Molecules and Cells

Minireview

Cancer prognosis using base excision repair genes

Jeongeun Kim[1,2,†], Su-Jin Kang[3,†], Nayoon Jo[1,2], Seung-Jin Kim[4,*], and Sunbok Jang[1,2,*]

[1]College of Pharmacy, Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, Republic of Korea, [2]Gradutate Program in Innovative Biomaterials Convergence, Ewha Womans University, Seoul 03760, Republic of Korea, [3]College of Pharmacy, Dongduk Women's University, Seoul 02748, Republic of Korea, [4]Department of Biochemistry, College of Natural Sciences, Kangwon National University, Chuncheon 24341, Republic of Korea

*Correspondence: sjk@kangwon.ac.kr (S.-J. Kim), sunbok.jang@ewha.ac.kr (S. Jang).

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ABSTRACT

The base excision repair (BER) pathway is a critical mechanism in genomic stability. This review investigates the role of the BER pathway in advanced cancer therapies considering the pivotal role of genetic factors in cancer patient responses and prognosis. BER factors significantly influence genetic instability and cancer prognosis, as well as the effectiveness of chemotherapy and radiation therapy. In various cancers such as breast, colon, lung, and bladder, BER factors have shown potential as critical biological markers for predicting cancer outcomes. This study focuses on the polymorphisms and expression levels of key BER genes, including OGG1, XRCC1, APE1, and Polβ. Our findings demonstrate that the expression levels of BER genes and proteins are closely associated with the risk, progression, treatment response, and prognosis of various cancers. These insights could improve cancer treatments and aid in the development of drugs targeting BER proteins. Ongoing research in this field requires extensive statistical analyses and large-scale prospective studies to effectively utilize BER protein levels. Ultimately, these results suggest that the BER pathway represents a potential target for cancer diagnosis, prognostic prediction, and the development of personalized therapeutic strategies. This paves the way for effective cancer treatment in the future.

Keywords: Base excision repair pathway, Biomarkers, Cancer, DNA repair, Polymorphisms

INTRODUCTION

Cancer therapies include systemic chemotherapy, radiotherapy, targeted drugs, and in some cases, immunotherapy. These treatments typically have clear limitations, as even minor fluctuations in drug concentrations can lead to significant changes in patient responses (Urruticoechea et al., 2010). Genes significantly contribute to this variability in drug efficacy and safety. They play a substantial role in influencing how patients respond to treatments and how their cancer prognosis evolves (Evans and McLeod, 2003).

Cells constantly endure endogenous and exogenous DNA damage, totaling around 30,000 events per cell per day, caused by UV light and ionizing radiation (Nemec et al., 2010; Prasad et al., 2020). The base excision repair (BER) mechanism is essential for correcting DNA damage. This process primarily eliminates faulty DNA bases and repairs single-strand breaks (SSBs) (Krokan and Bjørås, 2013; Krwawicz et al., 2007). Additionally, the BER pathway repairs various types of DNA lesions, including apurinic/apyrimidinic (AP) sites and base alterations caused by oxidation, alkylation, or deamination (Gohil et al., 2023). Therefore, BER is critical for maintaining genomic integrity. Unless these lesions are repaired, genomic instability can occur, leading to double-strand breaks, genomic mutations, cancer, and cell death (Karahalil et al., 2012; Prasad et al., 2020; Spiegel et al., 2021).

Cancer cells utilize the DNA repair mechanisms of the BER pathway to resist the impacts of DNA-damaging chemotherapy and radiation therapy. BER genes have been identified as potential focal points for therapeutic intervention and as contributors to chemotherapy resistance in various cancer types (Dorjsuren et al., 2012; Wallace et al., 2012). This resistance is primarily attributed to the overexpression of BER pathway proteins, although gene overexpression may also play a role in certain contexts. Consequently, BER genes may serve as valuable indicators or biomarkers for predicting the prognosis of different cancers. This review will discuss the prognostic value of BER pathway genes in several major cancers.

This review expands on the existing literature by integrating recent advancements in BER-related biomarkers and therapeutic strategies. Unlike previous studies that have primarily focused on individual cancer types or limited genetic markers, this work

† These authors contributed equally to this work.

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uniquely synthesizes evidence across breast, colon, lung, and bladder cancers. Moreover, it highlights the potential for personalized therapeutic approaches based on BER protein expression levels and genetic polymorphisms, providing a comprehensive framework for future research and clinical applications.

Cancer Therapy and BER Pathway

BER plays a crucial role in cancer cell survival and treatment resistance (Visnes et al., 2018). Inhibiting BER is a promising therapeutic strategy, as it prevents cancer cells from repairing DNA damage caused by chemotherapy or radiation (Grundy and Parsons, 2020). Traditional BER inhibitors target key enzymes like poly(ADP-ribose) polymerase1 (PARP1), AP endonuclease 1 (APE1), and DNA polymerase β (Polβ), enhancing the efficacy of existing treatments and overcoming resistance. PARP inhibitors have shown significant success in treating BRCA-mutated breast and ovarian cancers through synthetic lethality (Curtin Nicola, 2005).

Recent advancements include proteolysis targeting chimeras (PROTACs) and photodynamic therapy (PDT) with photosensitizers. PROTACs selectively degrade specific proteins, offering more complete and lasting inhibition compared to traditional inhibitors (Li and Song, 2020). This approach could effectively overcome resistance mechanisms (Cheng et al., 2024). PDT combines BER protein targeting with localized activation of photosensitizers, minimizing systemic side effects. Activated by specific wavelengths, these photosensitizers generate reactive oxygen species (ROS), causing oxidative stress and DNA damage in cancer cells, while inhibiting the BER pathway (Mossakowska et al., 2022) (Fig. 1).

These strategies highlight the importance of BER pathway genes as therapeutic targets and biomarkers. The efficacy of treatments may depend on the expression levels and functional

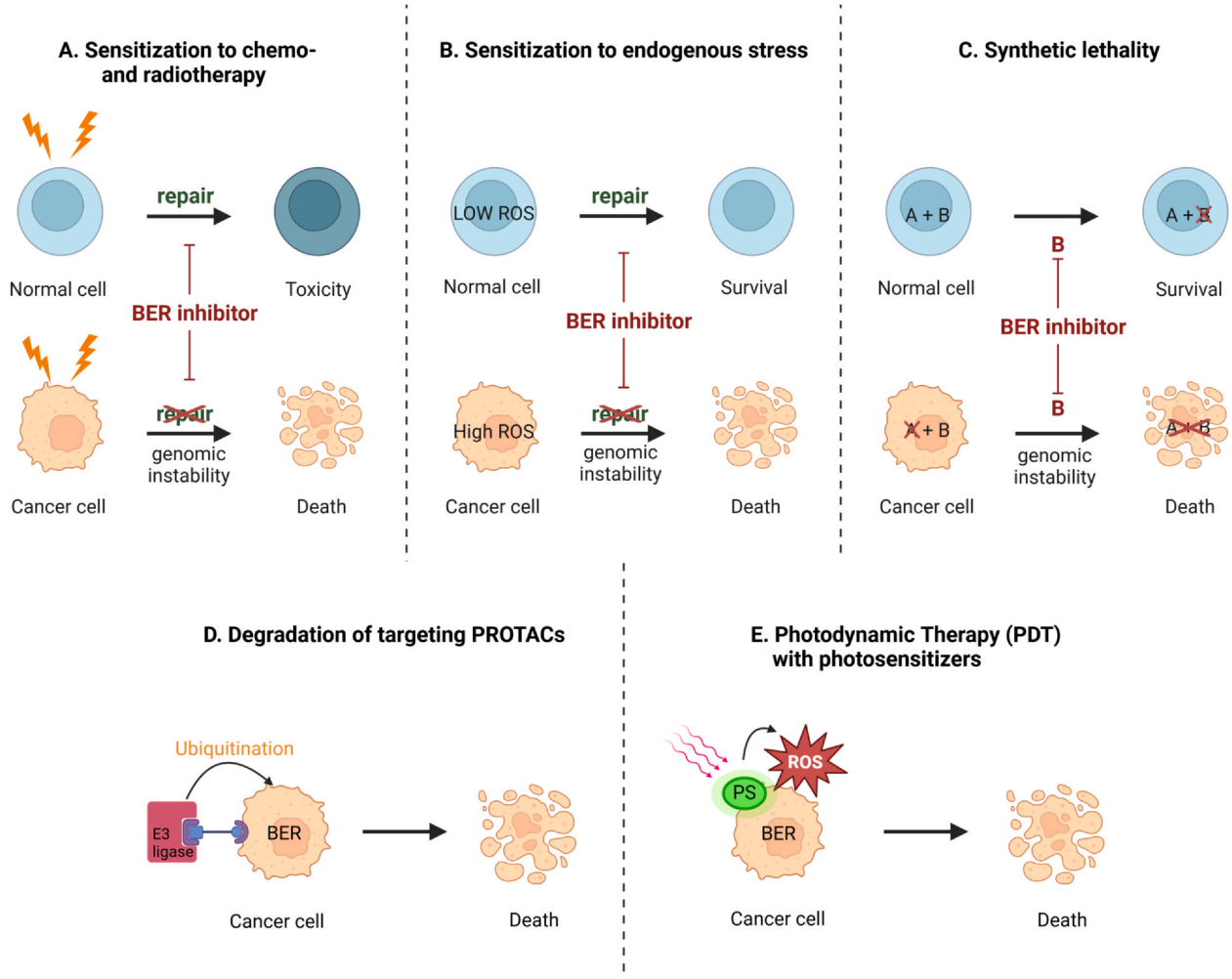

Fig. 1. Therapeutic strategies for BER inhibitors in cancer treatment. Created in BioRender. (A) Cancer cells with high genomic instability are selectively killed by BER inhibition, while normal cells survive due to greater stability. (B) BER inhibitors enhance chemo- and radiotherapy effects, targeting rapidly proliferating cancer cells but risking toxicity to normal cells. (C) BER inhibition causes cell death in cancer cells lacking compensatory repair pathways, while normal cells with intact pathways survive. (D) PROTACs operate by binding to the target BER protein and subsequently recruiting an E3 ligase, which facilitates the ubiquitination of the target protein, marking it for degradation by the proteasome. (E) A photosensitizer binds to the target BER protein and, upon light activation, generates ROS, causing oxidative damage to the BER protein and surrounding biomolecules.

status of BER genes in tumors, emphasizing the need for understanding the predictive and prognostic value of BER genes in cancers.

Tumors with variant alleles of functional BER genes may be more susceptible to certain treatments that cause DNA damage, which may also affect the effectiveness of anticancer treatments (Gossage et al., 2012; Marsden et al., 2017). Many anticancer drugs work by damaging tumor cell DNA (Reuvers et al., 2020). Therefore, understanding BER protein levels in tumors could help predict how well patients will respond to specific cancer treatments (Ali and Madhusudan, 2017). At the genetic level, variants in BER genes are associated with cancer predisposition, and certain genotypes have been reported in cancers such as stomach, lung, colon, breast, ovarian, and prostate cancers (Marsden et al., 2017; Visnes et al., 2018). Many studies have addressed the correlation between the BER pathway and cancer. This review will focus on the most studied cancers: breast, colon, lung, and bladder cancer. Monitoring these gene levels can provide valuable insight into the prognosis and potential treatment outcomes of cancer patients.

BER Pathway

The BER pathway includes short patch repair (SP-BER), which involves various proteins in repairing short damaged SSBs. It also includes long patch repair (LP-BER), where 2 to 8 newly synthesized nucleotides are used for repair. This process excises small regions of DNA damage to form SSB intermediates (Grundy and Parsons, 2020; Spiegel et al., 2021) (Fig. 2).

The initial phase of the BER pathway is the identification and removal of the damaged base by a damage-specific glycosylase, which cleaves the N-glycosyl bond and creates an abasic site. This abasic site is then cleaved by AP lyase or AP endonuclease (Jacobs and Schär, 2012). When DNA glycosylase is monofunctional and creates an abasic site, it is recognized and cleaved by APE1, generating an SSB with a 3' OH and a 5' deoxyribose phosphate (5'-dRP) termini (Kim and Wilson, 2012; Wallace et al., 2012). Bifunctional DNA glycosylases cleave the DNA backbone, creating a single-stranded nick (McCullough et al., 1999). At this point, PARP1 recruits DNA repair proteins to the site of DNA damage and protects the strand break (Woodhouse et al., 2008). Subsequently, the terminal ends of the sugar backbone are removed using a lyase or phosphodiesterase. APE1 both acts as an AP endonuclease and exhibits 3'-phosphodiesterase activity, which is required for DNA repair synthesis by removing 3'-PG residues. Polynucleotide kinase phosphatase (PNKP) is a bifunctional DNA repair enzyme that prepares nicked DNA for ligation, combining both DNA kinase and phosphatase domains (Barnes and Lindahl, 2004; Grundy and Parsons, 2020). Polβ has both polymerase activity and dRP lyase activity to remove 5'-dRP (Asagoshi et al., 2010). Finally, gap filling by Polβ and sealing the nick by DNA ligase IIIα (LigIIIα) in complex with X-ray repair cross-complementing protein 1 (XRCC1) complete the short patch

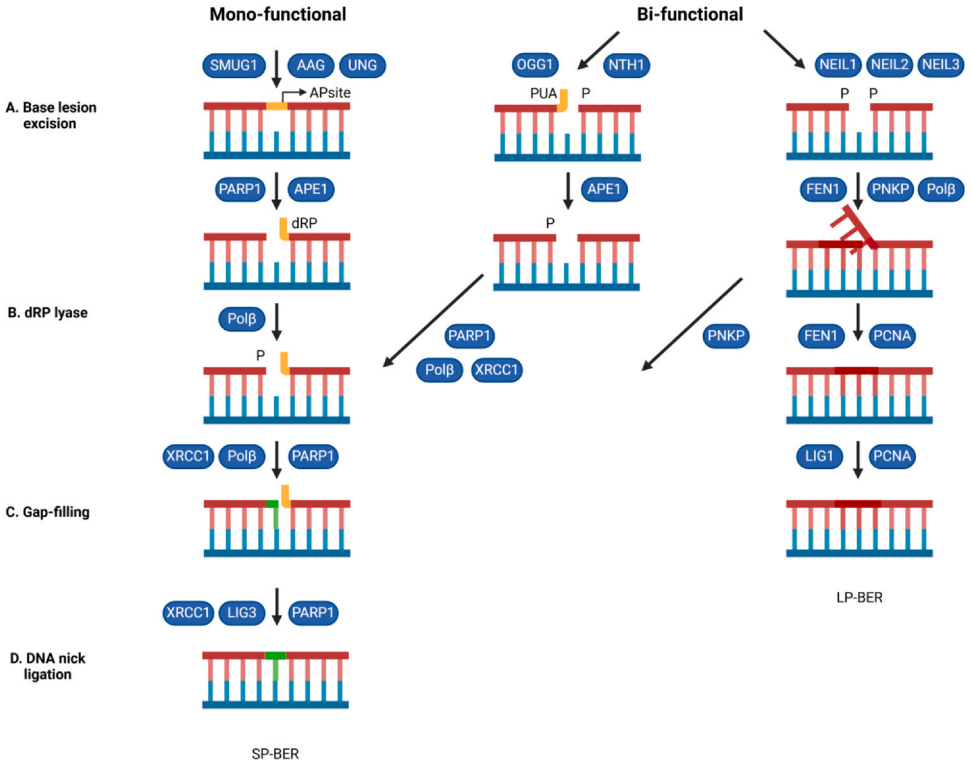

Fig. 2. Overview of the BER pathway. Created in BioRender. (A) Damaged bases (eg, oxidized guanine) are identified within the DNA structure. (B) DNA glycosylase excises the damaged base, generating an AP site. Then, AP endonuclease incises the AP site, creating an SSB in the DNA backbone. (C) DNA polymerase inserts a new nucleotide at the site of damaged base removal, effectively filling the gap. (D) DNA ligase catalyzes the formation of a phosphodiester bond between neighboring nucleotides, finalizing the repair process, and restoring the continuity of the DNA strand.

repair process (Beard et al., 2019; Kim and Wilson, 2012). Long patch repair is used when the 5' DNA ends are not suitable for Polβ action (Balakrishnan and Bambara, 2013). In these cases, either Polβ or other polymerases initiate strand DNA synthesis that relies on proliferating cell nuclear antigen (PCNA), forming a multinucleotide repair flap. Flap endonuclease 1 (FEN1) activity then removes the repair flap, and DNA ligase I or ligase IIIα seals the nicks (Asagoshi et al., 2010; Kim and Wilson, 2012).

Breast Cancer

Approximately 12% of women worldwide suffer from breast cancer (McGuire et al., 2015). Factors causing breast cancer include lifestyle, other medical conditions, family history, and genetic susceptibility (Pharoah et al., 2002). When a mutation occurs in a BER-related gene, the repair function is changed, significantly increasing the probability of developing cancer (Qiao et al., 2018). Numerous studies have investigated the relationship between susceptibility to breast cancer and single nucleotide polymorphisms (SNPs) in BER genes. SNPs are DNA-base variants with an allele frequency exceeding 1% in the population (Kwok and Gu, 1999). Both regulatory SNPs and nonsynonymous SNPs can reduce DNA repair capacity, leading to increased mutation rates and higher cancer risk (Karahalil et al., 2012; Moullan et al., 2003).

Studies on the association of genetic polymorphisms and breast cancer have shown that breast cancer can be initiated by somatic mutations that may be introduced during error-prone repair processes at estrogen-induced base sites. SNPs, including *XRCC1 Arg194Trp, Arg399Gln, APE1 Asp148Glu,* and *8-Oxoguanine glycosylase (OGG1) Ser326Cys,* may modulate breast cancer risk (Kang et al., 2013; Moullan et al., 2003; Smolarz et al., 2014). Combinations of *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms were linked to an increased breast cancer risk (Silva et al., 2007). *XRCC1 Arg399Gln* significantly increased the risk of developing breast cancer in Asian countries (Saadat, 2010). A significant association was found between breast cancer risk and the *APE1 Asp148Glu* genotype in the Saudi population (AlMutairi et al., 2015). In addition, a meta-analysis found that the *OGG1 Ser326Cys* allele significantly impacts breast cancer prevention in Asian women (Kang et al., 2017).

Some studies calculated a proprietary DNA repair index prognostic (DRPI) score using XRCC1, Polβ, FEN1, and BRCA1, which are known breast cancer factors for breast cancer-specific survival, and identified 2 prognostic groups (DRPI-PG). The results showed that XRCC1, Polβ, FEN1, and BRCA1 protein levels were significant independent predictors of breast cancer-specific survival in estrogen-estrogen receptor (ER)-negative and triple-negative breast cancer. Patients in the DRPI-PG2, which had high scores, were at a higher risk of death and exhibited unfavorable clinicopathological characteristics, such as higher grade and lymphovascular invasion, compared to those in DRPI-PG1 with lower DRPI scores (Abdel-Fatah et al., 2015). Additionally, researchers divided patients into 4 prognostic groups using DRPI scores for single-strand-selective monofunctional uracil-DNA glycosylase 1 (SMUG1) and APE1 in ER-driven breast cancer, indicating that BER-directed stratification may lead to appropriate treatments (Abdel-Fatah et al., 2014).

SMUG1 initiates DNA-base damage repair through the BER pathway by removing uracil from single-strand DNA, such as U:G mismatches and several pyrimidine oxidation products (Raja and Van Houten, 2021). One study found that uracil-DNA glycosylase (UNG) and SMUG1 work synergistically in uracil repair in mice, indicating that SMUG1 is important for uracil repair in vivo (Lirussi et al., 2022). C-to-T mutations in UNG/SMUG1 knock-out (KO) mice indicate that SMUG1 may influence gene regulation. Therefore, SMUG1 may affect cancer risk through antimutagenic function and gene regulation. Several studies have shown that SMUG1 status is associated with modified cancer risk and response to therapy because it is upregulated in breast cancer and cancer cell lines. Antibody-based staining of breast cancer tissue arrays showed that low expression of SMUG1 protein was associated with aggressive breast cancer, suggesting it could serve as an independent prognostic biomarker for ER-positive breast cancer and a predictive marker for response to adjuvant chemotherapy (Abdel-Fatah et al., 2013; Lirussi et al., 2022).

Colorectal Cancer

Colorectal cancer is one of the most prevalent tumors and ranks second among cancer-related deaths (Azambuja et al., 2018). Sporadic colorectal cancer, which accounts for more than 80% of all cases, is the most common form, but its etiological causes are not well known (Nojadeh et al., 2018). Colorectal cancer usually begins as a benign lesion and accumulates DNA damage along the way to full-fledged cancer. The determination of the pathological stage constitutes the singular prognostic parameter utilized for the allocation of adjuvant chemotherapy in clinical settings (Matsuda et al., 2021; Mirza-Aghazadeh-Attari et al., 2018). Moreover, drug resistance is important for colorectal cancer patients receiving comprehensive treatment and is directly related to the absence of predictive markers (Hossain et al., 2022).

In one study, the expression of N-methylpurine DNA glycosylase (MPG), Polβ, XRCC1, and FEN1 proteins was evaluated in tumor samples from 72 patients through immunohistochemistry (Azambuja et al., 2018). The correlation of molecular data with tumor-node-metastasis (TNM) staging was analyzed using clinical characteristics, prognosis predictor, and disease-free survival. High expression levels of MPG, Polβ, and XRCC1 were associated with unfavorable pathological outcomes such as cancer cell differentiation and TNM progression. In particular, overexpression of MPG and Polβ is associated with colorectal cancer. High expression of MPG shortens the disease-free survival of colorectal cancer patients and causes recurrence. BER proteins appear to be suitable candidates for improving the current TNM staging of colorectal cancer.

Another comprehensive study of single genes with common polymorphisms was performed to evaluate gene-environment interactions by examining both the risk of colorectal cancer and the prognosis of patients (Kabzinski and Majsterek, 2022). The *OGG1 Ser326Cys* and *PARP1 Lys940Arg* polymorphisms have been linked to an elevated risk of colorectal cancer in younger populations, whereas the *Polβ Pro242Arg* variant appears to

confer a protective effect against the development of colorectal cancer (Liu et al., 2019; Moreno et al., 2006). *XRCC1 Arg399Gln* and *ERCC1 Cys8092Ala* in multivariate analysis had significant results and may have an impact on responsiveness and prognosis in patients receiving adjuvant chemotherapy (Dai et al., 2015; Kabzinski and Majsterek, 2022).

In another study, sporadic colon tumor samples were analyzed to determine the gene expression of the BER pathway and the clinical and pathological characteristics of patients. Mismatch repair (MMR)-deficient colon cancer cells (HCT116) overexpressing MPG or XRCC1 were treated with 5-FU and evaluated for viability and metabolic levels (Leguisamo et al., 2017). The results showed that increased expression of BER genes and proteins was associated with aggressive tumor characteristics in colorectal cancer. Tumors with reduced gene expression in MMR also exhibited low expression of MPG, OGG1, and PARP1. An imbalance of BER due to overexpression of MPG sensitizes MMR-deficient colon cancer cells to 5-FU and TMZ and results in ATP depletion and lactate accumulation. MPG overexpression alters DNA repair and metabolism, suggesting it is a potential strategy to overcome 5-FU chemotherapy resistance in MMR-deficient colorectal cancer.

Lung Cancer

Many studies have reported that attenuated DNA repair capacity exhibits a significant association with heightened predisposition to lung cancer (Schwartz et al., 2007; Wang et al., 2013). Problems with DNA damage repair pathways precipitate an accumulation of somatic mutations, resulting in the loss of tumor suppressor functionality and oncogenic activation, subsequently inducing dysregulated cellular proliferation and malignant transformation (Sevilya et al., 2014). More than 80% of lung cancer cases are non–small cell lung cancer (NSCLC), and chemotherapy remains the cornerstone treatment for patients with advanced and recurrent lung cancer (Felip et al., 2005; Siegel et al., 2014).

The relationship between lung cancer and proteins in the BER pathway has been mostly studied across the genome using SNPs. In particular, SNPs in DNA glycosylase, which removes oxidatively generated DNA lesions, are susceptibility factors for lung cancer (D'Errico et al., 2017). For OGG1, variant homozygous carriers exhibit a reduced ability to remove 8-oxoguanine. The association of the *hOGG1 Ser326Cys* polymorphism with lung cancer risk has been noted in many epidemiological studies (Bravard et al., 2009; Matullo et al., 2005; Paz-Elizur et al., 2003; Zhong et al., 2012). In a follow-up study of patients with NSCLC, those with OGG1 mutations had a low survival rate (Su et al., 2015).

Experiments were conducted in KO model mice to examine the correlation between the inferred functions of DNA glycosylase and the gene and protein levels. Double-KO mice, which are defective in biallelic-inherited mutations of the human MutY homolog gene involved in MUTYH and OGG1 activities, show a clear increase in tumor frequency, mainly lung tumors, and lymphomas. In another study, MUTYH, OGG1 double-KO mice showed an age-dependent accumulation of 8-oxoguanine in most tissues and an increased incidence of lung and small intestine cancers (Russo et al., 2004). Additionally, the incidence of lung adenoma and hepatocarcinoma increased in endonuclease VIII-like 1 (NEIL1) KO-aged mice and a clear lung cancer-prone phenotype was observed in NEIL1 and NTH1 double-KO mice. Radak's study also showed that deletion of NTH1 results in a marked increase in pulmonary tumors in humans (Chan et al., 2009; Radak et al., 2005).

UNG has been identified as a prognostic indicator in NSCLC (Saviozzi et al., 2009). High UNG protein expression in lung adenocarcinoma tissues has been associated with reduced survival rates and advanced disease stages. UNG protein expression and transcript levels were significantly higher in lung cancer cell lines than in normal cell lines. The expression of UNG correlates with cell proliferation, as was observed in replication foci associated with the initiation of BER, indicating coordination of DNA replication and uracil-DNA repair (Berger et al., 2008). Significant variation in UNG expression was found between histological subtypes when UNG expression was measured in primary human lung cancer tissue cDNA microarray. UNG expression was increased in lung cancer compared to nonmalignant tissue cDNA (Weeks et al., 2013).

Many studies have specifically reported that the XRCC1 SNP is associated with the progression of advanced NSCLC in lung cancer (De las Peñas et al., 2006; Gurubhagavatula et al., 2004). Several studies have shown that carriers of the *XRCC1 Arg399Arg* genotype have a higher risk of lung cancer. An increasing number of XRCC1 variant alleles was associated with lower overall survival, and the *XRCC1 Arg399Arg* genotype was associated with a higher risk of death (Sreeja et al., 2008). Additionally, reduced DNA repair capacity has been reported in cells expressing XRCC1 mutant alleles, while some studies have reported no differences in cell survival after treatment with alkylating agents (Qu et al., 2005; Taylor et al., 2002).

Another study found that the *XRCC1 Gln399Gln* genotype was associated with a trend toward better survival after platinum-based chemotherapy (Giachino et al., 2007). Genes within the XRCC1 gene have been investigated as potential predictive markers for radiotherapy toxicity. Despite unclear research results, XRCC1 may serve as a valuable biomarker and a prognostic indicator in lung cancer (Gossage et al., 2012).

Bladder Cancer

Bladder cancer constitutes one of the most common malignant tumors of the urinary tract, and epidemiological studies indicate that environmental exposures and genetic susceptibility are the main causes of bladder cancer (Horikawa et al., 2008). Environmental factors, including cigarette smoke components, cause DNA damage through ROS-mediated mechanisms (Smal et al., 2018). A reported 98% of bladder cancers are epithelial malignancies, with transitional cell carcinoma accounting for the majority (Volanis et al., 2010). Interindividual differences in susceptibility to bladder cancer may be due to genetic polymorphisms in important genes, including DNA repair pathway genes (Wu et al., 2004).

In a case-control study of bladder cancer patients and controls, individual SNP analysis identified *SMUG1 rs2029167* as an important gene that increased the risk of bladder cancer. SMUG1 removes uracil, 5-hydroxyluracil, and several nucleotide derivatives from DNA. If they are not repaired, DNA lesions

can lead to nucleotide base transfer and conversion, which can affect cancer risk (An et al., 2007). This suggests that genetic mutations in BER pathway genes regulate the risk of bladder cancer. In particular, classification and regression tree analysis, which detects the cumulative effect of SNPs and gene-gene interactions in high-risk subjects, shows that risk increases with increasing number of unfavorable genotypes in the BER pathway and genetics as a predictor of bladder cancer risk (Xie et al., 2015). The *OGG1 Ser326Cys* polymorphism is known to reduce the ability of human blood lymphocytes to repair oxidative and radiation-induced DNA damage (Vodicka et al., 2007). Analyses of SNPs by visualization through polymerase chain reaction-restriction fragment length polymorphism showed that polymorphisms in OGG1 were associated with increased mutation frequency in urothelial carcinoma and affected promoter methylation (Bayraktar and Kreutz, 2018; Smal et al., 2018). Methylated genes can be prognostic biomarkers that can predict clinical outcomes and consider appropriate treatments accordingly.

While SMUG1 has been a focus, recent studies on XRCC1 underscore its relevance in bladder cancer. The *XRCC1 Arg399Gln* polymorphism has been associated with increased bladder cancer risk, while higher XRCC1 expression levels correlate with advanced tumor grade and poor prognosis. These findings suggest that XRCC1 plays a significant role in modulating DNA repair efficiency, which may affect cancer susceptibility and treatment response (Mao et al., 2013; Yang et al., 2014).

In qPCR, genotyping and statistical analyses, APE1 polymorphism was significantly associated with cancer mortality. In addition to APE1, studies have shown that transcript expression levels of XRCC1 and Polβ were significant regardless of tumor grade. Polβ transcripts were observed in 77% of high-grade tumors (Chantre-Justino et al., 2015). The *APE1 Asp148Glu* polymorphism is an allelic mutation known to affect patient mortality and recurrence, and other meta-analyses have shown that patients with the G allele have a higher cancer risk (Gu et al., 2009).

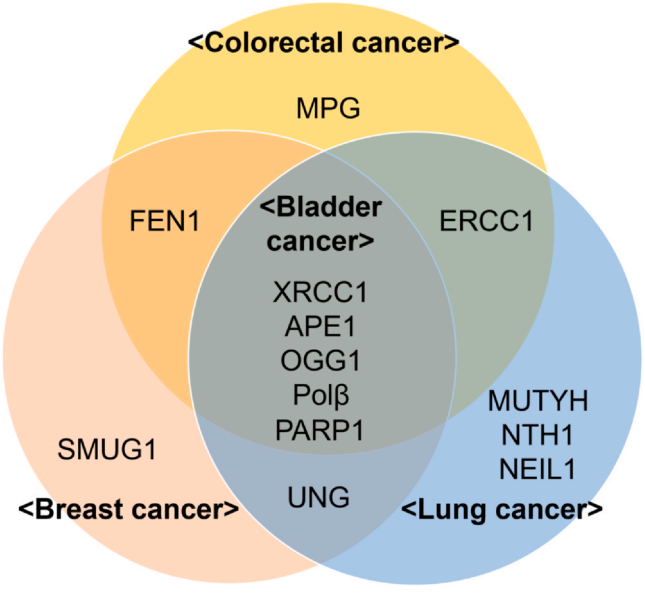

Fig. 3. Correlation with each cancer and BER gene. This Venn diagram illustrates the overlap of genes associated with 3 types of cancer: colorectal cancer (yellow), breast cancer (orange), and lung cancer (blue). The intersections highlight genes common to multiple cancer types.

CONCLUSION

The BER pathway is a major cellular repair system that repairs damaged DNA base. Damaged DNA can reduce cell function and cause diseases such as cancer. When base damage occurs, BER proteins recognize and remove the damaged base. Then, enzymes like DNA polymerase and DNA ligase replace the damaged bases and repair the DNA.

In this review, we discussed the expression level of BER proteins and their value as prognostic and predictive biomarkers for breast, colorectal, lung, and bladder cancer (Fig. 3). These studies suggest that the expression levels of BER proteins may play an important role in predicting cancer prognosis. Studies are underway to evaluate the expression levels and prognostic value of BER proteins in other types of cancer. Therefore, it is important to keep in mind the potential possibilities ahead. Additionally, to use BER protein as a biomarker, extensive statistical analyses and large-scale prospective studies are required. These studies suggest the potential therapeutic utility of effective cancer treatment targets by increasing the efficacy and reducing resistance to current radiotherapy and chemotherapy. In the future, it may also contribute to the development of drugs targeting these BER proteins and the development of cancer treatment techniques using synthetic lethality. Through this, we can look forward to a future in which we can effectively respond to cancer.

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AUTHOR CONTRIBUTIONS

Jeongeun Kim: Writing – review & editing, Writing – original draft, Conceptualization. **Su-Jin Kang:** Writing – review & editing, Writing – original draft. **Nayoon Jo:** Investigation. **Seung-Jin Kim:** Writing – review & editing, Supervision, Funding acquisition. **Sunbok Jang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ORCID

Jeongeun Kim: 0009-0005-0060-1660
Su-Jin Kang: 0000-0003-3276-8957
Nayoon Jo: 0009-0002-3292-2029
Seung-Jin Kim: 0000-0002-6062-1736
Sunbok Jang: 0000-0001-7371-0124

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