Pharmacological Modulation of DNA Damage Response Pathway in Breast Cancer Therapy: A Comprehensive Review

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Abstract

Breast cancer remains a leading cause of cancer-related morbidity and mortality among women worldwide. A hallmark of cancer cells, genomic instability, often arises from defects in the DNA damage response (DDR) pathways—complex cellular networks that detect, signal, and repair DNA lesions. This comprehensive review explores the pharmacological modulation of key DDR pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ), in the context of breast cancer therapy. Central to DDR activation are damage sensors such as the MRN complex and PARP1, which recognize DNA lesions and recruit transducer kinases—ATM, ATR, to propagate damage signals and coordinate repair. The review also discusses mechanisms of therapeutic resistance, tumor heterogeneity, and the role of combination therapies to overcome these challenges. Furthermore, the importance of predictive biomarkers and personalized DDR profiling for optimizing treatment outcomes is highlighted. We discuss clinical study of DDR-targeting agents such as PARP inhibitors (e.g., Olaparib), mechanisms of resistance, and future directions in harnessing DDR for improved therapeutic outcomes in breast cancer patients.

Keywords: ATM; ATR; DDR inhibition; PARP; breast cancer;

1. Introduction

The DNA damage response (DDR) is a complex network of signaling pathways that detect, signal, and repair DNA lesions to maintain genomic integrity. In cancer, especially breast cancer, many DDR components are frequently mutated or dysregulated, providing opportunities for targeted therapy [1]. For example, inhibitors targeting key DDR proteins such as PARP1, ATR, ATM, and CHK1 are being explored for their potential to selectively kill tumor cells with specific DNA repair defects while sparing normal cells [2,3]. Moreover, combining DDR inhibitors with other treatments—such as immunotherapy or chemotherapy—can enhance therapeutic efficacy and potentially overcome resistance [4]. Breast cancer accounted for 2.3 million new cases and 685,000 deaths worldwide in 2020 [5]. Breast cancer is a heterogeneous disease with four major molecular subtypes influencing prognosis and therapy. Luminal A tumors are ER/PR positive, HER2 negative. Luminal B tumors are ER/PR positive with either HER2 positivity. TNBC and BRCA1/2-mutated subtypes show homologous recombination deficiency (HRD), making them particularly sensitive to DDR-targeting agents like PARP inhibitors [6]. Despite advancements in breast cancer therapy, resistance, tumor heterogeneity, and relapse remain

major challenges due to factors like diverse subclonal populations, alternative signaling activation, and survival of therapy-resistant cells [7].

Genomic instability is a hallmark of cancer and plays a pivotal role in breast cancer initiation, progression, and therapy resistance [8]. It involves various DNA alterations, including mutations and chromosomal abnormalities, which contribute to tumor heterogeneity. In triple-negative and BRCA-mutated breast cancers, defective DNA repair mechanisms lead to high genomic instability and aggressive clinical behaviour [9].

2. DNA Damage and the DDR Pathway

2.1 Types of DNA Damage

- Single-strand breaks (SSBs):

SSBs can arise in many ways, in both a programmed manner as part of endogenous DNA metabolic processes and stochastically as unscheduled products of DNA damage and decay. Most of the major DNA repair pathways are represented by diseases in which that pathway is absent or impaired. The repair of direct and indirect SSBs has collectively been termed single-strand break repair (SSBR), primarily because the same group of proteins appear to repair both types of breaks [10].

SSBR can be divided into four basic steps

I) beginning with DNA damage binding

II) DNA end processing

III) DNA gap filling

IV) the integrity of the phosphodiester backbone is restored by DNA ligation. [11].

- Double-strand breaks (dsbs)

The DNA double-strand break (DSB) is the principle cytotoxic lesion for ionizing radiation and radio-mimetic chemicals but can also be caused by mechanical stress on chromosomes or when a replicative DNA polymerase encounters a DNA single-strand break or other type of DNA lesion. [12]. In contrast to single-strand DNA breaks (SSBs), in which the genetic information retained on the complementary strand is still available to template repair, faithful restoration of DSBs can be problematic.In addition to loss of genetic information, DSBs can lead to fragmentation, loss or rearrangement of chromosomes. DSBs are also generated during normal cell metabolism.[13] Double-strand breaks (DSBs), among the most lethal DNA lesions, are repaired via homologous recombination or nonhomologous end joining; defects in HR (e.g., BRCA1/2 mutations) or misrepair by cNHEJ contribute to genomic instability and breast cancer progression.[14]

- Crosslinks
DNA crosslinks, especially interstrand crosslinks (ICLs), block replication and are highly cytotoxic. In BRCA1/2-deficient breast cancers with impaired HR, agents like cisplatin are particularly effective. PARP inhibitors, such as olaparib, enhance this effect by inducing synthetic lethality in HR-deficient tumors [15]
- Base Modifications

Base modifications such as oxidation and alkylation are repaired by the base excision repair (BER) pathway, involving enzymes like OGG1 and DNA polymerase β. Oxidative lesions like 8-oxoG, if unrepaired, contribute to mutagenesis and breast cancer progression. BER modulation using agents like methoxyamine enhances chemotherapeutic efficacy by blocking repair [16].

2.2 Major DDR Pathways

- Base excision repair (BER)

Base excision repair (BER) is a cellular mechanism that corrects small base lesions caused by oxidative stress, deamination, and alkylation that do not significantly distort the DNA helix. The process is initiated by DNA glycosylases that recognize and excise damaged bases, leaving behind a basic (AP)sites. These sites are then processed by either short-patch or long-patch repair pathways involving different sets of proteins. BER is essential in protecting against cancer, aging, and neurodegeneration and operates in both the nucleus and mitochondria [17].

- Nucleotide excision repair (NER)

Nucleotide excision repair (NER) is the primary DNA repair mechanism in eukaryotes responsible for removing bulky DNA lesions, such as those caused by ultraviolet (UV) light, environmental mutagens, and certain chemotherapeutic agents. It operates through two sub-pathways: global genome NER (GG-NER) and transcription-coupled NER (TC-NER), both of which use a common set of core proteins. The NER mechanism involves recognition of DNA damage, unwinding of the DNA helix, excision of a short single-stranded DNA segment containing the lesion, DNA synthesis to fill the gap, and ligation. Defects in this pathway are linked to disorders such as xeroderma pigmentosum (XP), characterized by extreme sensitivity to sunlight and a high risk of skin cancer. [18].

- Mismatch repair (MMR)

Mismatch repair (MMR) is a critical DNA repair mechanism that corrects base-base mismatches and insertion–deletion loops formed during DNA replication. It plays a pivotal role in maintaining genomic stability by recognizing and repairing erroneous mismatches that escape proofreading by DNA polymerases. MMR involves key proteins such as MutS and MutL homologs, which detect and initiate the repair process. Deficiencies in MMR are strongly associated with microsatellite instability and several cancers, most notably Lynch syndrome (hereditary nonpolyposis colorectal cancer)[19].

- Homologous recombination (HR)

Homologous recombination (HR) is a critical DNA repair mechanism that accurately repairs double-strand breaks (DSBs) by using a homologous DNA sequence as a template. This process involves strand invasion, DNA synthesis, and resolution through pathways such as double-strand break repair (DSBR) and synthesis-dependent strand annealing (SDSA). HR plays a crucial role not only in preserving genomic integrity but also in promoting genetic diversity during meiosis. Defects in HR are linked to increased cancer susceptibility, particularly in cases involving BRCA1 and BRCA2 mutations[20].

- Non-homologous end joining (NHEJ)

Non-homologous end joining (NHEJ) is the primary pathway for repairing DNA double-strand breaks (DSBs) in human cells, accounting for up to 80% of such repair events. It functions throughout the cell cycle and involves the direct ligation of DNA ends without the need for a homologous template. The pathway begins with recognition of DSBs by the Ku70/80 complex, followed by recruitment of DNA-PKcs, end processing if needed, and final ligation by the XRCC4-Ligase IV complex. While efficient, NHEJ is error-prone and can lead to mutations or chromosomal translocations if misregulated, contributing to genomic instability and cancer [21].

2.3 Core DDR Components

- Sensors (e.g., MRN complex, PARP1)

MRN Complex & PARP1

The MRN complex (MRE11-RAD50-NBS1) is a key sensor of DNA double-strand breaks, initiating repair by recruiting ATM and activating HR and NHEJ pathways. It also contributes to telomere stability and meiotic recombination. PARP1, in contrast, detects single-strand breaks and facilitates base excision repair. Though acting in different contexts, MRN loss can sensitize cells to PARP inhibitors, highlighting synthetic lethality in cancer therapy [22].

- Transducers (ATM, ATR)

ATM (Ataxia-Telangiectasia Mutated)

Function: ATM is activated primarily by DNA double-strand breaks (DSBs), often resulting from ionizing radiation.

Mechanism: Once activated, ATM phosphorylates downstream targets like p53, Chk2, BRCA1, and NBS1 to enforce cell cycle checkpoints and DNA repair mechanisms.

Clinical Relevance: Mutations in ATM cause Ataxia-Telangiectasia, a disorder marked by neurodegeneration, radiosensitivity, and cancer predisposition.

Pathway Role: Plays a dominant role in G1/S, S, and G2/M checkpoints after DSBs.

ATR (ATM and Rad3-Related)

Function: ATR responds to a broader range of DNA damage, especially replication stress and UV-induced lesions.

Mechanism: ATR activation leads to phosphorylation of targets like Chk1 and p53, regulating the intra-S and G2/M checkpoints.

Essentiality: ATR is critical for cell survival; its complete loss results in embryonic lethality in mice.

Specialization: ATR is more involved in replication-associated damage, showing minimal redundancy with ATM despite some overlapping substrates [23].

Effectors (CHK1, CHK2, BRCA1/2, p53)

3. DDR Dysregulation in Breast Cancer

3.1. BRCA1/2 mutations and homologous recombination deficiency (HRD)

Mutations in BRCA1/2 impair homologous recombination, a critical DNA repair pathway. This leads to homologous recombination deficiency (HRD), resulting in genomic instability. HRD is a hallmark of certain hereditary breast cancers and increases sensitivity to PARP inhibitors. [24].

3.2. Triple-negative breast cancer (TNBC) and DDR vulnerabilities

TNBC lacks estrogen, progesterone, and HER2 receptors and often exhibits DDR gene alterations, especially HRD. These tumors are more dependent on alternative repair mechanisms like NHEJ, making them vulnerable to DNA-damaging agents and DDR inhibitors (e.g., PARP and ATR inhibitors). [25].

3.3. p53 mutation and its implications

TP53, the gene encoding p53, is mutated in ~30–50% of breast cancers, especially in

TNBC. Loss of p53 function disrupts cell cycle arrest, DNA repair, and apoptosis, allowing the proliferation of genomically unstable cells. This mutation contributes to resistance to certain therapies and affects DDR pathway regulation [26]. The expression levels of DDR genes (e.g., BRCA1, ATM, CHEK1) are increasingly used as biomarkers to predict prognosis and therapeutic response. Low expression may indicate sensitivity to PARP inhibitors, while high expression could signal resistance. DDR gene signatures are also being explored in guiding personalized breast cancer treatment [27].

4. Pharmacological Modulators of DDR in Breast Cancer

4.1 PARP Inhibitors

Mechanism of Synthetic Lethality: PARP inhibitors block the repair of single-strand breaks, leading to double-strand breaks that cannot be repaired in BRCA-deficient cells, causing synthetic lethality.

FDA-approved Agents: Olaparib and Talazoparib are approved for BRCA1/2-mutated HER2-negative metastatic breast cancer, improving progression-free survival.

Indications & Trials: Olaparib showed significant benefit in the OlympiAD trial, extending PFS by ~3 months in BRCA-mutated patients.

Resistance Mechanisms: Resistance may develop due to BRCA reversion mutations, restoration of HR function, or upregulation of drug efflux pumps [28].

4.2 ATM and ATR Inhibitors

Role in DDR: ATM responds to DSBs while ATR senses replication stress; both activate checkpoints to prevent mitotic entry and allow repair.

Agents Under Evaluation: Agents like AZD0156, BAY 1895344, and Berzosertib (ATR inhibitor) are under clinical trials for breast and other solid tumors.

Combination Therapies: ATR/ATM inhibitors show synergy with DNA-damaging agents like cisplatin or radiotherapy, especially in HR-deficient and p53-deficient tumors. [29].

4.3 CHK1/CHK2 Inhibitors

Checkpoint Regulation: CHK1 and CHK2 are downstream of ATR/ATM and mediate cell cycle arrest; inhibiting them forces cell cycle progression with unrepaired DNA, leading to cell death.

Drugs: Prexasertib (CHK1 inhibitor) and SRA737 are in clinical trials and show promise, particularly in TNBC and p53-mutant tumors, which lack a functional G1 checkpoint.

Therapeutic Potential: CHK1 inhibition is especially effective when combined with DNA-damaging agents, exploiting replication stress and genomic instability in TNBC [30].

4.4 WEE1 and DNA-PK Inhibitors

DDR Roles: WEE1 regulates mitotic entry by inhibiting CDK1, while DNA-PK is a key component of non-homologous end joining (NHEJ) repair of DSBs.

Key Agents: AZD1775 (WEE1 inhibitor) sensitizes tumor cells to chemotherapy by overriding G2/M checkpoint and is in trials with platinum agents or PARP inhibitors.

DNA-PK Inhibitors: Agents like M3814 (peposertib) and NU7441 are in preclinical and clinical studies, especially in HR-deficient settings [31].

5. Combination Therapies

5.1.DDR inhibitors with chemotherapy, radiotherapy

DNA Damage Response (DDR) inhibitors represent a promising approach in combination cancer therapy, particularly when used alongside radiotherapy and chemotherapy. These inhibitors target key proteins in DNA repair pathways—such as ATM, ATR, and PARP—disrupting cancer cells' ability to recover from genotoxic stress caused by radiation or cytotoxic drugs.The ATM inhibitor AZD0156, ATR inhibitor AZD6738, and PARP inhibitor olaparib were tested in combination with both single-dose and fractionated ionizing radiation (IR) in breast cancer cell lines (MDA-MB-231 and MCF-7). The results showed that all three DDR inhibitors significantly enhanced radiosensitivity, particularly under fractionated IR. AZD6738 and olaparib also showed notable sensitizing effects during fractionated IR. The combination impaired DNA double-strand break repair and disrupted cell cycle recovery, ultimately increasing cancer cell death. These findings highlight the potential of DDR inhibitors to overcome radioresistance when integrated with clinically relevant fractionation schedules [32].

5.2. Synergy and synthetic lethality

Combining PARP inhibitors (PARPi) with MYC blockade results in synthetic lethality, independent of BRCA mutation status in triple-negative breast cancer (TNBC). Specifically, the CDK inhibitor dinaciclib downregulates MYC and RAD51, impairing homologous recombination repair and sensitizing resistant TNBC cells to the PARPi niraparib. This synergistic effect was also observed across other MYC-driven cancers, highlighting the therapeutic potential of this combination in overcoming resistance mechanisms.[33].

6. Clinical Trials Landscape

Clinical Study (Olaparib in BRCA Mutation Carriers):

In Phase 1 clinical trial evaluated the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of olaparib, a potent oral PARP inhibitor, in 60 patients with advanced solid tumors. The study included a subgroup of 22 BRCA1/2 mutation carriers and one additional patient had a strong family history of BRCA-associated cancers but declined genetic testing. The patient population had a mean age of 54.8 years (range 19–82 years), with 67% female and 33% male participants. Many patients were heavily pretreated, with 53% having received four or more prior lines of therapy. In terms of efficacy, antitumor activity was observed exclusively in patients with BRCA1 or BRCA2 mutations. Among 19 evaluable BRCA mutation carriers with breast, ovarian, or prostate cancer, 12 patients (63%) experienced clinical benefit, including 9 objective responses (partial or complete responses) and 3 cases of prolonged disease stabilization for four months or longer. Specific responses included a complete remission in a patient with BRCA2-associated breast cancer, partial responses in eight patients with ovarian cancer, and a significant PSA decline and resolution of bone metastases in a BRCA2-mutated prostate cancer patient. The study concluded that olaparib is well tolerated, has a favourable pharmacokinetic and pharmacodynamic profile, and exhibits promising antitumor activity in patients with BRCA-associated cancers, supporting the concept of synthetic lethality as a targeted therapeutic strategy.

Table No. 1. Summary of the Clinical Study on Olaparib [34].

Study Type	**Phase 1 Clinical Trial**
Drug Studied	Olaparib (AZD2281) – Oral PARP inhibitor
Participants	60 patients with advanced solid tumors
BRCA Mutation Carriers	22 confirmed BRCA1/2 mutation carriers + 1 with strong BRCA family history
Cancer Types	Ovarian, breast, prostate, and others
Main Objective	Assess safety, dose-limiting toxicity, pharmacokinetics, pharmacodynamics, and antitumor activity
Key Results	Antitumor activity observed only in BRCA mutation carriers (ovarian,breast, prostate cancer); 12/19 showed clinical benefit
Adverse Effects	Mostly mild (grade 1–2): nausea (32%), fatigue (30%), vomiting (20%)
Dose Range Tested	10 mg daily → 600 mg twice daily (continuous dosing)

Maximum Tolerated Dose (MTD)	400 mg twice daily
Conclusion	Olaparib is well-tolerated, shows synthetic lethality in BRCA-mutated tumors, and avoids toxicity of conventional chemotherapy

7. Challenges and Future Directions

7.1 Identification of Reliable Predictive Biomarkers

The lack of consistent and clinically validated biomarkers limits the ability to predict patient response to DDR-targeted therapies. While BRCA1/2 mutations are established markers for PARP inhibitor sensitivity, other markers like genomic instability scores, HRD scores, and expression levels of repair proteins require standardization and validation across clinical settings.[35] Developing a robust biomarker panel is critical for patient stratification and treatment optimization.[36]

7.2. Novel DDR Targets (e.g., POLθ, RAD51 inhibitors)

Beyond traditional targets like PARP, new DDR components such as DNA polymerase theta (POLθ) and RAD51 are emerging as promising candidates, particularly for tumors with homologous recombination deficiency. POLθ inhibitors exploit synthetic lethality in BRCA-mutated cancers, while RAD51 inhibitors can impair HR activity and sensitize tumors to genotoxic agents. However, these agents are still under preclinical and early clinical development [37].

7.3. Personalized Medicine and DDR Pathway Profiling

Integrating personalized medicine with DDR pathway profiling enables tailored treatment approaches based on individual tumor repair capacity [38]. Comprehensive genomic and transcriptomic analyses can identify unique DDR deficiencies, guide therapy selection, and reduce unnecessary toxicity. This precision strategy is gaining momentum with the rise of next-generation sequencing and functional assays in clinical oncology [39].

8. Conclusion

Pharmacological targeting of DDR pathways holds transformative potential in breast cancer therapy, particularly for HR-deficient and triple-negative subtypes. The expanding repertoire of DDR inhibitors and combination strategies heralds a new era of personalized oncology. However, challenges such as resistance and optimal patient selection remain. Continued translational research and clinical validation are essential to realize the full promise of DDR-targeted treatments in breast cancer.

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