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Review Article

Base excision repair targets for cancer therapy

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Abstract: Cellular DNA repair is a frontline system that is responsible for maintaining genome integrity and thus preventing premature aging and cancer by repairing DNA lesions and strand breaks caused by endogenous and exogenous mutagens. However, it is also the principal cellular system in cancer cells that counteracts the killing effect of the major cancer treatments e.g. chemotherapy and ionizing radiation. The major goal of this review is to critically exam the base excision repair pathway and mechanisms regulating base excision repair capacity as a potential targets for improving cancer therapy.

Keywords: DNA repair, base excision, chemotherapy, ionizing radiation, cancer therapy

Base excision repair mechanism

Base excision repair (BER) is initiated by damage specific DNA glycosylases that release the corrupted base by hydrolysis of the N-glycosylic bond linking the DNA base to the sugar phosphate backbone. The arising abasic site (AP-site) is further processed by AP-endonuclease 1 (APE1) that cleaves the phosphodiester bond 5'- to the AP-site, generating a DNA single strand break (SSB) with a 5'-sugar phosphate. This SSB is then repaired by a DNA repair complex that includes DNA polymerase β (Pol β), XRCC1 and DNA ligase IIIα (Lig III) [1, 2]. Pol β possesses AP lyase activity that removes the 5'-sugar phosphate and also, functioning as a DNA polymerase, adds one nucleotide to the 3'-end of the arising single-nucleotide gap [3]. Finally, Lig III seals the DNA ends, therefore accomplishing DNA repair (reviewed in [4]). This pathway is commonly referred to as the short patch BER pathway, through which cells are accomplishing the majority of repair (**Figure 1**, left branch) [5-7]. However, if the 5'-sugar phosphate is resistant to cleavage by Pol β, then after addition of the first nucleotide by Pol β, a switch to Pol δ/ε occurs that adds 2-8 more nucleotides into the repair gap, therefore generating a flap structure that is removed by flap endonuclease-1 (FEN-1) in a PCNA-dependent manner. DNA ligase I then seals the remaining nick in the DNA backbone and this process is commonly referred to as long patch BER [8, 9] (**Figure 1** right branch).

BER targets for cancer therapy

Every time before DNA replication and cell division (late G1-phase of the cell cycle) the quality of DNA is checked and if DNA damage is detected, this leads to the activation of the cellular DNA damage response. Accumulation of the p53 tumour suppressor protein in response to DNA damage is a hallmark of this process [10]. There are several outcomes of increased p53 levels: if DNA damage is not significant and can be promptly repaired, then p53 activates a group of genes responsible for cell cycle delay to provide a time frame for DNA repair prior to replication [11]. Pre-replicative DNA repair is mainly accomplished by BER, that removes base lesions and SSBs and nonhomologous end joining (NHEJ) is responsible for processing of DNA double strand breaks (DSBs), **Figure 2**. Alternatively, if the DNA damage is recognised as beyond the repair capacity of the cell, p53 activates programmed cell death (apoptosis) to eliminate the damaged cell.

More evidence is accumulating to support the idea that the majority of cancer cells either have

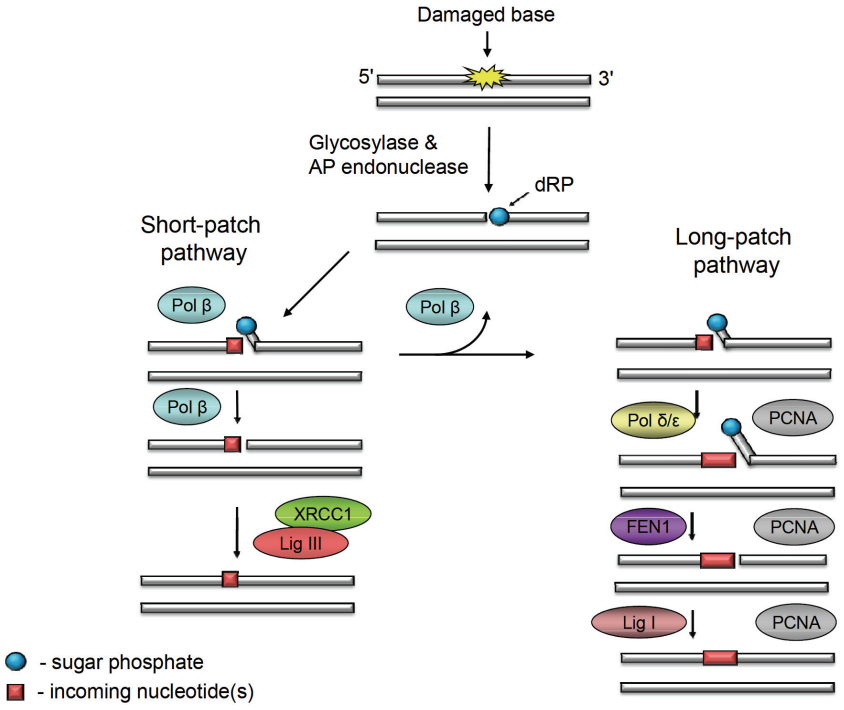

Figure 1. BER pathways BER is initiated by a damage specific DNA glycosylase and APE1 that excise the damaged base and incise the arising abasic site, respectively generating a DNA single strand break with a 5'-sugar phosphate. Pol β removes the 5'-sugar phosphate and also adds one nucleotide into the single-nucleotide gap. Finally, XRCC1-Lig III complex seals the remaining DNA ends. This pathway is commonly referred to as the short patch BER pathway (left branch). However, if the 5'-sugar phosphate is resistant to cleavage by Pol β, then Pol δ/ε adds 2-8 more nucleotides into the repair gap, generating a flap structure that is removed by FEN -1 in a PCNA-dependent manner. Lig I then seals the remaining DNA ends. This pathway is commonly referred to as long patch BER (right branch).

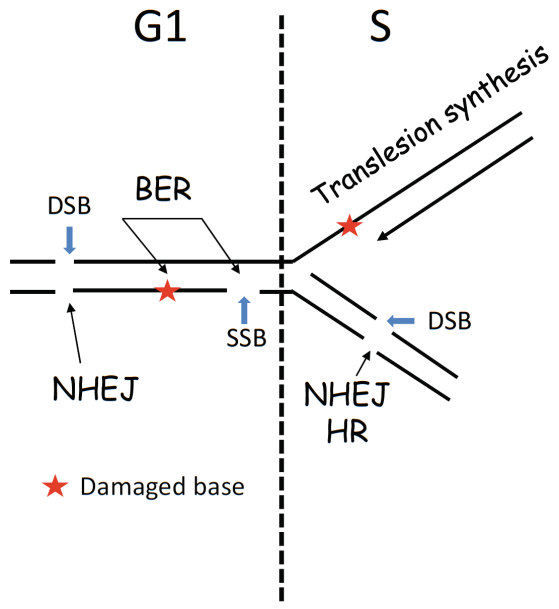

Figure 2. Involvement of DNA repair pathways through the cell cycle. In the G1 phase of the cell cycle, BER and nonhomologous end joining (NHEJ) are the major DNA repair pathways responsible for the removal of DNA base damage and DNA single and double strand breaks (SSBs and DSBs). During S phase, unrepaired DNA base lesions and DNA strand breaks are bypassed by translesion DNA polymerases or repaired by homologous recombination (HR), respectively.

increased level of DNA lesions induced by endogenous mutagens, or are deficient in at least one of the DNA repair systems [12]. If this happens in normal cells, they will be eliminated through apoptosis, however in the majority of cancer cells the DNA damage response is inactivated. This is achieved either by deletion or mutation of the p53 protein, inactivation or deletion of the ARF protein that is involved in DNA damage signalling or finding some other ways to incapacitate the DNA damage response [13, 14]. However, to accomplish replication of the damaged DNA, cancer cells are dependent on DNA repair systems operating in S-phase. In particular, translesion synthesis DNA polymerases are important for replicating through the damaged DNA bases and NHEJ and/or homologous recombination (HR) are important for removal of the DSBs. The major goal of cancer therapy mediated through DNA base damage, is to overload the cellular DNA repair capacity and initiate preferential elimination of the cancer cells whilst keeping normal cells intact. In this aspect the concept of synthetic lethality provides such an opportunity [15, 16]. Most probably, since the majority of BER genes are essential for normal and cancer cells, genetic instability in cancer cells is caused by mutation in one of the repair pathways that remove DNA lesions

other than those processed by BER, but plays an important backup role in processing DNA lesions normally removed by BER. This means that reducing BER capacity will preferentially overload DNA repair capacity of these backup repair pathways in replicating cancer cells and thus induce their elimination. However normal cells will survive since they will still have efficient backup repair systems. Since BER is one of the major DNA repair pathways responsible for repair of damaged DNA, reducing BER capacity is a very promising approach for cancer treatment. I will next discuss the feasibility of inhibiting different stages of BER to achieve the final goal of overloading repair capacity of cancer cells to promote their death.

DNA glycosylases

DNA glycosylase knockout mice, generated so far, develop normally and although they accumulate lesions in DNA, the majority of them did not show any significant increase in cancer initiation rates [17]. This suggest that since DNA glycosylase substrate specificity is quite overlapping and also because human cells are able to correctly replicate through damaged DNA bases using lesion bypass polymerases, inactivation of individual glycosylases in normal cells is not that toxic. However, inactivation of specific DNA glycosylase may increase killing of cancer cells if overexpressing of that particular DNA glycosylase is a requirement for cancer cell survival. There are a number of examples of overexpression of DNA glycosylases in cancer cells and it was suggested that it may lead to drug resistance (reviewed in [18]). In this case, inactivation of DNA glycosylases may have a positive impact on cancer therapy.

AP endonuclease

APE1, like many other BER proteins, is often overexpressed in cancer cells [19-22] and was implicated in cancer resistance to therapy [23]. However, the therapeutic window for APE1 is very questionable since APE1 is an essential enzyme and its knockdown in mice is embryonic lethal. Moreover, even cultured cells are not viable without APE1 [24] suggesting that APE1 inhibitors may be very toxic for both normal and cancer cells.

DNA polymerases

The major DNA polymerase involved in BER is Pol β [9, 25] although Pol λ contributes to repair of oxidative lesions [26, 27, Amoroso, 2008 #11237, 28, 29]. Knocking down of these polymerases increase cell sensitivity to irradiation and chemical mutagens [30]. However, human cells have multiple DNA damage bypass DNA polymerases that can replace BER DNA polymerases at the sites of DNA damage to accomplish DNA replication [31, 32]. In many cases these DNA polymerases are important for cancer cell survival and their overexpression negatively correlates with the efficiency of cancer therapy [33-36]. Inhibition or inactivation of these DNA polymerases in addition to BER DNA polymerases should increase the efficacy of cancer treatment, however since there are at least 11 bypass DNA polymerases, it is quite difficult to choose one of them as a target without preliminary knowledge as to which one is important for survival of a particular cancer.

DNA ligases

There are two human DNA ligases implicated in BER: DNA ligase IIIα (Lig III) and DNA ligase I (Lig I), **Figure 1.** Of those, Lig I is involved in long patch BER and also plays a major role in DNA replication [37]. Thus inhibiting Lig I may have a preferential effect on actively dividing cancer cells, but it still maybe quite toxic for normal cells as well. The same is probably true for Lig III. Even it is mainly a BER DNA ligase, it is essential for both mitochondrial and nuclear DNA repair in normal cells and its inhibition maybe toxic for cells [38]. The DNA repair function of Lig III can also be partially substituted by Lig I that will significantly reduce the therapeutic effect of Lig III inhibition [39].

Enzymes involved in regulation of BER capacity as potential targets for cancer therapy

Poly(ADP-ribose) polymerase-1

Poly(ADP-ribose) polymerase-1 (PARP-1) is one of the most abundant cellular proteins that is required for cellular resistance to DNA damaging agents, including ionising radiation. PARP-1 is a multi-functional molecule, whose catalytic activity is involved in a wide variety of cellular responses [40]. Although the molecular mechanisms are not clear, it is believed that PARP-1 plays a major role in DNA damage signalling and promotes DNA repair. PARP-1 binds to the DNA single strand breaks (SSB) as a dimer and this binding activates the poly (ADP-ribosyl)ation

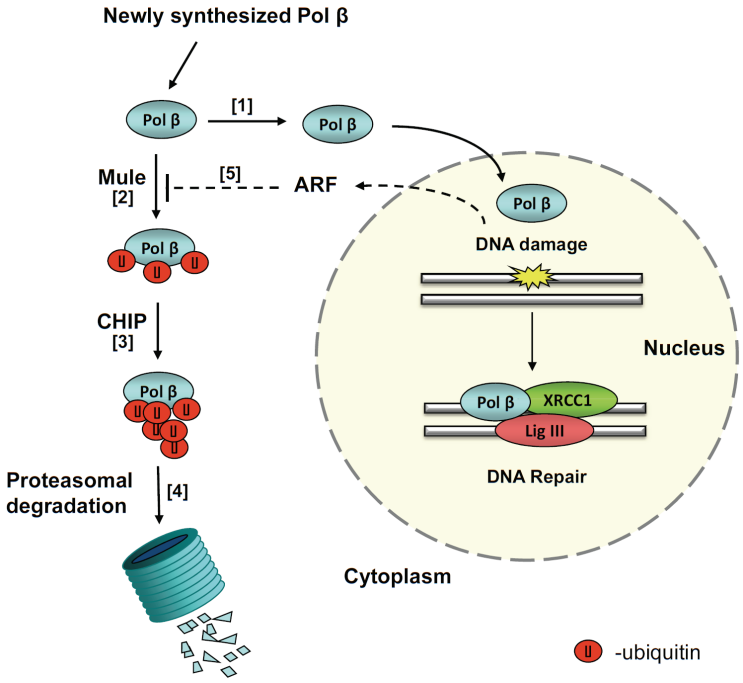

Figure 3. Regulation of base excision repair by Mule, CHIP and USP47. Depending on the amount of Mule, newly synthesised Pol β is either directly transferred to the nucleus [1] or ubiquitylated by Mule [2]. Ubiquitylated Pol β is then a target for CHIP mediated polyubiquitylation [3] and subsequent degradation by the proteasome [4]. However, if DNA damage is detected, the activity of Mule is inhibited by ARF [5] which then generates more active Pol β that is able to enter the nucleus to participate in DNA repair. Adapted from (58).

activity of PARP-1. The primary target of poly (ADP)ribosylation is the other PARP-1 molecule within the dimer bound to the SSB. Accumulation of the negatively charged poly(ADP-ribose) polymers stimulates PARP-1 dissociation from the DNA (reviewed in [40]. This binding-dissociation cycle can be repeated many times to protect SSB from deterioration by the cellular milieu [41]. We have previously demonstrated that PARP-1 plays a role in BER by increasing its capacity [42, 43]. We showed that since only a limited amount of BER enzymes are present in mammalian cells, in the case of extensive DNA damage, DNA repair is accomplished in several rounds. During this process, PARP-1 binding protects the excessive DNA SSB from converting into DNA DSB, thus preserving them for subsequent rounds of repair by BER enzymes. This suggests that PARP-1 plays an important role in BER by extending the ability of BER enzymes to process DNA SSB arising directly after extensive DNA damage. Recently, the idea of preventing BER by inhibiting PARP-1 function on a DNA repair deficient background (concept of synthetic lethality) has been proposed for selective killing cancer cells [16, 44]. The advantage of using PARP-1 inhibitors is that, unlike core BER proteins, PARP-1 is not essential and is only required for the BER of excessive DNA damage and thus should be less toxic to normal cells.

Enzymes involved in controlling proteasomal degradation of BER proteins

To support error-free transcription and replication, BER proteins should be present in adequate amounts to be able to promptly repair DNA. Indeed, mutations affecting the amounts or enzymatic activities of these proteins increase genome instability and reduce cell viability in response to DNA damage [45-50]. On the other hand, the amount of BER enzymes should be tightly controlled since when overproduced, BER enzymes may affect other DNA transactions and also lead to genome instability and cancer [18, 35]. The amount of DNA lesions in human cells originates from the chemical instability of the DNA molecule itself, but also depends on cellular metabolism and exposure to exogenous mutagens [51]. A combination of these factors leads to variations in DNA damage levels and BER should be responsive to the changing environment and indeed, as it has been recently demonstrated, the amount of BER enzymes present within a cell at any time (the steady-state level of BER enzymes), is tightly regulated and is linked to the amount of DNA lesions [52]. This is achieved by controlling the nuclear pool of three major BER enzymes (XRCC1, DNA ligase III and Pol β) through targeted proteasomal degradation. Proteins tar-

geted for degradation are marked with a chain of ubiquitin (small 76 amino acid protein) molecules. Polyubiquitylated proteins are recognised by the 26S proteasome that unfolds the protein, removes the polyubiquitin chains and degrades the protein (for review see [53]).

If the levels of BER proteins exceed the level of DNA lesions, then the excessive BER enzymes are ubiquitylated and thus labelled for proteasomal degradation. For example, sequential ubiquitylation of Pol β by the E3 ubiquitin ligases Mule (ARF-BP1) and CHIP leads to Pol β degradation and down regulates its steady state level [54]. However, when more Pol β is required for DNA repair, Mule activity is down regulated by the ARF tumour suppressor protein [55, 56], whose release is modulated in response to DNA damage [57]. Release of ARF, and the consequent Mule inhibition, leads to accumulation of Pol β and increased DNA repair (**Figure 3**). However, as well as inhibiting E3 ubiquitin ligase activities, in many cases the steady state level of proteins is also controlled by an opposing activity. In this scenario, ubiquitylation leading to protein degradation is counteracted by deubiquitylation, primarily by ubiquitin specific proteases (USPs) that are the major class of deubiquitylation enzymes. Recently, the deubiquitylation enzyme USP47 has been shown to deubiquitylate Pol β and thus generate more protein required for DNA repair [58]. Subsequently, modulation of ubiquitylation and deubiquitylation activities of enzymes involved in the regulation of BER may be an interesting novel approach for cancer treatment.

In summary, BER potentially has a number of promising targets for improving cancer therapy. However, it is quite clear that a better understanding of the molecular defects of the individual cancers is required for developing an effective therapy.

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