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DNA repair pathways in cancer therapy

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Abstract
DNA damage has long been understood to play a causative role in the emergence of cancer. Cells go through a malignant transition that results in cancerous growth when incorrect DNA repair causes mutations or chromosomal abnormalities affecting oncogenes and tumour suppressor genes. Cancer can be caused by genetic abnormalities because some DNA repair mechanisms can be mutated to increase the vulnerability to different cancer forms. DNA damage, however, continues to be a key target for chemotherapy and radiation treatment in addition to being a primary contributor to the formation of cancer. Since the beginning of cancer therapy, genotoxic chemicals that set off DNA damage checkpoints have been used to slow the growth of cancer cells and cause them to undergo the apoptotic process that results in cell death. We give an outline of how DNA repair mechanisms contribute to the prevention of cancer.

Keywords: Genome, DNA repair pathways, DNA damage response, poly ADP ribose polymerase 1, homologous recombination, double strand break, chemotherapy, radiotherapy

Introduction
The critical responsibility of maintaining and faithfully transmitting the genome down through generations belongs to living things. Transmission of genetic information is always in a state of selection equilibrium between preserving genetic stability and preventing mutational change and the loss of evolutionary potential. Every cell is thought to encounter up to 105 spontaneous or induced DNA lesions per day, with the DNA molecule constantly coming under attack from a variety of endogenous and external genotoxic insults (De Bont R, van Larebeke N. (2004) [1]. By repairing damaged DNA that can contribute to carcinogenesis, DNA repair pathways are crucial for maintaining the stability and integrity of the genome. According to a number of studies, some malignancies are linked to a flaw or mutation in the proteins involved in nuclear or mitochondrial DNA repair processes. The harmful effects of several external and internal Geno-toxicants are continuously exposed to mitochondrial and genomic DNA molecules. As a result, organisms developed the DNA repair process as a form of defence. Genome stability and, inadvertently, chromosomal maintenance are both provided by guarding against damage to the human genome, including DNA lesions, mutations, strand breaks, interstrand, and DNA-protein connections. The DNA repair mechanism uses parallel pathways that are tailored to the type of damage and cell cycle. All live cells can be understood to have major routes for excision repair (BER, base excision repair; NER, nucleotide excision repair), mismatch repair (MMR), and recombination repair (NHEJ, non-homologous end joining; and HR, homologous recombination) (Lindahl T *et al*, 2000) [2]. A variety of inhibitors targeting DDR components have emerged, some of which are currently being studied in clinical settings, in tandem with advancements in tumour biology that identify DDR as possible therapeutic targets (Neizer-Ashun, *et al*, 2021) [20]. A combination of developing data on the sensitization impact of DDR inhibitors to conventional cancer therapies and the relationship between DDR pathways and immune checkpoint inhibitor (ICI) responsiveness support the development of medicines based on DDR inhibitors. Afterward, sensitivity to mutagens and carcinogens and an individual's propensity to acquire cancer were linked to DNA repair variability discovered in the later decades of the 20th century. Additionally, a low DNA repair potential was linked to an increased risk of developing cancer, and the genes that remained behind were called "low penetration genes." (Curtin NJ. 2012) [3, 18].

This recognition of this attribution as one of the hereditary risk factors for cancer was proven for a number of carcinogens and cancer types. An excellent example is the frequent and poor DNA repair potential of lung or laryngeal cancers caused by tobacco smokers who were exposed to the toxins in tobacco smoke. Nevertheless, it was discovered that polymorphisms contained gene variants known as "risk genes" or "at risk genes," indicating limited DNA repair ability. Gene variations with the capacity to repair DNA, on the other hand, were referred to as "protective genes." It should be acknowledged that numerous articles examining the relationship between genetic variation of DNA repair genes and cancer risk have generated a wealth of information, often in disagreement. Chemotherapeutic agents, industrial chemicals, and cigarette smoke are examples of chemical sources of damage in the environment. Their effects range from the generation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine 6-4 pyrimidone photoproducts (6-4PPs) after UV exposure to the introduction of single and double DNA strand breaks upon IR treatment, or to inter- and intrusive bacterial growth. DNA lesions can change the double helix's fundamental structure, which will impact transcription and replication. Erroneous repair of lesions can cause mutations in the genome, which can be passed on to daughter cells and have detrimental effects on a person's health. In this review, we will be discussing various DNA repair pathways in details and how it is linked with therapeutic approaches of cancer treatment.

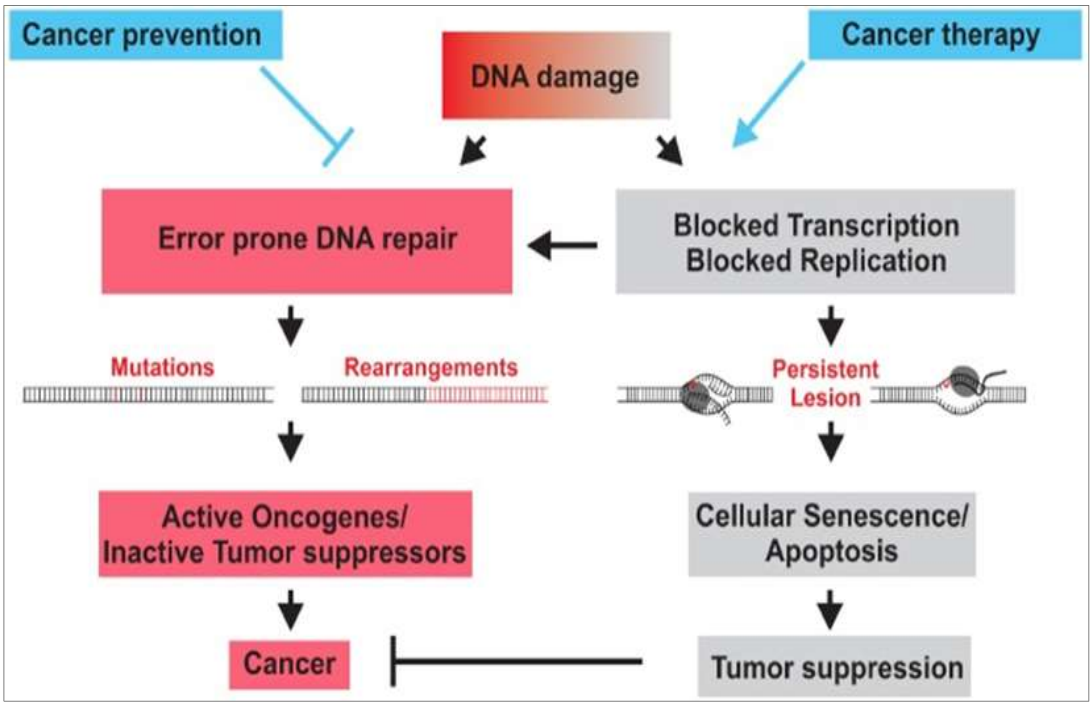

Fig 1: DNA damage checkpoints cause cellular senescence or apoptosis, which render injured cells inactive or kill them, suppressing carcinogenesis when DNA damage is persistent and prevents replication or transcription (grey). Cancer is prevented by DNA repair mechanisms that stop mutations**.** (DOI 10.3389/fgene.2015.00157)

Different dna repair pathways

Direct reversal pathway

Without the use of excision, resynthesis, or ligation, direct reverse repair removes some DNA and RNA alterations. Since the phosphodiester backbone is not broken during direct reversal repair, it is error-free and protects genetic information. N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), N-methyl-N-nitrosourea (MNU), and methyl methanesulfonate (MMS) are examples of DNA alkylating agents that react with DNA to produce a variety of O- and N-alkylated products. Direct reversal is generally employed to repair damage induced by these agents. O6-methylguanine-DNA methyltransferase (MGMT) and alkylated DNA repair protein B (AlkB) homologs are two distinct mechanisms that carry out DRR. Only one DNA methyltransferase protein, O6-methylguanine-DNA methyltransferase (MGMT or AGT), is present in mammalian cells, and it removes methyl groups from DNA's exocyclic ring oxygens. ALKBH proteins, which are a subfamily of the FeKGDs, carry out the second type of direct reversal repair. The elimination of alkyl damage in DNA has only been proven for four members of the ALKBH family of FeKGDs, ALKBH1 - 3 and FTO, despite the fact that the family consists of nine proteins with common active site domains.Each ALKBH protein can catalyse a variety of repair reactions to get rid of N-modifications of cytosine, adenine, thymine, and guanine residues, unlike repair by MGMT, which is inactivated after a single repair reaction (Gutierrez R., & O'Connor TR. 2021) [22].

Nucleotide excision repair pathway

The phases of the NER process in prokaryotes and eukaryotes can be separated into damage detection, damage verification, incision, excision, and DNA ligation. In prokaryotes, DNA repair is started in two main methods. First, when UvrA and UvrB work together to detect damage, this is possible. UvrA transmits the damage to UvrB, which then releases UvrA after separating the two DNA strands to confirm the location of the lesion. When UvrC arrives, UvrB creates a tight scaffold on the DNA for it. UvrC has two nuclease domains that cleave the phosphodiester links at

the damaged location, which are 8 nucleotides upstream and 4-5 nucleotides downstream. UvrD (helicase II) and DNA polymerase I (Pol I) function in tandem to excise the damage-containing oligonucleotide and allow turnover of the UvrB and UvrC proteins while filling in the resultant gap with the remaining complementary strand, creating the postincision complex. The DNA ligase enzyme closes the newly formed repair patch, completing the process. In the case of Eukaryotes, NER can be started by either the transcription-coupled NER (TC-NER) or the global genome NER (GG-NER) subpathway. The faster repair of lesions in the transcribed strand of active genes is carried out by TC-NER as opposed to GG-NER, which can occur anywhere in the genome. The GG-NER-specific factor XPC-RAD23B, often with the aid of UV-DDB (UV-damaged DNA-binding protein), initiates GG-NER. With the aid of the TC-NER-specific factors CSA, CSB, and XAB2, RNA polymerase that is stopped at a lesion initiates TC-NER. The core NER factors are required by both routes to finish the excision procedure. Only recently has it been discovered that a different class of enzymes called alkyltransferase-like (ATL) proteins can direct large O6-alkylguanine lesions into the NER pathway. In a NER-dependent manner, ATLs attach to these large alkyl lesions and aid in their elimination from DNA. It will be fascinating to find out if mammals have an equivalent repair route because there isn't another one known for bulky O6-alkylguanine damages in humans (Cai Y *et al*, 2020) [23].

Base excision repair pathway

The majority of endogenous base lesions and aberrant bases in the genome, as well as comparable lesions produced by various environmental agent groups or their metabolic intermediates, are repaired through the base excision repair (BER) system. The repair of DNA single-strand breaks also uses the BER pathway. These breaks, which are the result of deoxyribose residues reacting with free radicals, invariably have blocked termini. For the basic reaction steps in BER, DNA with AP sites or base damage can be repaired with only four or five enzymes. A DNA glycosylase, an AP endonuclease, a DNA polymerase, and a DNA ligase are a few of these. When the DNA glycosylase removes a damaged base, BER begins. The broken base's N-glycosidic bond causes the formation of an AP site. The APE cleaves the AP site in the subsequent step, producing the 3′ OH and 5′ deoxyribose phosphate (dRP) terminal. To close the single nucleotide gap left by the removal of the lesion base, the DNA polymerase is used in the pathway's third step (Hegde, M., *et al*, 2008) [21]. In mammalian cells, the repair DNA polymerase (Pol) contains an inbuilt dRP lyase activity that cleaves the dRP residue to yield 5′ phosphate. The resultant nick, following single nucleotide incorporation, is then sealed by the DNA ligase in the final step. Mammals and E. coli both produce the same BER enzymes.

Mismatch repair pathway

MMR is a biological mechanism that is highly conserved and shares striking parallels with the model MMR found in E. coli. These similarities include nick-directed strand selectivity, bidirectionality, and substrate specificity. Although the function of hemi-methylated dGATC sites as a signal for strand discrimination is not conserved from E. coli MMR to human MMR, it is assumed that both systems use a strand-specific nick to separate daughter and template strands because the hemi-methylated dGATC site directs MutH-dependent nicking (. MSHs are crucial components of the eukaryotic MMR system. It is similar to MutS. Both yeast and animals include the five highly conserved MSHs (MSH2-MSH6). There are two heterodimers of MSHs in the system, referred to as MutSa (MSH2/MSH6) and MutSb (MSH2/MSH3). About 80-90% of the MSH2 found in eukaryotic cells is represented by the MutSa complex. It has been discovered that the MutSa heterodimer's MSH6 protein is in charge of detecting the mismatch in the DNA duplex. It is crucial in the identification of mismatched DNA, the correction of base-base mis pairs, and several insertion/deletion loop (IDL) mis pairs. The repair of IDL mis pairs is the sole activity of the MutSb heterodimer.

Homologous recombination pathway

All forms of life utilise the homologous recombination (HR) DNA metabolic process, which offers high-fidelity, template-dependent repair or tolerance of complex DNA damages like DNA gaps, DNA double-strand breaks (DSBs), and DNA inter strand crosslinks (ICLs). Although limited to the S and G2 phases of the cell cycle, HR offers a high-fidelity method for repair in cycling cells. To restore any lost information, HR requires copying sequences from a donor who is still intact. As a way of overcoming replication stress and lesions brought on by replication fork obstruction, such as single-stranded DNA (ssDNA) gaps and one-ended DNA double-strand breaks (DSBs), HR is also crucial for the faithful duplication of the genome**.** Multiple sub pathways can be used for homologous recombination at DSBs, although the early steps are identical in function and include the same elements. In a nutshell, HR begins with the broad 5-3 resection of break ends by nucleases, resulting in 3 ssDNA overhangs that are then coated by replication protein A (RPA). In order to start the homology search for complementary sequences, the breast and ovarian cancer susceptibility protein 2 (BRCA2) first loads the recombinase RAD51 to ssDNA, replacing RPA (Sinha A. *et al*. 2020) [24]. Once homology has been identified, a displacement loop (D-loop) is created, where a primer-template junction enables DNA repair synthesis to take place. After repair synthesis is finished, HR can proceed by annealing to the complementary sequence at the non-invading end and displacing the prolonged break end from the D-loop, a process known as synthesis-dependent strand annealing (SDSA).

Non-homologous end joining pathway

The two termini of the damaged DNA molecule are processed to create compatible ends that are then directly ligated in NHEJ, a potentially less accurate kind of DSB repair. This technique may occasionally cause nucleotides to be lost, which would compromise the integrity of the genome. The cell-cycle stage must be a significant component in this choice, while it is still unclear what elements ultimately decide whether to use HR or NHEJ. Considering that only the S and G2 phases of the cell cycle contain the homologous template required for HR, this is not surprising. Therefore, it is assumed that the dominant repair mechanism during the G1 and M phases is NHEJ, notwithstanding the possibility that this assumption may be mistaken. The NHEJ process's molecular workings appear surprisingly straightforward. A protein complex called the

Ku70/80 heterodimer binds to both ends of the damaged DNA strand to start the NHEJ process (Figure 1B). A DNA end's connection with the Ku heterodimer is thought to act as a scaffold, allowing the other important NHEJ enzymes to be assembled. The DNA-PKCS, the catalytic subunit of DNA-dependent protein kinase, is drawn to the DSB by the DNA-Ku scaffold. The production of a synaptic complex, which connects the two DNA ends, is one of the many functions of this kinase. Final repair of the DSB requires processing of non-ligatable DNA termini after the two DNA ends have been trapped and anchored in a protein complex made up of DNA-PKCS and Ku. The ability to either eliminate or fill-in single-stranded, incompatible overhangs has been attributed to a number of enzymes, including nucleases and polymerases. Finally, the treated DNA ends are ligated by the ligase IV/XRCC4 complex. The recently identified protein XLF/Cernunnos may facilitate this ligation process.

Role of sensors in DNA damage response

Cells have developed a variety of interrelated systems to protect against DNA damage, or they have even used DNA damage to provide new natural selection chances. The DNA damage response, or DDR, has been given the name for these pathways. In DDR mechanisms, repair factors move to cluster at damage sites and feedback signals from the damage sites are also present. Mutations and tumour heterogeneity are frequent and pervasive because cancer cells have the typical genetic instability. Cancer cells may become more dependent on other DDR components for survival as a result of acquiring certain mutations (Neizer *et al*, 2021) [20]. Both mutagenic and non-mutagenic events are required for the onset of cancer. Throughout the course of cell oncogenesis, cells exposed to endogenous and exogenous mutagenic agents exhibit effects, but these effects are more pronounced in cancer cells with mutant or defective DDR genes. Several DNA damage sensors, including H2AX, the Mre11-RAD50-NBS1 complex, Ku70/Ku80, MDC1 and 53BP1, can start the damage signalling that causes the DDR to occur. According to a study, it is evaluated that H2AX expression increased after hepatocellular carcinoma therapy. Following chemotherapy and radiotherapy, there was a considerable rise in Ku70/Ku80 expression in patients with rectal cancer. Rectal cancer's responsiveness to chemoradiotherapy can be predicted using the molecular cluster expression of Ku70/Ku80. DDR sensors are currently in the early phases of molecular characterisation, and more research is needed to determine how they might be used to detect DNA damage and signalling, monitor cancer progression, and treat patients.

DNA damage repair as a target for cancer treatment by chemotherapy

Currently, the most popular clinical option for treating cancer is chemotherapy. The four main mechanisms for repairing DNA damage are BER, NHEJ, alt-NHEJ, and HR. APE1, XRCC1, DNA ligase III, KU70/Ku80, DNA-PK, Artemis, XRCC4, and XLF are important proteins in the BER route. PARP-1, XRCC1, and DNA ligase III are important proteins in the alt-NHEJ pathway. Numerous studies have shown that abnormalities in DNA repair pathways promote genomic instability, which increases cancer cell growth and survival time (Verma *et al*, 2017) [15]. Though Cancer cells still rely on their potential for DNA repair to shield them from harm. A crucial new target in the treatment of cancer is the nuclear poly (ADP-ribose) polymerase-1 (PARP-1). For base excision repair of single strand DNA breaks, the enzyme is crucial. The "synthetic lethality" effect of PARP-1 inhibition is directed at tumours with abnormalities in homologous recombination-defective DNA repair, more especially tumours with mutations in the breast cancer-associated BRCA1 and BRCA2 genes. Recent clinical data supported the findings of the early *in vitro* investigations and suggested that PARP-1 inhibitors could be employed as single agents as well as chemosensitizers to specifically kill tumours with impaired DNA repair by homologous recombination) (Cipak *et al*, 2010) [11]. This idea of "synthetic lethality"-targeting a second DNA repair pathway to kill tumours that have lost one DNA repair pathway represents a ground-breaking treatment approach (Harrision D. *et al*, 2020) [25]. APE2, APEX2, or APN2 is a newly discovered essential protein that plays a role in maintaining the integrity of the genome and epigenome (McMahon *et al*, 2023) [12]. Recent research has clarified the role and mechanism of APE2 in the immune response and DNA damage response, despite the fact that its catalytic function as a nuclease in DNA repair is generally accepted. APE2 has been recognised by several genome-wide screens as a synthetic lethal target for BRCA1, BRCA2, or TDP1 defects in cancer cells. Several reports have showed that, APE1 expression was related to intrinsic radiation sensitivity for cervical cancer (Herring CJ. *et al*, 1998) [26]. Particularly in cisplatin-resistant tumours, lung cancer tissues exhibit significant levels of APE1 expression. Other research has demonstrated a strong correlation between APE1 expression and DNA repair ability in cancer tissues such seminomas and malignant teratomas. To support its usage as a target for anticancer medicines, attempts have been made to create medications that impede APE1 action or exhibit significantly increased sensitivity to DNA base lesions. APE1 inhibitors have been created over the past ten years through cell, animal, and clinical research. Other genes like a XRCC1 are known as molecular scaffold protein which facilitate the recruitment of various enzymatic agents, including DNA kinase and DNA phosphatase, to enhance the repair of DNA single-strand breaks. Its interaction with its protein companion, PARP1, is one of the actions of XRCC1 that is of great interest. A growing body of research indicates that XRCC1 mutations are closely linked to a number of illnesses, including cancer and neurological conditions.

DNA damage repair as a target for cancer treatment by radiotherapy

Radiotherapy is a component of the cancer treatment for more than half of cancer patients. Ionising radiation (IR) used in radiotherapy causes DNA double-strand breaks (DSBs), which are regarded as the most dangerous type of DNA damage and a major factor in cell death (Huang, R *et al*, 2020) [7]. Numerous genetic and epigenetic abnormalities are present in many malignant cells, which may obstruct vital DSB repair pathways. A multicomponent signal transduction network called the DNA damage response (DDR) is also activated as a result of IR exposure. DDR triggers cell cycle checkpoints and causes homologous or non-homologous recombination (HR) to repair DSBs in the nucleus (Toulany M, 2019) [13]. However, cancer cells have

developed escape routes that enable them to withstand radiotherapy. Therefore, it is anticipated that focusing on these rescue mechanisms will be a successful therapeutic strategy for lowering cancer recurrence or increasing radiation sensitivity. Prior research has been done to ascertain the impact of using NHEJ-related proteins as effectiveness targets on the results of cancer radiation (Dong *et al*, 2020) [19]. In multiple cell and animal research looking into the impacts of its malfunction, DNA-PKcs, a crucial component of the NHEJ pathway, was discovered to increase radiation sensitivity. The radiation sensitivity of several malignancies was improved by using NU7441 to downregulate DNA-PKcs expression (Ciszewski *et al*, 2014) [18]. Cancer cells capable of rapid replication frequently use the HR-mediated DSB repair pathway as opposed to the NHEJ repair mechanism. So, it would be advantageous to design new strategies for examining radiotherapy resistance if we understood how cancer cells react to radiation through the HR pathway (Dong *et al*, 2020) [19]. Cancer cells were made more sensitive to chemo- and radiotherapeutic drugs due to HR deficit, indicating that this condition offers a useful method for enhancing radiation resistance. Promoter methylation, BRCA1/2 mutations, and somatic HR mutations are a few factors that affect how HR insufficiency develops. The most frequent cause of HR deficit is BRCA1/2 mutations. BRCA2-deficient cancer cells respond better to radiation therapy when heat is employed to block the HR pathway. For tumours with HR deficit, combining a PARP inhibitor with heat shown good therapeutic effectiveness (Harrision *et al*, 2020) [25]. A variety of inhibitors that work against both the HR and NHEJ pathways have been created to enhance radiation resistance. The pancreatic adenocarcinoma cells are made radiosensitive by the MEK1/2 inhibitor GSK212, commonly known as trametinib, which has demonstrated potential anticancer activity (Estrada-Bernal, A. *et al* 2015) [27]. The utility of this dual targeting strategy in various malignancies has been documented in additional trials. Valproic acid, a histone deacetylase inhibitor, increased radiation-induced DNA DSBs by doubly targeting HR and NHEJ in squamous cell carcinoma of the head and neck cells, enhancing the radio sensitizing impact. According to some publications, BEZ235 operates as a dual inhibitor of PI3K and mTOR, dramatically increasing radiation sensitivity by inactivating HR and NHEJ proteins in radioresistant prostate cancer cells (Herring *et al*, 1998) [26]. Some of these substances, including the calcium channel blocker mibefradil dihydrochloride, have also received FDA approval and have been expected to function as radiosensitizers and inhibitors of HR and NHEJ repair.

Conclusion

Cancer researchers, medical professionals, and surgeons are interested in DNA damage, response, and repair, and extensive study has led to new, fundamental understandings of the mechanisms underpinning cancer growth and cancer therapy-induced resistance. A new treatment approach has been developed to boost the effectiveness of DNA damaging agents by combining them with inhibitors of DNA repair pathways, which is based on the link between DNA repair pathways and the onset and progression of cancer. A number of DNA repair pathway inhibitors have been created, and several of them are presently undergoing clinical testing. Further research should be done to determine the therapeutic benefits of these drugs in the treatment of cancer, and more focused inhibitors should be created to lessen the negative effects on healthy tissues and cells.

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