DNA Damage Response in Cancer: Molecular Mechanisms and Therapeutic Exploitation

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Abstract

The DNA damage response (DDR) represents a highly conserved network of signaling pathways and repair mechanisms that are crucial for preserving genomic integrity. Cancer, which is marked by extensive genomic instability, often develops due to inherited or acquired deficiencies within these pathways. Paradoxically, these very defects can make tumor cells susceptible to therapeutic approaches that target the systems they are unable to regulate effectively. This review offers a thorough synthesis of DDR mechanisms, their dysfunction in the context of oncogenesis, and the emerging paradigm of targeting DDR components in cancer treatment. Particular emphasis is placed on the notion of synthetic lethality and its clinical application through poly(ADP-ribose) polymerase (PARP) inhibitors in tumors with BRCA mutations. Additionally, we explore new resistance mechanisms, the influence of the tumor microenvironment, and future prospects for functional biomarkers and personalized therapeutic strategies.

Keywords: DNA damage response, genomic instability, cancer, DNA repair, homologous recombination, PARP inhibitors, synthetic lethality, cancer therapy.

Introduction

Genomic instability is a hallmark of cancer, arising from persistent DNA damage and a diminished capacity for repair. Under normal physiological conditions, cells utilize a comprehensive DNA damage response (DDR) network that includes sensors, transducers, mediators, and effectors to identify, signal, and rectify DNA lesions.In contrast, tumor cells often exhibit mutations or epigenetic changes in DDR genes (such as BRCA1, BRCA2, ATM, MSH2) that enhance carcinogenesis by promoting the accumulation of mutations and chromosomal rearrangements. Paradoxically, this genomic vulnerability creates

therapeutic opportunities that can be targeted pharmacologically. This review examines the biology of DDR, its disruption in cancer, and both current and future therapeutic strategies. Cells respond to DNA damage by activating the DNA damage response (DDR), which halts cell cycle progression and facilitates repair of DNA lesions to prevent mutagenesis and genomic instability. In the context of overwhelming DNA damage in replicating cells the DDR activates programmed cell death, resulting in tumour regression[1]. Cancer cells can become resistant to this process by deregulation of DRR. This concept has particular relevance to cervical cancer, of which 99% are associated with highrisk human papillomavirus (HPV) infection (HPV [2].

1. Molecular Components of the DNA Damage Response

1.1 Base Excision Repair (BER):

BER rectifies minor, non-helix-distorting base lesions through the action of glycosylases, AP endonucleases, and DNA polymerase β. PARP1 functions as a sensor for single-strand breaks (SSBs), triggering the recruitment of repair complexes.

1.2 Nucleotide Excision Repair (NER):

NER addresses large helix-distorting lesions. It is divided into two subcategories: transcription- coupled NER (TC-NER) and global genome NER (GG-NER), both of which necessitate ERCC1– ERCC4 for the excision process.

1.3 Mismatch Repair (MMR):

MMR rectifies errors that occur during replication, including base mismatches and insertion-deletion loops. The primary components involved are MSH2, MSH6, MLH1, and PMS2. Deficiencies in this pathway result in microsatellite instability (MSI), which is a characteristic of hereditary non- polyposis colorectal cancer.

2. Double-Strand Break Repair Mechanisms

2.1 Homologous Recombination (HR):

This is an error-free repair mechanism that is active during the S/G2 phases of the cell cycle, utilizing proteins such as BRCA1, BRCA2, RAD51, and PALB2.

2.2 Non-Homologous End Joining (NHEJ):

DNA-PKcs and KU70/80 are involved in this error-prone repair mechanism, which operates during the whole cell cycle.This creates an initial scaffold that enables the recruitment of other NHEJ components, including X-ray cross complementing protein 4 (XRCC4), DNA Ligase IV, and the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), to create a bridge and join the two ends of the broken DNA strands[3,4,5,6,].

2.3 Alternative DSB Pathways

Template switching and translesion synthesis By using certain low-fidelity polymerases, these tolerance mechanisms allow DNA replication to avoid unrepaired lesions.

2.4. PARP inhibitors:

The DDR is significantly influenced by the PARP protein family. These proteins alter the chromatin structure around the damaged DNA after SSBs, bind firmly to DNA breaks, and attract DNA repair effectors. Although the several therapeutically established PARP inhibitors exhibit comparable catalytic inhibitory effects against PARP, their cytotoxic potencies are also correlated with differences in their PARP-trapping capabilities (talazoparib > niraparib > olaparib = rucaparib > veliparib)[7,8,9,10,].

Inhibitors of DDR Pathways Other than PARP Inhibitors:

The majority of DNA damage is caused by SSBs, although DSBs are more harmful to cells. As a result, the majority of DDR-targeted treatments have concentrated on blocking checkpoint molecules that act after these repair processes or on changing how the repair machinery linked to DSBs functions.

2.5 DNA-PK inhibitors:

DNA-PK, or DNA-dependent serine/threonine protein kinase catalytic subunit, is essential for NHEJ repair because it functions as a sensor of DNA damage. In a number of tumor models, high levels of DNA-PK are associated with a poor prognosis and resistance to chemotherapy and radiation. Small- molecule-based DNA-PK inhibition has shown very potent results when paired with DSB-inducing treatments such topoisomerase inhibitors and radiation therapy. Patients with solid and hematological neoplasms are presently undergoing

clinical trials with DNA-PK inhibitors either alone or in conjunction with chemotherapy or radiation therapy[11,12,].

2.6 CHK1/2Inhibitors

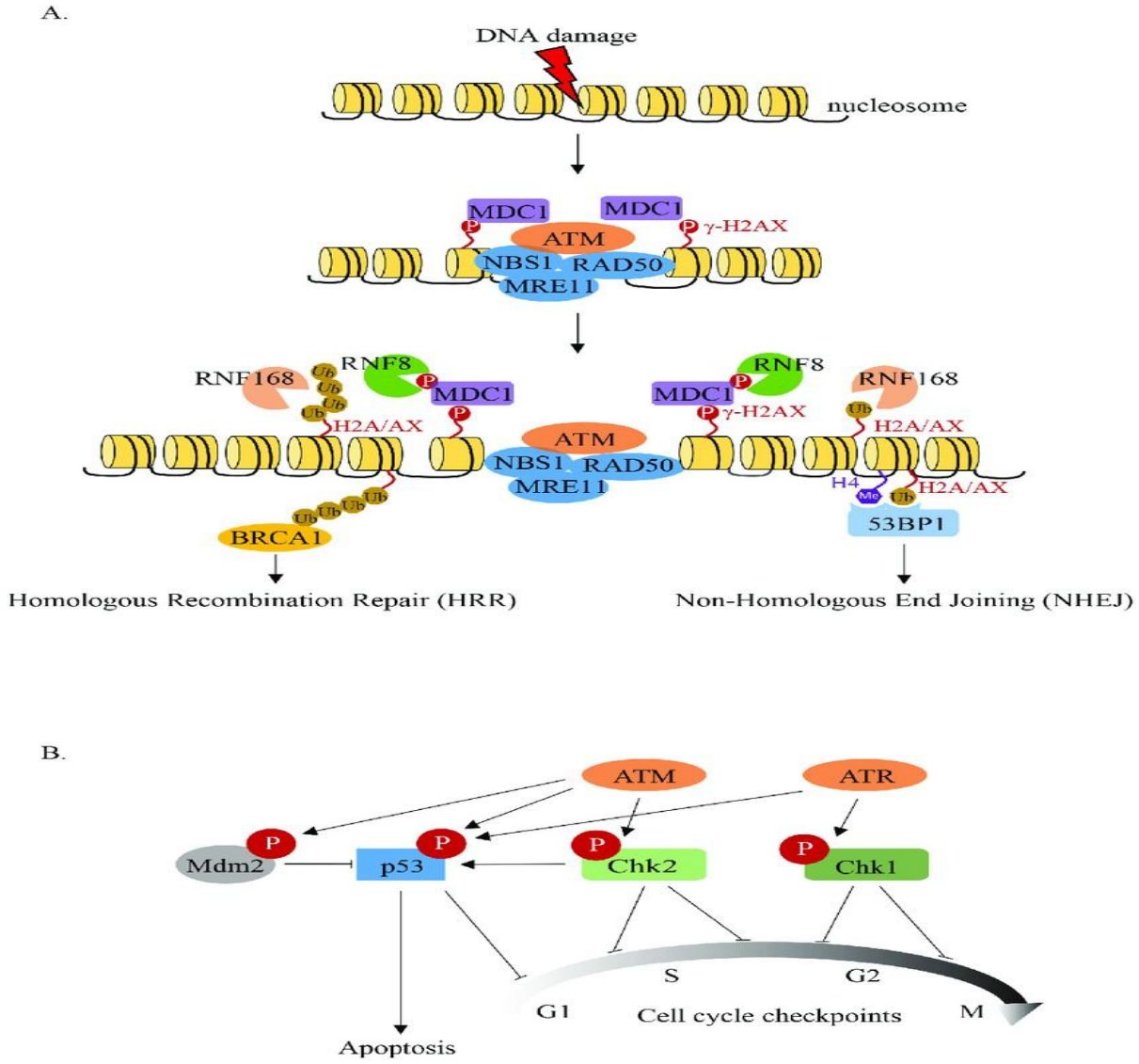
Cell Cycle Checkpoint CHK1 and CHK2 are important downstream regulators of ATR and ATM, respectively232,233 (Figure 4). Although the ATR-CHK1 and ATM-CHK2 axes are activated under distinct situations, the substrates and signaling circuits of CHK1 and CHK2 are partially overlapping. In terms of DDR-associated cell cycle regulation, CHK2 is primarily involved in the G1 checkpoint, whereas CHK1 is principally activated in the intra S and G2/M checkpoints. CHK1 deletion in mice resulted in early embryonic death, but CHK2 knockout animals developed properly, suggesting that CHK1 is more necessary than CHK2[21]. Although ATR inhibitors are hypersensitive in ATM- deficient circumstances, the synthetic lethal connection between CHK1 and CHK2 remains unknown. Most clinical-stage CHK1 inhibitors may be classed as CHK1-selective (for example, rabusertib and SRA737) or CHK1/2 dual inhibitors (for example, AZD7762, PF-477736, and prexasertib). Despite entering clinical trials for more than a decade, there has been a lengthy history of deprioritization in the development of CHK1 inhibitors, regardless of CHK1/2 selectivity. Notably, prexasertib (Fig. 6c) and LY2880070 are still being actively developed.

Resistance Mechanisms

Therapeutic resistance to DDR inhibitors arises through:

- Reversion mutations restoring HR competency (e.g., *BRCA* reversion).
- Upregulation of drug efflux pumps (e.g., P-gp for PARPi).
- Activation of compensatory repair pathways (e.g., NHEJ when HR is blocked).
- Tumor microenvironmental factors such as hypoxia affecting DDR gene expression.

These resistance mechanisms necessitate the identification of **functional biomarkers** (e.g., RAD51 foci, genomic scar scores) for patient stratification and therapy optimization.



Fig(1). DNA Double strand breaks

The DNA Damage Response to Double strand Breaks

Homology-Directed Repair versus Non-homologous DNA End Joining

There are two main types of DNA repair that can restore the duplex structure when double-strand breaks occur in any cell, whether prokaryotic or eukaryotic. It is possible to use homology-directed repair if the organism is diploid, even if the diploidy is just temporary, as in the case of replicating bacteria or haploid yeast. With the largest sequence homology requirements between the donor and acceptor DNA, homologous recombination, or HR for short, is the most popular type of homology- directed repair. Single-strand annealing (abbreviated SSA) and breakage-induced replication are two other homology-directed repair techniques that necessitate shorter sequence homology than HR [13,14,].

There is no homology donor close by in nondividing haploid organisms or in diploid species that are not in S phase. Nonhomologous DNA end joining (NHEJ) comprises a group of DNA enzymes with the mechanistic flexibility to offer a survival benefit, which made it possible for another type of double-strand break repair to offer an advantage early in evolution [15].

Research on how the cell decides whether to repair a break using HR or NHEJ is still ongoing. There may be some practical significance to the HR versus NHEJ determination [16]. HR cannot proceed and NHEJ is the only choice if a homologue is absent close to a DSB during S/G2. A homology donor for HR is provided by the sister chromatid's physical proximity during the S phase.

NHEJ is, in fact, the much favored choice outside of S/G2. Beyond questions of closeness and potential rivalry between Ku and RAD51 or 52, the specific molecular events remain unclear [16- 18]. The DNA ligase IV complex may play a crucial role in inhibiting the DNA end resection required to start HR, according to recent evidence from S. cerevisiae [19].

Clinical Applications and Future Directions

PARP inhibitors are FDA-approved for *BRCA*-mutated breast, ovarian, prostate, and pancreatic cancers. Current trials are expanding their use to non-BRCA HRD tumors.

Emerging DDR-targeted combinations include:

- PARPi + ATR inhibitors
- DNA-PK inhibitors + radiation
- DDR inhibitors + immune checkpoint blockade

Personalized medicine approaches integrating genomic profiling and DDR functionality assays will be essential for maximizing therapeutic efficacy while minimizing resistance.

Conclusion

The DNA damage response represents both a guardian of genomic stability and a therapeutic Achilles' heel in cancer. Advances in our molecular understanding of DDR have led to the development of precise inhibitors that exploit repair defects in tumor cells. While clinical progress is evident, challenges remain in overcoming resistance and refining biomarker-based patient selection. Ongoing research will further unlock the therapeutic potential of DDR-targeted strategies, cementing their role in the era of precision oncology.

Future perspectives

The DNA damage response (DDR) is a critical cellular pathway that maintains genomic integrity by detecting and repairing DNA damage. In cancer, DDR is often dysregulated, contributing to tumor progression, resistance to therapy, and genomic instability. Understanding the molecular mechanisms of DDR and exploiting these pathways for therapeutic purposes hold immense potential for advancing cancer treatment.

1. Precision Targeting of DDR Pathways

Future cancer therapies will increasingly focus on precision medicine by targeting specific DDR pathway components, such as PARP, ATR, ATM, and DNA-PK, tailored to the genetic profile of individual tumors. Advances in genomic profiling and CRISPR-based screening will enable the identification of synthetic lethal interactions, allowing for more effective and less toxic treatments. For example, PARP inhibitors have shown success in BRCA-mutated cancers, and ongoing research aims to expand these strategies to other DDR deficiencies (Lord & Ashworth, 2017).

2. Combination Therapies to Overcome Resistance

A key future direction involves combining DDR-targeted therapies with immunotherapy, chemotherapy, or radiotherapy to overcome resistance mechanisms. For instance, combining ATR inhibitors with immune checkpoint inhibitors could enhance tumor immunogenicity by increasing neoantigen presentation due to unrepaired DNA damage. Clinical trials exploring these combinations are underway, with promising early results (Sen et al., 2019).

3. Biomarker Development for Patient Stratification

The development of robust biomarkers to predict DDR inhibitor response will be critical. Future research will focus on identifying novel biomarkers, such as homologous recombination deficiency (HRD) scores or specific DDR gene mutations, to stratify patients for targeted therapies. Advances in liquid biopsy

technologies and AI-driven analytics will further refine patient selection and monitoring (Pilié et al., 2019).

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