and 5-hydroxycytosine (5-OHC) while thymine DNA glycosylase (TDG) removes T in T·G mismatch or T generated by deamination of 5-methyl cytosine. The two-step mechanism involving base excision enzyme, DNA *N*-glycosidase and endonuclease II mediated strand incision at the generated AP site, was reported for repair of alkylated DNA [17]. The mammalian AP-endonuclease APE1 (ortholog of endonuclease III or Xth in *E. coli*) hydrolyzes the phosphodiester bond 3′ to an AP site and produces 3′OH and 5′ deoxyribosephosphate (5′dRP) termini [18, 19]. Several groups subsequently established that oxidized base-specific glycosylases, e.g. 8-oxoguanine DNA glycosylase (OGG1), endonuclease III-like protein 1 (NTH1), NEIL1–3 which are orthologs of *E. coli* Fpg, Nth and Nei, respectively, are bi-functional by having both base excision and intrinsic AP lyase activity. These enzymes cleave the phosphodiester bond after base removal to generate SSB without requiring AP endonuclease activity [17, 20]. OGG1 and NTH1 possess β-elimination lyase activity to generate a 3′ phospho α,β-unsaturated aldehyde (3′PUA), chemically called phosphor 4-hydroxylpentenal at the strand break along with 5′phosphate (P) terminus, while NEILs carry out β, δ-elimination to form 3′P and 5′P termini [6]. In subsequent end cleaning reactions in mammalian cells, 5′dRP is removed by 5′dRP lyase activity of Polβ followed by

incorporation of the correct base to fill the gap. 3′PUA is cleaved by mammalian APE1 to produce the 3′OH terminus. In contrast, the 3′P generated by NEILs is removed by polynucleotide kinase/3′-phosphatase (PNKP) [21]. Thus, for oxidized bases, DNA glycosylases that carry out either β-elimination or β,δ-elimination determine the subsequent OGG1/APE1- or NEILs/PNKP-dependent steps, respectively. In the minimal BER pathway, excision of damaged base by OGG1/APE1 or NEILs/PNKP leaves a 1-deoxynucleotide gap whose repair (single nucleotide/short patch BER: SN/SP-BER) involves a DNA polymerase (Polβ), and a DNA ligase (Lig3α).

The second BER sub-pathway, known as long patch (LP) BER, which involves displacement and resynthesis of 2–8 nts following excision of the base lesion was reported by Dogliotti, Wilson, Klungland and their colleagues [22–24]. While the factors regulating pathway choice between SN- vs. LP-BER is incompletely understood, it was suggested that the latter occurs when Polβ fails to remove the modified or oxidized 5′ deoxyribose termini at the strand break [6]. In that case Polβ or Polδ/ε with the help of the replication sliding clamp, proliferating cell nuclear antigen (PCNA) and the clamp loader replication factor C (RFC) displace the damage containing strand and incorporates >2 nts producing a 5′-single stranded flap structure, which is cleaved by flap endonuclease 1 (FEN1). Ligation of the nick in LP-BER is usually mediated by DNA ligase 1 (Lig1) [25]. In addition to the oxidative modification of the 5′ sugar moiety, low ATP concentration may also guide the pathway to LP-BER [26].

The end processing, gap filling and ligation reactions in SSBR broadly share proteins and reaction steps with BER, although, additional factors may be involved in SSB recognition and stabilization inducing the SSB sensor PARP1 and scaffold protein X-ray repairs cross-complementing protein 1 (XRCC1).

Unique BER sub-pathways for repair during DNA replication and transcription

The unfolding of chromatin required at the replication fork or in the transcription bubble renders DNA more prone to oxidative damage than in condensed chromatin [27, 28]. While replication of unrepaired oxidized base lesions, most of which do not block DNA or RNA polymerases, could be mutagenic, their transcription could produce mutant proteins, which could be toxic and/or inactive. Contrary to the bulky adducts which block replication or transcription and are recognized by nucleotide excision repair (NER), recognition and repair of oxidized lesions is not understood. While, there is an urgency to repair these lesions during all DNA transactions, how these are recognized in replicating template or transcribed strand is not clear. Recent studies by us and others have suggested that there are distinct BER sub-pathways for transcriptionally active versus inactive genomes as well as for quiescent versus replicating genome [12, 29–32]. Our initial studies showed that both NEILs are active on bubble and fork-structured DNA substrates that mimic transcription and DNA replication intermediates, respectively [32]. However, only NEIL1 is upregulated during the S-phase, based on which we had proposed that NEIL1 is preferentially involved in replication-associated BER (RA-BER) [33] and NEIL2 in transcription-coupled BER (TC-BER) as demonstrated by Hazra and colleagues, where it specifically associates with RNA polymerase II and heterogeneous nuclear ribonucleoprotein U (hnRNP-U) [29].

Replication-associated BER is critical for preventing mutations in cycling cells

Template strand-specific pre-replicative versus progeny strand-specific post-replicative base damage repair at the replication fork

An unusual feature of oxidized bases is their formation in free nucleotide pool and incorporation into nascent DNA. In this situation, repair of an incorrect or oxidized base incorporated from the nucleotide pool, immediately after replication has been described as post-replicative repair [34, 35]. This ‘progeny strand-specific post-replicative repair’ as we would prefer to call it, is also tightly coupled to replication machinery, and has been described for the base incorporated opposite to U or unrepaired 8-oxo-G. When 8-oxo-G is not repaired prior to replication, replicative DNA polymerases (Pol δ/ε) may incorporate an A (or the normal base C) opposite the 8-oxo-G, generating an A:8-oxo-G mispair [10]; the mammalian homolog of *E. coli* MutY, MYH excises this mispaired A (Fig. 1b) [35–37]. Similarly, a U:A mispair generated during replication of U opposite an A, was shown to be repaired *post-replicatively* by UNG2 (nuclear form of UDG) [34]. Both UNG2 and MYH associate with PCNA at the replication foci [34, 38], which appears to recruit these glycosylases to the replication sites, facilitating their repair only in the progeny strand [34, 35]. Thus, these glycosylases interact with the replication machinery, analogous to the classical mismatch repair (MMR) pathway targeting the nascent DNA for post-replicative repair [35].

However, unlike U, which is misincorporated in the progeny strand during replication could be specifically repaired by UNG2, U generated in the template strand due to deamination of C needs to be repaired prior to replication to prevent fixation of mutation. Similarly, other oxidative lesions such as 5-OHU and thymine glycol,

major substrates of NEIL glycosylases, need to be repaired *pre-replicatively* in the template strand to maintain genomic integrity. Moreover, increased preference of TLS polymerase Polι to insert G opposite 5-OHU rather than A also reduces mutagenic potential of 5-OHU [9]. It is thus evident that efficient recognition of these lesions is a prerequisite for efficient pre-replicative repair. The two RA-BER pathways—template strand-associated pre-replicative and progeny strand-specific post-replicative BER are schematically illustrated in Fig. 2.

How can a damaged base be repaired in the single-stranded DNA template prior to replication?

We recently provided direct evidence for NEIL1's ability to repair oxidized bases by co-opting DNA replication proteins [31]. NEIL1 is present in cells as a component of the DNA replication complex where it carries out surveillance of oxidized bases in the replicating template. Thus, it acts as a 'cow-catcher', which is in consistence with its preference for binding to lesions in the ss DNA. However, if it excises oxidized bases and cleaves the template strand in replicating DNA a double-strand break will be generated. To avoid this, the ss DNA-binding protein RPA, essential for replication and other DNA transactions, coats the ss DNA template at the replication fork, and inhibits NEIL1's activity via direct interaction [39]. Further, we observed in in vitro reaction that NEIL1 inhibits primer elongation of RPA-coated template by Polδ, thereby stalling the replication complex at the lesion site. The replication is expected to cause regression of the replication fork causing fork collapse. Reannealing of the unwound region spanning the lesion by a helicase such as SMARCAL1 or Werner helicase (WRN) [40, 41] would then allow repair of the lesion by NEIL1 which is activated by PCNA [33]. Repair synthesis and ligation to seal the nick would be finally carried out by the replicative polymerase Polδ followed by Lig1 rather than by the canonical BER enzymes Polβ and Lig3α.

Oxidatively damaged bases such as spiro- and imino-hydantoins and thymine glycol block replication and were shown to be repaired by NEIL1 [42–44]. NEIL1 also functions in repairing replication blocking oxidative genome lesions, as indicated by the inhibition of DNA chain growth in oxidatively stressed NEIL1-deficient cells [31].

Backup function of NEIL2 in pre-replicative BER

We showed earlier that NEIL2, with similar activity on ss DNA as NEIL1 but without S phase-specific activation, has been linked to repair during transcription [45]. As far as its role in RA-BER is concerned, NEIL2 deficiency alone does not inhibit DNA replication after oxidative stress but enhances replication inhibition in NEIL1-deficient cells. This suggests that in the absence of NEIL1, NEIL2 acts as a 'relief pitcher' in removing cytotoxic base lesions from the replicating genome. The broad and overlapping substrate range of oxidized base-specific glycosylases ensures their ability to provide the backup function when needed [6, 46–48]. This is consistent with the observation that mouse mutants and cells lacking individual glycosylases are viable without a strong phenotype [49–51]. However, combined deficiency of two glycosylases strongly increases cancer susceptibility [52–54].

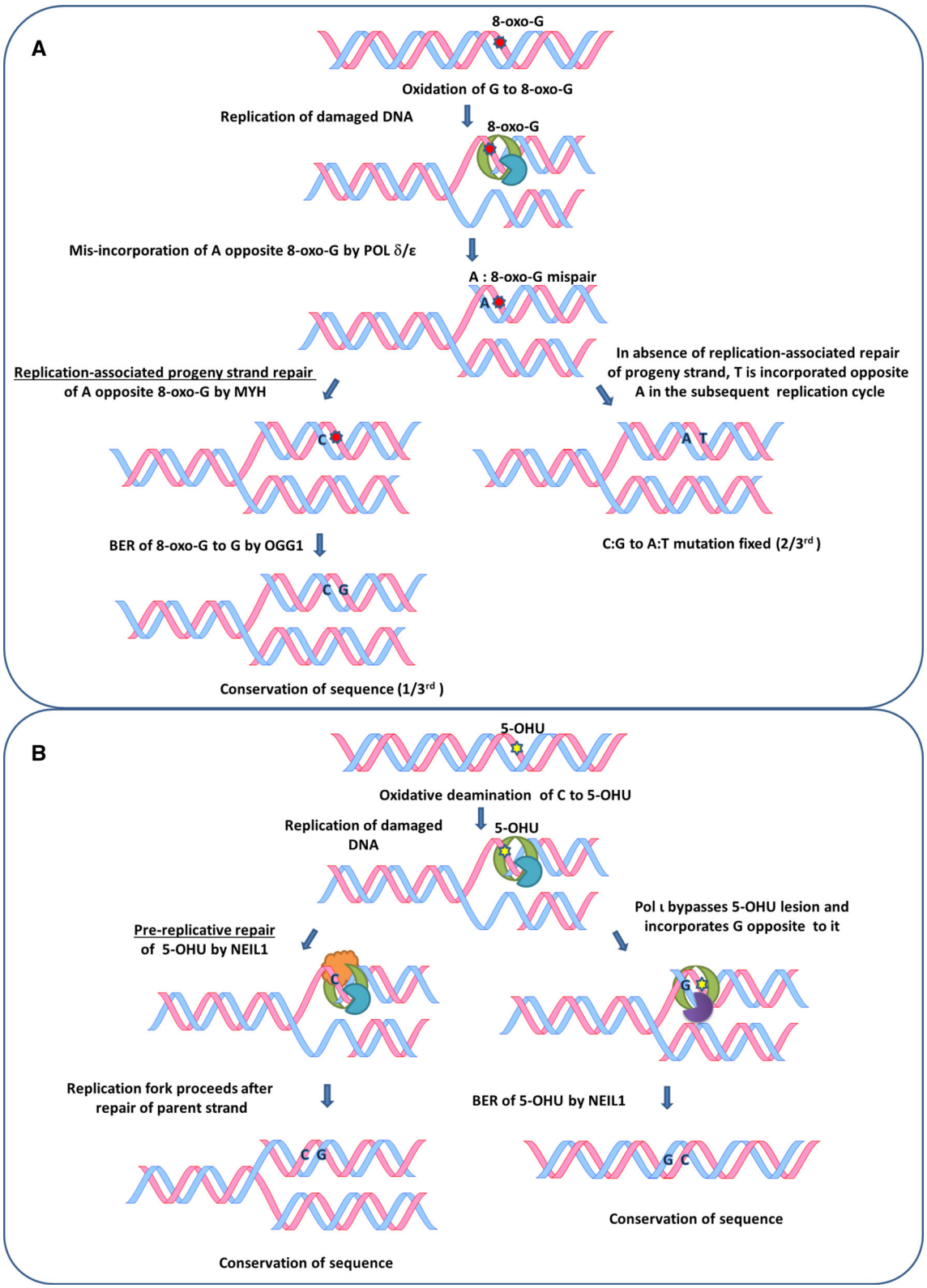
Role of 9-1-1 in repair at stalled replication forks

Upon genotoxic stress, Rad9–Rad1–Hus1 or 9-1-1, a heterotrimeric doughnut-shaped sliding clamp, structurally similar to the replication clamp PCNA [55], and active after DNA damage, is loaded onto DNA by a clamp loader, an RFC variant containing Rad17 which ensures stabilization of the replication fork through Chk1-mediated G2/M arrest [55]. Moreover, 9-1-1 protects stalled replication forks via recruitment of WRN helicase [56, 57]. It has also been implicated in BER. While 9-1-1 mediated stimulation of NEIL1, TDG and Polβ [58–60] (but not replicative polymerases Polα and Polδ) via physical interaction suggests its direct involvement in SP-BER, stimulation of FEN1 and Lig1 by 9-1-1 suggests its role in repair at stalled replication forks via recruitment of the LP-BER machinery [61, 62].

New paradigm: DNA repair complexes are formed via disordered segments

While the minimal BER/SSBR reaction reconstituted in vitro requires only four or five enzymes [6], we and others have demonstrated that the in vivo repair is highly complex, particularly in the mammals. The basic repair reactions for oxidative genome damage are conserved from the bacteria to humans; however, additional complexities have evolved in higher organisms, which include cross-talk between BER/SSBR with other metabolic pathways in the cell including DNA replication, transcription and cell cycle regulation, as already discussed. In addition, post-translational modifications of repair proteins, e.g. acetylation could also regulate repair [63, 64].

Secondary structure prediction of human (and other mammalian) BER enzymes revealed terminal disordered segments, which likely evolved to cope with the complexities of BER/SSBR pathways in higher organisms. Unlike their bacterial orthologs, human DNA glycosylases as well as APE1 have unstructured domains either at the C or the N terminus which are required for the enzymes' critical functions including DNA scanning, protein–protein interactions


A
8-oxo-G
Oxidation of G to 8-oxo-G
Replication of damaged DNA
8-oxo-G
Mis-incorporation of A opposite 8-oxo-G by POL δ/ε
A : 8-oxo-G mispair
A
Replication-associated progeny strand repair of A opposite 8-oxo-G by MYH
In absence of replication-associated repair of progeny strand, T is incorporated opposite A in the subsequent replication cycle
C
A T
BER of 8-oxo-G to G by OGG1
C:G to A:T mutation fixed (2/3rd)
C G
Conservation of sequence (1/3rd)
B
5-OHU
Oxidative deamination of C to 5-OHU
Replication of damaged DNA
5-OHU
Pol ι bypasses 5-OHU lesion and incorporates G opposite to it
Pre-replicative repair of 5-OHU by NEIL1
C
G
Replication fork proceeds after repair of parent strand
BER of 5-OHU by NEIL1
C G
G C
Conservation of sequence
Conservation of sequence

◀**Fig. 2** A model for replication-associated progeny strand versus template strand repair. **a** Progeny strand-specific post-replicative repair: Mismatch repair protein MYH recruited by PCNA at the replication fork removes A misincorporated opposite 8-oxo-G in the template, followed by gap filling with C. 8-oxo-G is subsequently repaired through BER initiated by OGG1. In absence of such post-replicative repair of the progeny strand, T could be incorporated during replication of the progeny strand, thus fixing the C:G to A:T transversion. **b** Template strand-specific pre-replicative repair: NEIL1, as part of the replication complex, acts as a 'cow-catcher' for surveillance of the template strand, prior to DNA synthesis. On encountering a lesion, NEIL1 non-productively binds the oxidized base in RPA-coated single strand template to stall Polδ. Subsequent fork regression brings the lesion back in the parent duplex segment, which is repaired by NEIL1 and replication proteins. On the other hand, Polι may correctly bypass the lesion followed by its repair through BER

and subcellular localization [6]. The N terminal tail (1–95 residues) of NTH1 containing nuclear and mitochondrial localization signal sequences also negatively regulates its activity by reducing product dissociation [65]. Human NEIL1 has a 100 residue long non-crystallizable C-terminal segment, which is absent in the bacterial ortholog Nei [66]. During the past few years, our lab has extensively characterized the role of NEIL1's C-terminal tail critical in stabilizing NEIL1's structure and enhancing its overall repair activity through interaction with various conventional and non-canonical BER proteins [67, 68]. Based on small angle X-ray scattering (SAXS), fluorescence-based experiments and molecular modeling, we have suggested that the flexible domain, normally packed in folded structure of the core is released, presumably to facilitate 'DNA scanning' and interaction with various BER proteins [69]. As already stated, NEIL1 via its C-terminal tail not only interacts with downstream SN-BER proteins such as Polβ, Lig3α and XRCC1 but also co-opts LP-BER proteins like FEN-1, PCNA, RPA and Polδ for pre-replicative repair [31]. In another example, the disordered N-terminal (1–61 amino acids; aa) domain of APE1, which is absent in bacterial prototype Xth was found to be dispensable for its DNA repair-linked AP-endonuclease activity [70, 71], but has a critical role in interactions in multiprotein complexes of higher eukaryotes [72–75]. Furthermore, NEIL1-initiated BER activity has been shown to be stimulated by non-canonical DNA repair proteins like WRN [76] and hnRNP-U, an RNA-binding protein [77], whose precise in vivo role is still not understood.

Involvement of accessory proteins in mammalian BER/SSBR and their emerging role(s) in repair regulation

One unique feature of mammalian BER/SSBR is the involvement of several accessory and non-canonical proteins as observed in *in-cell* repair. While the list of non-canonical proteins implicated in BER/SSBR is growing, here we will discuss the role of scaffold factor XRCC1, SSB sensor PARP1, RNA-binding protein hnRNP-U, high mobility group box 1 protein (HMGB1) and Y-box-binding protein 1 (YB-1). Such accessory proteins may not only induce structural changes at the damaged site, enabling their rapid detection by conventional damage sensor/repair initiating proteins but also facilitate protein–protein interactions to enhance coordination among the repair steps (Table 1). Through literature-based Ingenuity pathway analysis (IPA) tool, we analyzed the interactome of these accessory factors with various chromatin modifying proteins, DNA polymerases, DNA end-processing enzymes, ligases, DNA glycosylases and non-homologous end joining (NHEJ) proteins (Fig. 3).

The accessory proteins may also be important in stabilizing large dynamic 'repairosome' complexes by providing extended interaction surface area. As observed for early BER/SSBR proteins [78], many of these accessory proteins possess disordered regions either as a terminal appendage or as an internal segment which are commonly involved in protein–protein interactions [79]. We mapped these disordered segments using 'Predictor Of Naturally Disordered Regions' (PONDR) algorithm (Fig. 4). The unique structural features of these proteins and how their deficiency or mutation may impact BER/SSBR could be important for establishing their role in cancer and also for exploring them as targets for cancer adjuvant therapy.

Scaffolds and damage sensors

XRCC1 (X-ray cross-complementing factor 1)

XRCC1, a scaffold protein with no known enzymatic activity, was shown to co-ordinate BER/SSBR by forming multiprotein repair complexes [80]. It stabilizes Lig3α and at least 80 % of cellular Lig3α was found to be bound to XRCC1 [81]. Human XRCC1 with 633 residues (~85 kDa) consists of three interactive domains—the N terminal domain (NTD) and two BRCA1 C Terminus (BRCT) domains along with a nuclear localization signal, and each domain has unique interacting partners (Fig. 4).

PONDR analysis reveals two highly disordered segments in XRCC1 located between NTD-BRCT1 (183–315 aa) and BRCT1–BRCT2 (403–538 aa), each of which has unique binding partners. While the first disordered region binds to PCNA, APE1and OGG1 [82–84], the second has affinity for PNKP [85] (Fig. 4). DNA glycosylases NTH1, NEIL2, OGG1and MPG interact with the BRCT1 region of XRCC1 [86]. Co-localization of XRCC1 and PCNA in replication-specific foci [82] and role of XRCC1–PCNA interaction in LP-BER [87] suggest

Table 1 Roles of scaffold factors—XRCC1 and PARP1, accessory proteins—HMGB1, hnRNP-U and YB-1 and clamp 9-1-1 in interacting with and/or stimulating various DNA repair and replication proteins and chromatin modification factors with their corresponding references (derived from IPA analysis, Fig. 3)

Accessory protein	BER/SSBR protein	Interactive roles
HMGB1	FEN1	Stimulates FEN1 activity and promotes Polβ mediated LP-BER [139, 142]
	APE1	Stimulates APE1-mediated incision at AP sites and enhances CAG repeat expansion [139, 142]
	MSH2	Cooperates with MSH2/MSH3 to stabilize hairpins and stimulates FEN1 "alternate cleavage" [141, 179]
	ACF/CHRAC	Binds with distorted/damaged DNA and stimulates CHRAC- and ACF-mediated nucleosome remodeling [143] [144]
PARP1	NEIL1, OGG1	Physically interacts with DNA glycosylases NEIL1 and OGG1 to inhibit their incision activities; OGG1 stimulates poly ADP-ribosylation activity of PARP1 [110] [180]
	APTX	Helps in recruitment of APTX at SSBs at blocked termini [181]
	FEN1	PARP1 inhibition reduces FEN1 accumulation at DNA damage sites [182]
	PNKP	PNKP physically interacts with PARP1, through FHA domain [183]
	PCNA	Regulates function of PCNA during replication of damaged DNA site [184]
	Pol β	Stimulates Pol β activity in LP-BER [185]
	Lig3α	Recruits Lig3α after PARylation at DNA strand breaks and modulates its activity [186]
	WRN	Regulates activity of WRN at DNA strand breaks depending upon its PARylated state [187]
	DNA-PK	Interacts with DNA-PK [188]
XRCC1	PARP1	Recruited by PARP1 through interaction via BRCT domains which negatively regulates its activity [189]
	PNKP	Recruits PNKP and enhances its 3′-phosphatase activity [85]
	NEIL1, NEIL2, OGG1, NTH1, MPG	Recruits multiple DNA glycosylases at base damage sites [86]
	APTX	Phosphorylated XRCC1 binds to Aprataxin via its FHA domain, enhancing stability of XRCC1 [190]
	APE1	Physically interacts with APE1 through its N-terminal region and stimulates its activity [83]
	Polβ	Interacts with Pol β via N-terminal domain and enhances BER [191, 192]
	Rev1	Interacts with Rev1 for post-replication repair [88]
	Polδ, Polλ	Interacts with Polδ and Polλ [89, 90]
	Lig3α	Stabilizes Lig3α through interaction via BRCT domains [193, 194]
	PCNA	Interacts with PCNA for G1/S-phase-specific role of XRCC1 in replication-coupled repair [82, 195]
	DNA-PK	Interacts with DNA-PK (via XRCC1 BRCT1 domain) and gets phosphorylated at serine 371 after IR treatment; stimulates DNA-PK activity [196]
hnRNP-U	NEIL1	Interacts with NEIL1 and enhances BER [77]
	NEIL2	Binds and stimulates NEIL2 activity [29]
	DNA-PK	DNA-PK phosphorylates hnRNP-U at Ser59 in response to DNA DSBs [127]
	PNKP	Interacts with FHA domain of PNK [183]
YB-1	NEIL2	C-terminal disordered tail of YB-1 interacts with NEIL2 N-terminal region and stimulates its incision activity [134]
	NTH1	Interacts with NTH1 and stimulates its DNA glycosylase and AP lyase activity [136]
	APE1	APE1 (preferably acetylated) interacts with YB-1 C-terminal disordered tail, enhancing its binding to Y-box elements but stimulation of APE1's activity could not be detected [72]
	Polβ	Interacts with Polβ [134]
	PCNA	Interacts with PCNA to exert its regulatory role in mismatch repair pathway [132, 197]
	Lig3α	Interacts with Lig3α [134]

Table 1 continued

Accessory protein	BER/SSBR protein	Interactive roles
9-1-1 (Rad9–Rad1–Hus1)	NEIL1	Interacts with NEIL1 and stimulates its activity [58]
	TDG	Interacts with TDG and stimulates its activity [59]
	Polβ	Interacts with and stimulates strand displacement synthesis by Polβ but not replicative DNA polymerases, Polα and Polδ [60]
	FEN1	Stimulates FEN1 activity, favoring LP-BER [62]
	WRN	Interacts with WRN helicase through Rad1 subunit which has crucial role in preventing DNA damage during replication fork stalling [56]
	LIG1	Modulates activity of Lig1 required in LP-BER [61]

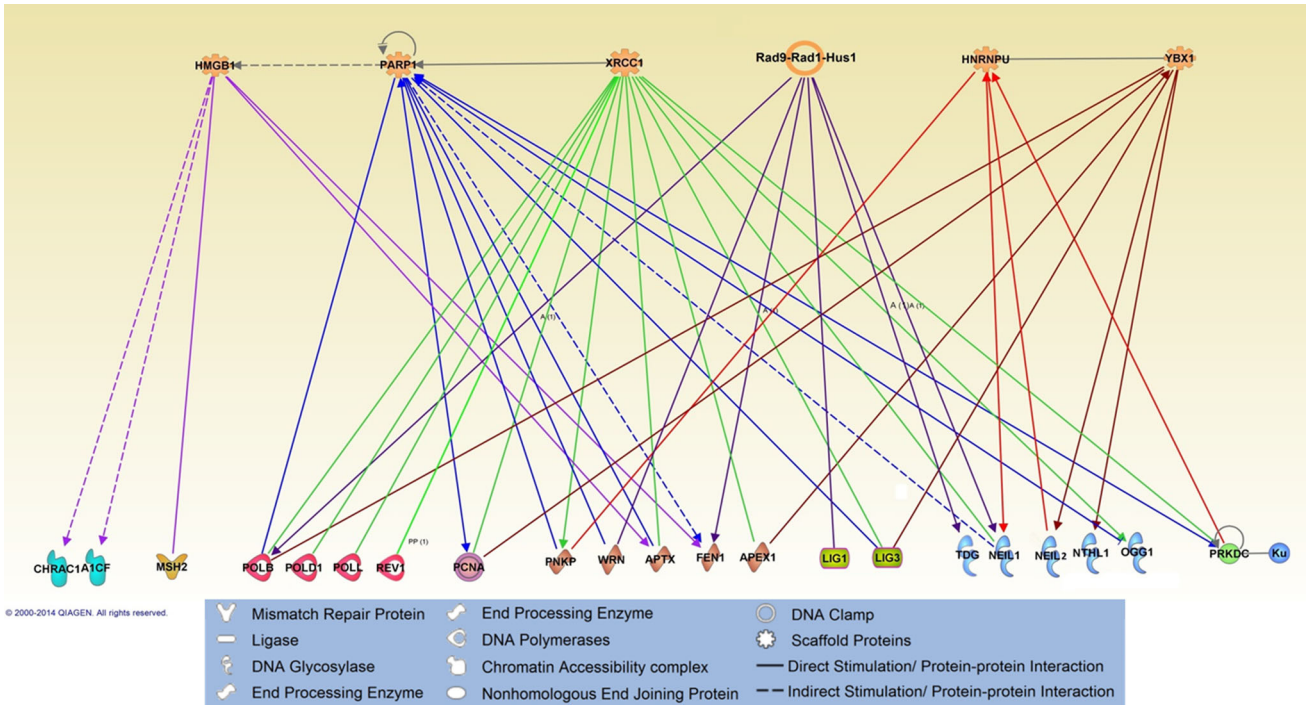


Fig. 3 Ingenuity pathway analysis (Qiagen) of accessory proteins that interact and/or stimulate various DNA repair and replication proteins and chromatin modification factors (see Table 1 for references derived from the IPA analysis)

XRCC1's role in replication-associated repair. XRCC1 also interacts with DNA polymerases Rev1 [88], Polδ and Polλ [89, 90]. While some of these interactions, mostly identified in vitro or in tumor cells with ectopic expression may imply their participation in specific repair sub-pathways, the in vivo significance is not known.

XRCC1's NTD (1–183 aa) has a beta sandwich domain that was shown to interact with nicked and gaped DNA substrates as well as with the palm–thumb domains of Polβ near the latter's active site [91–93]. Biochemical and molecular modeling studies suggest that the NTD via its interaction with both the SSB in DNA and Polβ surrounds the damaged site and performs dual function of protecting the DNA and recruiting the repair enzymes [94]. C12A XRCC1 mutant cells (defective in interaction with Polβ) are hypersensitive to H_2O_2 similar to the XRCC1 null cell lines. This underscores the biological role of XRCC1–Polβ interaction in oxidative stress-induced DNA repair [95]. Thus, XRCC1's scaffolding function is critical in formation of distinct repair complexes, particularly in response to oxidative DNA damage.

PARP (poly ADP-ribose polymerase)

The PARP family of proteins includes DNA break sensors (PARP1–3) which synthesize linear and branched chains of

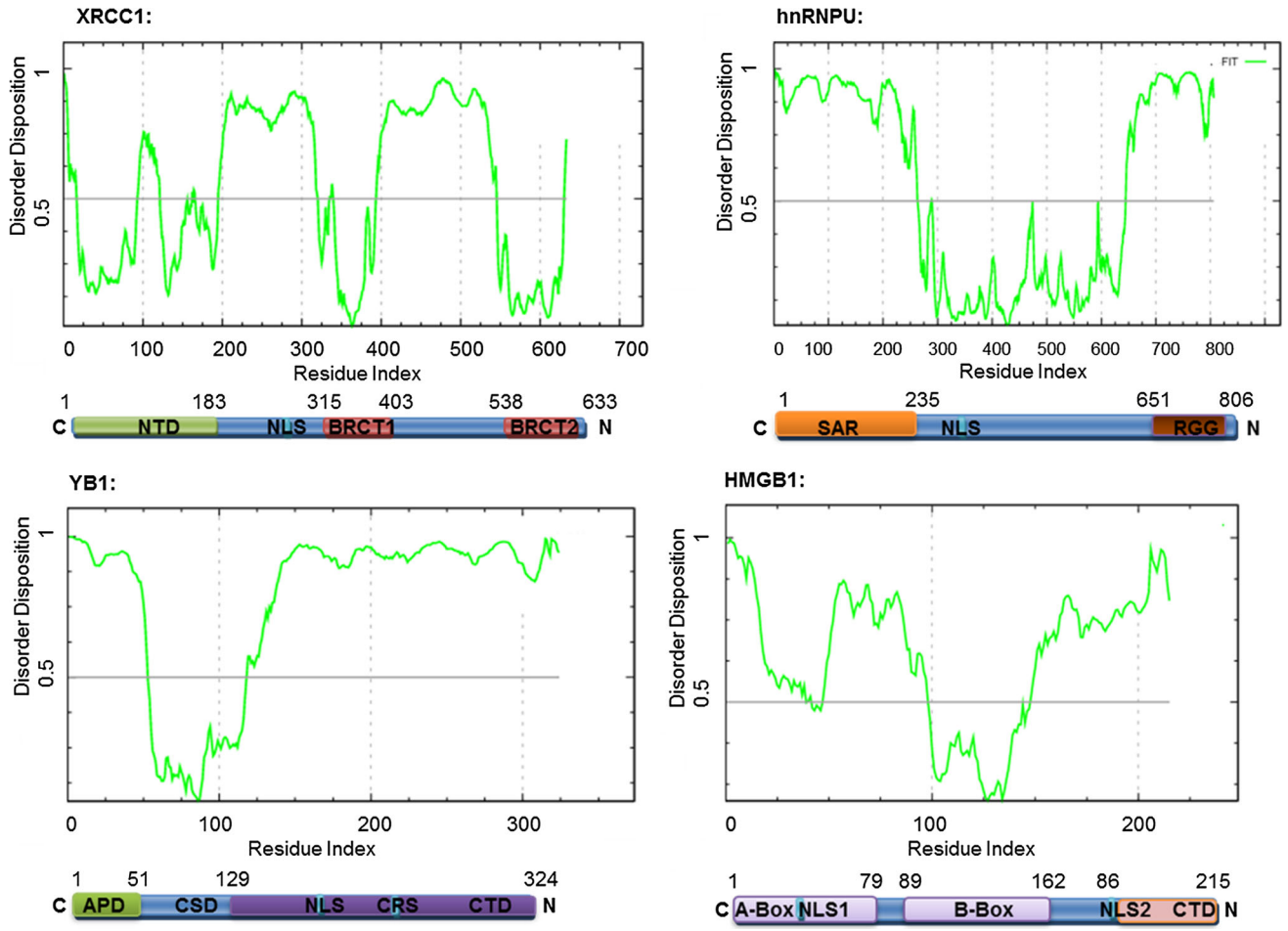


Fig. 4 PONDR-FIT analysis for determining intrinsic disorderness in the accessory proteins—XRCC1, hnRNP-U, YB-1, and HMGB1 and (http://www.disprot.org/pondr-fit.php). *AS* active site, *APD* alanine/proline-rich domain, *C* C terminal, *CD* catalytic domain, *CRS* cytoplasmic retention domain, *CSD* cold shock domain, *CTD* C terminal domain, *N* N terminal, *NTD* N terminal domain, *NLS* nuclear localization signal, *SAR* scaffold associated region, *RGG* arginine–glycine–glycine domain, *ZnF* zinc finger

poly ADP-ribose (PAR) using NAD+ as the substrate, after activation as a result of binding to DNA SSB. These chains are covalently attached to several nuclear proteins including themselves, histones, possibly some SSBR proteins and PARP itself [96]. PARP1 is the first identified member of the PARP family and its exact role in DNA damage response, particularly in base damage repair, is still ambiguous [97], presumably because of its dual role in chromatin unfolding via PARylation of histones [97], and recruitment of XRCC1 at SSB sites [94] to initiate SSBR. PARPs also stimulate apoptosis in a caspase-independent fashion by triggering release of apoptosis inducing factor (AIF), presumably to ensure cell death when the genome damage is beyond repair [98]. PARP1 was also shown to have a role in transcriptional regulation [99].

Human PARP1 is a 113 kDa nuclear protein containing three primary structural domains. It has an N terminal DNA-binding domain (DBD) containing two zinc finger motifs (ZnF1 and ZnF2) important for recognition of DNA strand break, an autoPARylation domain (AD) with BRCT motif, and a highly conserved C terminal catalytic domain that carries out mono/poly ADP-ribosylation. The DBD also contains a bipartite nuclear localization signal (NLS) and a third zinc finger motif (ZnF3), which is not required for DNA binding but promotes structural changes after DNA binding for enzymatic activation [100] and regulates PARP1's role in chromosome unfolding [101]. PARP1's tryptophan-, glycine-, arginine-rich (WGR) domain is conserved among the PARP family members but its function is not yet characterized. It has been suggested that PARP1 remains non-specifically associated with the chromatin via weak interaction of the ZnF1 motif with the sugar phosphate backbone [102, 103]. Upon encountering any discontinuity in the DNA backbone, the DBD engages at the major groove of the damaged site resulting in conformational changes followed by dimerization via DBD. Such DNA break-induced PARP1 dimerization exposes the AD of one molecule to the catalytic domain of the other

resulting in its trans-autoPARylation [103]. This facilitates unfolding of the chromatin by negatively charged PAR groups making the damaged site accessible to DNA repair proteins. The bulky mesh of PAR polymer recruits many DNA repair proteins but reduces PARP1's affinity for DNA due to large negative charge density. The turnover of PAR chains is crucial for SSBR and is carried out by poly ADP-ribose glycohydrolase (PARG) [104]. At SSBs PARP1 recruits XRCC1 via BRCT1 domains, forming XRCC1–PARP1 heterotetramer [105], further facilitating assembly of the BER/SSBR complex. PARP1 also PARylates XRCC1 at LL360/361DD preventing its degradation by poly ubiquitylation and thus enhancing its retention till the oxidative lesion is repaired [106]. At DSB sites, PARP1 and Ku compete with each other [107], possibly for pathway choice of alternative end joining (Alt-EJ) vs. NHEJ for DSB repair [108, 109]. Alt-EJ, which is prevalent in NHEJ-deficient conditions, is sensitive to PARP1 inhibitors [108]. We propose that BER/SSBR and Alt-EJ utilize common protein complexes recruited by PARP1 (and/or XRCC1) at secondary DSBs generated at closely localized SSB/base lesions, or an SSB close to replication fork. Moreover, NEIL1 has been shown to stimulate PARP1 while it itself is inhibited by the same through direct physical interaction, which suggests PARP1's direct role in coordination of BER/SSBR in addition to scaffolding function [110]. PARP1 can interfere with NHEJ pathway by inhibiting the binding of Ku and DNA-dependent serine/threonine protein kinase (DNA-PK) at the DSB and promote homologous recombination (HR), as observed in DT40 and mammalian cells [111]. Recent studies have implicated PARP1's role in Ku-independent alternative DSB repair pathways, through recruiting MRE11 and promoting end resections [112, 113]. PARP1 was shown to slow down the replication rate in response to CPT-induced DSBs in mammalian cells and recruit HR-protein RAD51. Thus, PARP1 may be involved in HR-coupled replication fork progression [114]. Increased PARP1 activity and degradation of stalled replication fork after PARP inhibition in BRCA2-defective cells have been linked to its role in protecting stalled replication forks through preventing end resection via PAR formation [115]. Pharmacologically blocking PARP1 with small molecule inhibitors has shown to delay SSB and DSB repair and radio-sensitize HR compromised BRCA-deficient breast cancer cells [116, 117]; a similar effect was found with PARG depletion due to prevention of removal of PAR scaffold that is necessary for providing access to BER proteins at oxidized DNA lesions [118].

PARP2 is the second member of PARP family which recognizes gaps and flap structures and less efficiently SSB [119]. It has been reported that PARP2's delayed recruitment at SSBs is dependent on PARP1 [120], indicating that PARP2 might be required either in later steps or merely act as a backup protein for PARP1. Though currently PARP2's role in DSB repair is elusive it has been shown that it suppresses chromosomal translocations [109].

PARP3 has been recently implicated in DSB repair pathway choice. PARP3 promotes NHEJ by stabilizing Ku70–Ku80 heterodimer at DSB and prevent MRE11/CtIP-mediated end resection required for HR or Alt-EJ [121, 122] and recruiting histone chaperone APLF to accelerate XRCC4-ligase IV mediated DSB repair [123].

RNA binding and other non-canonical proteins in BER

HnRNP-U (heterogeneous ribonucleoprotein-U)

HnRNP-U or scaffold attachment factor (SAF-A), belongs to the family of heterogeneous nuclear RNPs, which have conserved RNA-binding domain (RBD), in concert with other essential hnRNPs and have several roles in mRNA metabolism including packaging of nascent mRNAs, alternative splicing and regulation of translation [124]. HnRNPs have been subsequently shown to be involved in DNA metabolism and transcriptional regulation [125]. Post-translational modifications or degradation of various hnRNPs in response to IR-induced damage has implicated these in DSBR pathway choice [126]. HnRNP-U is phosphorylated by DNA-PK, a key enzyme involved in non-homologous end joining, in response to DSBs induced by etoposide and IR [127]. We recently showed that hnRNP-U, which was previously implicated in TC-BER in collaboration with NEIL2 [128], enhances the 5-OHU excision activity of NEIL1 by direct interaction, particularly in oxidatively stressed cells, supporting its role in stress-induced enhancement of BER activity [77].

HnRNP-U has two disordered domains—the C-terminal AT-rich SAR (scaffold attachment region) domain that binds to DNA, and the RNA binding N-terminal domain with the arginine-glycine-glycine (RGG) motif. Both of these domains are conserved in the hnRNP family members (Fig. 4). The terminal, disordered segments provide the binding interfaces for interaction with NEIL1 [77]. While the N-terminal segment is usually sufficient for stimulating NEIL1 activity to the same extent as the full-length protein, the C-terminal segment presumably helps stabilize the interaction. It is also possible that two termini are in close proximity in the native protein. Phosphorylation of hnRNP-U at Ser59 residue by DNA-PK and its association with NHEJ proteins XRCC4 and Ligase IV, first directly linked this otherwise RNA metabolism protein with DNA repair for the first time [129]. HnRNP-U-like proteins (hnRNPUL-1/2) have been shown to be binding partners of the DSB sensor and NHEJ factor MRN complex

and these also promote recruitment of BLM-helicase at the DSB site [130].

YB-1

YB-1, also a DNA/RNA-binding ribonucleoprotein, is primarily involved in transcriptional regulation, mRNA splicing, translation which is attributed to its nucleic acid chaperone activity. The observed association of YB-1 with DNA repair is not completely understood. It is a nucleo-cytoplasmic shuttling protein and its nuclear localization has been linked to multiple drug resistance of malignant cells and resistance to xenobiotics and IR-induced damage [131]. YB-1 was shown to interact via formation of multimeric complexes and to stimulate activity of several DNA proteins involved in BER, NER, MMR and DSBR [72, 132–134]. Increase in the YB-1 level in mammalian cells was also found to correlate with the increase in replication proteins PCNA, DNA topoisomerase IIα, and Polα, indirectly suggesting YB-1's involvement in replication [131].

YB-1 has two intrinsically disordered domains—a long C-terminal domain (CTD) containing alternating clusters of positively and negatively charged amino acid residues (129–324) and an N-terminal alanine/proline-rich domain (APD) (1–51) (Fig. 4). YB-1's interaction with DNA repair and other partner proteins is facilitated through type II polyproline (poly(Pro) II) helix conformation in the CTD while the basic residue clusters are responsible for interaction with DNA [135].

YB-1 binds to cisplatin–DNA adducts, AP sites and mismatched DNA with high affinity enhancing localized melting of the duplex DNA and stabilizing the single stranded form, presumably enhancing their repair efficiency. YB-1 has weak $3' \rightarrow 5'$ exonuclease activity on ss DNA and weak endonuclease activity on duplex DNA. YB-1 stimulates NTH1 and NEIL2 for the release of oxidized bases, and also enhances their AP lyase activity by increasing formation of Schiff base enzyme/substrate intermediates [134, 136]. YB-1 as a component of the oxidative stress-induced NEIL2-initiated BER complex, physically interacts with NEIL2, Lig3α and Polβ [134]. On the other hand, Pestryakov et al. [137] reported that YB-1, like RPA, suppresses NEIL's AP lyase activity on ss DNA substrates with AP sites while moderately stimulating the same with duplex DNA longer than 48 nts. These could implicate role of YB-1 in transcription/replication-associated repair where it simultaneously prevents induction of breaks at single stranded DNA and enhances repair of oxidized bases in ds DNA. Interestingly, it was recently shown that DNA damage stress-induced proteasome-mediated cleavage of YB-1 results in loss of its cytoplasmic retention sequence and thus increases its nuclear accumulation in primary cancer cells. This may contribute to multidrug resistance phenotype of cancer cells [138]. Truncated YB-1 retains its interaction with DNA damage response proteins γH2AX, MRE11, Rad50, Ku80 and WRN and in multiprotein repair complexes. YB-1's interaction with PCNA further suggests its role in NER and replication-associated repair [131].

HMGB1

HMGB1 belongs to the family of abundant high mobility group (HMG) of non-histone nuclear proteins whose common nuclear functions are not completely understood. HMGB1 functions as a DNA chaperone in regulating chromatin conformation and transcription. It also has a critical role in inflammation signaling. Furthermore, HMGB1's affinity for bent and distorted non-B DNA structures helps its binding to DNA lesions and inducing further DNA bending for lesion-detection by DNA repair proteins [139]. HMGB1 has been reported to interact with various repair proteins of disparate DNA repair pathways like XPC in NER [140, 141]; Ku, DNA-PK and Ligase IV in NHEJ [139, 141] and BER enzymes like APE1, Polβ, etc. and enhance their activity and regulates sub-pathway choice [139, 142]. Moreover HMGB1 also facilitates unfolding of the chromatin by stimulating chromatin remodeling factors ACF and CHRAC [143, 144], presumably to provide access to the repair proteins at lesion sites buried within the nucleosome.

HMGB1 with a proposed role in sensing oxidatively damaged DNA, contains A and B box domains, each containing 80–90 basic amino acids and share ~30 % sequence identity which assigns HMGB1 its affinity for bent, distorted, looped or other non-B DNA structures. After binding to such DNA structures HMGB1 introduces its bulky hydrophobic amino acid residues of the A and B box between successive base pairs in the minor groove resulting in further distortion which is stabilized by basic residues flanking the hydrophobic residues; these structural changes at the DNA lesion enhances recognition by a number of DNA damage response proteins. At the same time, HMGB1 physically interacts with and stimulates some DNA repair proteins, thus enhancing their DNA repair activity. *In vitro* studies have shown affinity of HMGB1 for BER substrate intermediates including AP site, nicked DNA and gapped DNA and with the highest affinity for 5′dRP intermediate. It can form Schiff base intermediate with the 5′dRP which could lead to stable crosslinks [142]. HMGB1 also stimulates activity of APE1 and strand displacement activity of Polβ and FEN1 mediated cleavage of 5–6 nts DNA flap with 5′dRP termini, thus facilitating LP-BER [139]. Thus HMGB1, itself not being a DNA repair protein, can stimulate disparate DNA repair

pathways including BER, MMR, NER and NHEJ because of its scaffolding ability [139].

HMGB1 has an acidic C terminal disordered tail (Fig. 4), which confers protein stability, enhances its DNA bending properties [145] and regulates repair at nucleosome via its acetylation [146]. Full-length HMGB1 has also been shown to inhibit replication, which is diminished upon its acetylation or due to phosphorylation by protein kinase C [147]. The C-terminal truncated mutant does not inhibit replication nor repair of cisplatin–DNA adducts in nucleosomes [146], further suggesting the functional importance of the disordered tail.

Defects in accessory proteins, BER deficiency and human diseases

Because of the role of BER/SSBR in genome surveillance against various endogenous and exogenous oxidative insults, defects in these repair pathways lead to cancer predisposition, aging and various neurodegenerative diseases [148]. Extensive studies have linked defects in or aberrant expression of core and also accessory BER/SSBR proteins to various pathophysiological conditions. For example, XRCC1 deficiency not only sensitizes mammalian cells to diverse DNA damaging agents such as IR, H_2O_2, alkylating agents and CPT, but also causes spontaneous chromosomal aberrations and deletions [94]. Thus, XRCC1 deficiency might increase cancer risk by promoting genomic instability. Certain polymorphic variants of human XRCC1 (e.g. R399G, R194W) have been associated with increased risk of cancer in the ovary, bladder, stomach, pancreatic, colon, skin, lung and of chronic myeloid leukemia [149–154]. Furthermore, it has been reported that XRCC1 is frequently mutated in familial breast and ovarian cancer [83, 155–157]. XRCC1 deficiency in breast tumors is associated with an aggressive phenotype and served as an independent predictor of poor clinical outcome [156]. The XRCC1 protein level is significantly downregulated in human gastric cancer tissues relative to the adjacent non-cancerous tissues [158]. Perhaps not surprisingly, null mutation of the XRCC1 gene is embryonic lethal in mice [159, 160].

PARP1 expression at both mRNA and protein levels is elevated in a variety of cancers, [161–167]. Furthermore, PARP1 overexpression is frequently correlated with poor outcome in breast cancer and ovarian serous carcinoma [168]. PARP1 overexpression could also be predictive for neoadjuvant chemotherapy [169]. More recently, PARP1 has been shown to have high expression in non-small cell lung cancer cell lines resistant to cisplatin, compared to those cisplatin-susceptible ones, suggesting its correlation with tumor resistance to therapy [170, 171]. These studies suggest that PARP1 expression level could be a prognostic biomarker in cancer. PARP inhibition is emerging as a promising therapeutic regimen, particularly in certain breast cancer patients [169].

BER/SSBR, an attractive anti-cancer target in synthetic lethality regimen

Genomic integrity is critical for health and survival of all organisms, which is maintained by highly evolved DNA repair machinery, involving multiple repair sub-pathways in mammals for both endogenous and induced genotoxic threats. Impaired efficiency in one or more DNA repair pathways is a major driver of carcinogenesis, aging and age-related chronic disorders. Moreover, robust DNA repair activity, particularly of BER/SSBR, plays a key role in highly pro-oxidant, acidic tumor micro-environment, needed to repair oxidative DNA damage. A large number of nucleotide polymorphic variants in BER/SSBR genes, many of which affect repair activity, have been identified in human population, which is often linked to pathogenicity [172]. Establishing BER/SSBR proteins as markers for cancer susceptibility and prognosis should be an important area. Early studies in this direction should be expanded [173].

Because most anti-cancer drugs and radiation kill cancer cells by inducing DNA damage including various oxidative damages besides DSBs, their efficacy and effective dosage are governed by specific DNA repair activities in tumor cells. Thus, the repair activity could be used as both prognostic and predictive markers for treatment. BER/SSBR is particularly important because their impairment could cause unrepaired SSBs which will be converted into lethal DSBs in the S phase in continuously multiplying tumor cells. Consequently, DNA repair inhibition and adoption of synthetic lethality (which targets the backup pathway) have recently been shown to have exceptional promise in cancer therapy. However, apart from the use of PARP inhibitors, the efforts to explore BER/SSBR inhibitors have not been successful in patient trial in spite of convincing data confirming their efficacy from *in-cell* and and in vitro studies. One reason for the failure may be the presence of multiple BER/SSBR sub-pathways, with overlapping and backup roles. Based on the relative success of synthetic lethality of PARP inhibitors with drug/radiation treatment of BRCA-negative breast cancer [174], BER/SSBR inhibitors could also provide effective alternative synthetic lethality strategy. In particular, DNA glycosylases, which we showed to regulate and control the complete repair sub-pathways [31, 68, 175] and/or Lig3α/Lig1, the two key nick-sealing enzymes [176, 177] have strong potential as synthetic lethality targets which is currently being explored by our and others' laboratories.

Conclusion and future perspectives

BER/SSBR, the predominant mode of repair for most oxidative genome damage (except DSBs) is critical in preventing mutations and maintaining genomic integrity. Considering the continuous generation of ROS in an aerobic cell due to respiration, and the abundance of oxidative insults inflicted on the genome, it is not surprising that BER/SSBR capacity broadly correlates with an organism's overall life span [178]. As most oxidative bases in the replication fork template fail to block replicative DNA synthesis, these lesions if remain unrepaired would often cause base mutations in the progeny strand. We believe that the 'cow-catcher' role of NEIL1 at replication fork is critical for preventing mutations in dividing cells. Thus, BER/SSBR initiating DNA glycosylases not only repair the base damage, but are also involved in damage recognition and pathway choice, the two under-studied aspects.

Another feature of BER/SSBR in higher eukaryotes is their collaboration with components of other cellular pathways which presumably allows tight regulation of the sub-pathways, and also for pathway choice. While many such non-canonical proteins have been shown in in vitro and *in-cell* studies to associate with BER/SSBR proteins and stimulate their function, their in vivo significance is still obscure. It is possible that these additional factors are utilized for specific repair events/conditions.

Other critical questions that need to be addressed include oxidized lesion scanning in chromatinized genome, repair in hetero versus euchromatin, and involvement of other accessory/non-canonical proteins, particularly factors involved in chromatin unfolding/remodeling in endogenous versus induced damage repair.

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