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BRCA1: Beyond double-strand break repair

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ABSTRACT

Since its discovery, the BRCA1 tumor suppressor has been shown to play a role in multiple DNA damage response pathways. Here, we will review the involvement of BRCA1 in base-excision DNA repair and highlight its clinical implications.

1. Introduction

1.1. BRCA1

The breast cancer susceptibility gene 1 (*BRCA1*) encodes a tumor suppressor that maintains genetic stability primarily through its involvement in DNA damage response pathways [1–3]. Since its discovery in 1994 [4], BRCA1 has been established as a key regulator of repair of double-strand DNA breaks *via* homologous recombination (HR) [5]. Interestingly, its involvement in other types of DNA repair has since come to light, including nucleotide-excision repair, base-excision repair (BER), and non-homologous end-joining [5–8]. While much remains to be learned about the mechanism by which BRCA1 functions in these repair pathways, evidence supports its involvement through transcription regulation and protein–protein interactions, and possibly through its E3 ubiquitin ligase activity [1–3].

Mutations in *BRCA1* may occur in each of the three main regions of the gene, including the (1) 5′ RING domain that harbors E3 ubiquitin ligase activity, (2) a central region that encompasses two nuclear localization signals (exon 11), and (3) two 3′ tandem BCRT domains that interact with a variety of proteins, including transcription regulators and effectors of DNA repair. However, deleterious mutations in *BRCA1* most frequently exist within exon 11, thereby precluding the localization of BRCA1 into the nucleus where it functions in DNA repair [9]. *BRCA1* mutations typically are inherited in the germline, and thereby confer an increased risk for breast and ovarian cancer. Indeed, *BRCA1*-mutated cancers comprise approximately 50% of hereditary breast cancer cases and more that 75% of hereditary ovarian cancer cases [10]. Furthermore, a subset of sporadic cancers harbor diminished BRCA1 expression (and function) due to epigenetic mechanisms. Together, these cancers are invasive and associate with an aggressive clinical course. They are relatively resistant to traditional anti-cancer strategies, but seem to respond best to therapies that exploit their defects in DNA repair [11,12].

This review will focus on the involvement of BRCA1 in base-excision DNA repair and address the clinical implications associated with such a role.

1.2. Base excision repair

DNA damage subject to BER is repaired *via* a short-patch or long-patch pathway [13,14]. Glycosylases initiate the process by acting in a lesion-specific manner to excise incorrect or damaged bases [15,16], and in turn, they generate an abasic or apurinic/apyrimidinic (AP) site. Table 1 lists common glycosylases discussed in this review. AP-endonuclease (APE1) then cleaves the phosphodiester backbone 5′ to the AP site, resulting in a

Abbreviations: 8oxoG, 8-oxo-guanine; 8oxodG, 8-hydroxy-2′-deoxyguanosine; AP, apurinic/apyrimidinic; APE1 (or APE1/REF1), AP-endonuclease (redox effector factor-1); ATR, ataxia telangiectasia and Rad3 related; ATM, ataxia telangiectasia mutated; BARD1, BRCA1-associated RING domain 1; BER, base excision DNA repair; BRCA1, breast cancer susceptibility gene 1; DNA-PKcs, DNA-dependent protein kinase; EndoIII, endonuclease III; FEN1, flap structure-specific endonuclease; Fpg, formamidopyrimidine [fapy]-DNA glycosylase; H_2O_2, hydrogen peroxide; HR, homologous recombination; IR, ionizing radiation; LIG3, ligase 3; MMEC, mouse mammary epithelial cell; MMS, methyl methansulfonate; MMTS, methyl methanethiosulfonate; NTH1 (or NTHL1), *n*th endonuclease III-like 1; OCDL, oxidatively-induced clustered DNA lesion; OGG1, 8-oxoguanine DNA glycosylase; Oct1, octamer binding transcription factor 1; PARP, poly (ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; POLB, polymerase beta; POLD, polymerase delta; POLE, polymerase epsilon; PNK, polynucleotide kinase 3'-phosphatase; ROS, reactive oxygen species; SMUG1, single-strand-selective monofunctional uracil-DNA glycosylase 1; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells.

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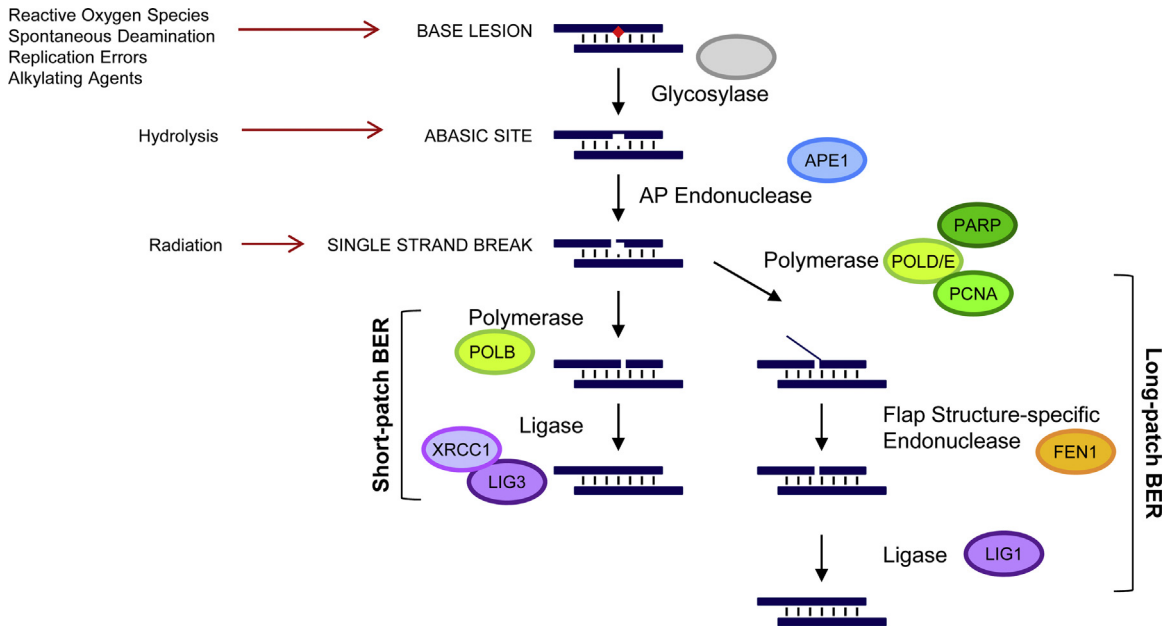

Fig. 1. DNA damage and base excision repair. Sources of the most common types of DNA damage are shown. Base excision repair occurs *via* the 'short-patch' or 'long-patch' pathway, and involves four major enzymatic activities: excision of a damaged/incorrect base by a lesion-specific glycosylase, incision of the phosphodiester backbone at the resulting abasic site by AP endonuclease, addition of nucleotide(s) and displacement of damage by polymerase (and flap structure-specific endonuclease), and re-formation of the phosphodiester bond by ligase. AP sites and single-strand breaks are intermediates in BER, therefore, their repair is intrinsic to the pathway. For each pathway, key enzymes and scaffolding proteins are depicted.

single-strand DNA break intermediate. In some cases, bifunctional glycosylases, which also cleave the phosphodiester bond adjacent to the damaged base, preclude the need for endonuclease activity of APE1, and instead, require polynucleotide kinase 3′-phosphatase (PNK) for single-strand break end-processing. In the short-patch pathway, DNA polymerase (POLB) displaces the AP-site and adds a nucleotide. Lastly, ligase (LIG3) forms a phosphodiester bond to complete repair. X-ray repair complementing defective repair in Chinese hamster cells 1 (XRCC1) is a scaffolding protein that brings POLB in close proximity to LIG3. In the long-patch pathway, DNA polymerase (POLB, POLD or POLE) displaces and adds >1 nucleotide, flap structure-specific endonuclease (FEN1) removes the displaced nucleotides, and ligase (LIG1) completes repair. Proliferating cell nuclear antigen (PCNA) is required for POLD function and acts as a scaffolding protein. Poly(ADP-ribose) polymerase (PARP) binds to and recruits essential mediators to single-strand break intermediates.

1.3. DNA damage

The types of DNA damage that are repaired by BER typically do not induce significant distortions to the DNA structure, and include single-base lesions, abasic sites, and single-strand breaks. This damage is frequently generated by endogenous sources, but on occasion includes damage induced by exogenous sources. They include reactive oxygen species (ROS), spontaneous deamination of bases, replication errors, alkylating agents, hydrolysis, or radiation (Fig. 1 and [15]). ROS form as byproducts of biological processes or arise from oxidizing agents to produce oxidative DNA damage. The most common oxidative lesion is 8-oxo-guanine (8oxoG). Spontaneous deamination most frequently affects cytosine, thereby producing uracil. Replication errors can result in the incorporation of incorrect or altered bases. Alyklating agents generate methylated or alkylated bases. Spontaneous hydrolysis of glycosidic bonds leads to abasic sites. Low doses of ionizing radiation (IR) produce single-strand breaks. Each of these forms of DNA damage tends to be mutagenic, and if left unrepaired, leads to DNA double-strand breaks, genomic instability, and ultimately tumorigenesis.

Table 1
Glycosylases examined in the context of BRCA1-mediated BER.

Glycosylase	Damage recognition	Function
NTH1 (NTHL1)	Oxidized pyrimidines	Bifunctional
OGG1	8-Oxo-guanine	Bifunctional
SMUG1	Uracil	Monofunctional
UNG	Uracil	Monofunctional
MPG	Methylated purine	Monofunctional

2. BRCA1 in BER

2.1. Implications for BRCA1 in BER

Perhaps the most preliminary lines of evidence implicating BRCA1 in BER derive from studies analyzing drug sensitivity to agents that induce DNA damage repaired by BER, such as oxidizing or alkylating agents and radiation [17–24]. Cells typically undergo apoptosis upon the accumulation of unrepairable damage, and thus, display sensitivity to agents that induce such damage. For example, Sgagias et al. suggested a role for BRCA1 in BER based on the finding that Brca1$^{-/-}$ mouse mammary epithelial cells (MMECs) exhibited greater sensitivity to methyl methansulfonate (MMS) alkylating agent than isogenic Brca1$^{+/+}$ MMECs [23]. Similarly, these Brca1$^{-/-}$ MMECs displayed greater sensitivity to hydrogen peroxide oxidizing agent (H_2O_2) than the Brca1$^{+/+}$ MMECs [22]. BER is an evolutionary conserved pathway across species, so the extrapolation of these findings to human cells seemed plausible. Indeed, human breast cancer cell lines with known mutations in *BRCA1* (or with a mutant BRCA1 phenotype) showed greater sensitivity to H_2O_2 than normal-like human breast cell lines [22].

2.2. Effects of BRCA1 on damage repaired by BER

Consistent with sensitivity to oxidizing agents, we found that Brca1$^{-/-}$ MMECs harbored significantly greater levels of