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Oxidant and environmental toxicant-induced effects compromise DNA ligation during base excision DNA repair

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Abstract

DNA lesions arise from many endogenous and environmental agents, and they promote deleterious events leading to genomic instability and cell death. Base excision repair (BER) is the main DNA repair pathway responsible for repairing single strand breaks, base lesions and abasic sites in mammalian cells. During BER, DNA substrates and repair intermediates are channeled from one step to the next in a sequential fashion so that release of toxic repair intermediates is minimized. This includes handoff of the product of gap-filling DNA synthesis to the DNA ligation step. The conformational differences in DNA polymerase β (pol β) associated with incorrect or oxidized nucleotide (8-oxodGMP) insertion could impact channeling of the repair intermediate to the final step of BER, *i.e.*, DNA ligation by DNA ligase I or the DNA Ligase III/XRCC1 complex. Thus, modified DNA ligase substrates produced by faulty pol β gap-filling could impair coordination between pol β and DNA ligase. Ligation failure is associated with 5′-AMP addition to the repair intermediate and accumulation of strand breaks that could be more toxic than the initial DNA lesions. Here, we provide an overview of the consequences of ligation failure in the last step of BER. We also discuss DNA-end processing mechanisms that could play roles in reversal of impaired BER.

Keywords

Base excision repair (BER); DNA polymerase β (pol β); DNA ligase; 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxoG); ligation failure; abortive ligation products

1. Repair of oxidant and environmental toxicant-induced DNA lesions by base excision repair

Environmental and endogenous stressors damage genomic DNA [1]. These stressors include radiation, base loss through spontaneous hydrolysis of the glycosidic bond and attack by

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Conflict of interest statement

None

reactive agents such as reactive oxygen and nitrogen species and alkylating agents [2]. One of the most abundant lesions in DNA is the abasic or apurinic/apyrimidinic (AP) site [3]. This lesion is mutagenic and can block DNA replication and transcription leading to cell death [4]. DNA bases also can become oxidized and one of the prominent oxidized bases is 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxoG) in DNA. Furthemore, the oxidized guanine base can be formed in the dNTP pool (8-oxodGTP), and the nucleotide pool can contain enough 8-oxodGTP to promote mutagenesis [5–8].

The primary defense mechanism against oxidative DNA damage and the AP-site lesion in cells is the DNA repair pathway known as base excision repair (BER) [9–11]. The overall BER process in mammalian cells consists of two sub-pathways: single-nucleotide (SN) or short patch BER, and long patch (LP) BER [12]. In SN-BER of the AP-site, the AP-site is recognized by apurinic/apyrimidinic endonuclease 1 (APE1), which cleaves the phosphodiester backbone leaving 3′-hydroxyl (3′-OH) and 5′-deoxyribose phosphate (5′-dRP) groups at the termini in a single-nucleotide gap (Fig. 1; *AP-site). DNA polymerase β (pol β), a bifunctional enzyme, removes the 5′-dRP group via its lyase activity, and then catalyzes single-nucleotide gap-filling DNA synthesis through its polymerase activity [13–15]. This generates a substrate for the final BER step accomplished by DNA ligase I or the XRCC1-DNA ligase III complex [16]. If the dRP group is modified so that it cannot be removed by the pol β lyase, BER switches to the alternate LP-BER sub-pathway. This involves damaged strand excision by flap endonuclease 1 (FEN1) and DNA polymerase replacement of several nucleotides ahead of the site of base damage [17].

BER repair of 8-oxoG is initiated by its removal by 8-oxoguanine DNA glycosylase (OGG1). Since the lyase activity of OGG1 is only weak, the resulting AP-site after base removal is processed by APE1 as described above [18, 19]. The negative cellular impact of 8-oxoG in DNA is mediated, in part, by replicative DNA polymerases [20–22]. These enzymes either fail to bypass the lesion when it persists in the template DNA or perform mutagenic repair by inserting a wrong, pro-mutagenic, nucleotide opposite the lesion [23–25]. In addition, during periods of oxidative stress, pol β can perform mutation-prone repair by inserting the oxidized dNTP pool nucleotide 8-oxodGTP (*syn*) opposite to template adenine base [26].

2. DNA ligation coupled to pol β gap-filling DNA synthesis in BER

BER is a sequential multistep process that is coordinated by protein-protein and enzyme-DNA interactions. BER appears to involve channeling of DNA intermediates through the repair pathway [27–30]; this may prevent accumulation of toxic repair intermediates once repair has been initiated. DNA intermediates were channeled or handed off from one step to the next *in vitro* [31]. In more recent biochemical studies with purified human BER enzymes, substrate channeling between pol β and DNA ligase was revealed (Fig. 1). After pol β dRP removal and gap-filling steps, the nicked DNA product was channeled to the ligation step where DNA ligase catalyzes phosphodiester bond formation between the 3′-OH and 5′-phosphate (5′-P) groups of the nick. On the other hand, environmental and metabolic sources of DNA damage can result in failed BER when the ligation step is not successful [32]. This involves ligase termination, premature ligation, and formation of the abortive

ligation product with the 5′-adenylate (5′-AMP) group at the nick [33, 34] (Fig. 2). Namely, DNA ligases fail when they engage damaged DNA structures including direct oxidative single-strand breaks, DNA nicks with 3′-AP-sites, and RNA-DNA junctions arising during ribonucleotide excision repair [35]. Moreover, during repair of AP-sites when the 5′-dRP group is not removed by pol β lyase prior to the ligation step, DNA ligases (*i.e.*, DNA ligase I or DNA ligase III/XRCC1 complex) can fail and the abortive ligation product with the 5′-adenylated-dRP-containing BER intermediate can be formed [36, 37] (Fig. 2A).

3. Impact of pol β structural conformations on channeling DNA intermediates to ligation step in BER

DNA polymerases select the proper nucleoside triphosphate from a pool of similar molecules to preserve the integrity of the genome during DNA synthesis [38]. Structural and biochemical data support the hypothesis that some DNA polymerases discriminate between alternate dNTP substrates through an “induced fit” mechanism where binding of the correct nucleotide leads to substrate/protein conformational adjustments that align catalytic groups to optimize chemistry [39–43]. Recently, time-lapse X-ray crystallography studies using natural substrates revealed high-resolution structures of novel catalytic intermediates within the pol β active site [44–46]. These intermediates provided structural insight into roles of active site conformational changes for phosphodiester bond formation and subsequent product release events that accelerate or hinder nucleotide insertion. From these molecular snapshots of pol β inserting an incoming correct nucleotide, the pol β active site undergoes molecular adjustments that optimize correct nucleotide insertion. On the other hand, the structure of ternary mismatch complexes showed important structural differences compared to correct nucleotide insertion. The key differences involved a lack of the structural changes that pol β normally undergoes in response to the incoming correct nucleotide. In addition, pol β kinetic data and ternary complex crystal structures with gapped DNA indicated that pol β can insert 8-oxodGMP opposite both adenine and cytosine bases in the template position [22, 24, 47, 48]. Time-lapse crystallography snapshots of 8-oxodGTP insertion opposite cytosine revealed surprising structural features [49, 50]. For example, the inserted 8-oxodGMP modulates the pol β active site, such that the conformation of the active site opens after the insertion event and the Watson-Crick base pair observed prior to insertion is lost. This is in contrast to the picture after insertion of the normal guanine nucleotide opposite template cytosine, where the active site remains closed and the base pair is maintained after insertion.

After an incorrect or oxidized (8-oxodGMP) nucleotide insertion into the single nucleotide gapped DNA intermediate by pol β, the resulting nicked product should be passed to the ligation step where DNA ligase would be responsible for nick sealing (Fig. 3). However, the presence of the modified or unnatural base pair at the 3′-margin of a nick could lead to ligation failure and formation of abortive ligation products with the 5′-AMP group at the resulting nicked DNA intermediate (Fig. 3). This would result in a lack of substrate channeling from the gap-filling DNA synthesis step to the ligation step in the BER pathway and subsequent impairment of normal coordination between pol β and DNA ligase. These 5′-adenylated BER intermediates with 3′-modified or unnatural bases could potentially

become cytotoxic and lead to abnormal DNA replication and double-strand breaks. Therefore, repair of the 5′-adenylated BER intermediates by DNA-end processing enzymes is critical to cell viability and genomic stability [35, 51].

4. Reversal of impaired BER by DNA-end processing mechanisms

The presence of a modified or unnatural base pair at the 3′-margin of a nick after pol β gap-filling and then ligation failure involving addition of the adenylate group at the 5′-phosphate of the nicked substrate could result in BER pausing. This type of paused intermediate could serve as a signaling mechanism triggering action by DNA-end processing enzymes, like 5′-end processing enzymes for AMP removal (Figs. 2B and 4) or 3′-end trimming for removal of problematic 3′-ends (Fig. 4). Therefore, after trimming, the gap-filling step may be allowed to start over again so that DNA ligase would be able to the join 5′-P and 3′-OH groups.

Aprataxin (APTX), a member of the histidine triad (HIT) superfamily, resolves the abortive DNA ligation products by 5′-AMP removal and thereby restores the 5′-P group at the 5′-terminus of the nicked DNA, and this will allow another attempt at ligation [52]. Another mechanism of removing 5′-end blocking lesions is the alternate BER sub-pathway, LP-BER. In this case, the role of FEN1 in processing of the 5′-adenylated BER intermediates via its flap excision activity is well known [36, 37]. Other blocked 5′-end reversal mechanisms, including polynucleotide kinase phosphatase (PNKP) or the Ku70/80 lyase activity, could play roles in 5′-DNA end-trimming as well [53, 54].

Regarding a blocked 3′-terminus, many repair mechanisms could serve to resolve a variety of problematic 3′-ends with modified or unnatural bases (Fig. 4). These enzymes include DNA glycosylases, APE1, APE2, and tyrosyl-DNA phosphodiesterase 1 (Tdp1), among others [55–57]. For example, OGG1 and nei endonuclease VIII-like 1 (NEIL1) can remove the 8-oxoG base lesion [58, 59] and APE1 can correct a 3′-mispaired nucleotide via its 3′-5′ exonuclease activity [60]. APE1 is known to interact with DNA ligase I and to stimulate its activity in BER [61]. In addition, a role of APE1 in the repair of DNA strand breaks with 3′-blocking damage has been shown in human cell extracts [56]. Therefore, APE1 appears to be actively involved in coordinating steps and proofreading errors during BER. Tdp1 is a general 3′-end-processing DNA repair enzyme that can function on mismatched 3′-end DNA [62].

Many examples of protein-protein interactions in the BER pathway have been reported, as discussed above. X-ray repair cross-complementing protein 1 (XRCC1) has been considered to be a scaffold protein facilitating multiprotein complex assemblies required in the BER pathway [63]. This role of XRCC1 involves its ability to form stable complexes with itself and other BER proteins, including DNA ligase III, PARP-1, PNKP and pol β [64–66]. Thus, XRCC1 could play a role in the recruitment of DNA-end processing proteins and factors involved in reversal of impaired BER due to lack of normal coordination between pol β and DNA ligase in the last step of the BER pathway. The coordination between BER proteins could also facilitate the removal of blocked DNA-ends after ligation failure (Fig. 4). For example, the BER enzymes pol β, APTX and FEN1 can coordinate in repairing blocked

DNA intermediates [36, 37]. These include 5′-adenylated-dRP either through 5′-AMP removal by APTX, excision of the AMP blocked 5′-dRP group plus one-to-two nucleotides by FEN1, or removal of the 5′-AMP-dRP group by the pol β lyase activity (Fig. 2C). These roles involving removal of blocked DNA-ends were found to be especially critical in biochemical studies of APTX-deficient cells isolated from Ataxia with oculomotor apraxia type 1 (AOA1) patients.

5. Concluding remarks and future directions

DNA ligases play important roles in maintaining genomic integrity by catalyzing the joining of breaks in the phosphodiester backbone of double-stranded DNA during repair, replication and recombination [67]. The final step in BER involves DNA strand sealing by DNA ligase, which indeed is a terminal or near-terminal step of almost all types of DNA repair pathways [68]. High-resolution crystallography has revealed that pol β shows different structural conformations upon correct versus incorrect or oxidized (8-oxodGMP) nucleotide insertion [50]. The question of how these structural adjustments could affect the pol β and DNA ligase interaction and the efficiency of BER is still unclear. Ligation failure in the last step of BER could be an important source of genomic instability and cytotoxicity in mammalian cells. The biochemical and cytotoxic effects of premature ligation during BER after pol β-dependent insertion of incorrect or modified nucleotides could mediate mutagenesis, influence cancer therapeutics, and impact bacterial antibiotic development [21]. Moreover, the cytotoxic nicked BER intermediate generated following ligation failure could increase the probability for apoptotic cell signaling [69, 70].

Finally, we highlight the well-known concept that DNA repair defects have been linked to many types of cancer, and inhibition of repair enzymes in tumors with DNA repair defects is of great interest [71]. Therefore, development of targeted DNA repair inhibitors is a therapeutic strategy toward selectively killing cancer cells. Because of the involvement of DNA ligases in replication and repair, inhibitors for DNA ligases have potential as cancer therapeutic agents [72, 73]. The development of DNA ligase inhibitors could provide for cancer specificity because of the high level of intrinsic oxidative stress in cancer cells and the attendant BER. In addition, such inhibitors will be useful in understanding the biological implications of DNA ligation failure in BER compromised by environmental toxicant-induced effects. Moreover, this could serve a strategy for understanding neurological disorders caused by deficiency in enzymes that play roles in repairing blocked DNA-ends after ligation failure in the BER pathway.

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Highlights

- BER is the DNA repair pathway responsible for repairing single strand breaks, base lesions and abasic sites in mammalian cells.
- BER intermediates are channeled during the pathway so that release of toxic repair intermediates is minimized.
- Handoff of repair intermediates from the pol β gap-filling to DNA ligation steps during BER pathway is important for genome stability.
- Structural differences that pol β shows after incorrect or oxidized nucleotide insertion could affect accuracy of BER.

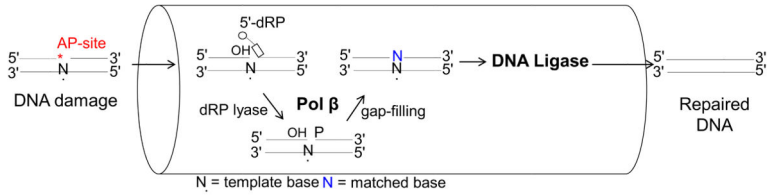

Fig. 1.

Substrate channeling between pol β and DNA ligase in the BER pathway

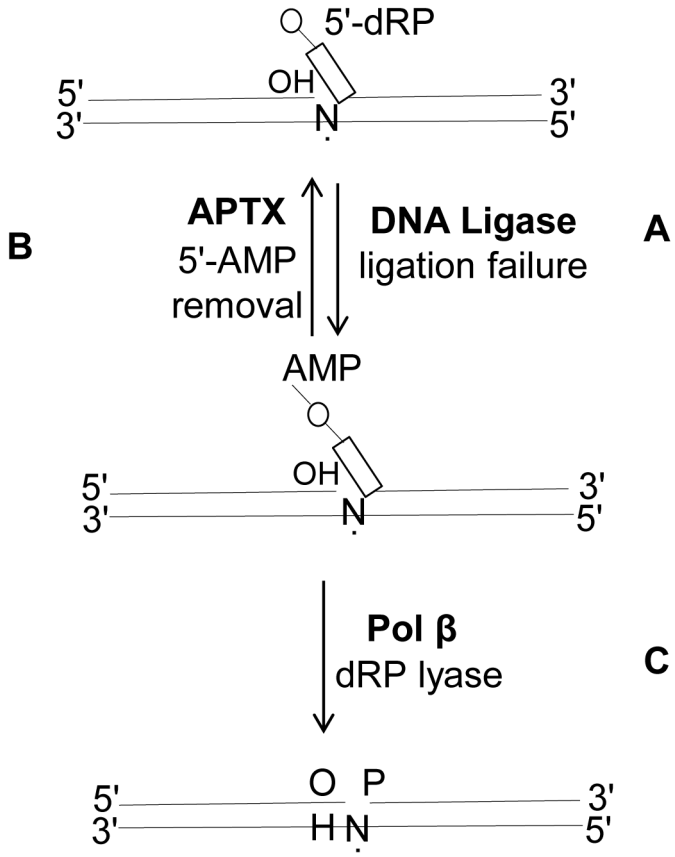

Fig. 2.

Ligation failure on the 5′-dRP-containing BER intermediate and repair of abortive ligation product with the 5′-adenylated-dRP by APTX and pol β

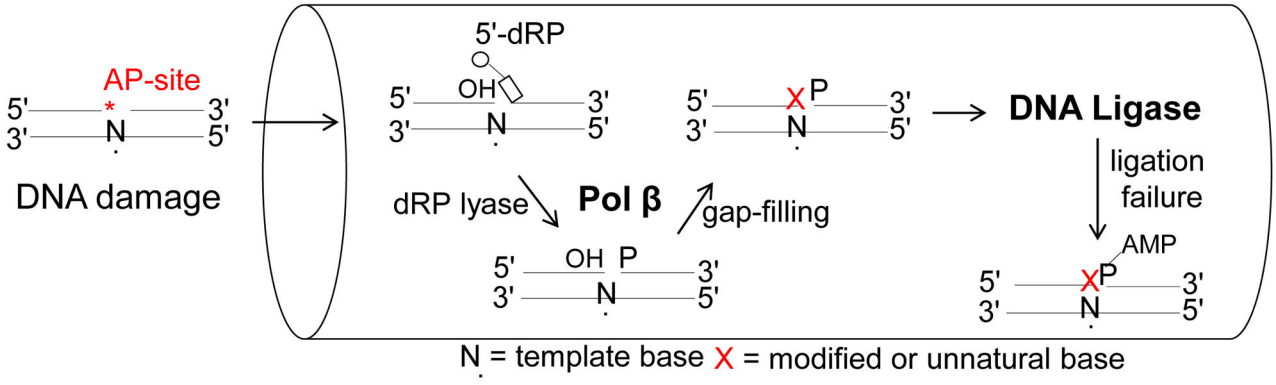

Fig. 3.

Impairment of substrate channeling from the gap-filling DNA synthesis to the ligation steps in the BER pathway

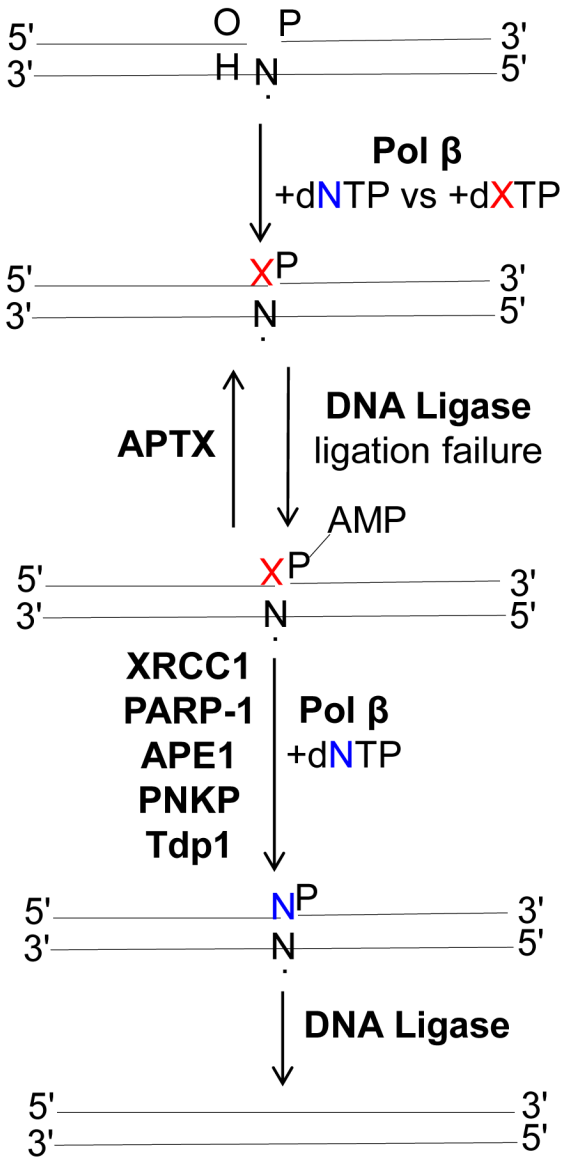

Fig. 4.
Reversal of impaired BER by DNA-end processing enzymes