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蔡木炎主任医师长期耕耘在临床病理诊断一线，诊断疑难病例约3 000例/年，疑难病例诊断能力达到国内领先水平。将临床病理诊断工作中发现的临床问题转化为科学问题，围绕“消化系统肿瘤生物标记物识别与临床应用”开展研究。发现了消化系统肿瘤病理分类诊断新标记，破解了国际诊断痛点，推动了国际指南修订；开发了消化系统肿瘤人工智能分类新方法，实现了基因不稳定亚型的精准诊断；鉴定出了识别消化系统肿瘤耐药的分层生物标记物，指导了临床分层治疗；提出了消化系统肿瘤基于DNA修复失衡的分子分型新方案，证实了DNA修复失衡指导下的新靶点治疗有效性，实现了新型标记物指导的精准治疗，引导了临床试验的开展。研究成果被写入国际多部肿瘤诊断指南。主持国家自然科学基金面上项目等10项课题，近年来以通信作者或第一作者(含共同)身份在*GUT*、*Cell Death Differ*、*J Hep*、*Nat Commun*、*Cell Rep Med*、*STTT*等期刊上发表高水平学术论文30余篇，其中ESI高被引论文2篇，研究成果被世界卫生组织肿瘤学分类指南引用，并以第一发明人身份获得国家发明专利授权4项。

谢丹教授主要运用分子肿瘤学和实验病理学等相关技术，进行多种人类实体肿瘤恶性分子表型的调控与蛋白修饰及肿瘤侵袭转移和分子诊断标记物的研究。近20年来，先后主持国家和省部级等科研课题20余项；在肿瘤学领域的相关主流学术(高水平)杂志上共发表高水平论著159篇，其中通信/共同通信作者论著76篇，第一/共同第一作者论著15篇，累计影响因子(IF)达900多分，许多论著发表在*Lancet Oncol*、*Gut*、*Cancer Res*、*Oncogene*、*Clin Cancer Res*、*PLoS Genet*、*J Phathol*、*Ann Oncol*等高影响力的肿瘤学主流杂志上；共申报肿瘤诊断标志物相关的专利5项。

DNA损伤反应及其抑制剂的现状与未来

郑雪怡　谢丹*　蔡木炎*

(华南恶性肿瘤防治全国重点实验室, 广东省恶性肿瘤临床医学研究中心, 中山大学肿瘤防治中心, 广州 510060)

摘要　DNA损伤应答(DDR)是真核生物细胞关键的响应机制，通过识别和修复DNA损伤以维持基因组稳定性。癌症常常伴有DDR通路的失调，导致基因组不稳定性增加和肿瘤进展。因此，靶向DDR通路已成为一种很有前景的肿瘤治疗方法。该综述首先阐述了DDR的关键修复通路。对这些通路分子机制的全面理解促进了抗肿瘤药物的开发，这些DDR抑制剂特异性地靶向DNA修复的关键介导者，包括PARP1、ATM、ATR、CHK1、CHK2、DNA-PK和WEE1。此外，该文探讨了DDR抑制剂应用的多方面挑战，包括肿瘤微环境的异质性、耐药机制的存在、抑制剂的选择性和毒性，以及临床试验设计的复杂性。最后，该文讨论了提高DDR抑制剂靶向治疗效果的策略，重点关注了生物标志物驱动的精准医疗、创新的联合治疗方法、先进的药物递送方式，以及人工智能在优化治疗效果中的潜在应用。

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*通信作者。Tel: 020-87342194, E-mail: xiedan@sysucc.org.cn; Tel: 020-87342775, E-mail: caimy@sysucc.org.cn
Received: December 6, 2024　　Accepted: January 2, 2025
*Corresponding authors. Tel: +86-20-87342194, E-mail: xiedan@sysucc.org.cn; Tel: +86-20-87342775, E-mail: caimy@sysucc.org.cn

关键词 DNA损伤反应; 抑制剂; 生物标志物

DNA Damage Response and Its Inhibitors: Current Perspectives and Future Directions

ZHENG Xueyi, XIE Dan*, CAI Muyan*

(*State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou 510060, China*)

Abstract The DDR (DNA damage response) is an essential cellular mechanism that detects and repairs DNA lesions to maintain genomic stability. Dysregulation of DDR pathways is frequently observed in human tumors, leading to increased genomic instability and promoting tumor progression. Consequently, targeting DDR mechanisms has emerged as a promising therapeutic strategy in oncology. This review provides an overview of the major DDR pathways, highlighting the roles of key proteins involved in various DDR processes. A detailed understanding of these molecular mechanisms has paved the way for the development of targeted antitumor agents, including inhibitors of PARP1, ATM, ATR, CHK1, CHK2, DNA-PK, and WEE1. Additionally, the significant challenges in the development of DDR inhibitors are examined, including tumor microenvironment heterogeneity, resistance mechanisms, issues with selectivity and toxicity, and the complexities associated with clinical trial design. Finally, future directions and emerging strategies to improve DDR-targeted therapies are discussed. These strategies include biomarker-driven precision medicine, novel combination therapies, advanced drug delivery systems, and the potential application of artificial intelligence to optimize treatment outcomes.

Keywords DNA damage response; inhibitor; biomarker

DNA, the blueprint of life, is constantly subjected to endogenous and exogenous threats that can compromise its structure. If left unrepaired, these damages can lead to mutations, genomic instability, and ultimately diseases such as cancer[1]. To preserve genomic integrity, cells have evolved a range of sophisticated DDR (DNA damage response) mechanisms[2-3]. In cancer cells, however, mutations in these repair pathways often create specific vulnerabilities that can be therapeutically exploited[4]. DDR inhibitors have emerged as a rapidly advancing class of therapeutic agents designed to target these weaknesses by blocking the repair machinery that cancer cells depend on for survival, opening new avenues in targeted cancer therapy[5].

PARP [poly (ADP-ribose) polymerase] inhibitors are among the most prominent DDR inhibitors, revolutionizing the treatment of cancers with HR (homologous recombination) repair defects, such as BRCA1- and BRCA2-mutated ovarian and breast cancers[6]. The clinical success of PARP inhibitors has sparked widespread interest in broadening DDR inhibition strategies, prompting the development of drugs targeting additional repair pathways, including ATM (ataxia-telangiectasia mutated), ATR (ataxia-telangiectasia and Rad3-related), and DNA-PK (DNA-dependent protein kinase)[7]. These inhibitors function through "synthetic lethality" wherein blocking a secondary repair pathway in cancer cells with an already compromised primary pathway results in cell death[8].

Despite the promising potential of DDR inhibitors in cancer therapy, significant challenges persist in managing resistance, toxicity, and patient selection. For instance, resistance to PARP inhibitors has been observed in certain cancers through mechanisms that restore HR repair, enabling cancer cells to survive despite treatment[9]. Moreover, developing reliable

biomarkers to predict patient response to DDR inhibitors beyond BRCA mutations remains an active area of research[10]. Addressing these issues is essential for optimizing the safety and effectiveness of DDR inhibitors and broadening their therapeutic applicability.

Looking forward, the field of DDR inhibitors is poised for significant expansion and refinement. This review will explore the underlying mechanisms, current clinical landscape, key challenges, and promising future directions of DDR inhibitors in cancer therapy, aiming to provide a comprehensive overview of their potential to transform cancer treatment strategies.

1 Key DNA repair pathways

DNA repair mechanisms are essential for maintaining genomic stability and cellular viability[11]. Each cell in the human body encounters tens of thousands of DNA lesions daily[12]. If these lesions are not repaired, they can result in mutations, chromosomal aberrations, and ultimately cancer. To prevent such outcomes, cells have evolved a variety of specialized pathways designed to recognize and repair different types of DNA damage.

1.1 BER (base excision repair)

BER is a crucial DNA repair pathway responsible for correcting small, non-helix-distorting base lesions in the DNA, which often arise from oxidative damage, deamination, or alkylation[13]. In humans at least 30 proteins are involved in both short patch repair, the removal of a single non-bulky damaged base; and long patch repair, where 2-8 nucleotides are synthesized to displace the damaged area[14]. The BER process begins with the recognition and removal of the damaged base by a specific DNA glycosylase, which cleaves the N-glycosidic bond, leading to the formation of AP (an abasic) site. This site is then processed by an AP endonuclease, which cuts the DNA backbone at the AP site, creating a single-strand break. Subsequently, DNA polymerase inserts the correct nucleotide, utilizing the complementary strand as a template, followed by the sealing of the remaining nick in the DNA backbone by DNA ligase[15]. This pathway is essential for maintaining genomic stability and preventing mutations that can lead to cellular dysfunction or cancer development. The efficiency of BER is vital for cellular health, as it ensures the rapid and accurate repair of damaged DNA bases.

1.2 NER (nucleotide excision repair)

NER is a critical DNA repair mechanism that removes a wide range of bulky, helix-distorting lesions, such as those caused by ultraviolet radiation, chemical adducts, and other forms of DNA damage[16]. The NER process begins with the recognition of the DNA lesion by specific proteins that distort the double helix structure. In the global genome NER pathway, damage recognition is facilitated by the XPC complex, while in transcription-coupled NER, RNA polymerase stalls at the lesion, recruiting repair factors[17-18]. Once the damage is recognized, an endonuclease cleaves the DNA strand on both sides of the lesion, resulting in the excision of a short, single-stranded DNA segment containing the damaged nucleotide. Following excision, DNA polymerase fills in the gap by synthesizing new DNA using the undamaged strand as a template, and the final nick in the DNA backbone is sealed by DNA ligase. The activity of NER proteins is tightly regulated by post-translational modifications[19]. In particular, the DNA-damage recognition steps are extensively regulated by complex ubiquitylation events. NER deficiency is exemplary of the severe consequences of DNA damage. Congenital defects in NER genes cause various human syndromes, which exhibit a wide range of clinical symptoms, including extreme (skin) cancer predisposition, severe neurodevelopmental defects, and premature ageing.

1.3 MMR (mismatch repair)

MMR is a vital DNA repair system responsible for correcting errors that occur during DNA replication, specifically mismatched bases and insertion-deletion loops that escape proofreading by DNA polymerases[20]. The MMR process begins with the recognition of the mismatch by a set of specific proteins, including MutS in prokaryotes (or its homologs, MSH proteins, in eukaryotes), which bind to the distorted DNA helix.

Once the mismatch is identified, MutS recruits another protein, MutL (or its homologs, MLH proteins), which serves as a bridge to coordinate the repair process[21]. The next step involves the identification of the newly synthesized strand, usually marked by nicks or other modifications, which allows the repair machinery to selectively excise the incorrect base or segment of DNA. Following excision, DNA polymerase fills in the gap by synthesizing the correct sequence using the complementary strand as a template, and DNA ligase seals the remaining nick in the backbone[22]. The MMR system is a major pathway that functions in the maintenance of genomic integrity, which is involved in mitotic and meiotic recombination, apoptosis, immunoglobulin gene rearrangement, somatic hypermutation, and other processes[23]. Deficiencies in mismatch repair give rise to hypermutability and the phenomenon called microsatellite instability[24]. Detection of deficient mismatch repair function or microsatellite instability is used diagnostically, predictively, and prognostically. Specifically, deficient mismatch repair function is used for screening of Lynch syndrome[25], determining patients who are likely to respond to immune checkpoint inhibition[26-27], and to contributes to an understanding of which cancer patients may pursue a more aggressive clinical course[28-29].

1.4 DSB (double-strand break) repair

DSBs are lesions formed when both strands of the DNA duplex are broken[30]. DSBs can arise pathologically following exposure to exogenous agents, such as ionizing radiation, but the major endogenous source occurs when DNA replication forks encounter unrepaired DNA lesions, triggering fork collapse. Regardless of their source, DSBs are highly toxic and can cause genome rearrangements and cell death. Cells have two primary pathways to repair DSBs.

HR repair is a precise DNA repair mechanism that addresses DSBs in DNA by utilizing a homologous DNA template, typically the sister chromatid, for accurate repair[31]. The HR repair process begins with the recognition of a DSB, which is typically sensed by the MRN (MRE11-RAD50-NBS1) complex[32-34]. This complex initiates the resection of the DNA ends, producing long 3′ ssDNA (single-stranded DNA) overhangs. These ssDNA regions are then coated by RPA (replication protein A), which stabilizes the ssDNA and prevents it from forming secondary structures. The next key step involves the replacement of RPA with RAD51[35], a recombinase that facilitates the search for homology between the ssDNA and the homologous template. Once homology is identified, RAD51 mediates the invasion of the ssDNA into the homologous double-stranded DNA, forming a D-loop (displacement loop)[36-37]. This structure allows for DNA synthesis to occur, where DNA polymerases synthesize new DNA using the homologous strand as a template, effectively repairing the break. Finally, the repair is completed through the resolution of the D-loop and ligation of the DNA strands, restoring the integrity of the DNA molecule. HR repair is essential for maintaining genomic stability, particularly in cells undergoing rapid division, and is crucial in processes such as meiosis and the generation of genetic diversity. Deficiencies in HR repair mechanisms, often associated with mutations in key genes such as *BRCA1* and *BRCA2*, can lead to increased susceptibility to cancer due to the accumulation of unresolved DNA damage[38].

NHEJ (non-homologous end joining) is a crucial DNA repair pathway that directly ligates DSBs without the need for a homologous template, making it a rapid and efficient mechanism for maintaining genomic stability, particularly during the G_1 phase of the cell cycle[39]. The NHEJ process begins with the recognition of DSBs by a protein complex that includes the Ku70/80 heterodimer, which binds to the DNA ends and protects them from degradation[40]. Following recognition, the Ku complex recruits the DNA-PKcs (DNA-dependent protein kinase catalytic subunit), forming the DNA-PK holoenzyme. This complex facilitates the processing of the DNA ends, which may involve trimming or filling in nucleotide gaps to prepare the ends for ligation[41]. Subsequently, the enzyme ligase IV, in association with

XRCC4 and XLF, catalyzes the final ligation of the processed ends, effectively sealing the break[42]. While NHEJ is generally accurate, it can introduce small insertions or deletions at the repair site, potentially leading to mutations. This pathway is essential for cellular responses to DNA damage and is particularly important in lymphocyte development, where it plays a critical role in the generation of antibody diversity through V(D)J recombination[43]. Dysregulation or deficiency of NHEJ components can result in increased susceptibility to genomic instability and cancer[44].

1.5 TLS (translesion synthesis)

TLS is a specialized DNA damage tolerance mechanism that enables DNA polymerases to replicate across non-canonical DNA lesions that will otherwise stall replication fork progression, thereby allowing cells to bypass bulky adducts or damaged bases[45]. TLS is primarily mediated by low-fidelity DNA polymerases, such as Pol η, Pol ι, and Pol κ, which can incorporate nucleotides opposite the damaged bases, albeit with lower fidelity compared to the high-fidelity replicative polymerases. The process begins when the replicative DNA polymerase encounters a lesion, where PCNA plays a central role in recruiting the TLS polymerases and effecting the polymerase switch from replicative to TLS polymerase[46]. When the fork is blocked, PCNA gets ubiquitinated. This increases its affinity for the TLS polymerases, which all have novel ubiquitin-binding motifs, thereby facilitating their engagement at the stalled fork to effect TLS. Once recruited, the TLS polymerase can insert nucleotides opposite the lesion, facilitating the continuation of DNA synthesis. After bypassing the lesion, the high-fidelity polymerase may resume replication, filling in the remaining gaps. While TLS allows for the completion of DNA replication, it carries the risk of introducing mutations due to the error-prone nature of the TLS polymerases[47]. As such, TLS serves a dual purpose: it helps maintain replication continuity under conditions of DNA damage while also contributing to the genetic variability that can be seen in evolutionary processes and disease states, including cancer[48-49]. Dysregulation of TLS can lead to increased mutagenesis and genome instability[50].

1.6 ICL (interstrand cross-link) repair

DNA ICLs are extremely toxic DNA lesions that prevent DNA double-helix separation due to the irreversible covalent linkage binding of some agents on DNA strands[51]. ICLs are induced by chemotherapeutics, endogenous metabolites, or microbial metabolites[52]. Their repair is a complex, multistep process involving several pathways. The first step is damage recognition, where proteins like FANCM in the Fanconi anemia pathway identify the ICL. Next, NER introduces single-strand incisions near the crosslink. During replication, stalled forks at the ICL trigger HR to bypass the lesion. Specialized TLS polymerases may then insert nucleotides opposite the crosslink. Finally, the ICL is resolved, and the DNA is restored to its native state through additional HR or excision steps. This coordinated mechanism maintains genomic stability, preventing mutations and ensuring proper cellular function[53]. Impaired repair of DNA ICLs poses significant risks to cellular and organismal health. ICLs block replication and transcription, leading to stalled replication forks and genomic instability. Inherited defects in ICL repair pathways, such as in Fanconi anemia, cause cancer and bone marrow failure[54].

2 Current status of DDR inhibitors

The field of DDR inhibitors has grown rapidly, driven by the clinical success of PARP inhibitors and the growing understanding of how cancer cells can be selectively targeted through deficiencies in DNA repair pathways. As a result, DDR inhibitors are now a critical component of precision oncology, offering a personalized approach to cancer treatment by exploiting tumor-specific vulnerabilities. DDR inhibitors target key proteins involved in DNA repair mechanisms, such as PARP, ATM, ATR, and DNA-PK. These inhibitors are actively being explored in phase I-II clinical trials for cancer therapies, particularly in combination with chemotherapy and radiation. In this section, we explore the current clinical landscape of DDR inhibitors,

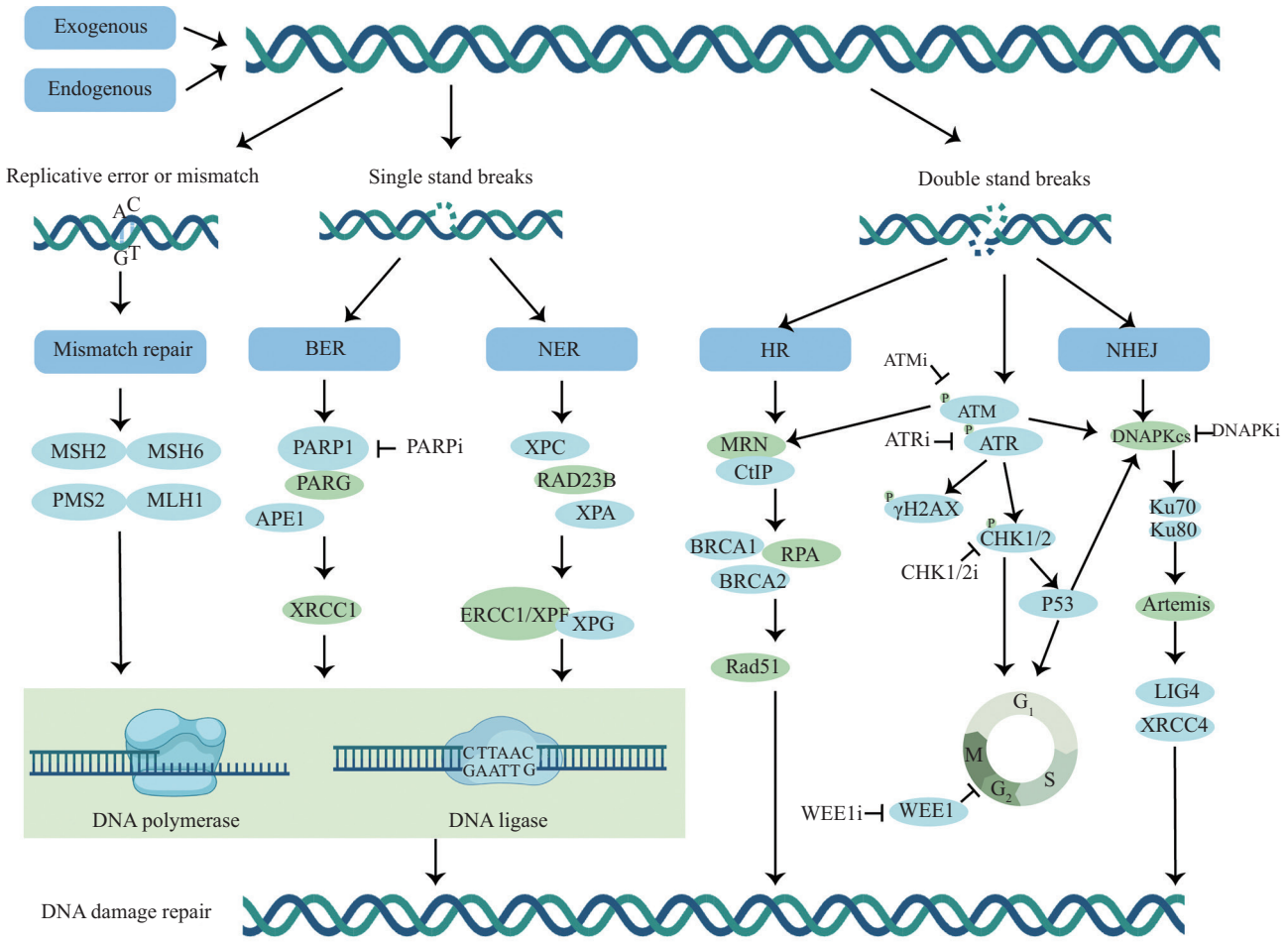
their applications across various cancer types, and the emerging use of these drugs in combination therapies (Fig.1 and Table 1).

2.1 PARP inhibitors

The PARP family comprises a group of nuclear proteins that are activated upon binding to damaged DNA and have crucial roles in various aspects of the DDR[55]. The main function of these proteins is to detect SSBs and DSBs, recruit the DNA repair machinery and stabilize replication forks during repair[56]. The key components of the DDR are the PARP1 and PARP2 enzymes, which act as DNA damage sensors and signal transducers. They function by synthesizing branched, negatively charged PAR [poly (ADP-ribose)] chains (a process known as PARylation) on target proteins as a form of post-translational modification. PARP1 binds damaged DNA at SSBs and other DNA lesions, an event that causes a series of allosteric changes in the structure of PARP1 that activate its catalytic function[57]. This leads to the PARylation and recruitment of DNA repair effectors such as XRCC1 as well as the remodeling of chromatin structure around damaged DNA as part of the DNA repair process. PARP1 eventually PARylates itself (autoPARylation)——the negative charge that PAR chains impart upon PARP1 likely causes its release from repaired DNA. PARylation process serves multiple functions: it facilitates the recruitment of DNA repair proteins to the damaged site, enhances the assembly of repair complexes, and promotes the stabilization of replication forks during the repair process[58]. By doing so, PARP plays a vital role in maintaining genomic integrity and preventing the accumulation of DNA damage.

PARP inhibitors operate through two primary mechanisms: the inhibition of PARP catalytic activity and the trapping of PARP on DNA[59]. The first mechanism involves the competitive binding of these inhibitors to NAD^+, which effectively blocks the PARP enzyme's ability to catalyze the addition of PAR chains. This inhibition hinders PARP's role in facilitating the repair of SSBs, resulting in the accumulation of unrepaired lesions. The second mechanism, known as PARP trapping, describes the capability of these inhibitors to stabilize PARP in a complex with damaged DNA, thereby preventing its release from the lesion site. This trapping is particularly detrimental, as it obstructs the recruitment of other essential DNA repair proteins, further exacerbating the accumulation of DNA damage.

The discovery and development of PARP inhibitors marked a breakthrough in cancer therapeutics, particularly for patients with BRCA1 and BRCA2 mutations[60]. PARP inhibitors have been approved for several cancer types, and they remain the most clinically advanced class of DDR inhibitors. Their ability to induce synthetic lethality in tumors with HR deficiencies has led to significant improvements in outcomes for patients with ovarian, breast, and prostate cancers[5]. Several PARP inhibitors have been approved by the FDA for the treatment of several types of cancers. For the treatment of ovarian cancer, the development of PARP inhibitors has provided robust clinical proof of concept and paved the way for the advancement of selective DDR inhibitors in cancer medicine. Currently, three agents——olaparib, rucaparib, and niraparib——have received approval for use in various therapeutic settings. For breast cancer, data from the phase III OlympiAD trial demonstrated a doubling of the ORR (objective response rate), a significant PFS benefit and a more favorable safety profile for olaparib versus single agent chemotherapy (not including platinum-based agents) in patients with germline BRCA1/2-mutant, HER2-negative, metastatic breast cancer, leading to FDA approval of olaparib in this patient population[61]. For patients with metastatic pancreatic cancer, the POLO trial, which investigated the efficacy of olaparib as a maintenance therapy in those who had germline BRCA mutations and had not progressed on platinum-based chemotherapy, demonstrated that olaparib reduced the risk of disease progression or death by 47% compared to placebo in patients whose disease had not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen[62]. For prostate cancer, clinical research on the use of PARP inhibitors has emerged as a promising area of investigation, particu-



各种类型的内源性或者外源性DNA损伤, 包括复制错配、DNA单链断裂(SSBs)和DNA双链断裂(DSBs), 能够触发特定的信号转导和修复级联反应。DNA损伤应答(DDR)通路在缓解复制应激和促进DNA修复过程中发挥着至关重要的作用; 这些通路的功能缺陷可能导致SSBs和DSBs的持续积累。聚(ADP-核糖)聚合酶(PARP)是激活多种下游修复过程的关键酶类, 尤其在SSBs修复和碱基切除修复(BER)过程中尤为重要。DSBs的修复主要通过两条途径实现: 快速但容易出错的非同源末端连接(NHEJ)途径, 以及相对缓慢但高度精确的同源重组(HR)途径。鉴于DNA复制在DNA损伤修复中的核心作用, 细胞周期调控机制、复制应激响应系统与DDR通路共同构成了一个精密而复杂的调控网络。其中, ATR和ATM激酶作为DDR信号通路和复制叉稳定性的核心调控因子, 通过与其下游效应分子CHK1和CHK2的协同作用, 精确调控细胞周期检查点。同时, DNA-PK在介导NHEJ修复和V(D)J重组过程中扮演着不可或缺的角色。核激酶WEE1则通过与DDR协同作用, 在调控细胞进入有丝分裂和维持核苷酸池稳态方面发挥着独特作用。目前, 这些DDR通路的关键组分, 如PARP1、ATM、ATR、DNA-PK、CHK1/CHK2和WEE1等, 已成为新药研发的重点靶点, 多个靶向这些分子的候选药物正处于临床试验阶段。PARP: 聚(ADP-核糖)聚合酶; NHEJ: 非同源末端连接; HR: 同源重组; BER: 碱基切除修复; NER: 核苷酸切除修复; PARPi: PARP抑制剂; ATMi: ATM抑制剂; ATRi: ATR抑制剂; DNA-PKi: DNA-PK抑制剂; CHK1/2i: CHK1/2抑制剂; WEE1i: WEE1抑制剂。

Various types of exogenous and endogenous DNA damage, including replication mismatches, SSBs (single strand breaks), and DSBs (double strand breaks), activate specific signaling and repair cascades. DDR (DNA damage response) pathways play a critical role in reducing replication stress and facilitating DNA repair; hence, defects in these pathways can lead to the accumulation of SSBs and DSBs. PARP [poly (ADP-ribose) polymerase] enzymes are pivotal in activating various downstream repair processes, especially in the context of SSBs repair and BER (base excision repair). DSBs repair is largely managed by two pathways: the fast but error-prone NHEJ (non-homologous end joining) pathway, and the slower, highly accurate HR (homologous recombination) pathway. Since DNA replication is essential for effective DNA repair, cell cycle regulation and replication stress responses are intricately connected to DDR pathways. The kinases ATR and ATM are central to DDR signaling and replication fork stability, collaborating with their downstream targets, CHK1 and CHK2, to manage cell cycle checkpoints. Furthermore, DNA-PK is crucial for NHEJ and V(D)J recombination. The nuclear kinase WEE1 also plays a unique role by regulating mitotic entry and nucleotide pool maintenance in coordination with DDR. Key DDR pathway components, including PARP1, ATM, ATR, DNA-PK, CHK1/CHK2, and WEE1, are now the focus of drug development efforts, with candidates currently undergoing clinical trials. DSBs: double strand breaks; SSBs: single strand breaks; DDR: DNA damage response; PARP: poly (ADP-ribose) polymerase; NHEJ: non-homologous end joining; HR: homologous recombination; BER: base excision repair; NER: nucleotide excision repair; PARPi: PARP inhibitor; ATMi: ATM inhibitor; ATRi: ATR inhibitor; DNA-PKi: DNA-PK inhibitor; CHK1/2i: CHK1/2 inhibitor; WEE1i: WEE1 inhibitor.

图1　DNA损伤反应通路及其抑制剂

Fig.1　DNA damage response pathways and their inhibitors

表1 DNA损失修复反应的靶蛋白及其抑制剂

Table 1 Target proteins and corresponding inhibitors in DNA damage response

靶标 Target	抑制剂功能 Inhibitor function	药物 Agent	分期 Phase	临床试验号 Trial number	癌种 Tumor
PARP	Inhibit PARP enzyme's ability and PARP trapping	Niraparib	III	NCT01905592	Breast cancer
		Niraparib	III	NCT01847274	Ovarian cancer
		Olaparib	IV	NCT02476968	Ovarian cancer
		Olaparib	III	NCT01844986	Ovarian cancer
		Olaparib	III	NCT02032823	Breast cancer
		Olaparib	III	NCT02000622	Breast cancer
		Rucaparib	III	NCT01968213	Ovarian cancer
		Talazoparib	III	NCT01945775	Breast cancer
		Veliparib	III	NCT02032277	Breast cancer
		Veliparib	III	NCT02264990	Lung cancer
DNA-PK	Disrupt the stabilization and processing of broken DNA ends, prevent the NHEJ process	CC-115	I	NCT01353625	Advanced solid tumor/hematologic malignancies
		CC-115	I	NCT02833883	Prostate cancer
ATR	Block the kinase activity of ATR, prevent it from phosphorylating key substrates, such as CHK1, RAD17, and H2AX	VX-970	I	NCT02723864	Refractory solid tumors
		VX-970	I	NCT02589522	Brain metastases
		VX-970	II	NCT02487095	Small cell cancers/extrapulmonary small cell cancers
		Elimusertib	I	NCT04267939	Advanced solid tumors and ovarian cancer
ATM	Inhibit ATM's kinase activity, block the phosphorylation of downstream targets of DSB	M4076	I	NCT04882917	Advanced solid tumors
		XRD-0394	I	NCT05002140	Advanced cancer
		AZD0156	I	NCT02588105	Advanced cancer
CHK1/CHK2	Block the kinase activity of these crucial checkpoint proteins, disrupt mediating cell cycle arrest and DNA damage repair in response to genotoxic stress	GDC-0575	I	NCT01564251	Advanced solid tumors or lymphoma
		MK-8776	II	NCT01870596	Myeloid leukemia
		Prexasertib	II	NCT02873975	Solid tumors
		Prexasertib	II	NCT02203513	Breast and ovarian cancer
WEE1	Abolish the G_2 checkpoint	AZD1775	II	NCT01164995	Ovarian cancer
		AZD1775	II	NCT01357161	Ovarian cancer
		AZD1775	II	NCT02037230	Adenocarcinoma of pancreas

PARP: 聚(ADP-核糖)聚合酶; NHEJ: 非同源末端连接; HR: 同源重组; BER: 碱基切除修复。

PARP: poly (ADP-ribose) polymerase; NHEJ: non-homologous end joining; HR: homologous recombination; BER: base excision repair.

larly for patients with mCRPC (metastatic castration-resistant prostate cancer) associated with DNA repair deficiencies, such as those with BRCA1 and BRCA2 mutations. One significant trial is the PROfound study, which evaluated the efficacy of olaparib in men with mCRPC who had specific gene alterations in DNA damage repair genes, including *BRCA1*, *BRCA2*, and *ATM*[63]. The study showed that olaparib significantly improved radiographic progression-free survival compared to the standard of care, reinforcing the role of PARP inhibitors in targeting specific genetic vulnerabilities in prostate cancer.

2.2 ATM inhibitors

ATM is a key protein kinase in the cellular response to DNA damage, particularly in the repair of DSBs. Upon sensing DNA damage, ATM is rapidly activated through autophosphorylation and subsequently phosphorylates a wide array of substrates involved in cell cycle control, DNA repair, and apoptosis[64]. Upon detecting DSBs, ATM undergoes autophosphorylation and becomes active, subsequently phosphorylating downstream targets to orchestrate DNA repair. ATM phosphorylates p53 to induce cell cycle arrest, allowing time for repair; it also activates CHK2, reinforc-

ing this arrest at both G_1/S and G_2/M checkpoints. By phosphorylating H2AX to generate γ-H2AX, ATM marks DSB sites, facilitating the recruitment of repair factors. Additionally, ATM phosphorylates BRCA1 to promote HRR and NBS1 in the MRN complex to enable efficient DNA-end processing, thus maintaining genomic stability[65].

ATM inhibitors function by binding to the ATM kinase, preventing its activation and subsequent autophosphorylation in response to DSBs[64]. By inhibiting ATM's activity, these compounds block the phosphorylation of downstream targets. This inhibition prevents cell cycle arrest and suppresses DNA repair processes, leaving damaged DNA unrepaired. ATM inhibitors are particularly valuable in cancer therapy, as they enhance the sensitivity to radiation and chemotherapy of cancer cells, especially those deficient in alternative repair pathways, like BRCA-mutated tumors, leading to increased cell death.

ATM inhibitors are currently being evaluated in several clinical trials to assess their efficacy and safety, particularly in combination with other cancer treatments. Trials focus on leveraging ATM inhibitors to enhance the effects of DNA-damaging therapies like chemotherapy and radiation, especially in cancers with inherent DNA repair deficiencies, such as BRCA1/2-mutated breast, ovarian, and prostate cancers. ATM inhibitors, including KU-55933, KU-60019, KU-59403, CP-466722, AZ31, AZ32, AZD0156, and AZD1390, have been evaluated for their antitumor effects[66]. Of note, among these ATM inhibitors, AZD0156 and AZD1390 achieve potent and highly selective ATM kinase inhibition and have an excellent ability to penetrate the blood-brain barrier. Currently, AZD0156 and AZD1390 are under investigation in phase I clinical trials[67-68]. These trials aim to determine the optimal dosing, therapeutic efficacy, and side effect profiles of ATM inhibitors. Some trials are also exploring the use of these inhibitors in combination with PARP inhibitors, targeting multiple points within the DNA repair pathway to maximize cancer cell vulnerability. Although results are still preliminary, ATM inhibitors hold promise as an emerging strategy for enhancing the effectiveness of existing cancer therapies, particularly for tumors with specific genetic vulnerabilities in DNA repair.

2.3 ATR inhibitors

ATR is a critical kinase in the DNA damage response, primarily activated by ssDNA regions that arise from DNA replication stress or stalled replication forks[69]. Once activated, ATR phosphorylates several downstream proteins to initiate cell cycle arrest and promote DNA repair. Key substrates of ATR include CHK1, which, when phosphorylated, triggers cell cycle checkpoints, particularly at the G_2/M boundary, allowing cells time to repair damaged DNA before mitosis. ATR also phosphorylates RAD17 and BRCA1, which stabilize replication forks and facilitate homologous recombination repair. Additionally, ATR phosphorylates H2AX, creating γ-H2AX, which serves as a marker for DNA damage and helps recruit repair proteins to ssDNA regions[65]. ATR plays an essential role in preventing genomic instability by safeguarding DNA integrity during replication. In cells with compromised ATR function, DNA replication stress leads to increased DNA damage, chromosomal instability, and, ultimately, heightened cancer risk.

ATR inhibitors function by selectively blocking the kinase activity of ATR, preventing it from phosphorylating key substrates involved in the DNA damage response, such as CHK1, RAD17, and H2AX. This inhibition disrupts ATR's ability to stabilize replication forks and activate cell cycle checkpoints, leading to the accumulation of DNA damage and replication stress in cancer cells[70]. ATR inhibitors are particularly effective in tumors with high levels of replication stress or defects in other DNA repair pathways, such as those with p53 or ATM deficiencies, as these tumors rely heavily on ATR for survival. By targeting ATR, these inhibitors make cancer cells more vulnerable to DNA-damaging agents, thereby enhancing the efficacy of chemotherapy and radiation therapies.

Four ATR inhibitors, M6620 (VX-970 or berzosertib), M4344 (VX-803), AZD6738, and

BAY1895344, are currently undergoing clinical trials as potential cancer therapeutics, particularly for tumors with high replication stress or deficiencies in other DNA repair pathways. M6620 is the first-in-class ATR inhibitor and has been tested as monotherapy and in combination with different chemotherapies, including topotecan, carboplatin, gemcitabine, and cisplatin. The maximum tolerated dose of M6620 in combination with chemotherapy was lower than the recommended phase II dose of M6620 monotherapy[71]. The safety and efficacy of AZD6738 monotherapy in patients with advanced-stage solid tumors had been investigated in the phase I PATRIOT study; two partial responses were observed, although one was unconfirmed[72]. In addition, a profound synthetic lethal interaction between ATR and the ATM-p53 tumor suppressor pathway in cells treated with DNA-damaging agents was reported and ATR inhibition was established to transform the outcome for patients with cancer treated with ionizing radiation or genotoxic drugs[73].

2.4 DNA-PK inhibitors

DNA-PK, a member of the PI3K-mTOR enzyme family, is a critical enzyme involved in the NHEJ pathway of DNA repair. Upon the recognition of DSBs, DNA-PK is rapidly recruited to the site of damage, where it forms a complex with the Ku protein (Ku70/Ku80 heterodimer)[74]. This complex facilitates the binding of DNA-PK to the broken DNA ends, promoting their stabilization. Once activated, DNA-PK undergoes autophosphorylation, which is essential for its kinase activity. This phosphorylation triggers several downstream processes, including the recruitment of additional repair proteins, such as Artemis, which processes the DNA ends to make them compatible for joining[7]. DNA-PK also phosphorylates and activates XRCC4 and ligase IV, which are critical for the final steps of NHEJ, where the processed DNA ends are ligated together to restore DNA integrity[5].

DNA-PK inhibitors function by specifically blocking the activity of DNA-dependent protein kinase, thereby impairing its ability to phosphorylate downstream targets essential for the NHEJ pathway of DNA double-strand break repair. By inhibiting DNA-PK, these compounds disrupt the stabilization and processing of broken DNA ends, preventing the recruitment of critical repair proteins such as Artemis and XRCC4-ligase IV. This disruption leads to an accumulation of unrepaired DNA breaks, heightened genomic instability, and increased sensitivity of cancer cells to DNA-damaging agents. The targeted inhibition of NHEJ makes this drug class particularly suitable for combination with radiation therapy, as NHEJ is the primary repair mechanism for traditional (non-heavy ion) radiation-induced DNA damage.

DNA-PK inhibitors are currently under investigation in phase I/II clinical trials, with several notable candidates, including VX-984, M3814 (nedisertib), and CC-115, showing promise in early-phase studies, though some adverse effects, such as hyperglycemia and mucositis, have been observed. CC-115, a small-molecule inhibitor targeting both DNA-PK and mTOR, was developed by optimizing a novel series of triazole-containing mTOR inhibitors. In a phase I trial (NCT01353625), CC-115 monotherapy was evaluated in an initial cohort of 44 patients across 10 dose-escalation groups[75]. VX-984 is also being assessed, both as a monotherapy and in combination with pegylated doxorubicin, in an ongoing phase I study (NCT02644278). This trial initially enrolled patients with advanced-stage solid tumors and later expanded to include patients with metastatic endometrial cancer who were unresponsive to prior platinum-based chemotherapy. Nnedisertib has been tested in combination with palliative radiation therapy in a phase I trial involving patients with tumors or metastases in the head, neck, or thoracic regions. Several additional trials are underway to evaluate nedisertib alone or in combination with definitive chemotherapy and/or radiotherapy[76].

2.5 CHK1/CHK2 inhibitors

CHK1 and CHK2 are critical kinases in the DNA damage response, playing essential roles in maintaining genomic integrity following DNA damage[77]. They are activated in response to various types of DNA dam-

age, particularly DSBs and replication stress, and are involved in signaling pathways that regulate the cell cycle. CHK1 primarily acts at the G_2/M checkpoint. Upon activation by ATM or ATR in response to DNA damage, CHK1 phosphorylates key substrates such as Cdc25C, leading to its degradation or inactivation. This prevents the activation of CDKs (cyclin-dependent kinases) and thereby halts the cell cycle, allowing time for DNA repair before the cell enters mitosis. CHK1 also plays a role in stabilizing replication forks and promoting DNA repair pathways, including homologous recombination and nucleotide excision repair. CHK2, on the other hand, is activated primarily by ATM in response to DSBs. Upon activation, CHK2 phosphorylates a variety of substrates, including p53, which enhances its transcriptional activity and leads to the expression of genes that induce cell cycle arrest and apoptosis. CHK2 also phosphorylates other proteins involved in the DNA repair process, including BRCA1 and Cdc25A, further coordinating the cellular response to DNA damage[78].

CHK1 and CHK2 inhibitors function by blocking the kinase activity of these crucial checkpoint proteins, thereby disrupting their ability to mediate cell cycle arrest and DNA damage repair in response to genotoxic stress. By inhibiting CHK1, these compounds prevent the phosphorylation and inactivation of Cdc25C, leading to uncontrolled progression through the G_2/M checkpoint, which can result in the accumulation of DNA damage during mitosis. Similarly, CHK2 inhibitors impair the phosphorylation of downstream targets such as p53 and other repair proteins, compromising the cellular response to DNA damage[7].

CHK1 and CHK2 inhibitors are being actively explored in clinical trials as promising therapeutic agents for cancer treatment. Historically, development of CHK inhibitors has faced challenges, with many candidates, including UCN-01, discontinued due to toxicity, before reaching phase III trials[79]. However, some agents, such as AZD7762, have advanced through early-phase trials, with studies exploring its use alone or in combination with chemotherapeutic agents like gemcitabine or irinotecan in patients with advanced-stage solid tumors[80]. Currently, three selective CHK1 inhibitors are undergoing clinical evaluation: prexasertib (LY2606368), GDC-575 (ARRY-575; RG7741), and CCT245737 (SRA737)[81]. Prexasertib, a second-generation CHK1-selective inhibitor, has shown significant activity but is associated with a high incidence of grade 4 neutropenia in early-phase trials, where it has been used as a single agent[82]. Importantly, this severe neutropenia has generally been transient and manageable, typically lasting fewer than five days. The targeted action of these inhibitors on cell cycle checkpoints holds promise for enhancing the efficacy of DNA-damaging therapies like chemotherapy and radiation, positioning CHK1 and CHK2 inhibitors as potential combination partners in cancer treatment.

2.6 WEE1 inhibitors

WEE1 is a pivotal kinase involved in the regulation of the cell cycle and the DNA damage response[83]. Its primary function is to inhibit the activity of CDKs, particularly CDK1, by phosphorylating them at specific tyrosine residues, notably Tyr15. This phosphorylation prevents the activation of CDK1, thereby halting the cell cycle progression at the G_2/M checkpoint in response to DNA damage. By doing so, WEE1 provides the cell with additional time to repair DNA lesions before entering mitosis, which is crucial for maintaining genomic stability. In the context of DNA damage, WEE1 is activated by various signaling pathways, including those mediated by ATM and ATR, in response to double strand breaks and replication stress. Upon activation, WEE1 phosphorylates CDK1, leading to cell cycle arrest and allowing the cell to initiate repair processes, such as homologous recombination or non-homologous end joining, to address the damage. Furthermore, WEE1 is also involved in the regulation of other cell cycle checkpoints, ensuring that cells do not prematurely enter mitosis with unresolved DNA damage[84].

Considering these effects, a strong biological rationale exists for targeting p53-deficient cells with WEE1 inhibitors. Given p53's pivotal role in regulating the G_1 checkpoint, p53-deficient cells show

increased dependence on the G_2 checkpoint for cell cycle control. Studies of MK-1775, a WEE1 inhibitor, demonstrate that it can abolish the G_2 checkpoint, rendering p53-deficient cells more susceptible to DNA-damaging chemotherapy and radiotherapy by inducing mitotic catastrophe[85]. Consequently, current development strategies focus on combining WEE1 inhibitors with other DNA-damaging therapies——including PARP inhibitors, chemotherapy, or radiotherapy——to treat tumors harboring TP53 mutations. Additionally, preclinical data suggest that WEE1 inhibition sensitivity can increase through mechanisms beyond cell cycle checkpoint defects, such as disturbances in the DDR and nucleotide depletion, showing single-agent efficacy even in TP53 wild-type cancer cells[86].

Adavosertib is the first WEE1 inhibitor and currently the only one in clinical development. In a phase I study, adavosertib monotherapy resulted in two partial responses among 25 evaluable patients, both of whom had refractory BRCA1-mutated solid tumors[87]. In another phase I study, adavosertib was also tested in combination with gemcitabine, cisplatin, or carboplatin, showing that TP53 mutations were only weakly associated with antitumor response across treatments, with the response rate in TP53-mutated patients (n=19) 21% compared with 12% in TP53 wild-type patients (n=33)[88]. In a phase II study of adavosertib plus carboplatin for patients with p53-mutated refractory ovarian cancer, the overall response rate was 43%, including one patient (5%) with a prolonged complete response[89]. In a subsequent phase II study, 121 platinum-sensitive ovarian cancer patients with TP53 mutations were randomized to receive carboplatin and paclitaxel, with or without adavosertib. The results indicated that adding adavosertib to chemotherapy improved progression-free survival[90].

3 Challenges in the development of DDR inhibitors

Given the significance of DDR in cancer biology, particularly in relation to tumor growth and response to therapy, inhibitors targeting various components of the DDR pathway have emerged as promising therapeutic agents. However, the development of these inhibitors presents several scientific, clinical, and regulatory challenges. This discussion explores the multifaceted challenges associated with the development of DDR inhibitors, emphasizing the heterogeneity of tumor microenvironment, resistance mechanisms, selectivity and toxicity, and clinical trial design.

3.1 Heterogeneity of tumor microenvironment

TME (the tumor microenvironment) plays a crucial role in influencing the effectiveness of DDR inhibitors. TME is a functional and structural niche where tumor progression occurs. It consists of cellular and molecular (extracellular matrix, cytokines, chemokines, and other molecules) components[91]. The microenvironment is composed of tumor stromal cells (cancer-associated fibroblast, mesenchymal stromal cells, endothelial cells, and immune cells (T cells, B cells, natural killer cells, dendritic cells, tumor-associated macrophages, tumor-associated neutrophils, myeloid-derived suppressor cells). The cells are not homogeneous in tumor. This heterogeneity can impact drug response in several ways. On the one hand, the TME can modulate immune responses, which may affect the therapeutic efficacy of DDR inhibitors. For instance, some DDR inhibitors may enhance the immunogenicity of tumors by inducing DNA damage that leads to the release of tumor-associated antigens, potentially improving immune recognition. Previous research has shown that DDR inhibition activates the STING/TBK1/IRF3 innate immune pathway, resulting in elevated levels of chemokines, such as CXCL10 and CCL5, which promote the activation and function of cytotoxic T lymphocytes[92]. On the other hand, cellular interactions between tumor cells and the surrounding microenvironment can alter DDR signaling pathways. Crosstalk between PARP inhibition and the tumor microenvironment related to STING/TBK1/IRF3 pathway activation in cancer cells governs $CD8^+$ T-cell recruitment and antitumor efficacy[93]. By understanding the diverse immune landscapes within tumors, we can better identify which specific features either support or hinder the effectiveness of DDR inhibition. Such in-

sights may allow for tailored strategies that adjust DDR inhibitor use based on the unique immune profile of each tumor, potentially improving treatment response rates, and overcoming resistance mechanisms of DDR inhibitors.

3.2 Resistance mechanisms

Resistance to DDR inhibitors poses a significant challenge in cancer treatment, particularly as these agents become more widely integrated into therapeutic regimens. DDR inhibitors, such as PARP inhibitors, exploit specific DNA repair vulnerabilities in tumor cells, leading to selective cancer cell death. However, resistance mechanisms often emerge, diminishing the long-term effectiveness of these therapies. One common resistance pathway is the restoration of HR repair, where secondary mutations can restore the function of previously deficient genes, such as *BRCA1* or *BRCA2*[94]. This recovery in DNA repair capability allows tumor cells to overcome the effects of DDR inhibition. Another mechanism of resistance involves upregulation of drug efflux pumps, which reduces intracellular concentrations of DDR inhibitors, lowering their efficacy. Furthermore, alterations in cell cycle checkpoint proteins or increased activity in alternative repair pathways, like the NHEJ pathway, can also contribute to resistance[5]. A deeper understanding of the molecular and environmental factors that drive resistance will be essential to developing next-generation DDR inhibitors and achieving more durable responses in cancer therapy.

3.3 Selectivity and toxicity

Selectivity and toxicity are significant concerns in the clinical use of DDR inhibitors, constraining their therapeutic window and limiting patient tolerance[95]. DDR inhibitors, such as PARP inhibitors, are designed to selectively target cancer cells with DNA repair deficiencies. However, they also impact healthy cells, especially those with high turnover rates or intrinsic vulnerabilities, such as hematopoietic cells in the bone marrow. This off-target activity can lead to hematologic toxicities, including anemia, thrombocytopenia, and neutropenia, which often become dose-limiting factors in DDR inhibitor therapies[96]. Besides hematologic effects, DDR inhibitors can induce gastrointestinal and systemic symptoms, such as nausea, fatigue, and diarrhea, affecting patients' quality of life and adherence to treatment. Additionally, concerns exist about cumulative effects from long-term use, including the risk of secondary malignancies from DNA damage accumulation in healthy cells. Managing these toxicities requires precise dose adjustments, supportive care, and regular monitoring, which may limit optimal dosing levels for effectiveness. When used in combination with other DNA-damaging therapies, such as chemotherapy or radiation, DDR inhibitors present an increased risk of overlapping toxicities[59]. Consequently, developing DDR inhibitors with enhanced specificity or identifying biomarkers to predict toxicity risk is critical to minimizing adverse effects and safely expanding the clinical use of DDR inhibitors in cancer treatment.

3.4 Biomarker development

The early identification of biomarkers that indicate DNA damage, response, and repair deficiencies is crucial for selecting appropriate cancer treatments. Although many such biomarkers have been reported over recent decades, most still require refinement for clinical utility. For example, the presence of RAD51 foci is used as a biomarker to assess DNA repair capacity via immunohistochemistry[97]. However, due to the complex detection methods and the influence of various external factors on results, this marker has yet to achieve widespread clinical use. In the era of personalized cancer therapy, advances in experimental methods necessitate the discovery of more functional biomarkers that can reveal early, precise changes in DNA damage, response, and repair processes. Moreover, there are ethical challenges to consider. In practice, testing patients for DNA repair deficiencies using these early biomarkers would require activating them with treatments like radiation, chemotherapy, or immunotherapy, raising ethical concerns about exposing patients to potentially harmful activators solely for diagnostic purposes. Therefore, ethical issues need to be carefully

addressed before these biomarkers can be clinically applied to predict patient responses and optimize cancer treatments.

4 Prospects and emerging strategies

4.1 Biomarker-driven precision medicine

One of the most promising advancements in DDR inhibitor therapy is the utilization of biomarkers to inform patient selection and treatment approaches. DDR deficiencies, such as BRCA1/2 mutations or HR deficiencies, make tumors particularly susceptible to PARP inhibitors and other DDR-targeted therapies. Identifying these biomarkers in patients enables the selection of those who are most likely to benefit from DDR inhibitors, thereby enhancing the chances of therapeutic success while reducing unnecessary side effects. With the emergence of advanced biomarker discovery technologies, including next-generation sequencing and liquid biopsies[98], DDR biomarker profiling is becoming increasingly accessible and precise. This profiling facilitates the matching of patients to DDR inhibitors that specifically target the genetic and molecular vulnerabilities of their tumors. Furthermore, the development of dynamic biomarkers capable of monitoring DDR activity in real time may enable clinicians to adjust treatment regimens based on changes in tumor biology, ultimately improving patient outcomes and addressing potential resistance mechanisms.

4.2 Combination therapy strategies

The lack of regular and prolonged responses to DDR inhibitors, even among biomarker-selected populations, highlight the presence of intrinsic or acquired resistance mechanisms to single-agent therapy. Generally, a tumor's sensitivity to and resistance against DDR inhibitors is significantly influenced by the remaining proficiency of SSB and DSB response and repair mechanisms, cell cycle regulation, chromatin remodeling pathways, and the activity of oncogenic pathways, all of which can affect DDR processes and the availability and utilization of cellular resources. Gaining insights into the systemic biology underlying these patterns of sensitivity and resistance can directly inform the development of combination treatment strategies. By pairing DDR inhibitors with therapies such as chemotherapy, radiation, immunotherapy, or other targeted agents, researchers aim to create synergistic effects that maximize DNA damage in cancer cells while minimizing the impact on healthy tissues. For instance, combining PARP inhibitors with platinum-based chemotherapies or immune checkpoint inhibitors can amplify tumor cell death by simultaneously inducing DNA damage and impairing the cancer cell's repair mechanisms[99]. Immunotherapy-DDR inhibitor combinations are particularly promising, as DDR inhibition can increase tumor mutational burden and antigen presentation, making the cancer cells more susceptible to immune attack[100]. In addition to these synergistic approaches, future combinations may utilize DDR inhibitors to sensitize tumors to emerge therapies like CAR T-cell or NK cell-based treatments, expanding the applicability of immuno-oncology.

4.3 Advanced delivery methods

Advanced delivery methods for DDR inhibitors are anticipated to greatly enhance their therapeutic precision, efficacy, and safety in cancer therapy. Cutting-edge drug delivery systems, such as nanoparticle-based carriers, are being explored to transport DDR inhibitors directly to tumor sites[101]. These nanoparticles can be specifically designed to target cancer cells by leveraging tumor-specific markers, ensuring that higher concentrations of the drug are delivered to the cancer while minimizing exposure to healthy tissues, thereby reducing side effects. In addition, nanoparticle formulations can be engineered for controlled drug release, which allows for sustained delivery of DDR inhibitors, potentially improving drug effectiveness by maintaining therapeutic levels over longer durations. Another promising approach is the utilization of antibody-drug conjugates that combine the specificity of monoclonal antibodies with the potency of DDR inhibitors, potentially reducing the severity of side effects by preferentially targeting their payload to the tumor site[102]. For DDR inhibitors that need to cross biological barriers, such as the blood-brain barrier in treating brain can-

cers, innovative strategies like receptor-mediated transcytosis and lipid-based carriers are being developed to enhance drug transport. These advanced delivery techniques offer significant promise for maximizing the therapeutic efficacy of DDR inhibitors in oncology.

4.4 AI (artificial intelligence) integration

AI holds immense potential in shaping the future of DDR inhibitor development[103]. As AI technologies advance, they are increasingly capable of identifying complex DDR-related vulnerabilities across various cancer types by analyzing large-scale omics data, such as genomics, transcriptomics, and proteomics. These insights allow researchers to discover previously unknown DDR targets, refine synthetic lethality concepts, and predict which specific DDR pathways can be targeted for optimal therapeutic outcomes. In drug discovery, AI models streamline the design of DDR inhibitors with higher potency and specificity by predicting molecular interactions, optimizing binding affinities, and even proposing chemical modifications for enhanced efficacy[104]. AI-driven algorithms can also simulate how different DDR inhibitors may work in combination therapies, identifying synergies with other treatments like immunotherapies or radiotherapy, thus personalizing therapeutic approaches to match individual cancer profiles. Beyond drug discovery, AI plays a crucial role in precision medicine, enabling real-time patient monitoring and predictive modeling to detect treatment responses and emerging resistance. AI tools integrated with digital health platforms allow continuous collection and analysis of patient biomarkers, predicting resistance pathways and enabling timely treatment adjustments.

Chemistry42 is a software platform for *de novo* small molecule design and optimization that integrates AI techniques with computational and medicinal chemistry methodologies[105]. Chemistry42 efficiently generates novel molecular structures with optimized properties validated in both *in vitro* and *in vivo* studies and is available through licensing or collaboration. ISM3091 is a cutting-edge small-molecule inhibitor of USP1, developed by Insilico Medicine using Chemistry42. This candidate drug has shown potent antiproliferative activity and exceptional selectivity in tumor cells with HR deficiency mutations, such as those in the BRCA genes.

5 Conclusions

The current landscape of DDR and its inhibitors underscores their transformative role in cancer treatment, particularly for cancers with genetic vulnerabilities like BRCA mutations. DDR inhibitors, especially PARP inhibitors, have opened new avenues for targeting tumor cells by exploiting compromised DNA repair pathways. However, apart from PARP inhibitors, no new classes of DDR inhibitors have advanced to later-stage clinical trials due to the complexity of the tumor microenvironment, challenges in identifying specific targets, difficulties in biomarker identification, and the need to overcome general resistance mechanisms. Looking ahead, the future of DDR therapies will focus on biomarker-driven approaches, innovative combination strategies, advanced delivery methods and formulations, and the integration of AI, all of which are expected to enhance the precision, efficiency, and personalization of cancer treatments.

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