# DNA Damage Response in Cancer: Mechanisms, Implications, and Therapeutic Opportunities

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**Abstract:**
The DNA Damage Response (DDR) constitutes an intricate network of sensing, signaling, and repair pathways that safeguards genomic stability against a constant barrage of endogenous metabolic by-products and exogenous genotoxic insults. Upon lesion recognition, specialized sensor complexes—such as the MRN (MRE11–RAD50–NBS1) and KU70/80 assemblies—activate master transducer kinases ATM, ATR, and DNA-PKcs, which in turn orchestrate a multilayered cascade of post-translational modifications, cell-cycle checkpoints, chromatin remodeling, and transcriptional re-programming. Downstream effector modules channel the repair of single- and double-strand breaks through error-free (homologous recombination, nucleotide- and base-excision, mismatch repair) or error-prone (non-homologous end-joining, translesion synthesis) mechanisms, thereby balancing genomic fidelity with cellular viability.

In oncogenesis, germline or somatic aberrations in DDR genes—exemplified by BRCA1/2, ATM, CHEK2, and mismatch-repair components—fuel genomic instability, clonal evolution, and therapeutic resistance. Paradoxically, these defects create synthetic-lethal vulnerabilities that can be therapeutically leveraged. The clinical success of PARP inhibitors in BRCA-mutant breast, ovarian, pancreatic, and prostate cancers has validated DDR targeting as a precision-oncology paradigm and catalyzed the development of next-generation agents against ATR, ATM, DNA-PK, CHK1/2, and WEE1. Combinatorial regimens coupling DDR inhibitors with immune checkpoint blockade, radiotherapy, and epigenetic modulators are broadening the therapeutic horizon, while circulating tumor DNA and functional genomic screens are refining patient stratification.

This review synthesizes current insights into DDR molecular circuitry, delineates how DDR dysfunction shapes the mutational landscape and tumor microenvironment, and critically appraises emerging translational strategies. By integrating mechanistic biology with clinical evidence, we highlight opportunities and challenges in harnessing DDR pathways to improve cancer prognosis and overcome resistance, paving the way for next-generation, genotype-directed interventions.

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## 1. Introduction

The genomic integrity of a cell is constantly challenged by a variety of intrinsic and extrinsic factors. Endogenous sources such as reactive oxygen species (ROS), which are by-products of normal cellular metabolism, spontaneous base hydrolysis, and replication errors, can induce various types of DNA lesions. Exogenous agents, including ultraviolet (UV) radiation, ionizing radiation (IR), environmental carcinogens, and chemotherapeutic drugs, further

contribute to DNA damage. If left unrepaired, these lesions can lead to mutations, chromosomal aberrations, and ultimately, cell death or malignant transformation.
To maintain genomic stability and ensure the faithful transmission of genetic information, eukaryotic cells have evolved an intricate surveillance and repair system known as the **DNA Damage Response (DDR)**. The DDR encompasses a highly coordinated network of cellular pathways responsible for recognizing DNA damage, halting the cell cycle to provide time for repair, recruiting the appropriate repair machinery, and either successfully repairing the damage or directing the cell towards apoptosis or senescence if the damage is irreparable. Key components of the DDR include sensors (e.g., the MRN complex), transducers (e.g., ATM, ATR kinases), and effectors (e.g., CHK1, CHK2, p53), which function together to preserve genome integrity.

The DDR is not a singular pathway but a collection of repair mechanisms tailored to different types of DNA lesions. These include **base excision repair (BER)** for small base modifications, **nucleotide excision repair (NER)** for bulky DNA adducts, **mismatch repair (MMR)** for replication errors, and **double-strand break repair mechanisms**, such as **non-homologous end joining (NHEJ)** and **homologous recombination (HR)**, which are vital for fixing the most lethal form of DNA damage—double-strand breaks (DSBs). The fidelity and efficiency of these repair processes are critical for cell survival and tumor suppression.

In the context of cancer, the DDR becomes a double-edged sword. On one hand, defects in DDR genes such as **BRCA1, BRCA2, ATM, TP53**, and **MLH1** can compromise repair fidelity, leading to increased mutation rates and genomic instability—a hallmark of cancer. These defects contribute to oncogenesis and tumor evolution, endowing cancer cells with heterogeneity and resistance mechanisms. On the other hand, these very defects can be exploited therapeutically. Tumors with specific DDR deficiencies become overly reliant on alternative repair pathways. By inhibiting these compensatory pathways—for instance, using **PARP inhibitors** in **BRCA-mutated** tumors—one can induce **synthetic lethality**, selectively killing cancer cells while sparing normal cells with intact DDR systems.

Recent advances in genomics and molecular oncology have highlighted the prognostic and predictive value of DDR gene alterations. Moreover, DDR-targeted therapies have emerged as a novel class of anticancer agents, ushering in a new era of precision oncology. As our understanding of DDR biology deepens, it holds promise not only for improving therapeutic efficacy but also for overcoming drug resistance and minimizing off-target toxicities.

This article aims to provide a comprehensive overview of the molecular mechanisms of the DNA Damage Response, its dysregulation in cancer, and the clinical strategies currently employed or under development to target DDR pathways in cancer therapy. Through this lens, we examine the dual role of DDR as both a barrier to tumorigenesis and a target for therapeutic intervention.

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## 2. **2. Overview of DNA Damage and Repair Mechanisms**

The integrity of the genome is constantly challenged by a variety of endogenous and exogenous agents. Endogenous threats include reactive oxygen species (ROS), replication errors, and metabolic by-products, whereas exogenous agents encompass ultraviolet (UV) light, ionizing radiation, and chemical mutagens. To preserve genomic stability, cells have evolved a complex and tightly regulated network known as the DNA damage response (DDR), which encompasses DNA repair pathways, checkpoint activation, and, when necessary, programmed cell death.

### 2.1 Types of DNA Damage

DNA lesions can manifest in several structural forms, each with distinct causes and cellular consequences:

- **Single-Strand Breaks (SSBs):**
  Caused primarily by oxidative stress, alkylation, or spontaneous hydrolysis. If left unrepaired, SSBs can convert into double-strand breaks during replication.
- **Double-Strand Breaks (DSBs):**
  Among the most deleterious DNA lesions, DSBs arise from ionizing radiation, replication fork collapse, or enzymatic cleavage. Unrepaired DSBs can lead to chromosomal translocations, deletions, or cell death.
- **Base Modifications:**
  These include oxidation (e.g., 8-oxoguanine), alkylation, and deamination events that alter the chemical structure of nucleobases, potentially leading to mutagenic base mispairing.
- **DNA Crosslinks (Interstrand and Intrastrand):**
  Induced by agents like cisplatin and mitomycin C, crosslinks tether one or both strands of the DNA helix, blocking transcription and replication processes.
- **Replication Stress-Induced Damage:**
  Stalled replication forks, often due to difficult-to-replicate sequences or oncogene activation, can give rise to fork collapse and subsequent DNA damage, including DSBs.

### 2.2 DNA Repair Pathways

Multiple overlapping and specialized DNA repair pathways have evolved to counteract specific types of DNA damage:

- **Base Excision Repair (BER):**
  Specialized in correcting small, non-helix-distorting lesions such as uracil, abasic sites, or oxidized bases. BER involves DNA glycosylases, AP endonuclease, DNA polymerase β, and DNA ligase III.
- **Nucleotide Excision Repair (NER):**
  Removes bulky adducts and helix-distorting lesions, including UV-induced pyrimidine dimers and chemical-induced DNA adducts. NER operates via two subpathways: global genome NER (GG-NER) and transcription-coupled NER (TC-NER).
- **Mismatch Repair (MMR):**
  Corrects base mismatches and small insertion/deletion loops arising during DNA replication. Key players include MSH2, MSH6, MLH1, and PMS2.
- **Homologous Recombination (HR):**
  A high-fidelity repair mechanism for DSBs, HR utilizes the undamaged sister chromatid as a template, making it active mainly during the S and G2 phases of the cell cycle. BRCA1, BRCA2, and RAD51 are central to HR.
- **Non-Homologous End Joining (NHEJ):**
  A more error-prone DSB repair pathway that ligates broken ends without the need for homology. Core components include Ku70/80, DNA-PKcs, XRCC4, and DNA ligase IV.
- **Fanconi Anemia (FA) Pathway:**
  Critical for the repair of interstrand crosslinks (ICLs), the FA pathway involves a complex network of proteins that coordinate incision, translesion synthesis, and HR-mediated repair.

## 3. DNA Damage Response (DDR) Signaling Pathways

### 3.1 Sensing and Signaling

The initial step in DDR involves the detection of DNA lesions by sensor proteins, which activate signal transduction cascades to halt cell cycle progression and initiate repair:

- **ATM (Ataxia Telangiectasia Mutated):**
  Primarily activated by DSBs, ATM phosphorylates a wide range of substrates, including CHK2 and p53, thereby triggering cell cycle arrest and DNA repair.
- **ATR (ATM and Rad3-related):**
  Activated in response to replication stress and single-stranded DNA regions coated with replication protein A (RPA). ATR, in concert with its partner ATRIP, phosphorylates CHK1 and promotes fork stabilization and repair.
- **DNA-PKcs (DNA-dependent Protein Kinase, Catalytic Subunit):**
  Functions in the NHEJ pathway. Upon binding to DSB ends via the Ku heterodimer, DNA-PKcs facilitates end processing and ligation.

These kinases further activate downstream effectors such as:

- **CHK1 and CHK2 (Checkpoint Kinases):**
  Mediators of checkpoint activation that enforce cell cycle arrest in G1, S, or G2 phases to allow time for DNA repair.
- **p53:**
  A tumor suppressor protein that acts as a transcriptional regulator of genes involved in cell cycle arrest (e.g., p21), DNA repair, and apoptosis.

### 3.2 Cell Cycle Checkpoints

DDR enforces cell cycle checkpoints to ensure DNA integrity before critical transitions:

- **G1/S Checkpoint:**
  Prevents the replication of damaged DNA, largely controlled by the ATM/CHK2/p53 pathway.
- **S-phase Checkpoint:**
  Slows or stalls replication in response to fork damage or stalling, with ATR/CHK1 playing a central role.
- **G2/M Checkpoint:**
  Delays mitotic entry until DNA repair is complete, primarily governed by ATM and ATR signaling cascades.

## 4. DDR Dysfunction in Cancer

### 4.1 Genomic Instability as a Hallmark of Cancer

Genomic instability, fueled by defective DNA repair pathways, is a defining feature of cancer cells. Mutations in DDR genes enable the accumulation of genetic alterations that drive malignant transformation and progression:

- **BRCA1/2 Mutations:**
  Associated with impaired HR-mediated DSB repair, leading to genomic instability and increased risk of breast, ovarian, and pancreatic cancers.

- **Mismatch Repair Deficiencies:**
  Result in microsatellite instability (MSI), characterized by length alterations in repetitive DNA sequences. MSI is a hallmark of hereditary nonpolyposis colorectal cancer (HNPCC) and certain sporadic tumors.
- **ATM Mutations:**
  Common in hematological malignancies, ATM loss disrupts DSB recognition and checkpoint activation, contributing to chromosomal aberrations.

### 4.2 DDR Mutations and Tumor Heterogeneity

Tumors often exhibit a mosaic of DDR deficiencies, contributing to both intratumoral heterogeneity and therapeutic resistance:

- **Subclonal Evolution:**
  Distinct tumor subpopulations may harbor diverse DDR alterations, complicating treatment strategies and facilitating resistance to genotoxic therapies.
- **Synthetic Lethality and Therapeutic Opportunities:**
  Exploiting DDR deficiencies, such as using PARP inhibitors in BRCA-mutant tumors, exemplifies the therapeutic potential of targeting DDR vulnerabilities.

In summary, DDR pathways are indispensable guardians of genomic fidelity. Their dysregulation not only promotes tumorigenesis but also represents a double-edged sword—posing challenges to treatment while offering unique therapeutic windows.

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## Therapeutic Exploitation of DDR in Cancer

The DNA Damage Response (DDR) pathway is increasingly recognized as a therapeutic vulnerability in cancer. As many tumors harbor defects in one or more components of DDR, these deficiencies can be strategically exploited to induce cancer-specific lethality. Among the most promising approaches are **synthetic lethality-based therapies**, **targeted DDR inhibitors**, and **combination regimens** that leverage DDR deficiencies to maximize treatment efficacy while minimizing harm to normal cells.

### *5.1 Synthetic Lethality*

The concept of **synthetic lethality** refers to a situation where the concurrent loss of two genes results in cell death, whereas the loss of either gene alone is non-lethal. This principle has been harnessed in cancer therapy by targeting compensatory DNA repair pathways in tumor cells with pre-existing DDR defects.

A landmark example is the use of **Poly(ADP-ribose) polymerase (PARP) inhibitors** in **BRCA1/2-mutated cancers**. BRCA1/2 genes are essential for homologous recombination repair (HRR) of double-strand breaks (DSBs). In BRCA-deficient cells, inhibition of PARP—an enzyme that repairs single-strand breaks (SSBs)—leads to accumulation of SSBs, which collapse replication forks and convert into toxic DSBs. As these cells lack efficient DSB repair via HR, they undergo apoptosis, sparing normal cells with intact BRCA function.

### *5.2 DDR Inhibitors in Clinical Use*

Over the past decade, multiple DDR inhibitors have progressed through clinical development, with some gaining regulatory approval. These include:

- **PARP Inhibitors**:
  - *Olaparib*, *Rucaparib*, *Niraparib*, and *Talazoparib* are approved for treating BRCA-mutated ovarian, breast, pancreatic, and prostate cancers.
- **ATR Inhibitors**:
  - *Berzosertib* and *Elimusertib* are under clinical investigation. ATR is crucial in the replication stress response; its inhibition sensitizes cells with ATM or TP53 mutations.
- **CHK1/2 Inhibitors**:
  - *Prexasertib* targets checkpoint kinases involved in cell cycle arrest and DNA repair, particularly effective in TP53-deficient tumors.
- **WEE1 Inhibitors**:
  - *Adavosertib* disrupts the G2/M checkpoint, forcing damaged cells into mitosis and enhancing the effects of DNA-damaging agents.

These agents are used both as monotherapies and in rationally designed combinations to maximize antitumor efficacy.

### *5.3 Combination Therapies*

DDR inhibitors are increasingly used in **synergistic combinations** to enhance therapeutic outcomes:

- **Chemotherapy**: DDR inhibitors amplify DNA damage induced by cytotoxic agents (e.g., platinum compounds, alkylators), overwhelming the repair machinery in cancer cells.
- **Radiation Therapy**: Radiotherapy-induced DSBs are particularly lethal in cells pre-treated with DDR inhibitors, such as PARP or ATM inhibitors.
- **Immunotherapy**: DDR deficiencies increase the accumulation of mutations and neoantigens, enhancing the immunogenicity of tumors and their responsiveness to **immune checkpoint inhibitors (ICIs)**. For example, tumors with HR deficiency often exhibit increased **tumor mutational burden (TMB)** and **microsatellite instability (MSI)**, both predictive of better ICI response.

## 6. Biomarkers and DDR-Directed Precision Medicine

With the advent of precision oncology, biomarker-driven treatment strategies have become critical in identifying patients likely to benefit from DDR-targeted therapies.

### *6.1 Predictive Biomarkers*

Several genomic and phenotypic biomarkers guide DDR-based therapeutic decisions:

- **BRCA1/2 Mutations**: Germline or somatic mutations are predictive of PARP inhibitor sensitivity.
- **Homologous Recombination Deficiency (HRD) Scores**: Composite metrics integrating loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions.

- **Microsatellite Instability (MSI)**: Associated with mismatch repair (MMR) deficiency, predictive of response to ICIs.
- **Tumor Mutational Burden (TMB)**: Elevated TMB suggests increased neoantigen load, making tumors more amenable to immunotherapy.

### *6.2 Companion Diagnostics*

Several FDA-approved companion diagnostics are available to guide DDR-based therapy:

- **Myriad myChoice® HRD test**: Quantifies HRD status using genomic instability scores.
- **FoundationOne® CDx**: Comprehensive genomic profiling tool used to identify actionable mutations, including those relevant to DDR pathways.

These assays ensure that patients receive the most appropriate, targeted, and effective treatment.

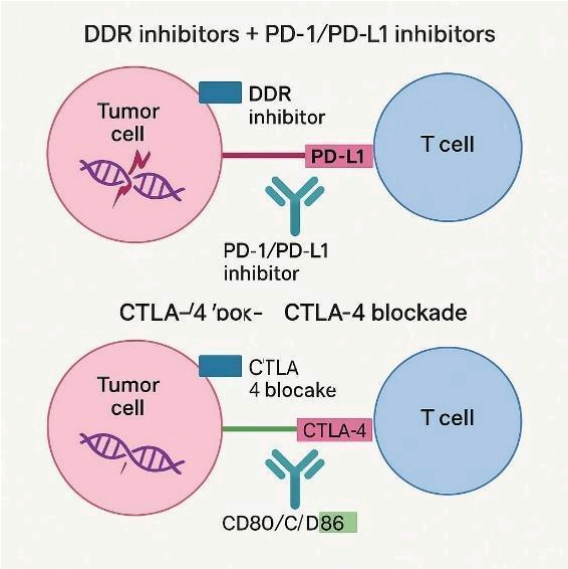


Fig :1: ddr inhibitors \

## 7. Challenges and Resistance Mechanisms

Despite promising clinical outcomes, therapeutic resistance remains a formidable challenge in DDR-targeted oncology.

### *7.1 Acquired Resistance to DDR Inhibitors*

Resistance to agents like PARP inhibitors often emerges via several mechanisms:

- **Reversion Mutations**: Secondary mutations in BRCA1/2 that restore functional protein expression and HR competency.
- **Upregulation of Drug Efflux Pumps**: Increased expression of ATP-binding cassette (ABC) transporters that reduce intracellular drug levels.

- **Compensatory Repair Pathways**: Activation of alternative DSB repair pathways such as **Polθ-mediated end joining (TMEJ)** can substitute for HR in some contexts.

### *7.2 Toxicity and Therapeutic Window*

Although DDR inhibitors are designed to target tumor-specific vulnerabilities, their action in proliferative normal tissues, such as bone marrow and intestinal epithelium, can cause:

- **Hematological Toxicities**: Anemia, neutropenia, thrombocytopenia.
- **Gastrointestinal Side Effects**: Nausea, vomiting, diarrhea.

Careful dose optimization and biomarker-driven patient selection are crucial to balance efficacy and safety.

## 8. Emerging Strategies and Future Directions

Ongoing research continues to unravel novel DDR targets and therapeutic strategies to overcome resistance and broaden the clinical applicability of DDR inhibitors.

### *8.1 Targeting Additional DDR Nodes*

- **POLQ (DNA Polymerase Theta)**: Key player in TMEJ, which serves as a backup for HR. Inhibiting POLQ in HR-deficient tumors induces synthetic lethality. First-in-class POLQ inhibitors are currently in preclinical development.
- **USP1 Inhibitors**: Deubiquitinating enzyme USP1 regulates turnover of FANCD2 and other DNA repair proteins. Its inhibition impairs interstrand crosslink repair and sensitizes cells to chemotherapy and PARP inhibition.

### *8.2 Immunotherapy and DDR*

DDR-defective tumors exhibit increased **neoantigen load**, **STING pathway activation**, and **type I interferon response**, rendering them more responsive to immunotherapy. DDR-targeting agents may **prime the tumor microenvironment** to potentiate checkpoint blockade, offering a rationale for combinatorial regimens involving:

#### DDR Inhibitors + PD-1/PD-L1 Inhibitors

*What are DDR inhibitors?*

DDR (DNA Damage Response) inhibitors target key proteins involved in the cellular pathways that detect and repair DNA damage. Common DDR targets include:

- **PARP inhibitors** (Poly (ADP-ribose) polymerase inhibitors)
- **ATR inhibitors** (Ataxia telangiectasia and Rad3-related protein)
- **CHK1/2 inhibitors** (Checkpoint kinase 1 and 2)
- **DNA-PK inhibitors** (DNA-dependent protein kinase)

DDR inhibitors impair the cancer cell's ability to repair DNA damage, causing accumulation of DNA lesions, genomic instability, and ultimately cell death, especially in cells already deficient in DNA repair (e.g., BRCA-mutated tumors).

*What are PD-1/PD-L1 inhibitors?*

- **PD-1 (Programmed cell death protein 1)** and **PD-L1 (Programmed death-ligand 1)** inhibitors are immune checkpoint blockers that release the "brakes" on T cells, enhancing immune system recognition and killing of cancer cells.

*Why combine DDR inhibitors with PD-1/PD-L1 inhibitors?*

- **Increased Tumor Mutational Burden (TMB):** DDR inhibition causes accumulation of DNA damage, increasing tumor mutational burden and neoantigen formation. This makes tumors more immunogenic and visible to T cells.
- **Activation of cGAS-STING pathway:** DNA damage can lead to accumulation of cytosolic DNA fragments, which activate the cGAS-STING pathway, resulting in type I interferon production and enhanced antitumor immunity.
- **Overcoming immune evasion:** Tumors with DDR deficiencies often have immune suppressive microenvironments; combining DDR inhibition with checkpoint blockade may reverse this immune suppression.
- **Synergistic efficacy:** Preclinical models show that DDR inhibitors sensitize tumors to PD-1/PD-L1 blockade, improving tumor regression and survival.

*Clinical insights:*

- **PARP inhibitors + PD-1/PD-L1 inhibitors** are being tested in various cancers (ovarian, breast, lung, prostate). For example, **olaparib (PARP inhibitor) combined with pembrolizumab (PD-1 inhibitor)** showed promising efficacy in BRCA-mutated and HRD (homologous recombination deficiency) tumors.
- Trials have shown that DDR inhibition may induce immune-related gene signatures predictive of better responses to immunotherapy.
- Combination regimens can improve progression-free survival (PFS) compared to monotherapy in some settings.

2. DDR Inhibitors + CTLA-4 Blockade

*What is CTLA-4 blockade?*

- **CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4)** is another immune checkpoint molecule expressed on T cells. CTLA-4 inhibitors (e.g., ipilimumab) block this negative regulator of T cell activation, enhancing T cell priming and proliferation.

*Why combine DDR inhibitors with CTLA-4 inhibitors?*

- **Priming of immune response:** CTLA-4 blockade acts more upstream in the immune activation cascade compared to PD-1/PD-L1 inhibitors. Combining it with DDR inhibitors could enhance initial T cell priming against neoantigens created by DNA damage.

- **Increased tumor antigenicity:** As with PD-1/PD-L1 blockade, DDR inhibitors increase neoantigen load, which CTLA-4 blockade can help the immune system recognize more effectively.
- **Potential to overcome resistance:** Some tumors resistant to checkpoint blockade may become susceptible with DDR inhibition by changing the tumor microenvironment.
- **Broad immunomodulation:** CTLA-4 blockade can modulate regulatory T cells (Tregs) that suppress immune responses, potentially enhanced by the immunogenic effects of DDR inhibition.

*Clinical insights:*

- Combination therapy involving **PARP inhibitors + CTLA-4 blockade** is under clinical investigation for various solid tumors.
- Preclinical data indicate enhanced antitumor effects with this combination due to improved T cell infiltration and activation.
- Toxicity can be a concern since CTLA-4 inhibitors have a higher immune-related adverse event profile, so dosing and scheduling optimization are critical.

Table:

| Combination | Mechanism | Key Effects | Clinical Status |
|---|---|---|---|
| DDR inhibitors + PD-1/PD-L1 | Increase neoantigens, activate cGAS-STING, enhance T cell killing | Higher immunogenicity, improved tumor control | Several ongoing clinical trials; promising in BRCA/HRD cancers |
| DDR inhibitors + CTLA-4 | Enhance T cell priming and reduce Treg suppression | Stronger initial immune activation, broader immune modulation | Early phase trials; managing toxicity is critical |

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*8.3 CRISPR Screens and Functional Genomics*

High-throughput **CRISPR-Cas9-based genome-wide screens** are revolutionizing our understanding of the DDR network. These screens:

- Identify novel synthetic lethal interactions (e.g., ATR + ARID1A).
- Reveal tumor-specific vulnerabilities.
- Enable the design of **next-generation precision therapies**.

Integration of **functional genomics**, **machine learning**, and **clinical genomics** is paving the way for a new era of personalized cancer therapy that is dynamically responsive to tumor evolution and resistance.

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9. **Conclusion**

The DNA damage response (DDR) is a highly intricate and evolutionarily conserved network that plays a pivotal role in maintaining genomic integrity and cellular homeostasis. In the context of cancer, DDR assumes a paradoxical role—while its impairment contributes to genomic instability and tumorigenesis, these very defects expose critical vulnerabilities that can be therapeutically exploited. The clinical success of PARP inhibitors, especially in BRCA1/2-mutated cancers, exemplifies how targeting specific DDR deficiencies can yield profound therapeutic benefit. However, the emergence of resistance mechanisms, off-target toxicities, and limited applicability to a broader spectrum of tumors remain significant hurdles.

A deeper understanding of the molecular underpinnings of DDR pathways, aided by advances in next-generation sequencing, functional genomics, and systems biology, holds the key to overcoming these limitations. The identification of novel DDR-related biomarkers, synthetic lethality networks, and context-dependent vulnerabilities offers promising avenues for expanding the scope of DDR-targeted interventions. Moreover, strategic combination therapies—such as pairing DDR inhibitors with immune checkpoint blockade, radiotherapy, or epigenetic modulators—are gaining traction for their potential to enhance efficacy and circumvent resistance.
As the landscape of cancer therapy shifts increasingly towards precision medicine, DDR continues to emerge as a cornerstone of personalized oncologic strategies. The future of DDR research lies not only in uncovering new therapeutic targets but also in fine-tuning patient stratification and optimizing treatment regimens based on individual molecular profiles. With ongoing translational research and clinical innovation, DDR-targeted therapies are poised to transform cancer care, bringing us closer to more effective, durable, and patient-tailored treatments.

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