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REVIEW

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DNA repair and the contribution to chemotherapy resistance

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Abstract

The DNA damage response comprises a set of imperfect pathways that maintain cell survival following exposure to DNA damaging agents. Cancers frequently exhibit DNA repair pathway alterations that contribute to their intrinsic genome instability. This, in part, facilitates a therapeutic window for many chemotherapeutic agents whose mechanisms of action often converge at the generation of a double-strand DNA break. The development of therapy resistance occurs through countless molecular mechanisms that promote tolerance to DNA damage, often by preventing break formation or increasing repair capacity. This review broadly discusses the DNA damaging mechanisms of action for different classes of chemotherapeutics, how avoidance and repair of double-strand breaks can promote resistance, and strategic directions for counteracting therapy resistance.

Keywords Chemotherapy resistance, DNA repair, DNA damage response

DNA damage and repair in cancer

Chemotherapeutics cause DNA damage through a variety of mechanisms that often converge at the generation of a double-strand DNA break (DSB). DSB persistence leads to cell death or senescence. Resistance to chemotherapeutics can occur through mechanisms that suppress DSB accumulation, either by avoiding the induction of breaks or through adaptations that enhance their repair.

Chemotherapy-induced DNA damage is addressed through a set of layered repair mechanisms. Most DNA damage can be addressed at multiple stages; first, the initial lesions may be substrates of base excision repair

(BER), nucleotide excision repair (NER), mismatch repair (MMR), or direct alkylation reversal reactions through methylguanine methyltransferase (MGMT) or AlkB family homolog (ALKBH) proteins (Fig 1A). If unresolved, damage encountered by DNA replication machinery can be processed by several pathways. These replication stress tolerance mechanisms include error-free template switching (TS), error-prone translesion synthesis (TLS), lesion bypass via repriming, or replication fork stalling and reversal that induce a replication pause to engage other repair mechanisms prior to replication restart (Fig 1B). Finally, if failures occur at these steps, a one-ended or two-ended DSB is generated by conversion of single-strand breaks (SSBs) or gaps to DSBs as the replication machinery passes, or through nucleolytic cleavage of unprotected single-stranded DNA [1–7] (Fig 1C).

DSB repair is the last line of defense to resolve many types of lesions that escape other repair processes. The detection of a DSB activates the DNA damage response kinases ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR) or DNA-dependent protein kinase (DNA-PK). Their activation triggers a cascade of phosphorylation events that integrate repair with cell cycle and fate decisions,

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including histone variant H2AX, checkpoint kinases CHK1 or CHK2, and the tumor suppressor protein p53 leading to activation of WEE1 and MYT1 kinases and regulation of CDK1, 2, and the cyclin proteins. Ultimately, these signal cascades induce cell cycle arrest, DNA repair, senescence, or cell death [8, 9]. Cell fate choices are influenced by multiple factors, such as the extent and type of DNA damage, and may trigger apoptosis through p53-upregulated modulator of apoptosis (PUMA), Bcl2-associated X protein (BAX), BH3-interacting domain (BID), NOXA, FAS, DR5, and others [10–12]. In the absence of apoptotic signaling, cell cycle checkpoints promote DSB repair.

Repair of DSBs can occur through several distinct pathways that function with some degree of redundancy. However, the varied mechanics of each pathway differentially impact genome stability with some pathways considered to be error-free while others highly mutagenic. Despite enormous efforts to decipher the mechanisms regulating pathway selection, the process remains ambiguous and dependent on numerous factors including cell cycle phase [13–19] and the damaged DNA substrate [19, 20]. The predominant DSB repair pathways are nonhomologous end joining (NHEJ) and homologous recombination (HR) repair (Fig 1D). NHEJ is an efficient ligation of DSB ends that often introduces small insertions or deletions [17]. NHEJ operates through DNA end binding by the Ku70/Ku80 heterodimer, a DNA-bridging synaptic complex formed with the catalytic subunit of DNA-PK (DNA-PKcs), XRCC4, XLF and PAXX, then DNA ligase IV-mediated end ligation following any necessary processing by the Artemis nuclease or Polymerases μ , λ , or Terminal deoxynucleotidyl transferase (TdT) to generate compatible ends [21]. In the absence of DNA end protection, broken ends are resected in 5' to 3' directions initially by the MRE11, RAD50, NBS1 complex (MRN) with involvement of BRCA1 followed by resection elongation by nucleases EXO1, DNA2, and WRN/BLM to generate substrates for other repair pathways [22]. HR repair utilizes the resultant single-strand DNA overhangs to recombine with a homologous sister chromatid, a process initiated by the BRCA1-PALB2-BRCA2-RAD51 complex, to achieve error-free repair. Alternative end joining (Alt-EJ), microhomology-mediated end joining (MMEJ), and Polymerase

θ -mediated end joining (TMEJ) all describe a pathway that uses small regions of microhomology to anneal and repair breaks at the expense of generating microhomology-flanked deletions or templated insertions [17]. Single-strand annealing (SSA) similarly involves annealing of homologous DNA regions, although it requires the RAD52 recombinase and facilitates substantial deletions between areas of DNA repeats [20, 23]. Each pathway uses a distinct set of repair proteins and resolves DSBs with varying consequences for genome integrity in an attempt to stave off apoptosis.

In this review, we address the complex role the DNA damage response plays in the context of cancer. We discuss why DNA damaging agents effectively treat cancers and how alterations in DNA repair responses can limit their efficacy from clinical and basic biology perspectives.

Chemotherapeutics and DNA damage-mediated cytotoxicity

Chemotherapeutic options vary across cancer types, yet most regimens induce DNA damage. Some agents produce DSBs through straightforward mechanisms while others generate damage indirectly through disruption of various cell processes. Why DNA damage effectively kills cancer cells is somewhat enigmatic because mutagenesis and genome instability are a characteristic feature of most cancers. Nevertheless, the tolerance for genome instability is not limitless, and certain genetic material remains indispensable. Thus, cancer cells, as well as normal cells, are reliant on DNA repair mechanisms to counteract catastrophic genome instability and cell death.

Cancer intrinsic determinants of chemo-response

Oncogenic processes strain the DNA replication machinery, induce DNA damage, and tax the DNA damage response. Breaks occur through cell cycle checkpoint disruptions, nucleotide metabolism dysregulation, replication/transcription interference, and deregulation of replication origin firing [24–26]. For example, MYC overexpression increases the density of early-replicating origins and replication fork collapse [27]. Overexpressed cyclin E acts with CDK2, induces replication stress, and suppresses senescence [28–30]. RAS, MYC, and cyclin E overexpression substantially elevates replication stress

(See figure on next page.)

Fig. 1 Layers of DNA repair. **A** Specific DNA damage lesions are substrates for direct reversal reactions. Unresolved damage can cause conflict with DNA replication machinery and/or induce double-strand DNA breaks (DSBs). **B** DNA replication forks that encounter a lesion are rescued through several pathways. **C** DSBs are generated when fork rescue mechanisms fail, and lesions are subject to further processing or a subsequent round of DNA replication. **D** DSBs are induced directly or arise indirectly as a result of problematic replication. Repair occurs through different mechanisms with varying consequences for genome stability. Created in BioRender

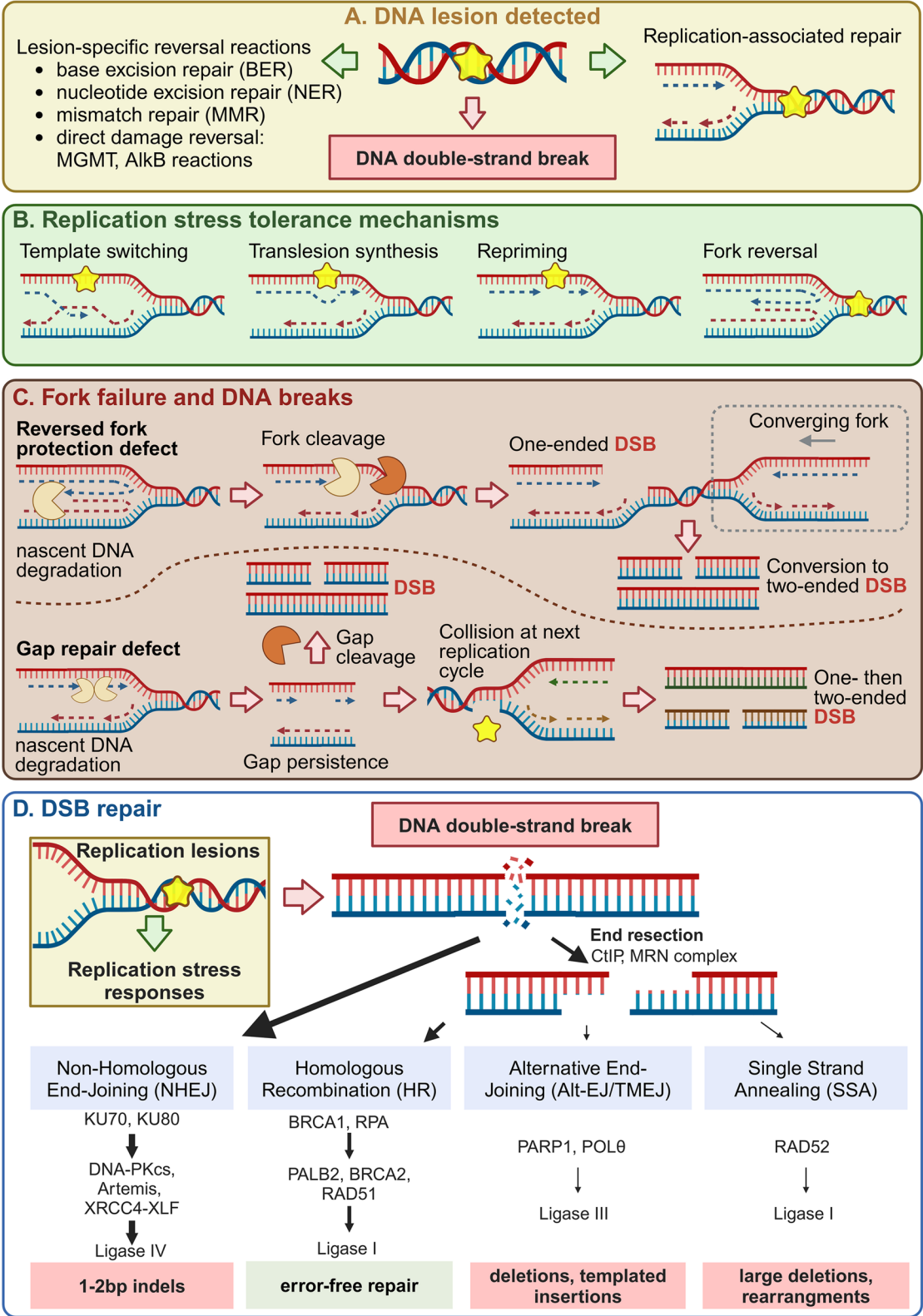


Fig. 1 (See legend on previous page.)

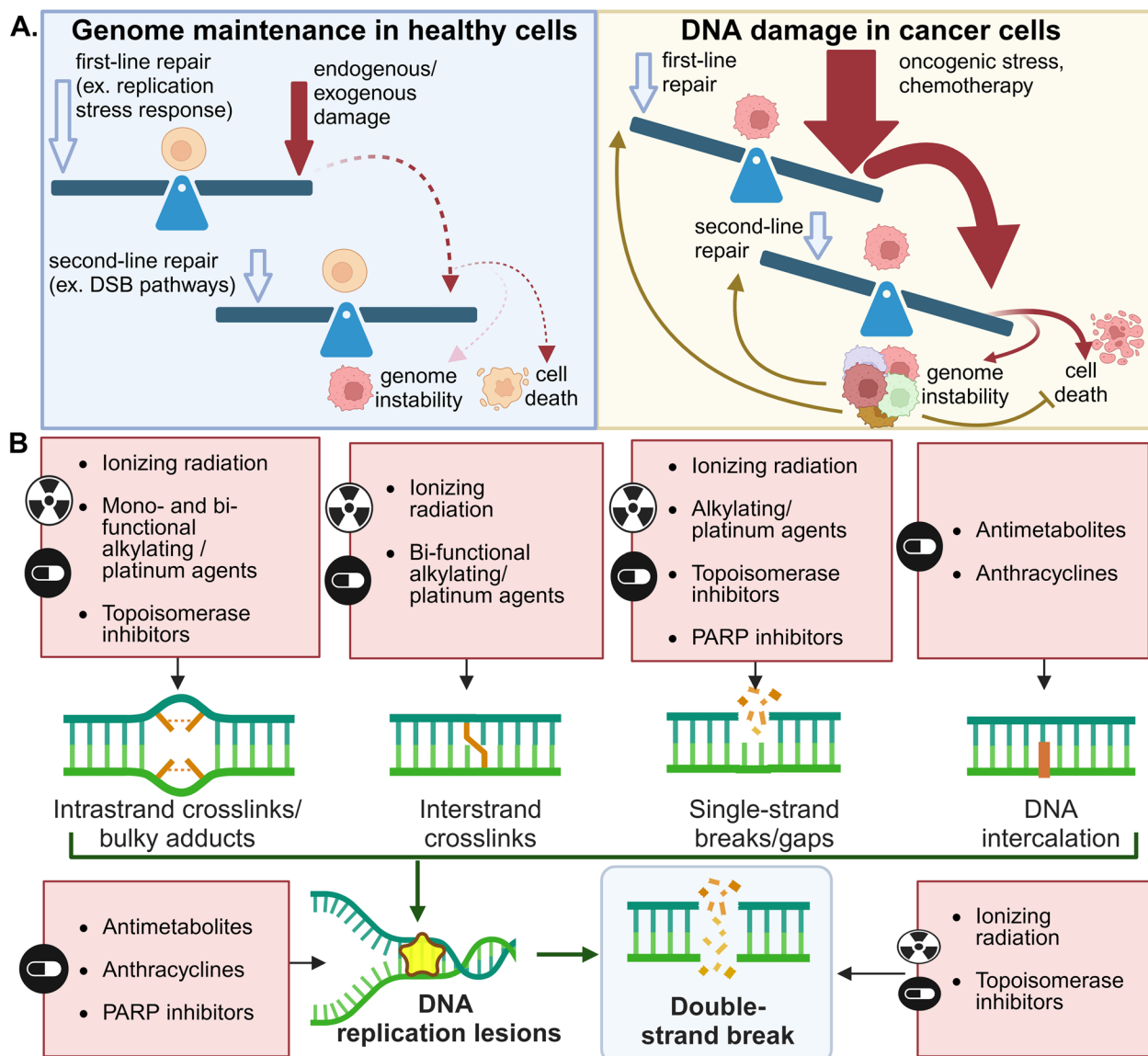


Fig. 2 Tolerance for DNA damage and chemotherapy. **A** Faithful DNA repair maintains genome stability. In contrast, mutagenic repair promotes cell survival at the expense of genome integrity and may contribute to tumorigenesis. DNA damaging chemotherapies push cells towards unsustainable levels of genome instability, potentially compounding DNA damage-causing oncogenic processes in cancer cells. DNA repair activity contributes to cell survival and alterations can drive radio- and chemoresistance. Genome instability resultant from mutagenic repair can promote adaptations that further enhance tolerance to therapy. **B** DNA damaging cancer treatments introduce distinct types of lesions that can ultimately result in DSBs. Created in BioRender

resulting from transcription-replication conflicts [31]. These oncogenic drivers differ between cancers; however, replication stress is a nearly universal feature of malignancy. Additional genome-destabilizing alterations, such as p53 pathway disruptions, allow continued replication despite genotoxic pressures [32, 33]. Exogenous, chemotherapy-induced DNA damage can overextend the DNA damage response in cancer cells already coping with oncogenic and replication stress-induced DNA

damage, mutagenesis, and genome instability [25, 34, 35] (Fig. 2A). Restated, chemotherapy pushes replicating cancer cells beyond an already stretched capacity for DNA repair [36, 37].

Altered DNA repair proficiencies contribute to tumor-intrinsic genome instability and can be a critical determinant of chemo-response. For example, defects in HR repair confer exquisite sensitivity to platinum agents and poly-ADP-ribose polymerase (PARP) inhibitors [38–40].

These defects arise from germline or somatic mutations in the *BRCA1* and *BRCA2* tumor suppressors [41–43], *BRCA1* promoter methylation [41, 44, 45], or mutations/methylation of other HR repair pathway genes such as *PALB2*, *RAD51C*, or *RAD51D* [45–50]. HR repair deficiencies are present in close to 50% of high-grade serous ovarian cancers, as well as a substantial proportion of triple negative breast cancers, prostate cancers, hematologic malignancies, and additional cancer types [45, 51–55]. Other repair gene mutations produce distinct sensitivity profiles. ATM defects lead to a pronounced radiotherapy sensitivity [56]. MGMT loss (often via hypermethylation in glioblastoma) or NER deficiencies (estimated for 10% of all cancers) confer hypersensitivity to alkylating DNA damage [57–60]. DNA mismatch repair defects (colorectal, endometrial, gastrointestinal, urinary tract, ovarian, pancreatic, breast, skin, and brain cancers [61–63]), through mutations or methylation of *MLH1*, *PMS2*, *MSH2*, *MSH6*, induce strong responses to antimetabolites and immunotherapies, but cause resistance to alkylating agents [64–69]. These instances of repair defects trigger the use of inappropriate or backup repair options rather than abrogating repair altogether. This repair activity contributes to a mutagenic environment in cancer, possibly to the initiation of cancer, and potentially to an adapted cancer state that no longer responds to the same therapeutics (or harbors the initial repair deficiency). For these reasons, the DNA damage response has been described as a “doubled-edged sword” that promotes cell survival and maintains genome stability yet encompasses mechanisms that contribute to mutagenesis, cancer cell survival, and therapy resistance.

Various routes to double-strand DNA breaks

DNA damage can take many forms, and the layered nature of the DNA damage response presents several opportunities to resolve issues, depending on the type of damage. The oncogenic processes, DNA repair alterations, and survival adaptations present within a particular cancer contribute to unique repair environments that may be more or less prepared to respond to different types of damage. DNA damaging anti-cancer agents function through different mechanisms of action and elicit specific DNA damage response pathways (Fig 2B and Table 1). Ultimately, repair failures often occur at multiple steps to generate a cytotoxic DSB. How chemotherapeutic agents induce damage determines which pathways might be engaged and whether a cell can mount a sufficient response to survive and avoid DSB accumulation.

Radiotherapy

Approximately 50% of all cancer patients receive radiotherapy [105, 106]. Radiotherapy is an effective and cost-efficient intervention across multiple cancer types, contributing to 40% of curative cancer treatments [107–109]. During radiotherapy, cancer cells are exposed to ionizing radiation, which causes the release of electrons from molecules within exposed tissue and generates ions that can directly break covalent bonds in the DNA backbone and also drives oxidative DNA damage [70, 110]. As a result, radiotherapy induces a range of DNA lesions, including damaged bases, DNA crosslinks, SSBs, and DSBs. Thus, DSBs occur directly from radiation exposure or as secondary events if other damage goes unrepaired and is then converted to breaks by nucleases or during replication [111, 112]. Given the breadth of DNA damage caused by radiotherapy, numerous DNA repair pathways are activated upon exposure, including HR, NHEJ, MMR, BER, and NER. Defects in any of these pathways sensitize cells to radiotherapy, and cancers with disruptive mutations (e.g. *ATM*, *ATR*, *CDKL1*, *PRKDC*, *PARP1*) are excellent responders. Small molecules targeting those pathways are being actively explored to enhance radiosensitivity [71, 113, 114]. Conversely, radio-resistance is often attributed to upregulated DNA repair capabilities, particularly the DSB response and most significantly, elevated NHEJ repair [109, 115, 116].

Alkylating and platinum agents

Alkylating agents add alkyl groups to DNA and cause DNA inter- and intra-strand cross-linking, RNA-DNA crosslinks, DNA mispairing, SSBs, and DSBs. Alkylators were among the first chemotherapeutics used with the nitrogen mustard Mechlorethamine deployed as a treatment against lymphomas, leukemias, and Hodgkin's disease [117]. Modern nitrogen mustard alkylators used as chemotherapeutics include cyclophosphamide, ifosfamide, melphalan, and chlorambucil. This class of therapeutics undergo metabolic processing to generate active compounds (at reduced toxicity compared to nitrogen mustard-based chemical warfare agents) and are bifunctional alkylators, meaning they possess two reactive groups capable of crosslinking DNA, RNA, and proteins. Other bifunctional alkylating chemotherapeutics include aziridines (mitomycin C, diaziquone, and thiotepa), nitrosoureas (carmustine, lomustine, nimustine), and platinum agents [77].

Approximately 10–20% of all cancer patients will receive a platinum drug during the course of their therapy [118]. Cisplatin, the first platinum-based alkylating chemotherapy drug, is effective against a variety of solid tumors, including testicular, ovarian, bladder, lung, and head and neck cancers [119]. Carboplatin

Table 1 Chemotherapeutics and activation of the DNA damage response

Therapeutic	Mechanism of action	Direct damage	Indirect damage	Repair activation	Examples
Radiotherapy	Ionizing radiation directly induces breaks in DNA and generates free radicals that cause further DNA damage [70, 71]	SSBs, DSBs [70, 71]	Base damage, abasic sites, SSBs, DSBs, crosslinks [70, 71]	Replication stress response, BER, NER, HR, NHEJ, SSA [70–72]	
Antimetabolites	Inhibits enzymes required for nucleotide synthesis [73] and/or incorporates into DNA to stall replication forks [74]	DNA replication lesions [74]	DSBs [74]	Replication stress response, BER, HR, NHEJ [75, 76]	See Table 2
Alkylating agents	Mono-functional Single reactive group modifies DNA base [77]	<i>N</i> ⁷ -methylguanine, <i>O</i> ⁶ -methylguanine, <i>N</i> ³ -methyladenine, Other <i>N</i> - and <i>O</i> -alkylated purines and pyrimidines [77]	DNA mispairing, DSBs [77]	BER, MMR, HR NHEJ [77]	Procarbazine, Dacarbazine, Methyl methanesulfonate (MMS), Temazolamide
	Bi-functional Alkylation by two reactive groups forms a crosslink [77]	Interstrand crosslinks, Intra-strand crosslinks, DNA protein crosslinks [77]	DSBs [77]	Fanconi anemia repair, NER, TLS, HR, NHEJ [77]	Nitrogen mustards: Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil Aziridines: Mitomycin C, Diaziquone, and Thiotepa Nitrosoureas: Carmustine, lomustine, Nimustine Platinum agents: Cisplatin, Carboplatin, Oxaliplatin
Topoisomerase inhibitors	Prevents the re-ligation of topoisomerase I and II induced DNA breaks [78, 79]	SSBs, DSBs [78, 79]	DSBs [78]	Replication stress responses, BER, HR, NHEJ [75]	Topoisomerase I inhibitors: Camptothecin, Topotecan, Irinotecan, SN38 Topoisomerase II inhibitors: Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone, Valrubicin, Mitoxantrone, Etoposide
PARPi	Traps PARP enzymes on DNA [80–83]	DNA replication lesions [80–82]	Persistent single-strand gaps and DSB with HR repair deficiency [81, 82]	Replication stress response (repriming, TS, TLS) [82, 84, 85], HR [86]	FDA approved: Olaparib, Rucaparib, Niraparib, Talazoparib

and oxaliplatin were subsequently developed to address toxicity and cisplatin resistance [119]. These agents primarily cause DNA damage via formation of intrastrand crosslinks, where covalent bonds form between adjacent guanine nucleotides of the same DNA strand, and are repaired by NER [119–121]. Interstrand (opposite DNA strand) crosslinks can also be formed to a lesser extent and are repaired by the Fanconi anemia pathway which combines the activities of NER, HR, and TLS [122, 123]. Intrastrand crosslinks distort the DNA structure and hinder essential processes like replication and repair, while interstrand crosslinks lock the DNA strands together and prevent them from separating during replication. The resulting distorted DNA structures impede both DNA replication and DNA repair processes, leading to catastrophic DNA damage (DSB and SSBs) and cell death [124].

Monofunctional alkylating agents retain a single reactive group and act through production of DNA adducts rather than crosslinks. These agents include procarbazine, dacarbazine, methyl methanesulfonate (MMS), and temozolomide [77]. These treatments result in methylation of DNA bases; predominantly N⁷-methyl guanine (N⁷mG) but also 3-methyl adenine (N³mA) and O⁶-methyl guanine (O⁶mG) [125]. BER rapidly resolves N⁷mG and N³mA lesions. In contrast, O⁶mG lesions are resolved by MGMT and can inappropriately activate MMR which is unable to repair the damage and instead interferes with replication fork progression, ultimately leading to DSBs [126, 127].

Antimetabolites

Antimetabolites are a large class of chemotherapeutics that interfere with DNA or RNA synthesis and are generally either folic acid, pyrimidine, or purine analogs (Table 2). Folate analogs, like methotrexate, inhibit dihydrofolate reductase (DHFR), an enzyme crucial for the synthesis of thymine nucleotides required for DNA replication. Pyrimidine analogs such as 5-fluorouracil (5-FU) interfere with DNA synthesis by inhibiting the enzyme thymidylate synthase, which is involved in the production of the nucleotide thymidine, required for DNA replication. Purine analogs, such as fludarabine, cladribine, mercaptopurine, and 6-thioguanine, instead mimic purine bases (adenine and guanine). Their incorporation into DNA terminates the DNA chain or stalls replication forks, causing DNA breaks if left unrepaired [73, 74]. Agent-specific mechanisms of action also contribute to cytotoxicity. For example, azacitabine and decitabine (5-Aza-2'-deoxycytidine) generate a DNA lesion that traps and crosslinks DNA methyltransferases (DNMTs) to the DNA, suppressing DNA methylation and forming

a DNA-protein crosslink that ultimately disrupts DNA replication and causes a DSB [128, 129].

Topoisomerase inhibitors and anthracyclines

Anthracyclines are potent DNA damaging chemotherapies derived from the bacteria *Streptomyces* spp. and include daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, and valrubicin. These compounds introduce DNA SSBs and DSBs through topoisomerase II inhibition, DNA intercalation, and free radical generation to varying extents depending on the drug [79, 130]. Topoisomerase II enzymes play a crucial role in managing DNA topology during replication and transcription by creating transient DNA DSBs to relieve topological stress caused by DNA supercoiling. Disrupting their activity can leave DNA in a state where cleavage occurs, but re-ligation is not possible. Mitoxantrone accomplishes this by intercalating into DNA and prevents re-ligation of topoisomerase II-mediated breaks, while etoposide directly inhibits the re-ligation activity [131]. Separate from topoisomerase II, topoisomerase I enzymes create SSBs to relieve torsional stress. Topoisomerase I inhibitor-mediated SSBs are converted to DSBs following continued DNA replication, likely through the MUS81-EME1/2 endonuclease, and can be suppressed by co-treatment with replication inhibitors [78, 132]. Topoisomerase I inhibitors include camptothecin, topotecan, irinotecan, and the irinotecan-derivative SN38. Topoisomerase inhibitors suffer from a variety of failure modalities, ranging from topoisomerase enzyme reductions to agent metabolism and other mechanisms that suppress DSB formation [133].

DNA repair pathway-targeted therapies

As of early 2025, PARP1/2 inhibitors (Olaparib, Rucaparib, Niraparib, Talazoparib) are the only DNA-repair targeted inhibitors approved by the U.S. Food and Drug Administration. PARP1/2 are nuclear poly(ADP-ribose) (PAR) polymerases with a broad range of cellular functions that impact BER repair, Okazaki fragment maturation, DSB signaling, telomere stability, DNA replication fork stabilization/reversal, and chromatin structure [134–136]. PARP1/2 inhibitors (PARPi) were originally developed as chemo-/radio-sensitizing agents but were found to be highly cytotoxic to BRCA1/2-deficient cells [38, 39] and effectively prolong survival in patients with HR repair-defective cancers [137, 138]. While the mechanisms underlying the targeted lethality for PARPi continue to be debated, there is an appreciation that PARPi trap PARP enzymes on DNA and induce replication-associated damage. Resultant DSBs are thought to be the primary cytotoxic lesion; however, single-strand DNA (ssDNA) gaps are also generated by

Table 2 Antimetabolite chemotherapeutics

Antimetabolite	Analogue	Primary target	Therapy	Cancer	References
5-fluorouracil	Pyrimidine	Thymidylate synthase, DNA/RNA incorporation	Carac, Tolak, Fluoroplex	Breast, colorectal, gastric, esophageal, head and neck, pancreatic, skin, cervical	[73, 74, 87]
6-thioguanine	Purine	Hypoxanthine-guanine phosphoribosyltransferase (HGPRTase), IMP dehydrogenase, DNA/RNA incorporation	Thioguanine, Tabloid	Acute myeloid leukemia (AML), chronic myeloid leukemia (CML)	[73, 74, 88]
6-mercaptopurine	Purine	HGPRTase, glutamine-5-phosphoribosylpyrophosphate amidotransferase, DNA incorporation	Purinethol	Acute lymphoblastic leukemia (ALL), Acute promyelocytic leukemia	[73, 74]
Azacitidine	Pyrimidine	DNA methyltransferase, DNA/RNA incorporation	Onureg, Vidaza	AML, chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS)	[73, 74, 89, 90]
Capecitabine	Pyrimidine	Metabolized to 5-FU	Xeloda	Breast, colorectal, gastric, esophageal, pancreatic	[73, 74, 91–93]
Cladribine	Purine	Ribonucleotide reductase, DNA incorporation	Mavenclad, Leustatin	Hairy cell leukemia, chronic lymphocytic leukemia (CLL)	[73, 74, 94]
Clofarabine	Purine	Ribonucleotide reductase, DNA polymerases, DNA incorporation	Clolar	ALL	[73, 74]
Cytarabine	Pyrimidine	DNA polymerases, DNA/RNA incorporation	Cytosar-U, DEPOCYT	Non-lymphocytic leukemia, ALL, AML, CML	[73, 74, 95]
Decitabine	Pyrimidine	DNA methyltransferase 1 (DNMT1)	Dacogen	MDS, CMML	[73, 74, 96]
Floxuridine	Pyrimidine	Metabolized to 5-FU	FUDR	Gastrointestinal	[73, 97]
Fludarabine	Purine	DNA polymerase α , ribonucleoside reductase, DNA primase	Fludara, Oforta	B-cell CLL	[73, 74]
Gemcitabine	Pyrimidine	DNA incorporation, ribonucleotide reductase	Gemzar, Infugem	Breast, non-small lung (NSCLC), ovarian, pancreatic, bladder, pancreatic	[73, 74, 98]
Hydroxyurea	Urea	Ribonucleoside reductase	Droxia, Hydrea	CML, head and neck	[73, 74, 99]
Methotrexate	Folate	DHFR, thymidylate synthase, aminoimidazole carboxamide ribonucleotide transformylase (AICART), amido phosphoribosyltransferase	Otrexup, Rasuvo, Trexall	Breast, bladder, head and neck, lung, osteosarcoma, ALL, AML, non-Hodgkin lymphoma	[100]
Nelarabine	Purine	Ribonucleoside reductase, DNA polymerases, DNA incorporation	Arranon	T-cell ALL and lymphoblastic lymphoma	[73]
Pentostatin	Purine	Adenosine deaminase (ADA), ribonucleotide reductase, DNA/RNA incorporation	Nipent	Hairy cell leukemia	[73, 94]
Pemetrexed	Folate	Thymidylate synthase, DHFR, Glycinamide ribonucleotide formyltransferase (GARFT)	Alimta, Pefmexy	Mesothelioma, NSCLC	[101]
Pralatrexate	Folate	DHFR	Folotylin	T-cell lymphoma	[102]
Trifluridine/tipiracil	Pyrimidine	Thymidylate synthase, thymidine phosphorylase, DNA incorporation	Lonsurf	Colorectal, gastric, esophageal	[73, 103, 104]

PRIMPOL-mediated repriming during replication, accumulate, and expand in PARPi-responsive contexts [80, 84, 139–141]. One model of reconciliation is that trapped PARP induces a replication block addressed through repriming where PARPi-sensitive cells subsequently fail to repair gaps, and unrepaired lesions get converted to DSB at the next round of DNA synthesis [82, 142]. Alternatively, a DSB-independent direct induction of apoptosis by gap accumulation may occur, particularly once cellular pools of the ssDNA protection protein RPA are

exhausted [81] (Fig 3A–D). Replication gaps are observed with other agents including platinum and hydroxyurea in specific genetic contexts so the cell death trigger could have broad implications for the understanding of various chemotherapy mechanisms of action [84, 141, 143, 144]. Ultimately, a model where chemotherapy-induced replication stress leads to accumulation of double-strand DNA breaks may be broadly applicable for both conventional and targeted therapeutic strategies.

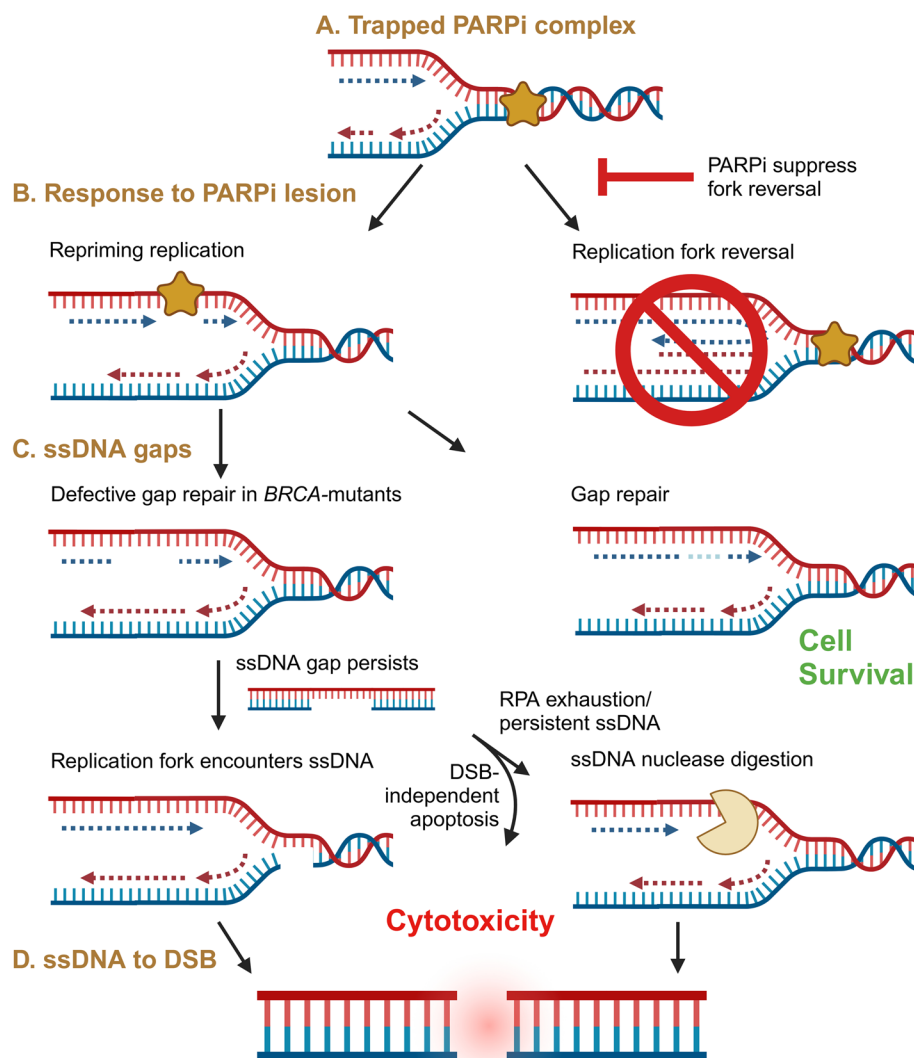


Fig. 3 PARP inhibition and DNA damage. **A** PARPi trap the PARP enzymes on DNA resulting in replication fork blockage. **B** PARPi prevent replication fork reversal and induce ssDNA gaps due to repriming. **C** Gap repair is defective in BRCA1 and BRCA2-deficient cancers and ultimately results in cell death. **D** DSBs can arise through several possible mechanisms. Additional chemotherapeutics induce gaps and may operate through similar pathways in HR repair-deficient cancers. Created in BioRender

DNA damage response contributions to chemoresistance

Chemotherapy resistance occurs through countless molecular possibilities, many specific to the mechanism of action of the individual agents discussed above. The DNA damage response contributes to several facets of resistance, ranging from the resolution of lesions prior to the induction of a cytotoxic DSB, to the repair of DSBs generated as direct or indirect consequences of treatment. Because many therapeutics ultimately trigger cell death via DSB induction, here, we categorically discuss chemotherapy tolerance with a DSB-centric focus by broadly classifying resistance as mechanisms that prevent

or repair DSBs. Notably, DNA repair is often imperfect and cell survival can come at the expense of genome instability and mutagenesis. As a result, the DNA damage response also contributes to a genomically diverse tumor microenvironment that can adapt to overcome selective/therapeutic pressures.

Limiting the cytotoxicity of DNA damaging chemotherapy Break suppression/avoidance

One route to avoiding the cytotoxicity of DNA damaging agents is to prevent the induction of DSBs. This can be accomplished by suppressing agent activity through metabolic or other processes, reducing drug target

availability, and repairing lesions prior to conversion to DSBs. A straightforward example of damage avoidance is through activity of drug efflux pumps [145, 146]. Not all chemotherapeutics are compatible pump substrates and the mechanics of each agent introduce unique molecular opportunities for resistance. *PARP1* mutations or loss may promote resistance to PARPi by preventing the trapping of PARP1 on DNA and suppressing the formation of DSBs [147]. Along similar lines, acquisition of topoisomerase I mutations present a specific example of drug target disruption by eliminating DNA cleavage activity and nullifying the effect of camptothecin [148–154]. Another unique example, discovered in the context of topoisomerase II-inhibition, is an upregulation of a RAD54L2-mediated mechanism to promote topoisomerase II turnover, thus limiting the ability of inhibitors such as etoposide to generate breaks [155, 156]. The pharmacologic and biological properties, as well as mechanism of action, of each agent determine the possible routes cancers could utilize to limit their capacity to induce DNA damage.

The initial DNA damage lesions generated by many chemotherapeutic agents are substrates for “direct reversal” reactions that detect and enzymatically remove damage before conversion to a DSB occurs [157]. In response to DNA alkylation, the repair protein MGMT directly removes the methyl group associated with O⁶mG in a stoichiometric reaction that restores the guanine base but results in an irreversible methylated MGMT protein that is then degraded. Unsurprisingly, MGMT expression levels correlate to response to alkylating agents. Expression levels are particularly important for predicting glioblastoma response to temozolamide with elevated expression indicating an increased repair capacity and chemoresistance [158–162]. Beyond MGMT, the ALKBH proteins participate in direct reversal of base alkylation (among other diverse functions). Of the ALKBH proteins, ALKBH2 and ALKBH3 are principally involved in removing the alkyl groups from DNA lesions through an enzymatic conversion of α -ketoglutarate to succinate and carbon dioxide. Expression and activity levels of the ALKBH proteins are also associated with resistance to alkylating damage [163–165]. In general, increased levels of the proteins responsible for directly counteracting lesions are associated with increased repair, lower DSB generation, and reduced responses.

Many chemotherapeutic agents induce DNA damage lesions that are addressed through BER, NER, or MMR mechanisms. Successful repair through these pathways prevents collisions with DNA replication machinery and conversion to DSBs. Overexpression of these repair pathway proteins, particularly if serving rate-limiting functions in repair, may drive enhanced repair and

chemotherapeutic tolerance. One example is APE1, a rate-limiting endonuclease essential to BER, that when overexpressed can promote cisplatin resistance through elevated BER [166–169]. Interestingly, and in contrast to elevated BER activity promoting resistance, MMR loss can drive resistance to various chemotherapeutics including some alkylating agents and antimetabolites [170–175]. The absence of MMR is thought to eliminate MMR-mediated nick and gap formation that ultimately result in DSBs during replication, following an inability to complete repair for some types of lesions (futile cycling) [176].

A significant proportion of chemotherapeutics directly or indirectly impact DNA replication by interfering with nucleotide availability, creating lesions or crosslinks that prohibit normal replication, or by disrupting the replication machinery itself. The activation of replication stress response mechanisms (Fig 1B) to resolve these lesions likely depends on the cell cycle stage, type of lesion, and affected strand [76, 177, 178]. Failures throughout these processes can result in DSBs (Fig 1C). Conversely, activation of these mechanisms can promote chemotherapy tolerance by avoiding DSB generation. Many of the proteins involved in TLS, TS, fork reversal, and repriming are upregulated in cancers and implicated in chemoresistance, reviewed extensively [76]. An intriguing element to the replication stress response and chemoresistance is the potential for adaptive mechanisms where cells reprogram their replication stress response to agents based on prior exposures [84]. The mechanisms of replication stress tolerance continue to be unraveled which may reveal additional pathways that suppress chemotherapy-induced break formation when activated in cancers.

Break repair

Elevated DSB repair capabilities can confer chemoresistance through a variety of possible alterations (Table 3). Overexpression of the DNA damage signaling kinases ATM, ATR, and DNA-PK are observed in numerous cancer types and associated with poor responses to various chemotherapeutics with several studies indicating improved DNA repair capacities [179–181]. Closely tied to kinase signaling, the cell cycle regulation machinery also plays an important role in DNA repair capabilities. When functional, checkpoint activations can pause the cell cycle and allow repair to occur. Overexpression and elevated activations of the checkpoint proteins ultimately suppresses accumulation of DNA breaks and promotes chemoresistance [182–186]. In addition, the two major E3 ubiquitin ligases responsible for recruitment of many DSB repair pathway proteins, RNF8 and RNF168, are overexpressed in a subset of cancers with poor chemoradio-therapy responses [187, 188]. Upregulation of

Table 3 DSB repair pathway alterations in radio- and chemoresistant cancers

Pathway	Protein	Alterations in cancer	Functional consequence
Damage detection, signaling, and pathway selection	ATM	Increased expression in radioresistant breast cancer cell lines [189] and high-mobility group A (HMGA) overexpressing neoplasias [190].	Elevated activity increases DNA damage signaling and may increase DNA repair capacity [189–191].
	ATR	Increased expression and activation in recurrent ovarian cancers [179].	Elevated activity improves DNA replication stress tolerance and repair capacity resulting in chemoresistance [179, 192].
	PARP1	Overexpressed in chemoresistant oral [193] and lung cancer cells [194].	Overexpression increases DNA damage tolerance [193] and may promote resolution of replication stress by restraining the replication fork [195].
	MDC1	Overexpressed in chemoresistant breast cancers [196].	Overexpression may promote DNA damage tolerance through enhanced recruitment of downstream repair factors [196].
	RNF8	Overexpressed and promotes DNA damage resistance in lung cancer cells [187].	Overexpression may promote DNA damage tolerance through enhanced recruitment of downstream repair factors [187].
	RNF168	Overexpression in chemoresistant breast, cervical, and multiple myeloma cell lines [188].	Overexpression may promote DNA damage tolerance through enhanced recruitment of downstream repair factors. Overexpression may also support resistance to proteasome inhibition [188].
	53BP1-Shieldin complex	Reduction observed in PARP1 resistant HR repair deficient ovarian cancers [197] with many functional characterizations in manipulated cell lines [198–203]. Similar outcomes are predicted for the Shieldin complex proteins (SHLD1–3, REV7) [200, 201]. Loss associated with resistance to 5-FU and other chemotherapies in colorectal cancer [203].	Loss results in activation of end resection and stimulation of HR [198, 199].
	MRN (MRE11, RAD50, NBS1)	Overexpression in platinum resistant ovarian [204], chemoresistant gastric [205] and radioresistant rectal cancers [206]. High expression is also associated with improved responses to radiotherapy in breast [207] and bladder cancers [208, 209].	MRN promotes DNA end resection and HR repair [210]. Overexpression of NBS1 increases HR repair efficiency [211].
	CtIP	Reduced expression or loss correlates with worse or improved outcomes depending on breast cancer subtype [212, 213].	CtIP promotes end resection and HR repair [214].
	EXO1	Overexpression correlates with poor outcomes in lung adenocarcinoma [215], hepatocellular carcinoma [216] and breast cancer [217].	Overexpression can increase repair efficiency, potentially through increased resection and replication stress responses [218].
DNA end resection	DNA2	Overexpressed in breast [219, 220] and ovarian [221] cancers with poor outcomes.	Overexpression promotes end resection and HR repair [219].
	RecQ helicases (BLM, WRN, RECQL4, RECQL5)	In general, overexpression may lead to increased chemoresistance [222] as observed for BLM overexpression in poor prognosis multiple myeloma [223] and glioma [224]. In contrast, BLM overexpression in platinum sensitive breast and ovarian cancer [225], topoisomerase inhibitor responsive in colorectal cancers [226], and CHK1 inhibitor responsive in ovarian cancer [227]. Low expression of WRN also correlates with poor breast cancer outcomes [228].	The RecQ helicases function in the replication stress response, in promoting resection at breaks, and in downstream HR repair processes [229]. Increased and decreased HR has been reported with overexpression, likely due to a diverse set of functions [222, 230, 231].
	RPA (RPA1, RPA2, RPA3)	Elevated expression in radioresistant glioma [232]. RPA1 overexpression induces gamma-radiation resistance in cell lines [233].	RPA overexpression has been linked to both increased repair efficiency and increased genome instability [233]. Overexpression is hypothesized to prevent RPA exhaustion, protect resected ssDNA from nucleolytic degradation, stabilize replication forks, and promote HR [139, 234].

Table 3 (continued)

Pathway	Protein	Alterations in cancer	Functional consequence
HR	DNA end resection and HR	Elevated expression in chemoresistant breast [235] and lung cancers [236]. Elevated expression in germline and somatic <i>BRCA1</i> mutant cancers through reversion or secondary mutations [237–243] or hypomorph expression [244–249].	Distinct activities promote the end resection and RAD51 loading steps of HR [250].
	RAD51	Elevated levels in pancreatic [251], breast [252], and chemoresistant ovarian cancers [253]. Elevated expression associated with poor survival outcomes in esophageal adenocarcinoma, colon, and breast cancers [254].	Biomarker of HR activity [255, 256]. Overexpression has been separately linked to both chemotherapy resistance and HR impairment [254, 257, 258].
	BARD1	Elevated expression in chemoresistant breast cancer [235]. High expression associated with worse prognosis in breast and ovarian cancer [259].	Required for <i>BRCA1</i> stability and HR [260].
	BRCA2	Elevated expression in germline and somatic <i>BRCA2</i> mutant cancers through reversion mutations [238, 241–243].	Required for HR [261].
	Ligase 1	Overexpression in ovarian cancers associated with platinum resistance and gemcitabine resistance in pancreatic cancer [262, 263].	Reduced DSB observed in LIG1 overexpressing cancers related to DNA repair or replication functions [262–264].
NHEJ	USP1	Overexpressed in ovarian [265] and gastric [266] cancers with poor outcomes.	USP1 promotes HR [267–269], though effects of alterations are confounded due to roles in replication, Fanconi anemia repair, and other processes [265].
	DNA-PKcs	Elevated in chemoresistant B-CLL [180], cervical cancer [181].	While not required for NHEJ, increased DNA-PKcs activation may elevate NHEJ and limit HR repair activity [180, 270].
	Ku70/Ku80	Elevated in chemoresistant B-CLL [180] and cervical cancer [181].	Overexpression may NHEJ activity [180], though has also been shown to suppress break repair in cell lines [271].
	XLF	Elevated expression in chemoresistant hepatocellular carcinoma [272], colorectal cancer [273], and <i>BRAF</i> ^{V600E} mutant thyroid cancers [274].	Overexpression increases NHEJ activity [274].
	XRCC4	Elevated expression associated with poor radiotherapy responses and survival in uterine, cervical [275], ovarian [276], and esophageal cancer [277].	XRCC4 impacts NHEJ efficiency and overexpression increases repair when Ligase 4 is co-elevated [278, 279].
TMEJ	Ligase 4	Upregulation in colorectal cancer cells leads to radioresistance [280]. Deficiency is associated with platinum resistance in ovarian cancer [262].	Overexpression increases NHEJ activity, however its loss can promote HR and TMEJ [281].
	Artemis	Increased levels in rectal cancers are associated with poor chemotherapy responses [282].	Overexpression may increase NHEJ activity and accelerate repair kinetics [283].
	Pol θ	Overexpression in thyroid [284], breast [285, 286], lung [287, 288], colorectal [289], hematologic [290] and ovarian cancers with poor outcomes [291].	Overexpression is associated with increased TMEJ repair and replication stress responses [288, 290].
SSA	Ligase 3	Overexpression in ovarian cancers with poor response [262].	Increased expression may be linked to elevated TMEJ [292].
	RAD52	Elevated in chemoresistant colorectal [293] and cervical cancers [294].	Potential upregulation of SSA [293].

Table 3 (continued)

Pathway	Protein	Alterations in cancer	Functional consequence
Cell cycle regulation	P53	Mutations drive chemoresistance across multiple cancer types (reviewed [295]).	Mutations disrupt apoptosis and other cell signaling pathways [12].
	WEE1	Increased expression in melanomas [296] and glioblastomas [182] with poor outcomes.	Overexpression enhances G2 cell cycle arrest and DNA repair (reviewed [297]).
	PKMYT1	Overexpression in esophageal [298], lung [299], breast [300], gastric [301], ovarian [302], liver [303], and kidney cancers [304] with poor responses.	Overexpression enhances G2 cell cycle arrest and DNA repair [305].
	CHK1	Upregulation associated with radioresistance in nasopharyngeal carcinoma (via MYC) [184] and in gastric cancer cells (via P53 and Rb1/EF2) [306].	Overexpression may reduce replication stress, potentially through activation of replication stress response pathways [307, 308].
	CHK2	Elevated CHK2 activation in platinum resistant colorectal cancer [186].	Overexpression is hypothesized to limit G1/S and G2/M cell cycle progression and enhance DNA repair (reviewed [309]).

the kinase and ubiquitin ligase signalers enhance repair of DSBs to promote chemoresistance, though in most cases, it is unclear whether this results from generalized increases in total repair activity or if specific DSB repair mechanisms are preferentially activated.

NHEJ is one of the dominant DSB repair mechanisms and, despite its error-prone nature, it effectively repairs breaks and prevents catastrophic loss of genomic content or activation of cell death signaling. Elevated NHEJ activity and repair protein expression are reported across cancer types and generally correlate with poor responses to treatments including radiation, etoposide, neocarzinostatin, and doxorubicin [180, 181, 310, 311]. Nearly all components of the NHEJ machinery have been implicated in therapy resistance when upregulated (Table 3).

The contributions of HR repair activity to therapy resistance are well established. HR repair defects, including *BRCA1* and *BRCA2* deficiencies, induce dramatic sensitivities to DNA damaging agents in pre-clinical and patient settings. HR repair reactivation is a dominant mechanism of resistance. In *BRCA1/2* mutant cancers, HR repair reactivation can occur through *BRCA1/2* reversion or secondary mutations [237–241], stabilization/expression of mutant *BRCA1* hypomorphic proteins [244–249], or through loss of the resection inhibitory 53BP1/Shieldin complex [198–201]. Notably, secondary mutations, which occur in 20–40% of post-platinum and 10–40% post-PARPi patients, and *BRCA1* hypomorph expression have been found to drive HR reactivation in patient tissue direct from the clinic [80, 249, 312, 313]. Outside of secondary mutations, frequency quantifications and validation of other mechanisms in clinical tissue is challenging due to limitations extracting protein level and functional information from clinical samples and the possibility that these resistance mechanisms do not necessarily require genetic changes to occur. HR repair activation has also been shown to drive chemotherapy resistance outside of the *BRCA1/2* mutant backgrounds (Table 3) and can occur through loss of *BRCA1* or *RAD51C* promoter methylation and gene silencing [44, 45, 50, 314], *RAD51* upregulation [257, 315, 316], *BRCA1*-*BARD1* complex upregulation/stabilization [235, 236, 317], and possibly other routes that remain to be defined. Restored HR repair capacity resolves chemotherapy-induced DSBs in an error-free manner that negates much of the treatment advantage present in HR repair-deficient scenarios. Elevated HR repair outside of HR gene mutated backgrounds may further reduce therapeutic windows for multiple treatments.

Upregulation of the end resection machinery (or loss of its negative regulators) can

promote chemoresistance in some cancer backgrounds (Table 3). Pro-resection factors include *BRCA1*, nucleases MRN (MRE11, *RAD50*, *NBS1*), CtIP, EXO1, and DNA2, and helicases BLM and WRN, while the anti-resection machinery comprise 53BP1, DYNLL1, PTIP, RIF1, Shld1, Shld2, Shld3, REV7, CST (Ctc1, Stn1, Ten1), and likely additional elements [22]. Resection activation is a well-established preclinical driver of resistance in some, but not all, *BRCA1* mutant backgrounds [318, 319]. Downstream of resection in the HR repair pathway, *BRCA1* localizes PALB2-*BRCA2*-*RAD51* to DSBs, so how this occurs in the absence of *BRCA1* remains an area of active investigation, with recent work suggesting that HR repair can occur through direct PALB2-chromatin or -RNF168 interactions [320–322]. Resection activation in *BRCA2* mutant backgrounds does not rescue HR repair proficiency, which may contribute to an increased higher frequency of *BRCA2* reversion mutations compared to *BRCA1* [198, 242]. Nevertheless, resection could stimulate enhanced activation of TMEJ or SSA repair which have less defined roles in managing therapy responses. Upregulation of these alternative repair mechanisms is a plausible route to gain tolerance to DNA damaging chemotherapeutics. Increased dependence on TMEJ, for example, is clearly evident in certain HR repair-deficient settings [19, 323–325]. Whether TMEJ or other pathways become essential for cancer cell survival in certain therapeutic contexts remains to be determined.

Creating a chemoresistant tumor environment

Beyond the immediate survival benefit of repairing DNA damage caused by cancer treatments, imperfect repair mechanisms create genetic opportunities for tumor evolution. Intratumoral heterogeneity is common for many solid cancers and similar diversity is found in hematologic malignancies [326–333]. Genome instability and mutagenesis create opportunities for therapy evasion and evolution of resistant clones (reviewed [334]). This heterogeneity allows for multiple drug resistance mechanisms to arise within different cells of the same tumor [249]. Acquired or selected resistance mechanisms with genomic origins, such as topoisomerase I mutations in the context of camptothecin treatments or *BRCA1/2* reversion mutations in PARPi or platinum-treated cancers, are potentially consequences of error-prone DNA repair processes. Some instances of these resistance causing mutations can be reasonably attributed to specific mutagenic repair events, such as microhomology flanked *BRCA1/2* reversions driven by TMEJ [242, 335]. Other events do not have clear origins with a specific pathway. It will be interesting to elucidate whether suppression of

mutagenic repair processes blocks or delays the onset of resistance.

In addition to providing an evolutionary catalyst, DNA damage response-induced mutagenesis increases potential neoantigen production and anti-tumor immunity [336]. Moreover, persisting DNA damage activates cGAS-STING proinflammatory signaling [337]. Pro-inflammatory signaling rapidly decreases with damage repair; however, chronic activation in some cancer settings can instead promote immune evasion, invasive phenotypes, and metastasis [338]. Thus, the complex interplay between DNA repair, therapy response, and immune activation is highly context dependent.

In summary, chemoresistance is often underpinned by the ability of the DNA damage response to prevent and repair DSBs through error-free or error-prone mechanisms. Furthermore, mutagenic repair of DNA damage may contribute to an adaptive response to therapy. Finding ways to overcome DNA repair-mediated chemoresistance is critical to improving treatments and patient outcomes.

Targeting DNA repair to improve patient outcomes

Deviations from the normal DNA damage response contribute to genome instability in cancer and dynamic alterations to repair pathway proficiencies can trigger a switch from therapy responsive to resistant states. The absence of normal repair regulation potentially introduces new therapeutic opportunities. The intricate and layered nature of the DNA damage response harbors partial repair redundancies that challenge these strategies to overcome therapy resistance. Recent advancements in profiling resistance mechanisms, new insights into the mechanics of the DNA damage response, and a rapidly expanding repertoire of DNA repair-targeted small molecules make the goal of combating chemoresistance through rationale therapeutic regimens that specifically eradicate cancers based on their altered DNA repair capabilities more achievable.

Comprehensive resistance profiling

The cancer genome provides essential clues into the history of the DNA repair environment within a tumor. The first cancer genome was sequenced and published in 2008, invigorating calls to incorporate individual genetic information into rational therapeutic approaches and clinical trial design [339–341]. Genomic data from thousands of cancers, often with paired normal tissue, are publicly available through The Cancer Genome Atlas and other studies. These efforts led to incredible insights into many oncogenic processes (reviewed [342]) including the prevalence of DNA repair deficiencies in cancers

and the conceptualization of many targeted treatment approaches [343]. Genetics-guided treatment decisions are already changing how many cancers are treated. Some clinical studies promote pre- and post-treatment sample collection, providing unparalleled clinically relevant insights into genetic determinants of response and resistance such as detection of primary and secondary mutations in DNA repair genes. Technological advancements in sequencing including single-cell DNA and RNA sequencing, cell-free DNA isolation and sequencing, cost-effective deep sequencing, and long-read sequencing with paired DNA modification analyses will further increase our capacity to understand treatment responses using clinical samples.

A large proportion of resistance mechanisms, and predictors of therapy responses, likely occur through epigenetic or protein-level alterations that impact the DNA damage response and are difficult to discern from sequencing data [158, 344]. Mutational signature analyses can probe specific DNA repair functionalities, though challenges deconvolving pre- and post-treatment states limit the utility of these approaches [345]. Functional assays to measure DNA repair proficiencies in live cells remain the gold standard for profiling the DNA damage response. Numerous approaches exist including flow cytometry-, microscopy-, and sequencing-based methods, and, in many cases, can distinguish specific repair pathway activations [346–349]. Predictive biomarker assays using fixed tissue are highly desirable and have the potential for clinical translation. One example is the analysis of HR repair status in formalin-fixed tumors by RAD51 foci quantifications now being explored for clinical samples [255, 256, 350, 351]. Overall, innovative developments to probe DNA repair proficiencies in patient samples will help clinicians provide the best treatment options for their patients.

Identifying resistance drivers in patients requires continued investment in dissecting treatment mechanisms of action and the molecular interactions driving repair of treatment-induced damage. Patient-derived xenograft (PDX) technologies have made incredible strides towards bridging biochemical understandings of DNA damage response processes with how patients respond to treatment. PDX allow propagation and expansion of tumor tissue in immune-compromised mice and typically capture patient responses while preserving the original tumor architecture [352]. PDX generated from pre-treatment tumor samples can also recapitulate the acquisition of therapy resistance in patients while providing ample tissue for functional investigations [249]. These and other pre-clinical advancements are critical to designing treatment strategies that capitalize on DNA repair alterations in cancer.

Table 4 Clinical development of DNA break repair-related inhibitors

Active clinical trials (<i>clinicaltrials.gov</i> accessed March 2025)		
Target	Inhibitor	Treatment
PARP1	AZD5305 (Saruparib)	Monotherapy and with radiotherapy, Darolutamide, Ceralasertib, Paclitaxel, Carboplatin, Trastuzumab Deruxtecan, Datopotamab Deruxtecan, Camizestran, Enzalutamide, Abiraterone, Darolutamide, Apalutamide, AZD5335, AZD8205, Rilvegostomig, Durvalumab
	AZD9574	Monotherapy and with Temozolomide, Trastuzumab Deruxtecan, Dato-potamab Deruxtecan
	IDE161	Monotherapy and with Pembrolizumab
	ETX-19477	Monotherapy
	ART4215	Monotherapy and with Talazoparib, Niraparib
Polθ	ART6043	Monotherapy and with Olaparib, Niraparib
	Novobiocin	Monotherapy
	GSK4524101	Monotherapy and with Niraparib
	MOMA-313	Monotherapy and with Olaparib
	RP-3467	Monotherapy and with Olaparib
ATR	AZD6738 (Ceralasertib)	Monotherapy and with Durvalumab, Acalabrutinib, Olaparib, Carboplatin, Etoposide, radiotherapy, trastuzumab deruxtecan, nab-paclitaxel
	Berzosertib	In combination with Lurbinectedin, Avelumab, Sacituzumab Govitecan, Gemcitabine, Carboplatin, Docetaxel, Topotecan, Irinotecan, Pembrolizumab, radiotherapy
	M1774 (Tuvusertib)	Monotherapy and with Avelumab, Niraparib, Cemiplimab, Fulvestrant, Lar-te-sertib, Temozolomide, Pepsosertib, ZEN-3694, M9466
	RP-3500 (Camonsertib)	Monotherapy and with Atezolizumab, Bevacizuma, Niraparib, Olaparib, Talazo-parib, Gemcitabine, RP-6306, radiotherapy
	BAY1895344 (Elimusertib)	Monotherapy and with Gemcitabine, Pembrolizumab, Cisplatin, Topotecan, Irinotecan, Fluorouracil, Leucovorin, radiotherapy
	ART0380	Monotherapy and with Gemcitabine, Irinotecan
	IMP9064	Monotherapy and with Senaparib
	ATRN-119	Monotherapy
	SC-0245	In combination with Irinotecan
	TCC1727	Monotherapy

Table 4 (continued)

Active clinical trials (clinicaltrials.gov accessed March 2025)		
Target	Inhibitor	Trial
ATM	AZD1390	In combination with radiotherapy, Durvalumab Phase 1: NCT05182905, NCT03423628, NCT05678010, NCT04550104, NCT05116254
	M4076 (Lartisertib)	In combination with Tuvusertib Phase 1: NCT05396833 Phase 2: NCT06433219
	SYH2051	Monotherapy and with SYH2051, radiotherapy Phase 1: NCT06775236, NCT06011291
	WSD0628	In combination with radiotherapy Phase 1: NCT05917145
DNA-PK	M3814 (Peposertib)	Monotherapy and with radiotherapy, Temozolomide, Tuvusertib, Lutetium Lu 177, Doxorubicin, Mitoxantrone, Etoposide, Cytarabine, Avelumab, Radium-223 dichloride Phase 1: NCT04555577, NCT05868174, NCT05687136, NCT04750954, NCT04092270, NCT04533750, NCT05711615, NCT03983824, NCT04172532, NCT04068194, NCT04071236, NCT02813135
	AZD1775 (Adavosertib)	Monotherapy and with Olaparib, Durvalumab, Gemcitabine, radiotherapy Phase 1: NCT02659241, NCT04197713, NCT02617277, NCT02546661, NCT04460937
WEE1	ZN-c3 (Azenosertib)	Phase 2: NCT04439227, NCT03284385, NCT03385655, NCT03668340, NCT02465060, NCT03579316, NCT03330847, NCT02101775
	Debio0123	Monotherapy and with Encorafenib, Cetuximab, Carboplatin, Doxorubicin, Paclitaxel, Gemcitabine, Bevacizumab, Trastuzumab Deruxtecan, Niraparib, Pembrolizumab Phase 1: NCT05743036, NCT04516447, NCT06364410, NCT04005690, NCT05198804, NCT04833582, NCT06351332
	APR-1051	Phase 2: NCT04814108, NCT05128825, NCT06015659, NCT06369155
	SY-4835	Monotherapy and with RP-6306, Carboplatin, Temozolomide, Etoposide, Sacituzumab govitecan, radiotherapy Phase 1: NCT04855656, NCT03968653, NCT05109975, NCT05765812, NCT06612203, NCT05815160
CHK1/2	LY2606368 (Prexasertib)	Monotherapy Phase 1: NCT06260514
	LY2880070	Monotherapy Phase 1: NCT05291182
	PEP07	Monotherapy and with Gemcitabine Phase 1: NCT05548296
	BBI-355	Monotherapy and with Gemcitabine Phase 2: NCT06597565
USP1	PHI-101	Monotherapy and with Gemcitabine Phase 1: NCT02632448
	KSQ-4279	Monotherapy and with Gemcitabine Phase 2: NCT05275426
	ASN-3186	Monotherapy Phase 1: NCT05983523, NCT05659732
	SIM0501	Monotherapy and with Erlotinib or Fufitinib Phase 1: NCT05827614
PKMYT1	XL309	Monotherapy and with Olaparib, Carboplatin Phase 1: NCT04678102
	RP-6306	Monotherapy and in combination with Olaparib Phase 1: NCT05240898
		Monotherapy and in combination with Olaparib Phase 1: NCT06787950
		Monotherapy and in combination with Olaparib Phase 1: NCT06331559
		Monotherapy and in combination with Olaparib Phase 1: NCT05932862
		Monotherapy and with folinic acid, 5-FU, Irinotecan, Gemcitabine, RP-3500, Debio0123, Carboplatin, Paclitaxel Phase 1: NCT05147350, NCT05147272, NCT04855656, NCT06107868, NCT05605509

New inhibitors and therapeutic strategies

New insights about the mechanics of DNA repair and therapy resistance have inspired the development of promising new inhibitors for DNA repair proteins (and related cycle regulators) in specific cancer contexts (reviewed [353–355]). A subset of these inhibitors are now in clinical trials including PARP1-selective [356–359], poly(ADP-ribose) glycohydrolase (PARG) [360], Polymerase θ (Pol θ) [361, 362], ATR [363], ATM [364], DNA-PK [365, 366], WEE1 [367], PKMYT1 [368], CHK1 [363, 369], and USP1 [370] inhibitors (Table 4). The list in clinical development expands significantly if considering other DNA repair-adjacent cell cycle regulatory kinases such as the CDKs, PLKs, and Aurora kinase A [371, 372].

PARP1-selective inhibitors have generated enormous interest due to its stand-alone synthetic lethality with HR repair deficiency and the increasingly supported possibility that PARP2 inhibition (as occurs with current generation PARPi) is responsible for dose-limiting hematological toxicities [373–375]. Preliminary reports for the PARP1-selective PARPi saruparib suggest increased potency and reduced toxicity [357–359]. Nevertheless, therapy resistance remains problematic [357]. A central nervous system-penetrant PARP1-selective inhibitor derivative AZD9574 is in clinical trials and could expand the types of cancers effectively treated by PARPi [376]. PARG inhibitors also target PAR signaling, though suppress PAR removal from DNA damage sites and may complement PARPi activity, even in PARPi resistant settings, by introducing replication lesions [360, 377]. In other contexts, PARG inhibition may limit PARPi efficacy though enhance sensitivity to other forms of DNA damage including radiation and temozolamide [378].

Pol θ inhibitors capitalize on a dependence for TMEJ repair in HR repair-deficient cancers [361]. Recent studies have considerably expanded our understanding of the biochemical and cellular functions of Pol θ with potential therapeutic implications. Like HR, TMEJ is capable of repairing resected DNA breaks. While resection may be impaired in *BRCA1* mutant cancers, *BRCA2* mutations do not lead to resection defects and may prime these cancers for response to Pol θ inhibition [19]. In addition to serving as a backup to HR, TMEJ is uniquely active in mitosis [18, 379]. This discovery could possibly expand the subset of cancers predicted to respond to Pol θ inhibitors such as those with defective G2/M checkpoints and increased mitotic DNA damage. Combining Pol θ and PARPi is another attractive approach to elicit synergistic cancer cell cytotoxicity and potentially circumvent the development of resistance by counteracting mechanisms that enhance resection or introduce secondary mutations via mutagenic (often TMEJ-mediated) repair [361, 380–382].

Complementary mechanisms of action can be achieved through a multitude of combination strategies that prevent or overcome resistance to monotherapies. PARPi combined with ATR inhibitors elicits a response in PARPi and platinum-resistant ovarian cancer models [383, 384]. PARPi induce a replication stress response that requires ATR for resolution and likely contributes to the combined efficacy. Clinical trials testing this approach are ongoing [385]. Similarly, ATR inhibition may be particularly effective when combined with other forms of replication stress, as is being tested in numerous studies (Table 4). Alternatively, concurrent targeting of parallel pathways such as ATM and ATR inhibitor combinations may eliminate repair redundancies and could be used to suppress backup repair options [386, 387]. Each approach requires careful vetting to ensure appropriate therapeutic windows for cancer over nonmalignant cells to limit adverse patient reactions.

These promising new strategies benefit from rational inhibitor combinations and synthetic lethal approaches that capitalize on DNA repair alterations in cancer cells. While the use of PARPi in HR repair-deficient cancers is the prime example of a successful synthetic lethal strategy, the advent of CRISPR/Cas9 screening approaches has dramatically accelerated the discovery of new potential synthetic lethal interactions that could be targeted to overcome resistance. Ongoing work that expands these investigations beyond HR repair-deficient settings is essential to maximize the impact for patients, specifically those with oncogenic driver mutations or amplifications like MYC, RAS, or Cyclin E [388, 389]. Additionally, insights into whether new vulnerabilities are created by overexpression of specific DNA repair proteins or hyperactivation of certain pathways (Table 3) could have enormous implications for how resistant cancers are treated.

Ultimately, uncovering the fundamental issues of DNA repair generates the tools to treat therapy-resistant cancers and pair individuals with the treatment strategies most likely to succeed. An increasing depth of understanding of the mechanics of DNA repair, combined with recent advancements in resistance mechanism profiling, sequencing technologies, and inhibitor development position the field to dramatically improve the effectiveness and tolerability of cancer treatments.

Abbreviations

DSB	Double-strand break
BER	Base excision repair
NER	Nucleotide excision repair
MMR	Mismatch repair
MGMT	Methylguanine methyltransferase
ALKBH	Alk B family homologs
TS	Template switching
TLS	Translesion synthesis
SSB	Single-strand break

NHEJ	Non-homologous end joining
HR	Homologous recombination
Alt-EJ	Alternative end joining
TMEJ	Polymerase Theta-mediated end joining
SSA	Single-strand annealing
PARP	Poly (ADP-ribose) polymerase
PARG	Poly (ADP-ribose) glycohydrolase
DHFR	Dihydrofolate reductase
DNMT	DNA methyltransferase
N ⁷ mG	N ⁷ -methyl guanine
N ³ mA	3-methyl adenine
O ⁶ mG	O ⁶ -methyl guanine
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3 related
DNA-PK	DNA-dependent protein kinase
TdT	Terminal deoxynucleotidyl transferase
MMS	Methyl methanesulfonate

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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