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PERSPECTIVE

Insights into the DNA damage response and tumor drug resistance

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Overview of the DNA damage response (DDR) in tumor cells

DDR is a highly coordinated signaling network that repairs DNA damage caused by intrinsic cellular processes and extrinsic insults, thereby preventing genome instability. Depending on the type of damage, distinct DNA damage repair and DNA damage tolerance (DDT) pathways are involved and coordinately regulated. Since the 1980s, an increasingly clear relationship between DDR and carcinogenesis has been demonstrated through extensive evidence. DDR-associated genes are frequently mutated in tumor cells, thus leading to genetic hypermutagenesis and consequently fueling carcinogenesis. In this context, inactivating mutations in DDR genes, such as the homologous recombination (HR) genes breast cancer type 1/2 susceptibility gene *BRCA1/2*; mismatch repair genes MutS homolog 2 (*MSH2*) or MutL homolog 1 (*MLH1*); and DNA translesion synthesis (TLS) polymerase genes, predispose individuals to the development of a wide range of tumor types[1].

Given the essential roles of the DDR in cell survival and proliferation, chemotherapeutic drugs have been developed and widely used to induce DNA damage in rapidly proliferating tumor cells, thereby inducing replication stress and cell death. Double-strand breaks (DSBs) and inter-strand or intra-strand crosslinks are typical types of harmful DNA damage induced by chemotherapeutic drugs, such as etoposide, cisplatin, and mitomycin (**Table 1**). DSB is among the most toxic forms of DNA damage and is repaired predominantly through the error-free HR and error-prone non-homologous end-joining (NHEJ) pathways. In general, platinum-induced intra-strand crosslinks are specifically bypassed by DNA polymerase eta (Polη), a classical factor in the TLS pathway, thus decreasing the anti-tumorigenic effect of platinum-based drugs[2]. Unfortunately, DDR defects in tumor cells not only confer sensitivity to DNA-damaging agents but also cause additional genetic mutations, thus promoting acquired chemoresistance and facilitating tumor recurrence. Therefore, DDR pathways have both benefits and drawbacks in cancer prevention and chemotherapy. This perspective is aimed at summarizing recent studies on the molecular mechanisms underlying DDR in chemoresistance, which have provided novel and promising biomarkers and strategies for improving the efficacy of chemotherapy.

Mechanisms of chemoresistance to DNA-damaging agents

DNA-damaging agents exert antitumor effects by inducing DNA damage. The mechanisms underlying DDR-related tumor chemoresistance identified to date can be categorized into 3 main groups: genetic mutation mechanisms, including genetic reversion of DDR defects, allelic variation in DDR genes and DDR pathway rewiring; post-translational modification (PTM) alteration mechanisms; and epigenetic remodeling mechanisms (**Figure 1**).

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Table 1 Summary of DNA-damaging chemotherapy drugs used in clinical settings

Action groups	Mechanism of action	Representative drugs
Alkylating agents	Induce DNA inter-strand or intra-strand crosslinks	Bendamustine, beusulfan, carboplatin, carmustine, cisplatin, cyclophosphamide, ifosfamide, lomustine, melphalan, mitomycin, oxaliplatin, temozolomide, thiotepa, trabectedin
Antibiotics	Interfere with DNA replication	Bleomycin, dactinomycin
Antimetabolites	Interfere with DNA replication	Doxorubicin, daunorubicin, epirubicin, 5-fluorouracil
Topoisomerase inhibitors	Induce DNA strand breaks	Camptothecin, etoposide, irinotecan, idrarubicin, mitoxantrone, topotecan, teniposide, valrubicin
DDR inhibitors	Interfere with DDR	ATMi, ATRi, CHK1/2i, DNA-PKi, HDACi, PARPi

Genetic mutation mechanisms of chemoresistance

During chemotherapy, tumor cells survive by acquiring genetic aberrations. Because the functions of DDR proteins can be either restored or abolished by mutations in DDR genes, genetic mutations have differential effects on therapy resistance. Genetic reversion of DDR defects, potential consequences of alternative splicing, frameshift mutations, or germline mutation correction, have been identified in DDR-deficient tumors with acquired chemotherapeutic resistance. The best-known example is poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi) drugs, which selectively kill HR-deficient tumor cells by inducing DSBs. PARPi treatment has shown great promise in the clinical treatment of BRCA-mutant ovarian and breast tumors. However, some BRCA-deficient tumors exhibit PARPi resistance driven by genetic restoration of BRCA protein function and reversal of HR activity[3]. In contrast, some mutations in DDR genes might partially or completely abolish the function of DDR proteins. Consequently, the existence of allelic variation in DDR genes has differential effects on therapy outcomes. The single-nucleotide polymorphism (SNP) rs4971059 enhances the expression of tripartite motif 46 (TRIM46), which in turn acts as an E3 ligase targeting histone deacetylase 1 (HDAC1) for degradation, thus leading to transcriptional upregulation of a panel of DDR genes endowing chemoresistance in breast cancer[4].

Moreover, DDR pathway rewiring in tumors contributes to the development of resistance to DNA-damaging agents. HR is essential for error-free S/G2 phase DSB repair, whereas defects in HR lead to PARPi hypersensitivity. The S/G2 phase-specific binding of BRCA1 to DSBs promotes DNA end resection and thereby prevents NHEJ. However, in some intrinsic HR-deficient tumors, suppression of the NHEJ pathway alleviates PARPi sensitivity, because of the shift from the NHEJ to the HR pathway. The loss of several critical factors that inhibit DNA end resection, such as p53 binding protein 1 (53BP1), the Shieldin complex, and REV7, promotes HR repair and leads to resistance in tumor cells with BRCA1 deficiency[5].

Alterations in PTM mechanisms in chemoresistance

Beyond genetic mutations in DDR genes, PTM alterations are considered critical in controlling chemotherapy outcomes by modulating the transduction of DDR signals, the stability of DDR proteins, and the dynamic phase separation of DDR factors. PTM involves dynamic and enzyme-mediated processes that covalently add functional groups at specific residues of substrate proteins. DDR proteins undergo multiple types of PTMs, including phosphorylation, ubiquitination, methylation, glycosylation, and lactylation. In particular, ataxia telangiectasia mutated (ATM), ataxia telangiectasia mutated and Rad3-related (ATR), and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) are 3 principal kinases triggered by DNA damage at early stages of DDR, their activation is responsible for the phosphorylation of downstream DDR effectors and the magnitude of the DDR signaling cascade. More recently, lactate-induced lactylation of DDR proteins, such as meiotic recombination 11 (MRE11) and Nijmengen breakage syndrome 1 (NBS1), have been shown to promote HR and contribute to clinical resistance to cisplatin or PARPi[6,7]. These findings suggest that tumor metabolites can modulate DDR and chemoresistance. To repair DSBs, numerous DDR factors, particularly 53BP1 and fused in sarcoma (FUS), concentrate

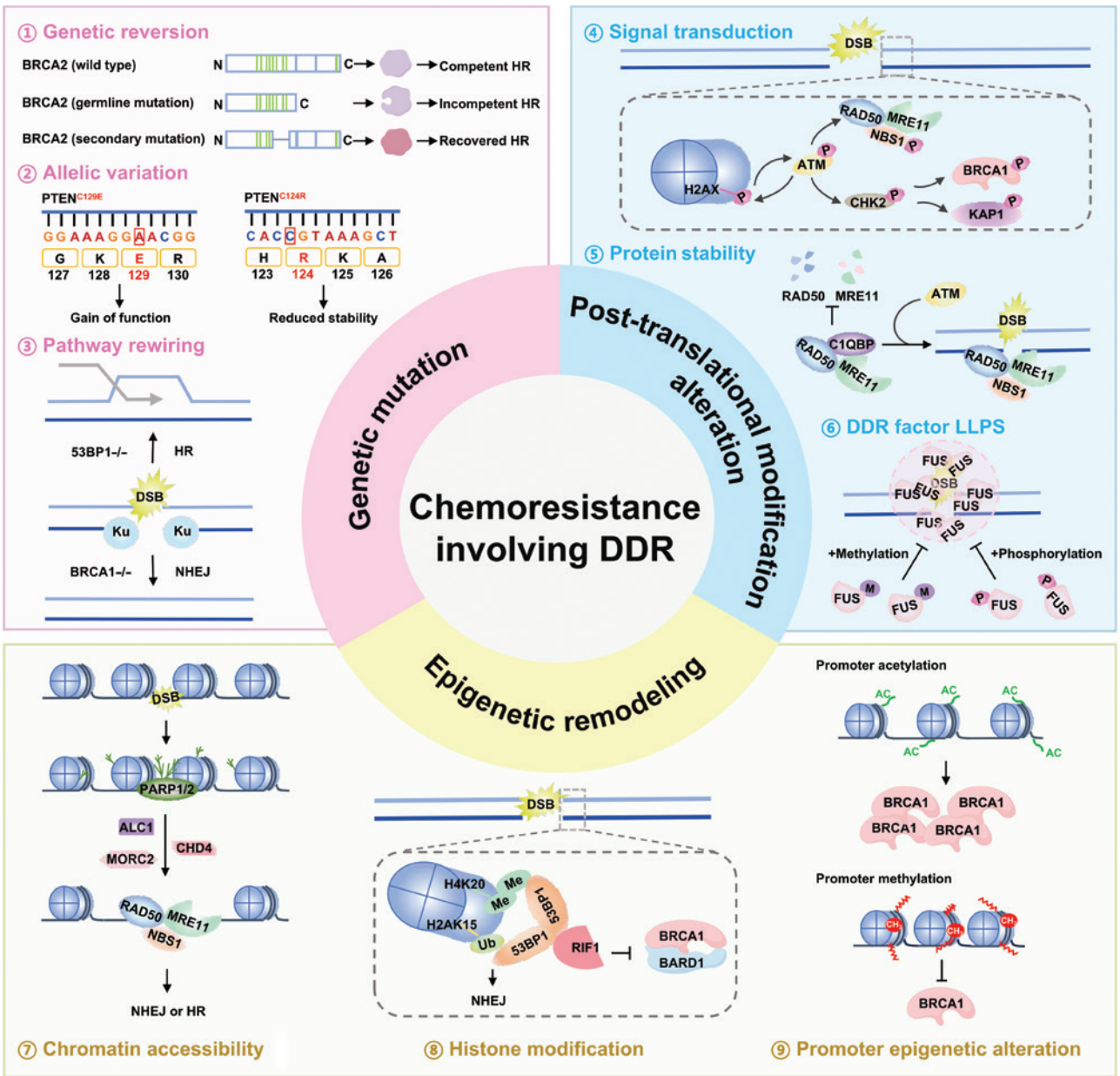


Figure 1 DDR-related mechanisms of chemoresistance to DNA-damaging agents. Resistance to DNA-damaging agents can result from recovery of DDR activity after genetic mutation of DDR genes, PTM alterations in DDR proteins, and epigenetic remodeling. ① Genetic reversion of DDR deficiency. Treatment with DNA-damaging agents can cause secondary mutations leading to partial or complete restoration of DDR protein activity, as shown for BRCA2. ② Allelic variation in DDR genes has differential effects on the chemotherapy response. C124R and C129E are 2 common missense mutations in PTEN that decrease PTEN stability or confer gain of function, respectively. ③ Pathway rewiring caused by genetic mutation of DDR genes shifts the balance among DDR pathways, such as 53BP1-mediated NHEJ and BRCA1-mediated HR. ④ PTMs modulate DDR signal transduction, as shown for ATM/CHK2-catalyzed phosphorylation after DSB induction. ⑤ PTMs regulate DDR protein stability. C1QBP stabilizes MRE11/RAD50 and protects it from degradation, and inhibits MRE11-dependent nonspecific resection in the absence of stress conditions. In the case of DSBs, ATM phosphorylates MRE11; subsequently, C1QBP dissociation from MRE11/RAD50 promotes MRE11/RAD50/NBS1 (MRN) complex assembly and DSB end resection. ⑥ PTMs control the phase separation of DDR factors. LLPS of FUS is inhibited by its methylation and phosphorylation. ⑦ Chromatin relaxation surrounding DNA damage sites is responsible for efficient DDR protein accumulation and the promotion of chemoresistance. After DSB formation, histone PARylation triggers nucleosomal disassembly, and chromatin remodelers such as ALC1, CHD4, and MORC2 orchestrate further alterations in chromatin structure. ⑧ Histone PTMs affect DDR

factor accumulation and DDR pathway choice. For example, H2AK15 monoubiquitination and H4K20 dimethylation promote 53BP1-mediated NHEJ and antagonize BRCA1-mediated HR at DSBs. ⑨ DNA epigenetic modifications modulate DDR protein expression, as shown for the promoter methylation or acetylation of BRCA1. 53BP1, p53 binding protein 1; ALC1, amplified in liver cancer 1; ATM, ataxia telangiectasia mutated; BARD1, BRCA1 associated RING domain 1; BRCA1, breast cancer type 1 susceptibility protein; BRCA2, breast cancer type 2 susceptibility protein; C1QBP, complement C1q binding protein; CHD4, chromodomain helicase DNA binding protein 4; CHK2, checkpoint kinase 2; DSB, double-strand break; FUS, fused in sarcoma; H2AK15, histone H2A lysine 15; H4K20, histone 4 lysine 20; HR, homologous recombination; KAP1, KRAB-associated protein 1; MORC2, microrchidia CW-type zinc finger 2; MRE11, meiotic recombination 11; NBS1, Nijmengen breakage syndrome 1; NHEJ, non-homologous end-joining; PARP1/2, poly(ADP-ribose) polymerase 1/2; PTEN, phosphatase and tensin homolog; RIF1, replication timing regulatory factor 1. Figure was created in Word Processing System (WPS) and Figdraw.

at damage sites and form droplet-like membraneless structures *via* liquid-liquid phase separation (LLPS)[8]. PTMs have been proposed to regulate LLPS of DDR factors, thereby contributing to the DDR process by altering protein conformation and protein–protein interactions. For example, arginine methylation, together with phosphorylation, has been found to interrupt FUS LLPS formation[9,10].

To date, extensive crosstalk among PTM types has been described in DDR. Dysregulated expression of the enzymes responsible for DDR protein PTMs has been observed in a variety of tumors and associated with poor outcomes of treatment with DNA-damaging agents. For example, the methyltransferase SYMD3—which functions in HR repair and genome stability through ATM methylation, thereby promoting the DDR signaling cascade—is dysregulated and contributes to chemoresistance in colorectal cancer, hepatocellular cancer, and breast cancer[11]. In response to cisplatin treatment, proliferating cell nuclear antigen (PCNA), a homotrimeric sliding clamp in the replisome, is mono-ubiquitinated by the E3 ubiquitin ligase RAD18 and subsequently initiates the TLS pathway. Beyond its role in TLS, RAD18 coordinates other DDR pathways, including HR and Fanconi anemia. However, the expression of RAD18 is altered in various tumors. Suppression of RAD18 decreases PCNA mono-ubiquitination, and increases tumor sensitivity to cisplatin, etoposide, and camptothecin. Collectively, DDR protein-related PTM alterations are potential drivers of acquired cancer drug resistance.

Epigenetic remodeling mechanisms of chemoresistance

Epigenetic remodeling mechanisms are responsible for DDR dysregulation and hence drug resistance. During DDR, chromatin undergoes transient relaxation, which in turn enables DDR proteins to access damaged DNA; after DDR completion, chromatin condensation occurs. Histones are essential in mediating chromatin conformation and DDR protein accumulation. In response to DNA-damaging agents, the dynamic conformational shift of chromatin relaxation relies strongly on nucleosomal disassembly triggered by the PARylation of core histones. After histone PARylation, chromatin remodelers such as amplified in liver cancer 1 (ALC1) and chromodomain helicase DNA binding protein 4 (CHD4) are recruited by PARP1 and PARylated histones. These remodelers further orchestrate alterations in chromatin structure, which are responsible for efficient DDR protein accumulation and promotion of chemoresistance. The expression of chromatin remodelers governs the efficacy of DNA-damaging agents. For example, ALC1 deficiency decreases chromatin accessibility and promotes apurinic/apyrimidinic endodeoxyribonuclease 1 (APE1)-dependent DSB formation and replication fork stalling, thereby resulting in PARPi hypersensitivity in BRCA-mutant cells[12]. A recent study has revealed that dynamic SUMOylation of microrchidia CW-type zinc finger 2 (MORC2), an ATPase-dependent chromatin remodeling enzyme, contributes to proper chromatin remodeling and DDR. Inhibition of MORC2 SUMOylation enhances the sensitivity of breast cancer cells to chemotherapeutic drugs[13]. Beyond chromatin remodeling, histone PTMs surrounding DNA damage sites directly affect DDR factor accumulation and DDR pathway choice. For example, the status of histone H2A lysine 15 (H2AK15) ubiquitination and histone 4 lysine 20 (H4K20) methylation determines whether 53BP1-mediated NHEJ or BRCA1-mediated HR occurs at DSBs[14]. Diacetylated H2A lysine 5 and lysine 9 (H2AK5acK9ac) around DSBs also antagonizes NHEJ repair by promoting BRD4-Ku80 LLPS. The mitotic deacetylase complex (MiDAC) removes di-acetyls from H2AK5K9 and suppresses BRD4-KU condensates, and therefore is a likely potential regulator in

tumor chemotherapy[15]. Moreover, DDR activity is altered by modulation of the expression of DDR proteins, such as BRCA1, *via* promoter epigenetic modifications, including DNA methylation and acetylation, which frequently occur in tumors. Hence, targeting epigenetic remodeling in combination with DNA-damaging agents might reverse tumor cell resistance.

Overcoming chemoresistance *via* the DDR pathway

Given the essential roles of DDR in intrinsic and acquired drug resistance during chemotherapy, efforts have been made to address chemoresistance by increasing the toxicity of DNA-damaging drugs during chemotherapy. In principle, beyond efforts to enhance drug uptake, intrinsic drug resistance in tumors could be avoided with precise medicine regimens emphasizing the precise matching of specific DDR-deficient patients to targeted therapies. To maximize the efficacy of chemotherapy and overcome adverse effects in normal cells, developing biomarkers of DDR pathways that predict the response to DNA-damaging agents is critical. Hereditary mutations or copy number aberrations of DDR genes are known as potential predictive biomarkers for selecting optimal therapeutics. For example, HR deficiency (HRD) phenotype detection is used for patient stratification in clinical PARPi treatment. Beyond the 2 most common indicators of HR activity, BRCA1 and BRCA2, a computational tool, signature multivariate analysis (SigMA), has been demonstrated to accurately detect HRD candidates[16]. Moreover, numerous DDR regulators, including proteins and noncoding RNAs, have been identified as potential functional biomarkers and druggable targets. For example, the long noncoding RNA CTD-2256P15.2-derived micropeptide PACMP, which plays a dual role in the maintenance of CtBP-interacting protein (CtIP) abundance and poly(ADP-ribosyl)ation stimulation, causes resistance to several DNA-damaging agents, including epirubicin, camptothecin, and PARPi[17]. Recently, vestigial-like 3 (VGLL3), an essential transcription cofactor, has been shown to promote HR repair, whose inhibition sensitizes tumor cells to etoposide treatment and further inhibits tumor progression[18]. Consequently, on the basis of numerous classical and potential DDR biomarkers, better therapeutic outcomes can be achieved through personalized drug treatment and novel drug development.

As discussed above, acquired drug resistance resulting from dysregulated DDR activity poses a major obstacle to the use of DNA-damaging agents in clinical settings. Combination therapy strategies that inhibit the response of key DDR proteins to chemotherapeutic agents or target specific DDR defects hold promise for re-sensitizing tumors to chemotherapeutics. Therefore, the development of DDR inhibitors is an attractive strategy for reversing drug resistance (**Table 2**). Given the primary roles of ATM and ATR kinases in DDR signaling cascade activation, the inhibition of ATM or ATR, coupled with chemotherapy drugs, increases antitumor efficacy[19]. Similarly, inhibitors of downstream targets of these kinases, such as checkpoint kinase 1 (CHK1), exacerbate the cytotoxicity of DNA-damaging agents[20]. The TLS pathway enables bypassing of cisplatin-induced intra-strand crosslinks and contributes to cisplatin resistance. However, increased TLS capacity has been observed in tumor cells, thus leading to cell survival and chemoresistance. Compounds that limit TLS activity are expected to be potential chemosensitizers in tumor treatment. Beyond the small chemical molecules that inhibit the TLS polymerase REV1, the natural TLS inhibitor ganoboninketal C, derived from *Ganoderma* mushrooms, has recently been reported to sensitize tumor cells to cisplatin treatment[21]. Moreover, restored HR activity in HR-deficient tumors can be eliminated by inhibitors targeting DDR proteins, including RAD51 and ATR, thus further enhancing the sensitivity of tumor cells to PARPi. Drug treatment-induced epigenetic adaptation contributes to the accumulation of drug-resistant cells. Therefore, targeting epigenetic regulators is an effective strategy to reverse drug resistance. Inhibitors of chromatin remodelers, such as HDACs, have synergistic killing effects when used in combination with PARPi treatment in triple-negative breast cancer; this regimen is of great interest in testing the reversibility of PARPi resistance.

Summary

Generally, most chemotherapy drugs are DNA-damaging agents that trigger distinct types of DNA damage and therefore cell death. However, the emergence of innate or acquired resistance occurs in many tumors during treatment. Tumor drug resistance is a multifactorial phenomenon closely associated with the DDR—a process crucial for genomic integrity. Three different but not mutually exclusive mechanisms involving genetic mutation, PTM alteration, and epigenetic remodeling have been implicated in the dysregulation of DDR

Table 2 DDR inhibitors used in tumor combination chemotherapy

Target	Inhibitors			Pathway	Combination
ATM	AZD0156[b] M4076[b] KU60019[b]	AZD1390[b] KU55933[c]	M3541[b] KU59403[c]	HR NHEJ	Irinotecan Olaparib
ATR	ART0380[b] AZD6738[b] Berzosertib[b] DN020198[b] HRS2398[b] M6620[b] Tuvusertib[b]	ATG-018[b] AZ20[c] Camonsertib[b] Elimusertib[b] IMP9064[b] RP-3500[b]	ATRN-119[b] BAY1895344[b] Ceralasertib[b] Gartisertib[b] M4344[b] SC0245[b]	HR	Carboplatin Cisplatin Gemcitabine Irinotecan Niraparib Olaparib Topotecan Veliparib
CHK1/2	AZD7762[b] LY2603618[b] PF-00477736[b] UCN-01[b]	GDC-0575[b] LY2880070[b] Prexasertib[b]	GNE-323[c] MK-8776[b] SRA737[b]	HR NHEJ	Cisplatin Gemcitabine Irinotecan Olaparib
DNA-PKcs	AZD7648[b] CC-115[b] M9831[b] Peposertib[b]	BY101801[b] LY294002[c] Nu7026[c] Samotolisib[b]	BY101298[b] M3814[b] NU7441[c] XRD-0394[b]	NHEJ	Capecitabine Doxorubicin Etoposide
FEN1	FEN1-IN-1[c] FEN1-IN-4[c] FEN1-IN-7[c]	FEN1-IN-2[c] FEN1-IN-5[c] FEN1-IN-SC13[c]	FEN1-IN-3[c] FEN1-IN-6[c]		Camptothecin Cisplatin Olaparib
MRE11	Antitumor agent-96[c] PFM01[c]	Mirin[c] PFM39[c]	PFM03[c]	HR	Carboplatin Cisplatin Doxorubicin Olaparib
OGG1	OGG1-IN-08[c]	TH5487[c]	SU0268[c]	BER	Olaparib
PARP	ABT-767[b] AZD9574[b] CK-102[b] Fuzuloparib[a] HWH340[b] NMS-293[b] RP12146[b] SC10914[b] Stenoparib[b] TSL1502[b]	AMXI-5001[b] Basroparib[b] CVL218[b] HS-10502[b] Nesuparib[b] Olaparib[a] Rucaparib[a] Senaparib[b] Talazoparib[a] Veliparib[b]	AZD-2461[b] BMN-673[b] E7016[b] HTMC0435[b] Niraparib[a] Pamiparib[b] Saruparib[b] Simmiparib[b] TQB3823[b] Venadaparib[b]	BER NHEJ	Cisplatin Irinotecan Temozolomide
PARG	COH34[c] ETX-19477[b] PDD00017272[c]	DAT-2645[b] IDE161[b] PDD00017273[c]	Ethacridine[c] JA2131[c] PDD00031705[c]	BER NHEJ	Olaparib
Polθ	ART4215[b] GSK4524101[c] RP-6685[c]	ART558[c] Novobiocin[b] ZM-2311[c]	ART6043[b] RP-3467[b]	MMEJ	Niraparib Olaparib Talazoparib
RAD51	B02[c] RI-1[c] Chicago Skye Blue[c]	DIDS[c] RI-2[c]	IBR2[c] RS-1[c]	HR	Cisplatin Mitomycin C Olaparib
RAD52	AICAR[c] NP-004255[c]	D-103[c] 6-Hydroxy-DOPA[c]	D-G23[c]	HR	Cisplatin Olaparib

Table 2 Continued

Target	Inhibitors			Pathway	Combination
REV1	JH-RE-06[c]			TLS	Cisplatin
RPA	HAMNO[c] JC-229[c]	TDRL-551[c] NSC15520[c]	ML367[c] Anti-osteoporosis agent-1[c]		Cisplatin Etoposide Olaparib
USP1	C527[c] ML-323[c] TNG348[c]	I-138[c] SJB3-019A[c]	KSQ-4279[b] SJB2-043[c]	TLS FA	Cisplatin Olaparib
USP7	GNE-6640[c] HBX-28258[c] P22077[c] XL177A[c] YCH3124[c]	GNE-6776[c] HBX41108[c] USP7-055[c] XL188[c]	HBX19818[c] P005091[c] USP7-797[c] YCH2823[c]	HR	Cisplatin Etoposide Olaparib
WEE1	AZD1775[b] Debio0123[b] SC0191[b]	Adavosertib[b] IMP7068[b] SY-4835[b]	Azenosertib[b] PD0166285[c] ZN-c3[b]	G2/M checkpoint	Carboplatin Cisplatin Doxorubicin Gemcitabine Olaparib Paclitaxel
WRN	H3B-968[c] NSC19630[c]	HRO761[b] NSC617145[c]	NCGC00029283[c] VVD-214[c]	HR	Irinotecan Mitomycin C Olaparib

Stage of DDR inhibitors: [a]approved, [b]clinical, [c]preclinical.
BER, base excision repair; FA, Fanconi anemia; FEN1, flap endonuclease-1; MMEJ, microhomology-mediated end joining; OGG1, 8-oxoguanine DNA glycosylase; PARG, poly(ADP-ribose) glycohydrolase; REV1, REV1 DNA directed polymerase; RPA, replication protein A; USP1, ubiquitin-specific protease 1; USP7, ubiquitin-specific protease 7; WEE1, WEE1 G2 checkpoint kinase; WRN, Werner syndrome RecQ helicase.

and poor chemoresponse in tumor cells. Inhibitors targeting DDR proteins, combination therapies involving DNA damaging agents, and novel DDR factor-targeting compounds are frequently used strategies to improve antitumor efficacy.

After exposure to DNA-damaging agents, cells rewire biological activities such as rRNA biosynthesis, protein translation, endomembrane morphological change, and energy metabolism, thereby integrating them with the DDR and fine-tuning the systemic stress response. In particular, whereas elevated levels of 2-hydroxyglutarate (2HG), succinate, and fumarate suppress HR, the accumulation of lactate, a byproduct of the Warburg effect, promotes DDR activity in cancer cells, thus demonstrating a strong synergy between oncometabolites and the DDR. Therefore, oncometabolite interventions may be a promising approach for improving chemotherapy outcomes. Recently, an inhibitor of lactate dehydrogenase (LDHA), the glycolytic enzyme catalyzing pyruvate to lactate, has been found to alleviate the resistance of cancer cells to DNA-damaging agents. The innate immune response can also be activated by the DNA lesions caused by DNA-damaging agents, and the combination of DDR inhibitors with immune checkpoint blockade is another promising strategy for reversing chemoresistance. Given the high molecular heterogeneity among patients with cancer, predictive biomarkers of DDR inhibitors should be rigorously validated in further studies and clinical trials. In conclusion, a deeper understanding of DDR regulation in tumor cells would not only reveal how chemoresistance occurs after DNA damage treatment but also aid in the development of strategies to overcome chemoresistance.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xiaolu Ma and Caixia Guo.
Wrote the paper: Xiaolu Ma and Zina Cheng.
Revised the paper: Caixia Guo.

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