DNA Damage Response and Cancer Treatment

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ABSTRACT

Throughout long-term evolution, cells have evolved sophisticated defence systems to counteract DNA damage, which are essential for preserving genomic stability and ensuring proper cellular function. The DNA damage response (DDR) is a complex network of cellular pathways that detect, signal, and repair DNA lesions to preserve genomic integrity. In cancer cells, these mechanisms are often dysregulated, leading to genomic instability—a hallmark of cancer. Paradoxically, this vulnerability also presents a therapeutic opportunity. This review explores the dual role of DDR in cancer development and treatment, highlighting the molecular pathways involved, including homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), and mismatch repair (MMR). Recent advancements in targeting DDR pathways have led to the development of novel therapies, such as PARP inhibitors, ATM/ATR inhibitors, and CHK1/CHK2 inhibitors, which selectively exploit defects in cancer cell repair mechanisms while sparing normal cells. We also discuss the concept of synthetic lethality and its application in precision oncology. Furthermore, we examine resistance mechanisms to DDR-targeted therapies and potential strategies to overcome them. The integration of DDR-targeted agents with immunotherapy and conventional treatments is also considered. This review underscores the critical importance of DDR in cancer biology and treatment, offering insights into how manipulating these pathways can lead to more effective and personalized cancer therapies.

Keywords: DNA damage response, synthetic lethality, PARP inhibitors, homologous recombination, genomic stability

1. INTRODUCTION:

Cancer is characterized by uncontrolled cell proliferation, often accompanied by genomic instability. The DNA Damage Response (DDR) plays a crucial role in maintaining genomic integrity by repairing DNA lesions caused by endogenous metabolic processes and exogenous insults. In many cancers, mutations in DDR genes—such as BRCA1, BRCA2, ATM, and p53—compromise repair fidelity, contributing to tumour evolution but also rendering these cells particularly susceptible to DDR-targeted therapies. DNA is inherently dynamic and susceptible to continual damage from both internal sources—such as replication stress and telomere attrition— and external factors like ultraviolet radiation and chemical agents. If not properly repaired, such damage can result in mutations, genomic instability, and cell death, ultimately contributing to the development of various diseases, including cancer[1]. As a result, cells have evolved intricate systems known collectively as the DNA damage response (DDR), which are essential for identifying and repairing DNA lesions, thereby safeguarding genomic integrity.

Pioneering researcher Phil Lawley significantly advanced the understanding of DNA damage and carcinogenesis by demonstrating that alkylating agents such as dimethyl sulphate can form harmful adducts with DNA, disrupting its normal function. This discovery led to the early hypothesis that certain cancer-related genes might be particularly susceptible to such agents, sparking extensive research. Over time, this foundational work paved the way for the development of chemotherapy and radiation therapies, which exploit DNA damage as a means to selectively target and kill cancer cells. Extensive research on cell cultures, animal models, and human tumours has consistently demonstrated that the accumulation of DNA damage and a weakening of the DNA damage repair function both play a crucial role in the onset and advancement of cancer, while simultaneously presenting potential avenues and targets for therapeutic intervention [2].Recent research has uncovered that organisms have developed an intricate system of DNA damage response (DDR) signalling pathways and repair processes to preserve genomic integrity. This review focuses on the major proteins central to the DDR and their functions in maintaining genome stability and cellular equilibrium, while also examining how disruptions in these pathways contribute to cancer development. Furthermore, it highlights key molecular targets and small-molecule inhibitors that have emerged as promising candidates for cancer therapy, offering valuable perspectives on the prevention and treatment of malignancies.

2. THE DNA DAMAGE RESPONSE: AN OVERVIEW

The DNA damage response (DDR) is a complex network of cellular processes that detect and repair DNA damage to maintain genome stability. This system is crucial for preserving the integrity of the genome and preventing mutations that could lead to diseases, including cancer. It involves multiple signaling pathways regulated by kinases, which are responsible for detecting and relaying DNA damage signals. The extent of the damage seems to dictate the cellular response, which may involve cell cycle arrest, repair mechanisms, or programmed cell death (apoptosis)[3]. The DDR begins with the detection of DNA damage, which can occur due to various factors, such as UV radiation, ionizing radiation, chemicals, or errors during DNA replication. Key sensors, such as kinases and receptors, are responsible for identifying damaged DNA. Once DNA damage is detected, a signalling cascade is triggered to activate a series of downstream proteins. This leads to the activation of checkpoint kinases, like CHK1 and CHK2, which regulate the cell cycle. These cellular checkpoints pause the progression of the cell cycle, providing time for damaged DNA to be repaired. The DNA damage response (DDR) signalling pathways are a network of interconnected processes that detect DNA damage, signal its presence, and coordinate appropriate cellular responses such as repair, cell cycle arrest, or apoptosis. These pathways ensure genomic integrity and are especially important in preventing diseases like cancer.

1. MAJOR DNA REPAIR PATHWAYS

DNA damage is typically categorized into two primary types according to its origin: internal (endogenous) and external (exogenous) sources. Endogenous damage primarily results from the inherent chemical reactivity of DNA, which undergoes hydrolytic and oxidative reactions with water and naturally occurring reactive oxygen species (ROS) within the cell[4]. DNA damage can arise from both internal factors, like replication stress and reactive oxygen species, and external factors such as ionizing radiation, chemotherapy drugs, ultraviolet (UV) radiation, and polycyclic aromatic hydrocarbons. This damage manifests in various forms, including single-strand breaks (SSBs), double-strand breaks (DSBs), base modifications, DNA crosslinks, and clusters of damaged sites. [figure 1]. Double-strand breaks (DSBs) represent the most harmful form of DNA damage; if not accurately and swiftly repaired, they can trigger cell death or drive the development of cancer. Research has shown that human cells experience around 70,000 occurrences of DNA damage each day.[5]. The majority of these damage instances are SSBs, which account for about 75% [6]. Single-strand breaks (SSBs) can result from oxidative stress generated during cellular metabolism or from base hydrolysis, and under certain conditions, these lesions may escalate into double-strand breaks (DSBs).

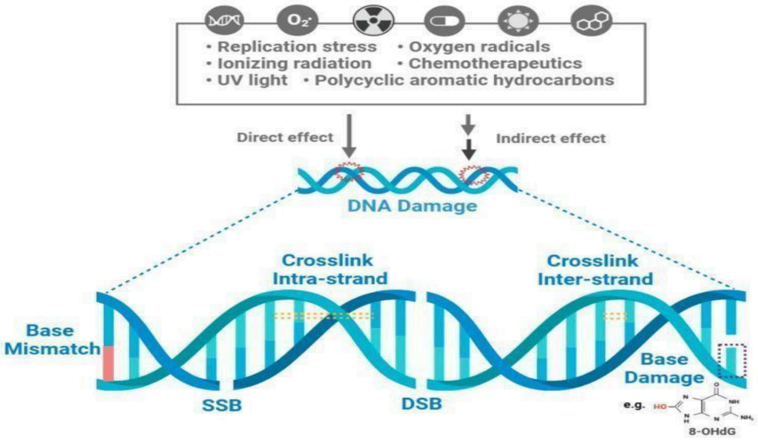
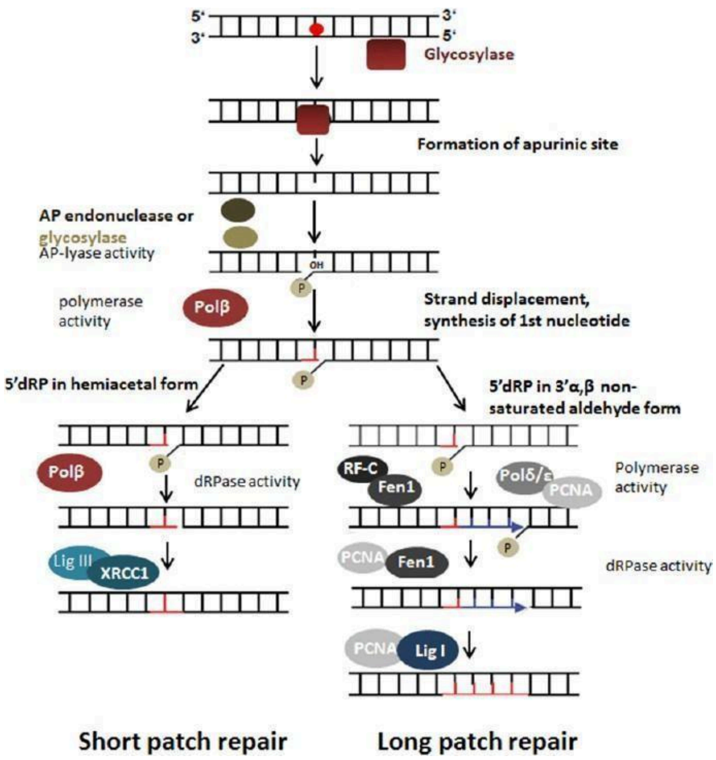


Figure 1. Types of DNA damage. DNA is susceptible to a broad spectrum of damage arising from both internal sources—such as oxidative stress and errors during replication—and external agents, including ionizing radiation,ultraviolet light, certain chemotherapeutic drugs, and environmental carcinogens like polycyclic aromatic hydrocarbons. These factors can compromise DNA either directly or through the generation of reactive intermediates, leading to the disruption of chemical bonds within the DNA structure. The resulting damage can alter both the integrity and function of the genetic material, manifesting in various forms such as single-strand breaks (SSBs), double-strand breaks (DSBs), oxidative base modifications (e.g., 8-oxoG), base mismatches, and intra- or inter-strand crosslinks.

1.1 Base Excision Repair

Base Excision Repair (BER) is a DNA repair pathway that removes damaged or modified bases and single-strand breaks from DNA. It's a crucial process for maintaining the integrity of the genome and preventing mutations. BER involves two main sub-pathways: short-patch BER (SP-BER), which repairs a single nucleotide gap, and long-patch BER (LP-BER), which repairs a gap of two or more nucleotides [figure



2] [7].

Figure 2. Base excision repair (BER) occurs through two distinct sub-pathways: short-patch and long-patch

repair. The process initiates with the detection of a damaged base, followed by its removal and the subsequent cleavage of the DNA strand at the site of the lesion. The choice between the short-patch and long-patch base excision repair (BER) pathways is primarily influenced by the status of the 5' deoxyribose phosphate (5'dRP) group at the site of repair. It plays a vital role in correcting a range of DNA base lesions—such as deamination, depurination, alkylation, and single-strand breaks (SSBs)—that are essential for preserving genome stability. Malfunctions in the BER system are strongly associated with the development of cancer, a relationship that is well- documented. [8]. On the other hand, modulating or modifying base excision repair (BER) pathways could serve as an effective strategy for enhancing survival under genotoxic stress[9].

1.2 Nucleotide Excision Repair

Nucleotide excision repair (NER) is a DNA repair pathway that eliminates large, helix-altering lesions induced by UV radiation, chemicals, and other mutagenic agents. It's a versatile pathway found in all organisms, crucial for maintaining genomic stability and preventing mutations. NER involves a "cut-and-paste" process where damaged DNA segments are removed and replaced with undamaged DNA, effectively repairing the DNA [figure 3] [10].

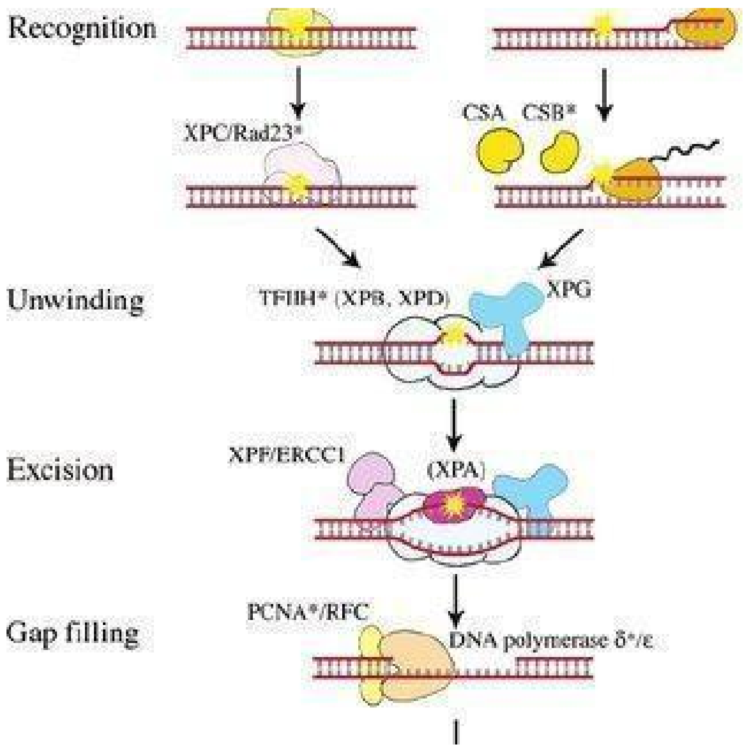


Figure 3. Nucleotide excision repair (NER). Nucleotide excision repair (NER) carries out its function through two major sub-pathways: global genome repair (GGR) and transcription-coupled repair (TCR). The NER

mechanism involves several key steps: detection of DNA lesions, local unwinding of the DNA helix around the damaged region, removal of the affected nucleotides, and restoration of the strand through DNA synthesis followed by ligation. Some of the proteins involved in this process, indicated in parentheses, have not yet been identified in plants. Proteins marked with an asterisk exist in multiple isoforms or gene copies [29].

1.3 Mismatch Repair

Mismatch repair (MMR) is a DNA repair pathway that corrects errors in DNA that arise during replication or

recombination, ensuring genomic stability. It primarily focuses on base-base mismatches and insertion/deletion mispairs, recognizing and repairing them on the newly synthesized strand [11]. The DNA mismatch repair (MMR) pathway, which is evolutionarily conserved, plays a key role in safeguarding genomic integrity by identifying and rectifying base-base mismatches and insertion/deletion loops generated during DNA replication and recombination. Additionally, MMR inhibits homologous recombination and has been recently implicated in DNA damage signalling within eukaryotic cells [figure 4].

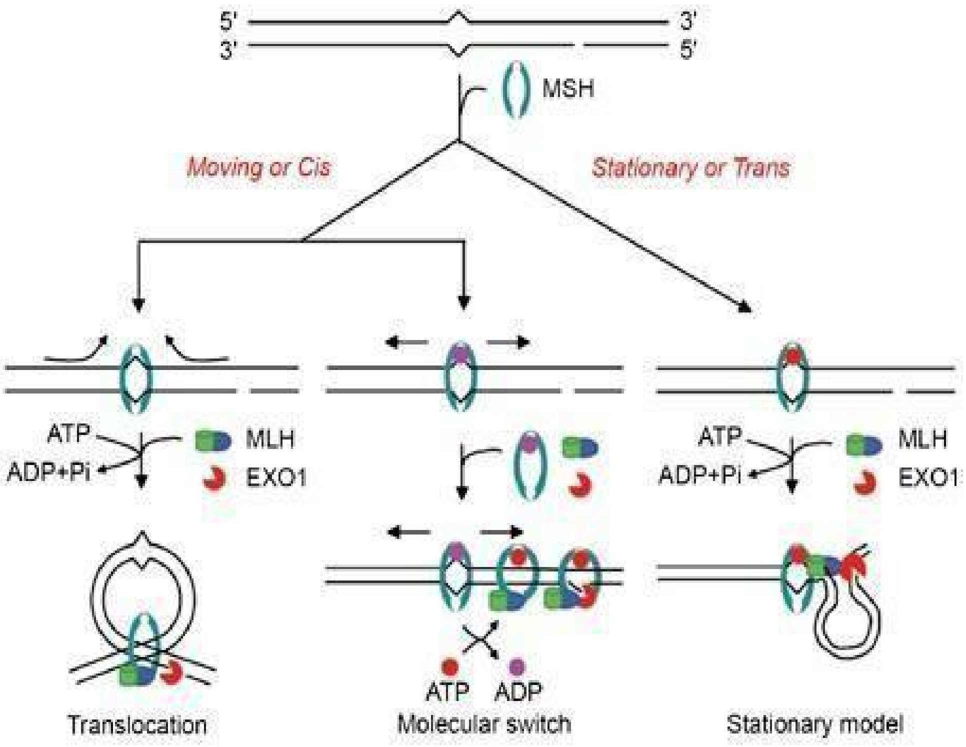


Figure 4. Proposed models for signalling events downstream of mismatch recognition in MMR are illustrated schematically, highlighting how communication occurs between the mismatch site and the strand discrimination signal, represented here by a 5′ nick. Comparable mechanisms are suggested for the 3′ nick-directed mismatch repair (MMR). In the 'stationary' or 'trans' model (right), MutS or its homologs (MSH proteins) remain bound at the mismatch site, and signal propagation occurs through protein-protein interactions that induce DNA bending or looping, effectively bridging distant sites in a trans configuration Alternatively, the two 'cis' or 'mobile' models—the 'translocation' model (left) and the 'molecular switch' or 'sliding clamp' model (center)— It is believed that MSH proteins initially attach to the mismatch site and then move along the DNA strand to identify the distinguishing signal that marks the correct strand. The translocation model suggests ATP hydrolysis powers unidirectional movement, forming an α-loop structure. Meanwhile, the molecular switch model involves an ADP- to-ATP exchange upon mismatch binding, enabling bi- directional sliding of MSH proteins away from the mismatch, which facilitates recruitment of additional MSH proteins. The mismatch repair process begins when an MSH protein complex detects and engages with a break in the DNA strand [28].

1.4 Double-strand DNA break repair

Among the various forms of DNA damage, double-strand breaks (DSBs) are regarded as one of the most critical and potentially harmful lesions. These breaks involve the cleavage of both strands of the DNA helix, significantly disrupting essential cellular processes such as transcription, replication, and chromosome segregation. If not properly repaired, DSBs can trigger cell death; if misrepaired, they may cause chromosomal translocations—key early events in cancer development. To counteract the threat posed by DSBs, cells have developed four distinct repair pathways, each contributing to the maintenance of genomic stability. These pathways, while mechanistically unique and outcome- specific, rely on a large network of shared DNA repair proteins and operate in a highly coordinated, interdependent manner.

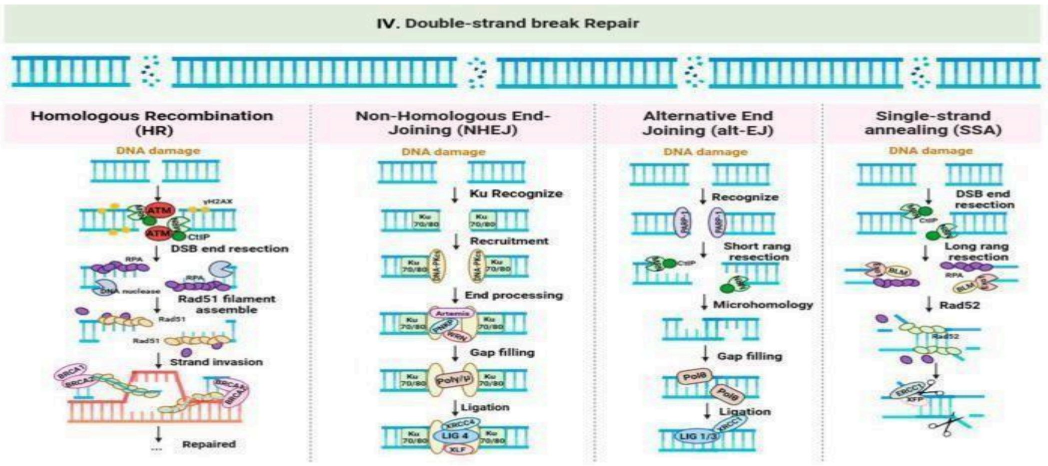


Figure 5. Repair of double-strand breaks occurs through mechanisms such as homologous recombination (HR), non- homologous end joining (NHEJ), alternative end joining (alt-EJ), and single-strand annealing (SSA) [12].

1.4.1 Homologous recombination repair

Homologous recombination repair (HRR) is a DNA repair pathway that utilizes a homologous DNA template, such as a sister chromatid, to repair double-strand breaks (DSBs) and other DNA damage with high accuracy. This mechanism is essential for safeguarding the genome's integrity and limiting the occurrence of genetic mutations. Homologous recombination (HR) is a highly accurate but complex DNA repair process that relies on a homologous template strand to direct precise DNA synthesis. This mechanism mainly takes place during the S and G2 phases of the cell cycle. When a double-strand break (DSB) occurs in DNA, one of the initial responders is the MRN complex— comprising MRE11, RAD50, and NBS1—which quickly identifies and binds to the broken DNA ends at the damage site [13].

1.4.2 Non-Homologous End Joining

Non-homologous end joining (NHEJ) is a crucial repair mechanism for double-strand breaks (DSBs), operating independently of any homologous template[14]. This error-prone pathway does not require sequence homology at the DNA ends and can operate throughout the cell cycle, though it is most active during the G1 phase. Repair proteins quickly assemble at the DNA break sites, facilitating the direct ligation of the ends with minimal or no processing.

1.4.3 Alternative End-Joining

Alternative end-joining (a-EJ) is a DNA repair pathway that acts as a backup for the major non- homologous end-joining (NHEJ) and homologous recombination repair pathways. It's particularly

active when NHEJ is impaired and when DNA ends have lost their associated chromatin structure, according to a study published in Frontiers. a-EJ is considered error-prone and can lead to genomic instability, including translocations and sequence alterations [15].

1.4.4 Single-strand Annealing

While both alt-EJ and SSA require 5′ end resection of DSB ends, SSA involves more extensive resection, as it relies on longer homologous sequences at the 3′ ends of the ssDNA tails—typically spanning from 25 to several hundred nucleotides—for strand annealing [16].

2. THERAPEUTIC TARGETING OF DDR IN ANTICANCER THERAPY

Over time, extensive research from multiple laboratories has revealed a remarkably complex network involving hundreds of proteins and protein complexes that detect and repair distinct types of DNA damage via specialized pathways. These repair mechanisms are precisely synchronized with cell cycle progression and function within the highly dynamic and structured chromatin landscape. DNA damage response (DDR) signalling proteins orchestrate a range of post-translational modifications and protein complex formations, amplifying and diversifying damage signals to elicit the appropriate cellular responses [17].

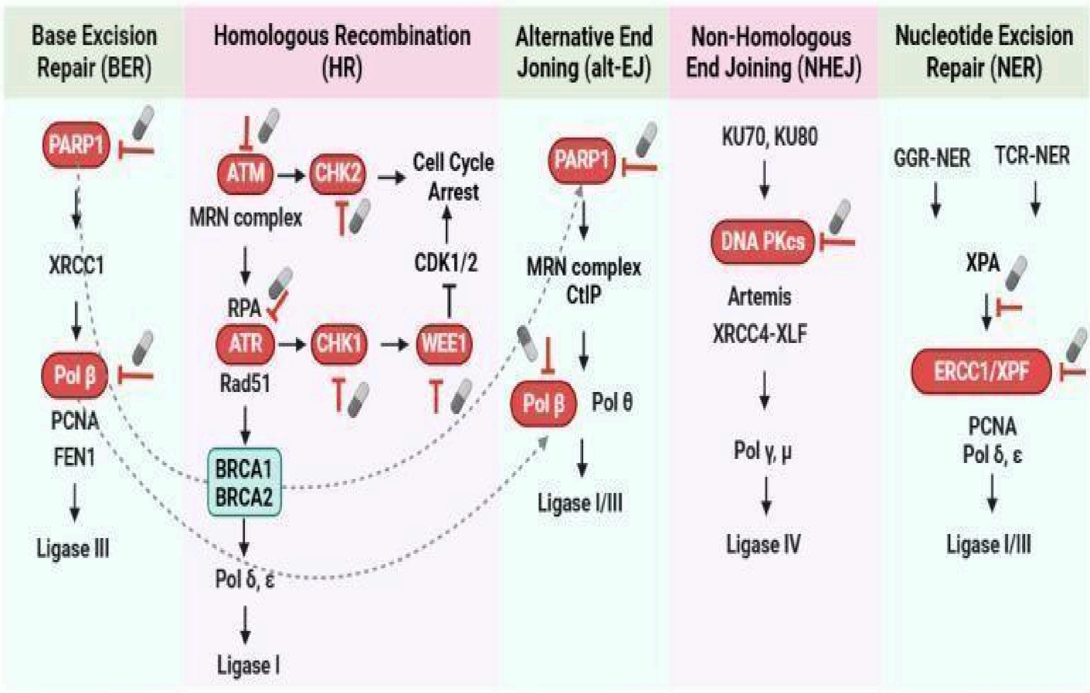


Figure 6. Targeting DNA damage response for cancer therapy [27].

Targeting DNA repair pathways offers a promising strategy for cancer therapy. Inhibitors such as PARP1 and Polβ disrupt base excision repair (BER) and alternative end-joining (alt-EJ) pathways, while ATM/ATR inhibition impairs the homologous recombination (HR) pathway. DNA-PKcs inhibitors compromise non-homologous end joining (NHEJ), and interference with interactions between XPA and ERCC1 or ERCC1 and XPF impairs the nucleotide excision repair (NER) pathway. These disruptions increase DNA damage and genomic instability in tumour cells. Additionally, checkpoint kinase inhibitors, including Chk1/2 and WEE1 inhibitors, override cell cycle arrest, forcing damaged cells into mitosis and inducing mitotic catastrophe. The BRCA genes play a crucial role in HR, and their mutation or loss renders tumour cells more reliant on alt-EJ pathways—particularly those involving PARP—for DNA repair. Consequently, PARP inhibitors are especially effective in BRCA-deficient tumours, leading to the accumulation of double-strand breaks (DSBs) and subsequent cell death. These insights highlight several targeted therapeutic opportunities using DNA damage response inhibitors.

3. COMBINATION STRATEGIES IN CANCER THERAPY

Utilizing multiple therapeutic agents simultaneously, known as combination therapy, represents a core approach in the treatment of cancer. By integrating different anti-cancer drugs, this approach often achieves greater effectiveness than single-agent treatments, as it targets critical cancer-related pathways in a synergistic or additive way. This strategy not only helps to minimize the development of drug resistance but also provides a range of therapeutic advantages, such as slowing tumor growth, limiting metastasis, halting the proliferation of mitotically active cells, reducing cancer stem cell populations, and promoting apoptosis [18].

Combination strategies in cancer therapy aim to enhance treatment efficacy, reduce resistance, and minimize toxicity by simultaneously targeting multiple cellular pathways. A common approach involves pairing traditional chemotherapy with targeted agents such as DNA damage response (DDR) inhibitors—like PARP, ATR, CHK1, or WEE1 inhibitors— which block cancer cells' ability to repair chemotherapy-induced DNA damage, leading to increased cell death. Another effective combination is chemotherapy with immunotherapy, where cytotoxic drugs promote tumour antigen release and immune checkpoint inhibitors enhance T-cell-mediated responses.

DDR Inhibitor	Target	Combined With	Cancer Type
PARP inhibitors (e.g., olaparib)	PARP1/2	Platinum-based drugs (cisplatin, carboplatin)	Ovarian, breast, prostate cancers
ATR inhibitors (e.g., ceralasertib)	ATR kinase	Gemcitabine, cisplatin	Lung, pancreatic cancers
CHK1 inhibitors (e.g., prexasertib)	CHK1	DNA-damaging agents (cytarabine)	Hematologic malignancies
WEE1 inhibitors (e.g., adavosertib)	WEE1 kinase	Carboplatin, paclitaxel	Ovarian, endometrial cancers

Table 1. DNA Damage Response (DDR) inhibitors are a class of targeted cancer therapies designed to disrupt the cellular pathways responsible for detecting and repairing damaged DNA. Cancer cells often exhibit defects in specific DNA repair mechanisms, such as homologous recombination (HR), making them heavily reliant on alternative repair pathways for survival. DDR inhibitors exploit this vulnerability by blocking key proteins involved in these alternative pathways, leading to the accumulation of unrepaired DNA damage, replication stress, and ultimately, cancer cell death—a concept known as synthetic lethality.

3.1 PARP1 Inhibitors

Initial studies indicated that PARP inhibitors promote the death of cancer cells via a process called "synthetic lethality." In this mechanism, mutations or deficiencies in the BRCA genes hinder DNA repair, making cancer cells more susceptible to the effects of PARP inhibition. This leads to the buildup of double-strand breaks (DSBs), which eventually results in cell death. BRCA genes have traditionally been recognized as key players in the homologous recombination (HR) repair pathway. When these genes are mutated, cells become dependent on alternative mechanisms—such as those mediated by PARP—to resolve DNA damage[19]. Nevertheless, mutations in BRCA1 or BRCA2 genes compromise the cell's ability to repair therapy-induced DNA double-strand breaks, rendering them vulnerable to cell death following PARP inhibitor treatment. Additionally, synthetic lethality can also arise through a different mechanism—excessive DNA damage during the S-phase may lead to replication catastrophe, ultimately resulting in cell death [20].

3.2 ATM/ATR Inhibitor

ATM is a vital protein kinase involved in the repair of DNA double-strand breaks (DSBs) and plays a key role in managing the cell's response to these types of damage throughout the cell cycle. Its activation is primarily mediated by its interaction with the MRN complex, particularly through the NBS1 subunit. Once activated, ATM phosphorylates histone H2AX, a rapid and essential event that initiates the recruitment of DNA repair machinery. Due to its central role in maintaining genomic stability, ATM has emerged as a promising target for cancer therapy. The findings suggest that ATM deficiency does not markedly affect sensitivity to PARP1 inhibitors but significantly enhances cellular sensitivity to ATR inhibitors, which target a related DNA damage response kinase [21].

3.3 CHK1/2 Inhibitors

CHK1 and CHK2, the primary downstream effectors of ATR and ATM respectively, play crucial roles in the DNA damage checkpoint response. Elevated levels of CHK1 and CHK2 have been associated with enhanced activation of this pathway, contributing to radioresistance. On the other hand, suppressing or eliminating CHK1 and CHK2 expression has been found to reduce radio resistance in both laboratory and animal models, especially in cancer cells with elevated c-MYC levels [22]. UCN-01 (7-hydroxystaurosporine) is an early-generation inhibitor of CHK1 [25]. Moreover, increasing the stability of CHK1 has been shown to support homologous recombination (HR)-mediated DNA repair and contribute to resistance against radiation therapy. These findings highlight CHK1 and CHK2 as valuable therapeutic targets in the treatment of cancer. Numerous CHK1/2 inhibitors have been developed, with many currently undergoing evaluation in clinical trials [26].

3.4 WEE1 Inhibitor

WEE1 acts as a tyrosine kinase that suppresses CDK1/2 activity, triggering the G2/M checkpoint and inducing cell cycle arrest to halt mitotic entry following DNA damage [23]. In preclinical studies, WEE1 inhibitors have shown promise in increasing the effectiveness of chemotherapy and radiotherapy, particularly in cancers with mutated or deficient p53, though their benefits may extend beyond these cases. This review explores the clinical

progress of WEE1 inhibitors when used in combination with chemotherapy or radiotherapy, as well as their application alongside concurrent chemotherapy and emerging novel treatments. [24].

1. CONCLUSION

As chemotherapy continues to evolve, one of the major obstacles in cancer therapy is the emergence of drug resistance.

Identifying the molecular pathways responsible for therapeutic resistance is fundamental to advancing cancer treatment strategies. In particular, unravelling how disruptions in DNA damage response (DDR) pathways contribute to cancer progression and resistance to treatment has become a key area of focus in both preclinical and clinical research. Investigating the intricate relationship between genomic instability and DNA repair processes offers crucial understanding of how cancer cells develop therapeutic resistance.

Clarifying the interplay, overlap, and prioritization among various DNA repair pathways can aid in developing synthetic lethality approaches—targeting vulnerabilities specific to cancer cells. Since many tumors exhibit deficiencies in DNA repair capabilities, selectively inhibiting certain DNA repair routes can enhance drug-induced cytotoxicity, overcome resistance, and improve therapeutic success. To boost treatment outcomes,

DDR inhibitors are being combined with agents targeting either DDR components or other molecular pathways, aiming to simultaneously disrupt multiple survival strategies used by cancer cells. Significant progress has been made in creating inhibitors that target DDR mechanisms. Combining these with traditional therapies—such as using PARP inhibitors to potentiate platinum-based regimens or pairing CHK1/2 and WEE1 inhibitors with
chemotherapy and radiotherapy—has shown promising results. Looking forward, personalized targeted therapies are expected to gradually replace conventional chemotherapy, offering the potential to minimize adverse effects while improving survival rates and quality of life for patients with advanced cancers.

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