Review

Targeting Cellular DNA Damage Response in Cancer and Bacterial Infections: Current Progress, Challenges, and Opportunities

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Abstract: Effective cancer treatment remains challenging due to the genomic instability of tumors and the frequent emergence of resistance. Traditional approaches such as radiotherapy, chemotherapy, and immunotherapy face limitations in addressing tumor heterogeneity and resistance mechanisms. Targeting the DNA damage response (DDR) pathway has emerged as an innovative strategy, either as monotherapy or in combination with conventional treatments. DDR-targeted therapies, including poly-ADP-ribose polymerase (PARP) inhibitors, have shown promise in reducing tumor growth and enhancing patient outcomes. Emerging targets such as ATM, ATR, CHK1/2, WRN, and PARG, coupled with cutting-edge technologies like CRISPR and proteolysis-targeting chimeras (PROTACs), have opened new avenues for precise and effective cancer treatment. Furthermore, combining DDR inhibitors with established therapies, such as immune checkpoint inhibitors, has demonstrated synergistic benefits, improving therapeutic efficacy and overcoming resistance. Beyond cancer, DDR inhibitors also offer the potential to combat bacterial pathogens by exploiting vulnerabilities in microbial DNA repair systems. This review focuses on the major advantages, challenges, and future directions of DDR-targeted therapies in cancer and bacterial infections. We also discuss the integration of these therapies with traditional approaches, highlighting their potential to enhance therapeutic outcomes across diverse applications.

Keywords: DNA damage response; drug targets; cancer therapy; bacterial infection treatment; challenges and opportunities

1. Introduction

The exploration of DNA damage has evolved significantly since the 1950s, beginning with early efforts to quantify and understand the effects of radiation on DNA integrity. In 1959, Mole and Temple utilized DNA content in the small intestine to measure radiation-induced cellular damage, establishing a correlation between radiation dose and DNA recovery [1]. This work laid the foundation for understanding DNA damage as a quantifiable response to external agents. Around the same time, Lerman and Tolmach explored the impact of ultraviolet light and heat on pneumococcal DNA, highlighting the susceptibility of DNA to various degradative treatments and proposing that DNA's genetic functionality is tied to its molecular integrity [2]. By 1960, Lett and Stacey linked DNA's molecular weight and viscosity as indicators of damage severity, showing how physical and chemical alterations in DNA could be systematically assessed using light scattering and viscosity measurements [3]. These foundational studies have paved the way for modern DNA damage detection and therapeutic interventions through the manipulation of DNA repair mechanisms.

DNA damage is a complex biological phenomenon that can be triggered by both endogenous metabolic processes and exogenous damaging agents. Endogenous DNA damage is primarily caused by internal cellular processes, such as oxidative stress, hydrolysis, and reactive metabolic byproducts, leading to various lesions and mutations [4]. Reactive oxygen species (ROS) generated during metabolism play a significant role, causing oxidative DNA damage, such as 8-hydroxydeoxyguanosine (8-OHdG), accumulating in both nuclear and

mitochondrial DNA [5]. Additionally, lipid peroxidation products, aldehydes, and S-adenosylmethionine can induce mutagenic lesions like etheno adducts, which are more common in tissues with higher metabolic activity, such as the brain [6]. Exogenous sources, such as ionizing radiation (IR), ultraviolet (UV) light, and carcinogenic chemicals, can cause more severe damage like double-strand breaks (DSBs), DNA-protein cross-links, and chemical adducts [7,8]. Hydroxyl radicals also generate specific lesions like 2,5-diaminoimidazolone, which interferes with DNA repair pathways, further increasing mutation rates [9].

The DNA damage response (DDR) is a general term for a series of cellular response mechanisms to DNA damage. The DDR pathway plays a pivotal role in preserving genomic stability and preventing the onset of various diseases. It is responsible for sensing, signaling, and repairing damaged DNA in order to maintain the stability of the genome [10]. In normal cells, the DDR machinery is essential for preventing mutations and maintaining cell function. For instance, ATM protein kinases play a central role in DSBs response and its absence causes cellular defects in DDR, cell cycle control, and telomere maintenance, thereby increasing cancer susceptibility [11]. Additionally, the cellular DDR mechanism can help prevent or slow down tumor development, thus serving as a potential anti-cancer mechanism [12]. For example, studies have found that DDR-related features in renal cell carcinoma (RCC) are closely related to the clinical stage and prognosis of tumors, suggesting the potential use of DDR in cancer treatment [13].

In recent years, much attention has been paid to the study of DDR as a target for anticancer therapies. By inhibiting key components of the DDR pathway in cancer cells, it is possible to make these cells more sensitive to chemotherapy or radiotherapy, or even to induce cell death without the use of conventional therapies. DDR-targeted drugs represented by poly-ADP-ribose polymerase (PARP) inhibitors have been successful in the clinic, and this progress has inspired further exploration of other DDR-related targets [14,15].

In bacteria and fungi, the DDR is critical for their survival and pathogenicity, especially under stress conditions like those imposed by host immune defenses. For example, pathogenic bacteria like *Salmonella* utilize DDR mechanisms to evade host immune responses, facilitating their intracellular survival and persistence [16]. Conversely, the toxin listeriolysin O (LLO) produced by *Listeria monocytogenes* suppresses the host's DDR by degrading key DDR proteins such as Mre11, thereby enhancing bacterial replication and infection efficiency [17]. Therefore, targeting DDR mechanisms in microbial pathogens offers a promising strategy for developing antifungal and antibacterial drugs. This approach exploits vulnerabilities in the DNA repair process of these pathogens, potentially enhancing the efficacy of existing treatments and counteracting drug resistance. Inhibitors of DNA topoisomerases has been shown to induce lethal DNA breaks in pathogens like *Candida. Albicans* [18], highlighting their potential for antifungal applications. Thus, DDR inhibitors have also emerged as a novel strategy to combat bacterial pathogens, particularly antibiotic-resistant strains.

This review provides a comprehensive overview of the DDR pathway, including its role in cancer and bacterial survival. We review the recent advancements in DDR-targeted therapies, and the challenges and opportunities in integrating DDR inhibitors into clinical applications for cancer treatment and combating antimicrobial resistance.

2. The DDR Pathway

Depending on the type of DNA damage and the cell cycle phase, the DDR pathway employs specific repair mechanisms, including direct lesion reversal, mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), non-homologous end-joining (NHEJ), homologous recombination (HR), the Fanconi anemia (FA) pathway, and the trans-lesion synthesis mechanism [19].

When DSBs occur, histone H2AX is phosphorylated by the kinases ATM, ATR, or DNA-PKcs forming γH2AX, which marks the site of DNA damage and recruits other repair proteins to the damaged region [20–23]. When BRCA1 is recruited, it interacts with CtIP to facilitate DNA end resection through direct interaction with PALB2, recruiting BRCA2 and RAD51 to the site of damage to mediate homologous DNA strand exchange, thereby directing the high-fidelity HR repair pathway (Figure 1) [24]. In contrast, the recruitment of 53BP1 protects DSB from resection [25]. Then, the Ku70/80 complex also binds to DSBs, guiding DSBs to be repaired via the NHEJ pathway primarily in the G1 phase (Figure 1) [26]. In the S and G2 phases, BRCA1 suppresses the activity of 53BP1, alleviating its inhibitory effect on DNA end resection, thereby shifting the repair pathway preference toward HR. Differently, members of the PARP family, such as PARP1 and PARP2, are activated mainly by single-strand breaks (SSBs) (Figure 1). Upon activation, these enzymes synthesize poly ADP-ribose chains at the damage sites, recruiting DDR-associated factors to the breaks [27].

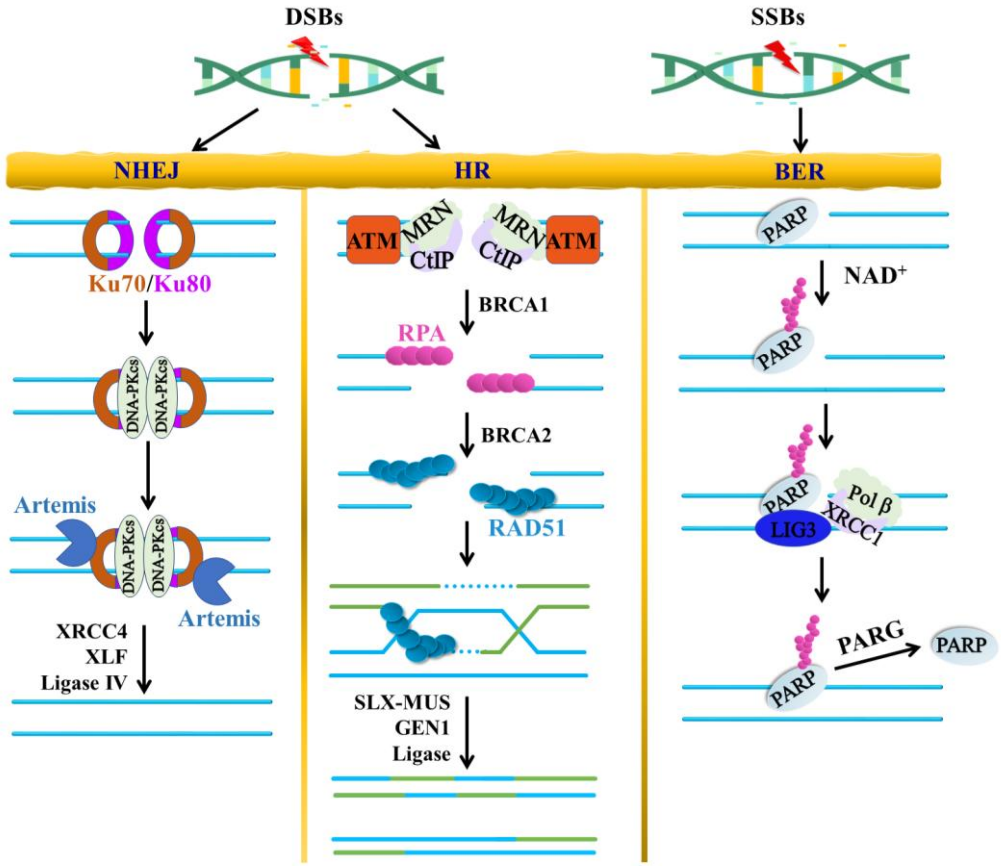

Figure 1. Mechanisms of DNA damage repair via the NHEJ, HR and BER pathways.

Once DNA damage is recognized, signal transduction mechanisms are activated to ensure an appropriate cellular response. Key nodes in this signaling include kinases such as DNA-PKcs, ATM, and ATR. These kinases phosphorylate downstream effectors, such as CHK1, CHK2, and p53, to initiate cell cycle arrest, DNA repair, or apoptosis [28–30]. For G1 phase response, ATM activates CHK2, which in turn activates p53. p53 inhibits the Cyclin E/CDK2 complex, preventing the cell from entering the S phase, and allowing time to repair DNA damage before replication begins [31]. For G2 phase response, ATR activates CHK1, which inhibits the Cyclin B/CDK1 complex, blocking entry into mitosis [29]. The subsequent phosphorylation of p53 by CHK1 or CHK2 induces DNA repair, cell cycle arrest, apoptosis, or cellular senescence. These processes prevent damaged cells from dividing further, thereby reducing the risk of mutation accumulation [31]. Together, the DDR pathway acts as the first line of defense in maintaining genomic stability and preventing the accumulation of mutations that can lead to diseases such as cancer.

3. Emerging DDR Targets in Cancer Therapies

The dysfunction of DDR can lead to increased genomic instability, facilitating cancer progression and metastasis. Mutations in DDR-related genes are commonly observed across various cancer types. DDR pathways also shape the tumor microenvironment, particularly through receptors such as discoidin domain receptors, which are linked to cancer cell proliferation and metastasis [32,33].

PARP inhibitors were the first approved cancer drugs that specifically targeted DDR. These molecules can bind to the NAD^+ binding pocket of PARP1 and PARP2, resulting in irreversible DNA-PARP association and the accumulation of DSBs. This ultimately triggers cell death in cells with HR repair deficiencies, such as those with BRCA1/2 mutations [15]. Olaparib was the first PARP inhibitor developed based on the concept of synthetic lethality, designed for the treatment of BRCA-mutated breast and ovarian cancers [34]. This breakthrough sparked a wave of interest in the synthetic lethality approach for new drug development. As a result, PARP inhibitors achieved significant success in drug research, with multiple PARP inhibitors now approved worldwide, including Fuzuloparib [35], Pamiparib [36], and AKEEGA™ (Niraparib + Abiraterone Acetate) [37].

While current PARP inhibitors have achieved significant clinical success, researchers continue to explore more efficient and selective molecules. Recent developments in DDR-targeted therapies highlight promising

advancements in drug discovery and clinical applications. For example, Senaparib, developed in collaboration between Junshi Biosciences and Impact Therapeutics, has recently had its new drug application accepted by the Center for Drug Evaluation (CDE) for maintenance therapy in patients with stage III-IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer [38].

In addition to well-established DDR pathway targets like PARP, ATM, ATR, WEE1, CHK1/2, and DNA-PKcs, a growing number of targets are being explored for cancer treatment. These include WRN, PARP7, PARG, USP1, POLQ, MUS81, Ku70/80, STAG1/2, KIF18A, MAT2A, PKMYT1, Pol θ [39] and PD-L1 [40]. Table 1 lists the clinical status of new potential targets in recent years.

Table 1. Clinical Progress of Emerging Targeted Drugs.

Target	Drugs	Clinical Trail	Indication	Identifier
WRN	HRO-761	Phase I	MSI-H or dMMR advanced unresectable or metastatic solid tumors, including colorectal cancers	NCT05838768
	RO-7589831	Phase I	Advanced solid tumors	NCT06004245
	IDE275	IND clearance	MSI-H solid tumors	-
	ISM-9342A	Preclinical	MSI-H cancers	-
PARP7	RBN-2397	Phase II	Advanced squamous non-small cell lung carcinoma	NCT05127590
	BY101921	Phase I	Malignant solid tumors	CTR20240141
	JBA-26766	CDE clearance	Solid Tumors	CXHL2300348 CXHL2300349
	(S)-XY-05	Preclinical	Tumors	-
PARG	IDE-161	Phase I	Advanced or metastatic solid tumors Breast cancer Ovarian cancer Pancreas cancer	NCT05787587
	ETX-19477	Phase I	Advanced or metastatic solid tumors Breast cancer Ovarian cancer Prostate cancer	NCT06395519
	DAT-2645	Phase I	Solid cancers BRCA mutation HRD cancer Breast cancer Prostate cancer Colorectal cancer Pancreatic cancer Endometrial cancer Gastric cancer Advanced cancer Metastatic solid tumors	NCT06614751
	JA2131	Preclinical	Tumors	-
	CC-006	Preclinical	Solid tumors	-
USP1	HSK39775	Phase I/II	Advanced solid tumors	NCT06314373 CTR20240645
	SIM-0501	Phase I	Advanced solid tumors	NCT06331559 CTR20240500
	ISM-3091	Phase I	Advanced solid tumors	NCT05932862
	KSQ-4279	Phase I	Advanced solid tumors	-
	APL-2302	IND clearance	Advanced solid tumors	-
	IMP-13	IND application	Tumors	-
	I-138	Preclinical	Tumors	-

POLQ	ART4215	Phase II	Advanced cancer Metastatic cancer Breast cancer	NCT04991480
	ART-6043	Phase I/IIa	Advanced solid tumor Metastatic solid tumor	NCT05898399
	GSK4524101	Phase I/II	Neoplasms	NCT06077877
	SIM-0508	Phase I	Advanced solid tumors	NCT06686745 CTR20244105
	RP-3467	Phase I	Advanced solid tumor	NCT06560632
	MOMA-313	Phase I	Advanced solid tumor Metastatic solid tumor Prostate cancer Pancreas cancer	NCT06545942
	SYN818	Phase I	Advanced solid tumor Metastatic solid tumor Ovarian cancer Breast cancer	NCT06666270
KIF18A	VLS-1488	Phase I/II	Advanced solid tumor High grade serous adenocarcinoma of ovary Squamous non-small-cell lung cancer Triple negative breast cancer Gastric adenocarcinoma Colorectal adenocarcinoma Esophageal squamous cell carcinoma Esophageal adenocarcinoma Gastroesophageal junction adenocarcinoma Transitional cell carcinoma of bladder Head and neck squamous cell carcinoma Ovarian carcinosarcoma Uterine carcinosarcoma Uterine serous carcinoma Endometrium cancer Chromosomal instability	NCT05902988
	Sovilnesib	Phase I	High grade serous adenocarcinoma of ovary Fallopian tube cancer Primary peritoneal carcinoma Chromosomal instability	NCT06084416
			Advanced solid tumors	NCT04293094
	GH2616	Phase I	Advanced solid tumors	NCT06329206 CTR20240250
	GenSci122	Phase I	Advanced solid tumors	NCT06772415 CTR20244917
	AM-1882	Preclinical	Breast cancer Ovarian cancer.	-
	ATX-210201	Preclinical	Tumors	-
MAT2A	IDE-397	Phase I/II	Advanced MTAP [1]-null solid tumors	NCT05975073
		Phase I	Advanced solid tumors	NCT04794699
	S095033	Phase I/II	Advanced or metastatic esophageal squamous cell carcinoma (ESCC)	NCT05312372
	S095035	Phase I	MTAP-deleted solid tumors	NCT06188702
	ISM3412	Phase I	Locally advanced/metastatic solid tumors	NCT06414460 CTR20243737

	SYH2039	Phase I	Advanced or metastatic MTAP-deleted solid tumors	NCT06568614
			Advanced tumors	CTR20242626
	SCR-7952	Preclinical	Tumors	-
	AGI-25696	Preclinical	Tumors	-
PKMYT1	RP-6306	Phase II	Breast cancer	NCT05601440
			Advanced Cancer	NCT05605509
		Phase I	Adult solid tumor	NCT05147272 NCT04855656 NCT05147350
	XL-495	Phase I	Solid cancers Solid tumor cancer Solid tumor malignancy Urothelial cancer (urinary bladder, ureters, or renal pelvis cancer) Metastatic solid tumor Locally advanced solid tumor Urothelial cancer of renal pelvis	NCT06630247
	ZM-2322	Preclinical	Breast cancer	-
	ALVX-A	Preclinical	Tumors	-
PKMYT1 × WEE1	ACR-2316	Phase I	Specific advanced solid tumors	NCT06667141
POLQ × TRPV4	GSK-101	Phase I	Solid tumors	-
PARP7 × PARP12	Cpd36	Preclinical	Tumors	-
USP1-UAF1	ML323	Preclinical	Non-small cell lung cancer	-
PARP × POLQ	SMU-CX1	Preclinical	SARS-CoV-2	-

[1] MTAP: Methylthioadenosine Phosphorylase.

3.1. Werner Syndrome Helicase (WRN)

WRN is an ATP-dependent DNA helicase in the RecQ family, playing a critical role in maintaining genomic stability, DNA damage repair, and cellular senescence [41]. It possesses dual helicase and exonuclease domains, enabling the unwinding of double-stranded DNA or RNA to facilitate processes like DNA replication, repair, transcription, recombination, and telomere maintenance [42]. Meanwhile, its exonuclease activity trims irregular structures at DSB ends, facilitating their ligation [43]. Mutations in the WRN gene cause Werner syndrome, a progeroid syndrome characterized by accelerated cellular aging, genomic instability, and increased susceptibility to various cancers [43]. Additionally, WRN also represents a promising therapeutic target for microsatellite instability-high (MSI-H) colorectal cancers, which often exhibit poor responses to conventional treatments such as chemotherapy [44]. The potent and selective allosteric WRN inhibitor HRO761, which causes DNA damage and suppresses tumor cell growth in MSI cancer cells [45], is currently in Phase I clinical trial (NCT05838768) in patients with MSI colorectal and other MSI solid tumors. Other WRN inhibitors are also under development, aiming to enhance antitumor efficacy and overcome the limitations of traditional therapies.

3.2. Poly (ADP-Ribose) Polymerase 7

PARP7, also known as TCDD-inducible poly-ADP-ribose polymerase (TIPARP), is a member of the PARP family. Its primary function involves mono-ADP-ribosylation, a process crucial for cellular responses to environmental stress, transcriptional regulation, immune responses, and DDR [46]. Unlike PARP1, which generates long ADP-ribose chains, PARP7 attaches a single ADP-ribose moiety to target proteins. This modification alters the function or stability of labeled proteins, thereby influencing various cellular pathways including lipid metabolism and transcriptional regulation [47], estrogen receptor α signaling [48], and the type I interferon response in cancer cells [49]. The selective PARP7 inhibitor BN-2397 has been shown to reduce tumor proliferation by stabilizing α-tubulin and enhancing immune-mediated responses when combined with chemotherapeutics like paclitaxel [50]. Clinical investigations (Phase I) revealed its tolerability and biological activity across advanced solid tumors, with noted adaptive immune induction, $CD8^+$ T cell infiltration, and immune checkpoint upregulation, supporting its synergy with immune checkpoint inhibitors like pembrolizumab [51]. In

addition, the orally bioavailable PARP7 inhibitor JAB-26766 displays synergistic effects when combined with STING agonists, enhancing antitumor immunity through increased CXCL10 secretion and tumor STAT1 phosphorylation [52]. These findings underscore the therapeutic promise of PARP7 inhibitors in overcoming immune suppression in tumors.

3.3. Poly (ADP-Ribose) Glycohydrolase (PARG)

PARG is responsible for the hydrolysis of poly (ADP-ribose) chains, breaking them down into shorter fragments or monomers of ADP-ribose. It ensures that PAR signaling is tightly controlled, facilitating DNA repair, chromatin remodeling, stress response, and energy homeostasis. Failure to degrade poly (ADP-ribose) results in embryonic lethality and increased sensitivity to genotoxic stress [53]. Therefore, targeting PARG has emerged as a promising cancer therapy strategy, particularly for tumors with homologous recombination deficiency (HRD) or those resistant to PARP inhibitors. IDE161, a small-molecule PARG inhibitor, is being developed for HRD solid tumors, including BRCA1/2-mutated cancers. Preliminary results of phase I trials indicate promising pharmacodynamic activity and tumor regression of HRD-positive cancers, such as ovarian and breast cancer [54]. In addition, another PARG inhibitor, ETX-19477, is currently in Phase 1 trials for advanced solid malignancies [55].

3.4. Ubiquitin-Specific Protease 1 (USP1)

FA pathway is a crucial DNA repair mechanism that is regulated by various proteins and enzymes. One such enzyme is the deubiquitinase USP1, which plays a critical role in the FA pathway by deubiquitinating key proteins involved in DNA repair processes [56]. For example, USP1 has been shown to regulate the monoubiquitination of proliferating cell nuclear antigen (PCNA), a DNA replication factor, to prevent error-prone translesion synthesis during DNA replication [57]. Additionally, USP1 is involved in the deubiquitination of the Fanconi anemia D2 protein (FANCD2), a critical protein in DNA crosslink repair [58]. Moreover, USP1 also deubiquitinates inhibitors of DNA binding (ID) proteins to preserve stem-like states in osteosarcoma, indicating its potential as a target for differentiation therapies [59]. Small-molecule inhibitors of USP1 have demonstrated promising therapeutic potential in leukemia treatment [60]. Additionally, the selective inhibitor of the USP1-UAF1 complex ML323 has been demonstrated to potentiate cisplatin cytotoxicity in non-small cell lung cancer and osteosarcoma cells [61]. Furthermore, the selective USP1 inhibitor HSK39775 demonstrates strong anti-proliferative effects against BRCA-mutant cancer cell lines. In a triple-negative breast cancer model, the combination of HSK39775 and PARP inhibitors such as olaparib produces synergistic effects, yielding up to 89% tumor growth inhibition [61].

3.5. DNA Polymerase Theta (POLQ/Polθ)

POLQ or Polθ is a critical enzyme in the microhomology-mediated end-joining (MMEJ) pathway. It has been suggested that targeting POLQ can be an effective treatment to cancers defective in HR [62]. POLQ is highly expressed in several malignancies, such as breast, cervical, and pancreatic cancers, and is associated with genomic instability and therapeutic resistance [63]. Inhibiting POLQ has emerged as a potential therapeutic strategy, particularly for HR-deficient cancers such as BRCA-mutated tumors [64]. POLQ inhibition has been shown to activate the cGAS-STING pathway, enhancing immune infiltration and $CD8^+$ T-cell activation, thereby boosting antitumor immunity in pancreatic ductal adenocarcinoma [65]. In ongoing Phase I/II trials, the orally bioavailable POLQ inhibitor ART4215 is being evaluated as a monotherapy and in combination with PARP inhibitors like talazoparib and niraparib [66].

3.6. Methyl Methanesulfonate and Ultraviolet Sensitive Gene Clone 81 (MUS81)

MUS81, a DNA endonuclease, is essential for processing replication forks and repairing DNA crosslinks, especially under conditions of DNA damage or replication stress [67]. In human cells, MUS81-EME1/2 cooperate with the SLX1-SLX4 to form a MUS-SLX complex to process Holliday junction (HJ), a DNA intermediate formed during HR and DNA repair (Figure 1) [68]. In BRCA2-deficient cancer cells, MUS81's cleavage activity facilitates chromosome segregation and adaptation to replication stress [69]. It has been demonstrated that the expression levels of MUS81 and EME1 are up-regulated in patient gastric cancer cells [70], whereas reducing MUS81 has been shown to enhance the sensitivity of ovarian cancer cells to chemotherapeutic agents, such as Olaparib [71]. Therefore, MUS81 is considered a potential novel target for cancer therapy. We previously performed fluorescence resonance energy transfer (FRET)-based high throughput screening and identified dyngo-4a as a potent small-molecule inhibitor of MUS81-EME1 and MUS81-EME2 complexes, with IC_{50} values of 0.57 μM and 2.90 μM,

respectively [72]. Cell-based studies indicate that dyngo-4a sensitizes MDA-MB-231 and A549 cells to DNA-damaging agents such as bleomycin and cisplatin, suggesting its potential in cancer treatments [72].

3.7. Ku70/80

The Ku70/80 protein complex is a key player in DSB repair via the NHEJ pathway (Figure 1), representing a promising therapeutic target. Overexpression of Ku proteins has been associated with radioresistance across various cancer types [73–76]. Conversely, lower Ku protein expression has been linked to improved responses to radiotherapy [77]. In a previous study, we identified UMI-77 as an effective inhibitor that disrupts the interaction between Ku and DNA (IC_{50} ~2.3 μM) and impairs bleomycin-induced DNA damage repair in HeLa cells. Cell-based and animal studies demonstrated that UMI-77 significantly sensitizes cancer cell to the DNA-damaging agents, enhancing the chemotherapeutic efficacy of etoposide with little adverse physiological effects [78].

3.8. Stromal Antigen 1 and 2

Stromal antigen 1 and 2 (STAG1 and STAG2) are mutually exclusive components of the cohesin complex, essential for maintaining centromeric and telomeric cohesion. In addition, STAG2 plays a key role in promoting HR repair by facilitating the recruitment of BRCA1 to chromatin [79]. Mutations in STAG2 are commonly observed in various cancers [80]. As STAG1 can partially compensate for the functions of STAG2, its inhibition induces synthetic lethality in STAG2-deficient cancer cells both in vitro and in vivo [81,82]. The recently identified inhibitor of STAG1/2, KPT-6566, has been shown to effectively impair DNA repair and exhibits synergy with the PARP inhibitor Olaparib or the NHEJ inhibitor UMI-77 in HeLa and HepG2 cells [83], demonstrating the potential of STAG1/2 as promising therapeutic targets in cancer treatment.

4. DDR Inhibitors in the Treatment of Bacterial Pathogens

Under environmental stressors such as radiation, chemicals, or antibiotics, the DDR pathway recognizes and repairs DNA damage, maintaining genomic integrity. DNA-damaging antibiotics are designed to kill bacteria by inducing DNA damages. However, these agents often trigger the bacterial SOS response, a repair mechanism regulated by the RecA protein, which promotes bacteria survival and contributes to antibiotic resistance [84].

4.1. RuvAB Inhibitors

RuvAB is a bacterial complex composed of the RuvA and the RuvB proteins, which play a critical role in resolving the HJ DNA intermediate [85]. The RuvA homotetramer specifically binds to the HJ core and recruits the RuvB hexamer to the HJ arms. RuvB acts as a motor protein, driving HJ branch migration in an ATP-dependent manner [86]. Our group identified three small-molecule inhibitors of *P. aeruginosa* RuvAB: Corilagin, Bardoxolone methyl, and SKQ1, with IC_{50} values of 0.40 μM, 0.38 μM, and 4.64 μM, respectively [87]. Corilagin inhibits RuvB's ATPase activity by binding near its catalytic ATP-binding domain, while BM and SKQ1 disrupt RuvA's interaction with HJ DNA. In plate-based anti-bacterial assays, these compounds sensitize *P. aeruginosa* to UV radiation [87], underscoring the potential of RuvAB as promising target for combating bacterial infections.

4.2. RecG Inhibitors

RecG belongs to the Superfamily-2 helicase and plays an important role in replication fork processing and DNA repair [88]. In addition to RuvAB, RecG also participates in the processing of HJ intermediate [89]. It has been shown that the inactivation of either RecG or RuvAB individually causes only mild sensitivity to UV irradiation in bacterial cells [90]. However, when both RecG and RuvAB are simultaneously inactivated, the sensitivity is markedly enhanced [90–92]. In a previous work, we identified two small-molecule RecG inhibitors of *P. aeruginosa*, Ebselen, and TPI-1, with IC_{50} values of 0.31 μM and 1.16 μM, respectively. Notably, these RecG inhibitors exhibit significant synergistic effects when combined with RuvAB inhibitors such as Corilagin and Bardoxolone methyl, enhancing the sensitivity of *P. aeruginosa* to UV radiation and ciprofloxacin [93].

5. Emerging Strategies to Target DDR Pathway

Novel technologies and biological insights have significantly expanded strategies for targeting DDR and enhanced drug screening efficiency. Innovations such as CRISPR gene-editing technology, proteolysis-targeting chimeras (PROTACs), and rational drug design. These methods have enabled more efficient identification of DDR targets and introduced new possibilities for drug development. Integrating these technologies will further enhance the precision and efficiency of DDR-targeted therapies.

5.1. Applications of CRISPR-Based Gene Editing

CRISPR technology, as a revolutionary gene-editing tool, has profoundly advanced biomedical research. In the DDR field, CRISPR is invaluable for identifying new DDR targets and facilitating drug development, particularly in synthetic lethality strategies, target validation, and novel drug screening. CRISPR-Cas9 gene-editing technology enables systematic knockout or mutation of DDR-related genes to observe their impact on cell survival and DDR functionality [94]. This approach rapidly identifies novel DDR targets and validates their roles in cancer. For instance, Clements et al. used whole-genome CRISPR screening to identify HUWE1 (a ubiquitin ligase) and KAT5 (a histone acetyltransferase) as regulators of PARP inhibitors resistance in BRCA2-deficient cells. These factors significantly reverse PARP inhibitors' sensitivity in BRCA2-deficient contexts [95]. In addition, CRISPR screening has identified PARP1 mutants that confer PARP inhibitors resistance both in vitro and in vivo [96]. A study by Choudhury et al. developed a CRISPR-programmable demethylase tool using Ten-Eleven Translocation (TET) dioxygenase1 (TET1CD) to demethylate the BRCA1 promoter region, reactivate gene expression, and restore BRCA1 function in breast and cervical cancers [97]. In addition, genome-wide CRISPR/Cas9 screening revealed that EXO1 and FEN1 are the major synthetic lethal interactors in PARG-deficient cells [98].

5.2. Proteolysis Targeting Chimeras

PROTACs represents a novel drug development strategy that induces protein degradation rather than merely inhibiting activity. Compared to traditional small-molecule inhibitors, PROTACs exhibit catalytic activity, enabling multiple rounds of target degradation, with greater selectivity and lower resistance risk [99]. PROTACs bridge target proteins and ubiquitin ligases, leading to target protein ubiquitination and degradation via the proteasome. These bifunctional molecules consist of a target-binding ligand that interacts with the protein of interest and an E3 ligase-binding ligand, connected by a linker [99]. In the DDR field, PROTACs have shown immense potential. For example, in MSI cells, PROTAC-mediated WRN degradation induces significant cytotoxicity and DNA damage, while sparing MSS cells, highlighting its therapeutic potential for MSI cancers [100]. Based on reported ATR inhibitors, Alfayomy et al. designed PROTACs targeting ATR, with PROTAC 42i reducing ATR levels to 40% of untreated cells at a concentration of 500 nM, without hitting related kinases ATM and DNA-PKcs [101]. Moreover, Zheng et al. synthesized dual-target PROTACs against EGFR and PARP, validating their effectiveness in cancer cells and providing innovative solutions for cancer therapy [102]. Collectively, PROTAC technology offers a flexible and efficient approach to protein degradation, demonstrating significant promise in DDR-target applications.

5.3. Artificial Intelligence in Drug Discovery

Artificial intelligence (AI) technologies, such as deep learning, machine learning, and AlphaFold, can rapidly process and analyze vast amounts of biomedical data to discover potential drug targets and accelerate drug discovery and optimization [103]. For example, Zhou et al. employed AI to discover a novel activator, H3, targeting the p53 mutant (Y220C) [104], which has been a great challenge in drug development. In addition, Subramanian et al. used AI to identify a completely new therapeutic target for liposarcoma in less than few months [105]. Furthermore, TumFlow, as a novel AI model, has shown significant potential in generating new anticancer molecules [106]. Overall, AI-driven drug discovery methods surpass traditional drug discovery approaches and are expected to have a significant impact on tumor drug development and repurposing.

6. Challenges in Clinical Research and Drug Development

While DDR targeted therapies have shown immense potential in cancer treatment—particularly through the success of synthetic lethality strategies—the transition from laboratory research to clinical application still faces numerous challenges. These challenges include addressing issues related to drug safety and efficacy, tumor heterogeneity, resistance, and individualized patient differences.

6.1. Drug Resistance

Drug resistance is a major obstacle in the clinical application of DDR-targeted therapies. For example, PARP inhibitors are highly effective in treating breast and ovarian cancers with BRCA1/2 mutations but often lose effectiveness due to resistance [15]. First, some cancer cells restore BRCA1/2 function through secondary mutations, enabling HR repair and negating the synthetic lethality mechanism of PARP inhibitors [107]. Second, when a single repair pathway is blocked, cancer cells may rely on other compensatory pathways instead to repair

DNA damage, potentially leading to drug resistance. For example, it has been shown that POLQ is up-regulated in subgroups of cancers associated with HR deficiency [64]. Third, upregulation of efflux proteins (e.g., P-glycoprotein) reduces intracellular drug concentration, diminishing efficacy [108]. Finally, mutations in DDR-related proteins (e.g., PARP, ATR, CHK1) can alter their activity, making drugs less effective. To overcome drug resistance, the following strategies can be employed: (i) Combination therapies: utilizing combination therapies that target compensatory repair pathways or introducing alternative therapies can prevent or delay the emergence of resistance mechanisms; (ii) Biomarker-driven approaches: biomarkers can be used to predict and monitor the onset of drug resistance, enabling timely adjustments in therapy; (iii) Next-generation inhibitors: developing inhibitors targeting specific compensatory repair pathways can provide more effective treatment options in resistant cancer cells.

6.2. Tumor Heterogeneity

Tumor heterogeneity complicates DDR-targeted therapy by creating variability in drug sensitivity and treatment outcomes. Genetic and phenotypic differences among cancer cells within the same tumor lead to varied dependencies on DDR pathways. For example, some cells rely on HR repair, while others depend on NHEJ, making it challenging for a single therapy to target all cells. Moreover, factors in the tumor microenvironment, such as angiogenesis, immune infiltration, and oxygen availability, influence drug distribution and efficacy, further complicating treatment [109]. Therefore, early identification of heterogeneity and adjustments to therapeutic strategies are critical for improving outcomes. To address tumor heterogeneity, the following strategies can be implemented: (i) Using advanced technologies such as single-cell sequencing and spatial transcriptomics to map tumor heterogeneity allows for more accurate identification of DDR dependencies and the potential for adaptive treatment strategies; (ii) Incorporating real-time monitoring tools to track tumor responses and dynamically adjust treatment plans based on evolving tumor characteristics; (iii) Developing inhibitors targeting multiple DDR pathways or employing drug combinations can help overcome heterogeneity and address shifts in repair dependency within the tumor.

6.3. Drug Selectivity and Side Effects

Although DDR inhibitors aim to selectively target tumor cells with DDR defects, achieving this balance remains a challenge. DDR pathways are essential in normal cells, and inhibiting key proteins can lead to DNA damage accumulation in healthy tissues, causing side effects such as nausea, anemia, and fatigue. Rare but severe side effects include acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), and myelodysplastic syndromes (MDS). For example, side effects have been observed in patients administered with PARP inhibitors like olaparib, niraparib, and rucaparib, such as pneumonia, headaches, hypertension, tachycardia, and elevated creatinine [34,110,111]. Therefore, improving the selectivity of DDR inhibitors while minimizing toxicity is a key focus of clinical research. To improve drug selectivity and minimize side effects, the following strategies can be considered: (i) Targeted drug delivery: employing nanoparticle-based drug delivery systems or other targeted approaches can enhance the accumulation of drugs in tumor tissues while reducing exposure to healthy cells; (ii) Protective strategies: combining DDR inhibitors with protectants such as antioxidants could help safeguard normal tissue integrity, reducing the risk of severe side effects.

6.4. Complexity of Personalized Treatment

Personalizing DDR-targeted therapies is challenging due to patient-specific genomic and phenotypic variability. Although advances in genetic testing enable the identification of DDR mutations, designing personalized treatments based on genotype and phenotype requires more clinical data. Additionally, reliable biomarkers to predict patient responses to DDR inhibitors are still lacking, making treatment optimization difficult. To address these challenges, the following strategies are recommended: (i) Biomarker discovery and validation: identifying new biomarkers that accurately predict patient responses to DDR-targeted therapies can enhance personalized treatment decisions; (ii) **Comprehensive** genomic testing: expanding access to genomic testing allows for better patient stratification and more precise treatment planning; (iii) **Artificial** intelligence and data integration: utilizing AI tools to analyze large datasets can optimize treatment recommendations based on patient-specific data and clinical outcomes. Establishing strong databases that link genomic profiles with clinical results will further facilitate the development of personalized therapies.

7. Conclusion and Future Perspectives

DDR-targeted therapies represent an effective approach in cancer treatment as well as bacterial infections. Future research may prioritize improving drug selectivity, identifying new therapeutic targets, and refining personalized treatment strategies to enhance clinical outcomes.

Combination therapies are a promising strategy for increasing efficacy and reducing resistance. Pairing DDR inhibitors with immunotherapy, chemotherapy, or radiotherapy has demonstrated synergistic potential. Furthermore, next-generation DDR-targeted drugs, including structurally optimized PARP inhibitors and PROTACs are under development. These advancements aim to improve drug selectivity, efficacy, and safety, minimizing adverse effects on normal tissues. Finally, the rise of precision medicine, driven by advances in genomics and biomarker technologies, is reshaping personalized cancer care. Biomarker-guided approaches further refine patient selection, ensuring that DDR inhibitors are used effectively in those most likely to benefit.

In bacterial infections, targeting DDR pathways offers a novel strategy to address antibiotic resistance. Inhibitors of bacterial DDR components, such as RuvAB and RecG, impair DNA repair, making bacteria more sensitive to genotoxic agents and reducing their resistance to antibiotics. Combining DDR inhibitors with traditional antibiotics has the potential to enhance existing treatments and tackle the global challenge of antimicrobial resistance.

With the advancements in combination therapies, precision medicine, and artificial intelligence in drug discovery, DDR-targeted therapies are expected to offer improved outcomes and expand treatment options in both oncology and combating antibiotic resistance in bacterial infections.

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