Genome Medicine

REVIEW

Open Access

DNA repair and the contribution to chemotherapy resistance

Ksenija Nesic[1,2], Phoebe Parker[3], Elizabeth M. Swisher[4] and John J. Krais[3*]

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,

*Correspondence:
John J. Krais
krais@wustl.edu
[1] The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia
[2] Department of Medical Biology, University of Melbourne, Parkville, VIC, Australia
[3] Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA
[4] University of Washington, Seattle, WA, USA

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

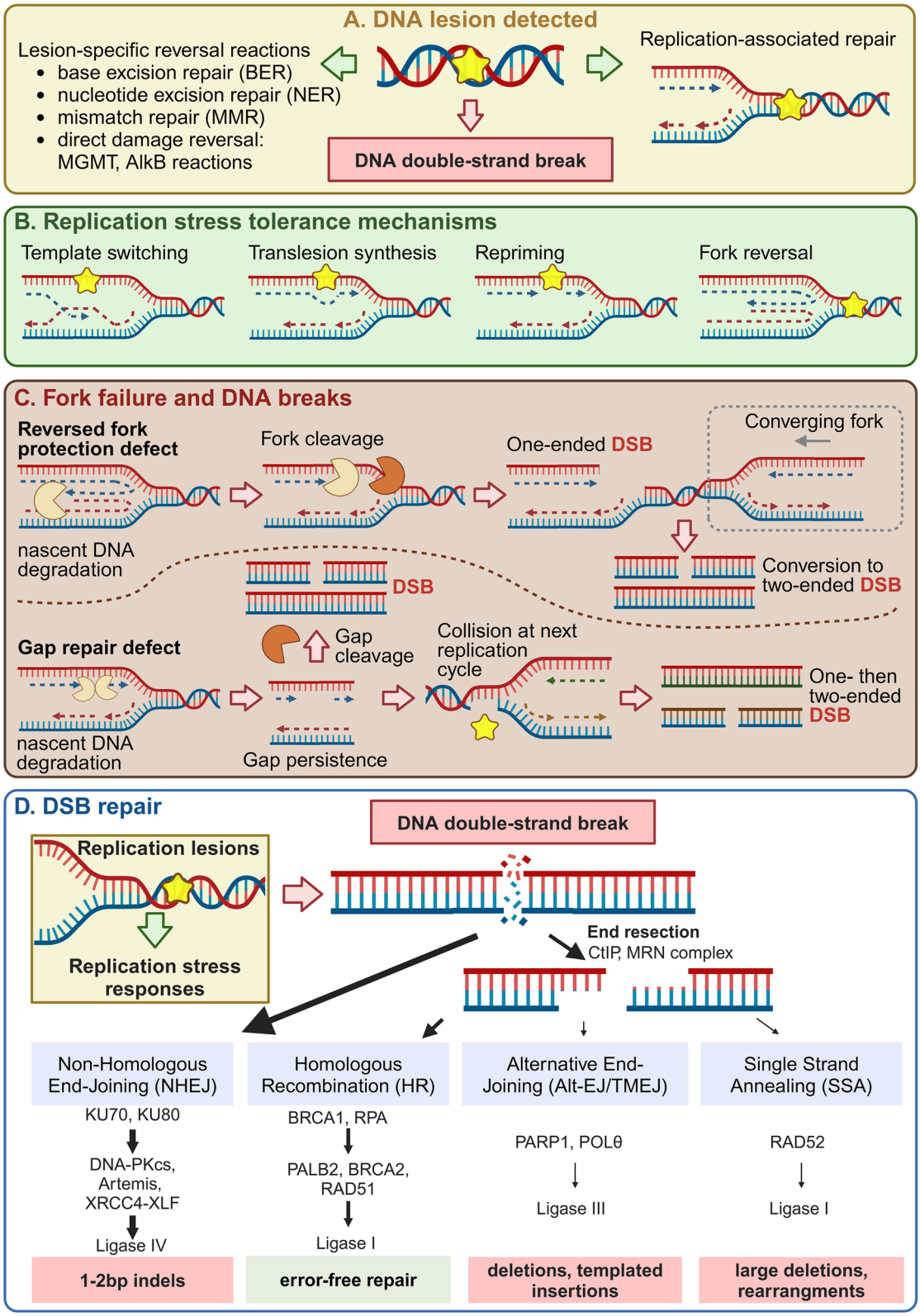

Fig. 1 (See legend on previous page.)

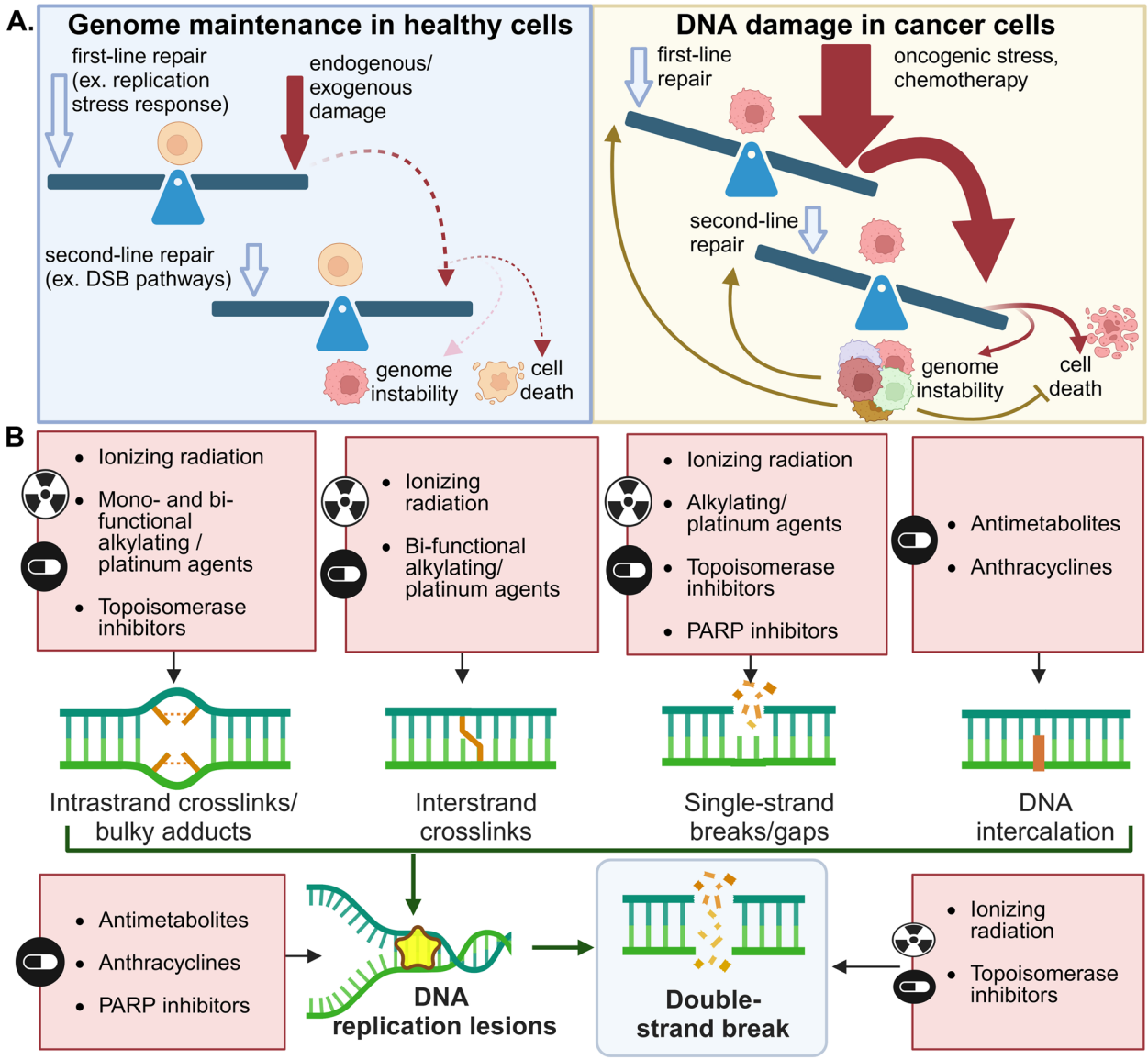

Fig. 2 Tolerance for DNA damage and chemotherapy. **A** Faithful DNA repair maintains genome stability. In contrast, mutagenic repair promotes cell survival at the expense of genome integrity and may contribute to tumorigenesis. DNA damaging chemotherapies push cells towards unsustainable levels of genome 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, CDK1, 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]	N^7-methylguanine, O^6-methylguanine, N^3-methyladenine, Other N- and O- 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, intrastrand crosslinks, DNA protein crosslinks [77]	DBSs [77]	Fanconi anemia repair, NER, TLS, HR, NHEJ [77]	Nitrogen mustards: Cyclophoshamide, Ifosfamide, Melphalan, Chlorambucil Aziridines: Mitomoycin C, Diaziquone, and Thiotepa Nitrosoureas: Carmustine, Iomustine, 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 N^7-methyl guanine (N^7mG) but also 3-methyl adenine (N^3mA) and O^6-methyl guanine (O^6mG) [125]. BER rapidly resolves N^7mG and N^3mA lesions. In contrast, O^6mG 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	Pyrimadine	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), myelodyplastic syndrome (MDS)	[73, 74, 89, 90]
Capecitabine	Pyrimadine	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	Pyrimadine	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	Gastrointenstinal	[73, 97]
Fludarabine	Purine	DNA polymerase α, ribonucleoside reductase, DNA primase	Fludara, Oforta	B-cell CLL	[73, 74]
Gemcitabine	Pyrimadine	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 caboxamide 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, Pemfexy	Mesothelioma, NSCLC	[101]
Pralatrexate	Folate	DHFR	Folotyn	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.

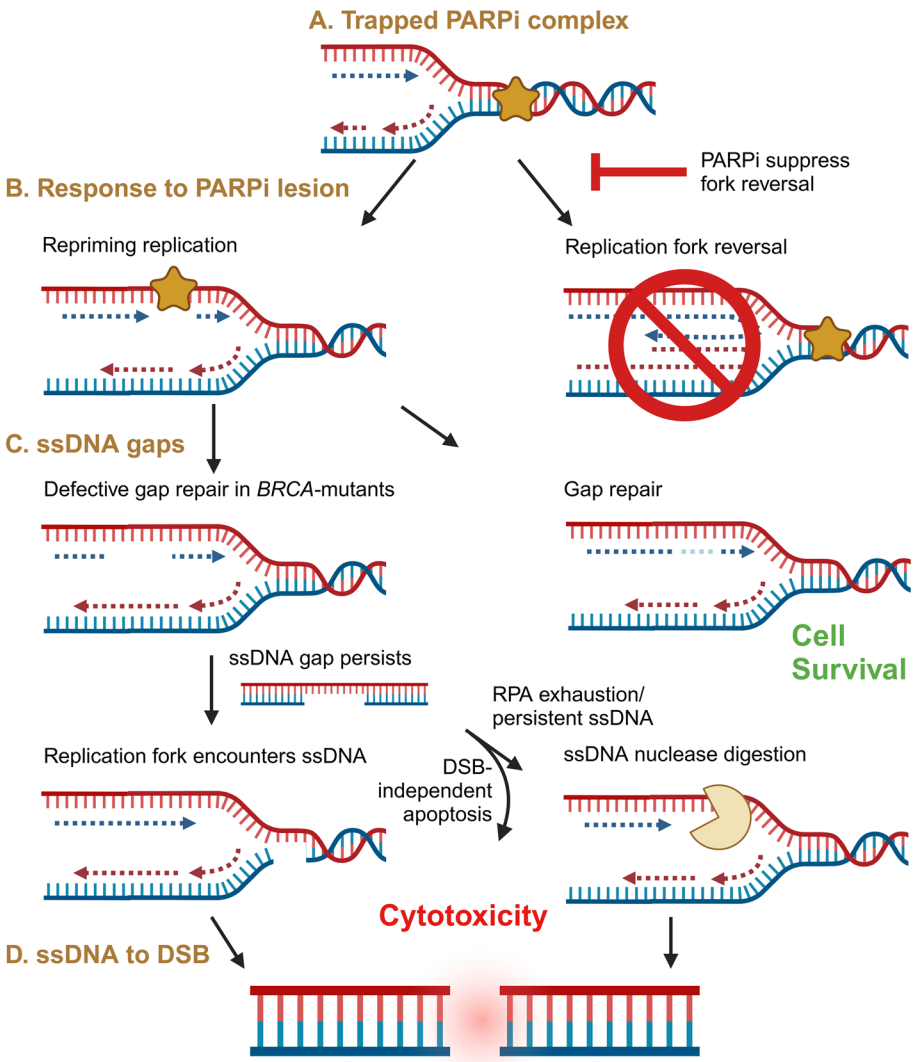

Fig. 3 PARP inhibition and DNA damage. **A** PARPi trap the PARP enzymes on DNA resulting in replication fork blockage. **B** PARPi prevent replication fork reversal and induce ssDNA gaps due to repriming. **C** Gap repair is defective in BRCA1 and BRCA2-deficient cancers and ultimately results in cell 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 O^6mG in a stochiometric 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 temazolamide 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 chemo- or radio-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 PARPi 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].
DNA end resection	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].
	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
DNA end resection and HR	BRCA1	Elevated expression in chemoresistant breast [235] and lung cancers [236]. Elevated expression in germline and somatic *BRCA1* 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].
HR	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 BRCA1 stability and HR [260].
	BRCA2	Elevated expression in germline and somatic *BRCA2* 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].
	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].
NHEJ	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 $BRAF^{V600E}$ 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].
	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].
TMEJ	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].
	Ligase 3	Overexpression in ovarian cancers with poor response [262].	Increased expression may be linked to elevated TMEJ [292].
SSA	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 caner 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 preclinical 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]. Proinflammatory 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

Target	Inhibitor	Active clinical trials *(clinicaltrials.gov accessed March 2025)*	
		Treatment	**Trials**
PARP1	AZD5305 (Saruparib)	Monotherapy and with radiotherapy, Darolutamide, Ceralasertib, Paclitaxel, Carboplatin, Trastuzumab Deruxtecan, Datopotamab Deruxtecan, Camizestran, Enzalutamide, Abiraterone, Darolutamide, Apalutamide, AZD5335, AZD8205, Rilvegostomig, Durvalumab	Phase 1: NCT06713369, NCT04005690, NCT05938270, NCT04550104, NCT02264678, NCT04644068, NCT05367440, NCT05797168, NCT05123482 Phase 2: NCT06769126 Phase 3: NCT06120491, NCT06380751
	AZD9574	Monotherapy and with Temozolomide, Trastuzumab Deruxtecan, Datopotamab Deruxtecan	Phase 1: NCT05417594
PARG	IDE161	Monotherapy and with Pembrolizumab	Phase 1: NCT05787587
	ETX-19477	Monotherapy	Phase 1: NCT06395519
Polθ	ART4215	Monotherapy and with Talazoparib, Niraparib	Phase 1: NCT04991480
	ART6043	Monotherapy and with Olaparib, Niraparib	Phase 1: NCT05898399
	Novobiocin	Monotherapy	Phase 1: NCT05687110
	GSK4524101	Monotherapy and with Niraparib	Phase 1: NCT06077877
	MOMA-313	Monotherapy and with Olaparib	Phase 1: NCT06545942
	RP-3467	Monotherapy and with Olaparib	Phase 1: NCT06560632
ATR	AZD6738 (Ceralasertib)	Monotherapy and with Durvalumab, Acalabrutinib, Olaparib, Carboplatin, Etoposide, radiotherapy, trastuzumab deruxtecan, nab-paclitaxel	Phase 1: NCT06754761, NCT05514132, NCT03328273, NCT02264678, NCT04550104, NCT04704661, NCT02813135 Phase 2: NCT04564027, NCT03801369, NCT05061134, NCT03334617, NCT03682289, NCT04065269, NCT04417062, NCT04090567, NCT03579316, NCT03787680, NCT03878095, NCT03330847, NCT03833440, NCT06769126, NCT05941897, NCT05582538, NCT06680050, NCT04699838 Phase 3: NCT05450692, NCT06732401
	Berzosertib	In combination with Lurbinectedin, Avelumab, Sacituzumab Govitecan, Gemcitabine, Carboplatin, Docetaxel, Topotecan, Irinotecan, Pembrolizumab, radiotherapy	Phase 1: NCT04802174, NCT04266912, NCT04826341, NCT02627443, NCT02595931, NCT04052555, NCT02589522, NCT04216316, NCT02567422 Phase 2: NCT02595892, NCT03517969, NCT04807816, NCT03896503, NCT03641313
	M1774 (Tuvusertib)	Monotherapy and with Avelumab, Niraparib, Cemiplimab, Fulvestrant, Lartesertib, Temozolomide, Peposertib, ZEN-3694, M9466	Phase 1: NCT04170153, NCT05882734, NCT05986071, NCT06308263, NCT05396833, NCT05691491, NCT05687136, NCT05950464, NCT06421935 Phase 2: NCT06518564, NCT06433219, NCT05828082, NCT05947500
	RP-3500 (Camonsertib)	Monotherapy and with Atezolizumab, Bevacizuma, Niraparib, Olaparib, Talazoparib, Gemcitabine, RP-6306, radiotherapy	Phase 1: NCT03337698, NCT04972110, NCT04497116, NCT05566574, NCT04855656 Phase 2: NCT04589845, NCT05605509, NCT05601440
	BAY1895344 (Elimusertib)	Monotherapy and with Gemcitabine, Pembrolizumab, Cisplatin, Topotecan, Irinotecan, Fluorouracil, Leucovorin, radiotherapy	Phase 1: NCT05071209, NCT04616534, NCT04576091, NCT04491942, NCT04535401, NCT04514497
	ART0380	Monotherapy and with Gemcitabine, Irinotecan	Phase 1: NCT04657068 Phase 2: NCT05798611
	IMP9064	Monotherapy and with Senaparib	Phase 1: NCT05269316
	ATRN-119	Monotherapy	Phase 1: NCT04905914
	SC-0245	In combination with Irinotecan	Phase 1: NCT05731518
	TCC1727	Monotherapy	Phase 1: NCT05970016

Table 4 (continued)

Target	Inhibitor	Active clinical trials *(clinicaltrials.gov accessed March 2025)*	
		Treatment	**Trials**
ATM	AZD1390	In combination with radiotherapy, Durvlaumab	Phase 1: NCT05182905, NCT03423628, NCT05678010, NCT04550104, NCT05116254
	M4076 (Lartesertib)	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
WEE1	AZD1775 (Adavosertib)	Monotherapy and with Olaparib, Durvalumab, Gemcitabine, radiotherapy	Phase 1: NCT02659241, NCT04197713, NCT02617277, NCT02546661, NCT04460937 Phase 2: NCT04439227, NCT03284385, NCT03385655, NCT03668340, NCT02465060, NCT03579316, NCT03330847, NCT02101775
	ZN-c3 (Azenosertib)	Monotherapy and with Encorafenib, Cetuximab, Carboplatin, Doxorubicin, Paclitaxel, Gemcitabine, Bevacizumab, Trastuzumab Deruxtecan, Niraparib, Pembrolizumab	Phase 1: NCT05743036, NCT04516447, NCT06364410, NCT04005690, NCT05198804, NCT04833582, NCT06351332 Phase 2: NCT04814108, NCT05128825, NCT06015659, NCT06369155
	Debio0123	Monotherapy and with RP-6306, Carboplatin, Temozolomide, Etoposide, Sacituzumab govitecan, radiotherapy	Phase 1: NCT04855656, NCT03968653, NCT05109975, NCT05765812, NCT06612203, NCT05815160
	APR-1051	Monotherapy	Phase 1: NCT06260514
	SY-4835	Monotherapy	Phase 1: NCT05291182
CHK1/2	LY2606368 (Prexasertib)	Monotherapy and with Gemcitabine	Phase 1: NCT05548296 Phase 2: NCT06597565
	LY2880070	Monotherapy and with Gemcitabine	Phase 1: NCT02632448 Phase 2: NCT05275426
	PEP07	Monotherapy	Phase 1: NCT05983523, NCT05659732
	BBI-355	Monotherapy and with Erlotinib or Futibatinib	Phase 1: NCT05827614
	PHI-101	Monotherapy	Phase 1: NCT04678102
USP1	KSQ-4279	Monotherapy and with Olaparib, Carboplatin	Phase 1: NCT05240898
	ASN-3186	Monotherapy	Phase 1: NCT06787950
	SIM0501	Monotherapy and in combination with Olaparib	Phase 1: NCT06331559
	XL309	Monotherapy and in combination with Olaparib	Phase 1: NCT05932862
PKMYT1	RP-6306	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 (Polθ) [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].

Polθ 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 Polθ 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 Polθ 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 Polθ inhibitors such as those with defective G2/M checkpoints and increased mitotic DNA damage. Combining Polθ 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 methytransferase
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^7mG	N^7-methyl guanine
N^3mA	3-methyl adenine
O^6mG	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

Acknowledgements
We thank Dr. Alessandro Vindigni and Dr. Priyanka Verma for input and discussions regarding the manuscript.

Authors' contributions
All authors read and approved the final manuscript.

Funding
K.N. receives support though AACR-AstraZeneca Ovarian Cancer Research Fellowship (2022), National Health and Medical Research Council (NHMRC Australia), and the Stafford Fox Medical Research Foundation. E.S. is funded by NIH NCI R01CA251817 and R01CA237600. J.K. receives support from NIH NCI 1K22CA276631-01, Ovarian Cancer Research Alliance #ECIG-2025-3-1966, Basser Center for BRCA, the Cancer Research Foundation, the Route 66 Endometrial Cancer SPORE CEP, and Alvin J. Siteman Cancer Center through The Foundation for Barnes-Jewish Hospital and the Alvin J. Siteman Cancer Research Fund.

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
K.N. reports research support (paid to institution) from AstraZeneca Pty Ltd and Boehringer Ingelheim outside the submitted work, and non-financial support from Clovis Oncology and Sierra Oncology. E.S. is on the Scientific Advisory Board for Ideaya Biosciences.

Received: 17 July 2024 Accepted: 14 May 2025
Published online: 26 May 2025

References

1. Hashimoto Y, Puddu F, Costanzo V. RAD51- and MRE11-dependent reassembly of uncoupled CMG helicase complex at collapsed replication forks. Nat Struct Mol Biol. 2011;19:17–24. https://doi.org/10.1038/nsmb.2177.
2. Hanawalt PC. The U.V. sensitivity of bacteria: its relation to the DNA replication cycle. Photochem Photobiol. 1966;5:1–12.
3. Hanada K, Budzowska M, Davies SL, van Drunen E, Onizawa H, Beverloo HB, Maas A, Essers J, Hickson ID, Kanaar R. The structure-specific endonuclease Mus81 contributes to replication restart by generating double-strand DNA breaks. Nat Struct Mol Biol. 2007;14:1096–104. https://doi.org/10.1038/nsmb1313.
4. Schlacher K, Christ N, Siaud N, Egashira A, Wu H, Jasin M. Double-strand break repair-independent role for BRCA2 in blocking stalled replication fork degradation by MRE11. Cell. 2011;145:529–42. https://doi.org/10.1016/j.cell.2011.03.041.
5. Lemaçon D, Jackson J, Quinet A, Brickner JR, Li S, Yazinski S, You Z, Ira G, Zou L, Mosammaparast N, Vindigni A. MRE11 and EXO1 nucleases degrade reversed forks and elicit MUS81-dependent fork rescue in BRCA2-deficient cells. Nat Commun. 2017;8:860. https://doi.org/10.1038/s41467-017-01180-5.
6. Pavani R, Tripathi V, Vrtis KB, Zong D, Chari R, Callen E, Pankajam AV, Zhen G, Matos-Rodrigues G, Yang J, et al. Structure and repair of replication-coupled DNA breaks. Science. 2024;eado3867:eado3867. https://doi.org/10.1126/science.ado3867.
7. Scully R, Walter JC, Nussenzweig A. One-ended and two-ended breaks at nickase-broken replication forks. DNA Repair (Amst). 2024;144:103783. https://doi.org/10.1016/j.dnarep.2024.103783.
8. Bartek J, Lukas J. DNA damage checkpoints: from initiation to recovery or adaptation. Curr Opin Cell Biol. 2007;19:238–45. https://doi.org/10.1016/j.ceb.2007.02.009.
9. Visconti R, Della Monica R, Grieco D. Cell cycle checkpoint in cancer: a therapeutically targetable double-edged sword. J Exp Clin Cancer Res. 2016;35:153. https://doi.org/10.1186/s13046-016-0433-9.
10. Hafner A, Bulyk ML, Jambhekar A, Lahav G. The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol. 2019;20:199–210. https://doi.org/10.1038/s41580-019-0110-x.
11. Roos WP, Kaina B. DNA damage-induced cell death by apoptosis. Trends Mol Med. 2006;12:440–50. https://doi.org/10.1016/j.molmed.2006.07.007.
12. Ozaki T, Nakagawara A. Role of p53 in Cell Death and Human Cancers. Cancers (Basel). 2011;3:994–1013. https://doi.org/10.3390/cancers3010994.
13. Mao Z, Bozzella M, Seluanov A, Gorbunova V. DNA repair by nonhomologous end joining and homologous recombination during cell cycle in human cells. Cell Cycle. 2008;7:2902–6. https://doi.org/10.4161/cc.7.18.6679.
14. Her J, Bunting SF. How cells ensure correct repair of DNA double-strand breaks. J Biol Chem. 2018;293:10502–11. https://doi.org/10.1074/jbc.TM118.000371.
15. Nakamura K, Saredi G, Becker JR, Foster BM, Nguyen NV, Beyer TE, Cesa LC, Faull PA, Lukauskas S, Frimurer T, et al. H4K20me0 recognition by BRCA1-BARD1 directs homologous recombination to sister chromatids. Nat Cell Biol. 2019;21:311–8. https://doi.org/10.1038/s41556-019-0282-9.
16. Pellegrino S, Michelena J, Teloni F, Imhof R, Altmeyer M. Replication-coupled dilution of H4K20me2 Guides 53BP1 to pre-replicative chromatin. Cell Rep. 2017;19:1819–31. https://doi.org/10.1016/j.celrep.2017.05.016.
17. Ceccaldi R, Rondinelli B, D'Andrea AD. Repair pathway choices and consequences at the double-strand break. Trends Cell Biol. 2016;26:52–64. https://doi.org/10.1016/j.tcb.2015.07.009.
18. Brambati A, Sacco O, Porcella S, Heyza J, Kareh M, Schmidt JC, Sfeir A. RHINO directs MMEJ to repair DNA breaks in mitosis. Science. 2023;381:653–60. https://doi.org/10.1126/science.adh3694.
19. Krais JJ, Glass DJ, Chudoba I, Wang Y, Feng W, Simpson D, Patel P, Liu Z, Neumann-Domer R, Betsch RG, et al. Genetic separation of Brca1 functions reveal mutation-dependent Polθ vulnerabilities. Nat Commun. 2023;14:7714. https://doi.org/10.1038/s41467-023-43446-1.
20. Bhargava R, Onyango DO, Stark JM. Regulation of single-strand annealing and its role in genome maintenance. Trends Genet. 2016;32:566–75. https://doi.org/10.1016/j.tig.2016.06.007.
21. Vogt A, He Y. Structure and mechanism in non-homologous end joining. DNA Repair (Amst). 2023;130:103547. https://doi.org/10.1016/j.dnarep.2023.103547.
22. Zhao F, Kim W, Kloeber JA, Lou Z. DNA end resection and its role in DNA replication and DSB repair choice in mammalian cells. Exp Mol Med. 2020;52:1705–14. https://doi.org/10.1038/s12276-020-00519-1.
23. Liang CC, Greenhough LA, Masino L, Maslen S, Bajrami I, Tuppi M, Skehel M, Taylor IA, West SC. Mechanism of single-stranded DNA

annealing by RAD52-RPA complex. Nature. 2024;629:697–703. https://doi.org/10.1038/s41586-024-07347-7.
24. Macheret M, Halazonetis TD. DNA replication stress as a hallmark of cancer. Annu Rev Pathol. 2015;10:425–48. https://doi.org/10.1146/annurev-pathol-012414-040424.
25. Kotsantis P, Petermann E, Boulton SJ. Mechanisms of oncogene-induced replication stress: Jigsaw falling into place. Cancer Discov. 2018;8:537–55. https://doi.org/10.1158/2159-8290.CD-17-1461.
26. Primo LMF, Teixeira LK. DNA replication stress: oncogenes in the spotlight. Genet Mol Biol. 2019;43:e20190138. https://doi.org/10.1590/1678-4685GMB-2019-0138.
27. Srinivasan SV, Dominguez-Sola D, Wang LC, Hyrien O, Gautier J. Cdc45 is a critical effector of myc-dependent DNA replication stress. Cell Rep. 2013;3:1629–39. https://doi.org/10.1016/j.celrep.2013.04.002.
28. Macheret M, Halazonetis TD. Intragenic origins due to short G1 phases underlie oncogene-induced DNA replication stress. Nature. 2018;555:112–6. https://doi.org/10.1038/nature25507.
29. Zeng J, Hills SA, Ozono E, Diffley JFX. Cyclin E-induced replicative stress drives p53-dependent whole-genome duplication. Cell. 2023;186:528-542.e514. https://doi.org/10.1016/j.cell.2022.12.036.
30. Kok YP, Guerrero Llobet S, Schoonen PM, Everts M, Bhattacharya A, Fehrmann RSN, van den Tempel N, van Vugt MATM. Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. Oncogenesis. 2020;9:88. https://doi.org/10.1038/s41389-020-00270-2.
31. Kotsantis P, Silva LM, Irmscher S, Jones RM, Folkes L, Gromak N, Petermann E. Increased global transcription activity as a mechanism of replication stress in cancer. Nat Commun. 2016;7:13087. https://doi.org/10.1038/ncomms13087.
32. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability–an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010;11:220–8. https://doi.org/10.1038/nrm2858.
33. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74. https://doi.org/10.1016/j.cell.2011.02.013.
34. Zeman MK, Cimprich KA. Causes and consequences of replication stress. Nat Cell Biol. 2014;16:2–9. https://doi.org/10.1038/ncb2897.
35. Clarke TL, Mostoslavsky R. DNA repair as a shared hallmark in cancer and ageing. Mol Oncol. 2022;16:3352–79. https://doi.org/10.1002/1878-0261.13285.
36. Gu L, Hickey RJ, Malkas LH. Therapeutic Targeting of DNA Replication Stress in Cancer. Genes (Basel). 2023;14:1346. https://doi.org/10.3390/genes14071346.
37. da Costa AABA, Chowdhury D, Shapiro GI, D'Andrea AD, Konstantinopoulos PA. Targeting replication stress in cancer therapy. Nat Rev Drug Discov. 2023;22:38–58. https://doi.org/10.1038/s41573-022-00558-5.
38. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434:917–21. https://doi.org/10.1038/nature03445.
39. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, Helleday T. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434:913–7. https://doi.org/10.1038/nature03443.
40. Mukhopadhyay A, Plummer ER, Elattar A, Soohoo S, Uzir B, Quinn JE, McCluggage WG, Maxwell P, Aneke H, Curtin NJ, Edmondson RJ. Clinicopathological features of homologous recombination-deficient epithelial ovarian cancers: sensitivity to PARP inhibitors, platinum, and survival. Cancer Res. 2012;72:5675–82. https://doi.org/10.1158/0008-5472.CAN-12-0324.
41. Network CGAR. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474:609–15. https://doi.org/10.1038/nature10166.
42. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30:2654–63. https://doi.org/10.1200/JCO.2011.39.8545.
43. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, Thornton A, Norquist BM, Casadei S, Nord AS, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014;20:764–75. https://doi.org/10.1158/1078-0432.CCR-13-2287.
44. Kondrashova O, Topp M, Nesic K, Lieschke E, Ho GY, Harrell MI, Zapparoli GV, Hadley A, Holian R, Boehm E, et al. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. Nat Commun. 2018;9:3970. https://doi.org/10.1038/s41467-018-05564-z.
45. Xu L, Liddell B, Nesic K, Geissler F, Ashwood LM, Wakefield MJ, Scott CL, Waddell N, Kondrashova O. High-level tumour methylation of BRCA1 and RAD51C is required for homologous recombination deficiency in solid cancers. NAR Cancer. 2024;6:zcae033. https://doi.org/10.1093/narcan/zcae033.
46. Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, Bowden G, Kalmyrzaev B, Warren-Perry M, Snape K, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011;43:879–82. https://doi.org/10.1038/ng.893.
47. Meindl A, Hellebrand H, Wiek C, Erven V, Wappenschmidt B, Niederacher D, Freund M, Lichtner P, Hartmann L, Schaal H, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010;42:410–4. https://doi.org/10.1038/ng.569.
48. Rafnar T, Gudbjartsson DF, Sulem P, Jonasdottir A, Sigurdsson A, Besenbacher S, Lundin P, Stacey SN, Gudmundsson J, Magnusson OT, et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet. 2011;43:1104–7. https://doi.org/10.1038/ng.955.
49. Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, Roeb W, Agnew KJ, Stray SM, Wickramanayake A, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011;108:18032–7. https://doi.org/10.1073/pnas.1115052108.
50. Nesic K, Kondrashova O, Hurley RM, McGehee CD, Vandenberg CJ, Ho GY, Lieschke E, Dall G, Bound N, Shield-Artin K, et al. *RAD51C* Promoter Methylation Loss Causes PARP Inhibitor Resistance in High-Grade Serous Ovarian Carcinoma. Cancer Res. 2021;81:4709–22. https://doi.org/10.1158/0008-5472.CAN-21-0774.
51. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC, Beral V, Berek JS, Birrer MJ, Blagden S, Bookman MA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer. 2015;15:668–79. https://doi.org/10.1038/nrc4019.
52. Kwok M, Agathanggelou A, Stankovic T. DNA damage response defects in hematologic malignancies: mechanistic insights and therapeutic strategies. Blood. 2024. https://doi.org/10.1182/blood.2023019963.
53. Telli ML, Timms KM, Reid J, Hennessy B, Mills GB, Jensen KC, Szallasi Z, Barry WT, Winer EP, Tung NM, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. Clin Cancer Res. 2016;22:3764–73. https://doi.org/10.1158/1078-0432.CCR-15-2477.
54. Nguyen L, WM Martens J, Van Hoeck A, Cuppen E. Pan-cancer landscape of homologous recombination deficiency. Nat Commun. 2020;11:5584. https://doi.org/10.1038/s41467-020-19406-4.
55. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 2007;7:152. https://doi.org/10.1186/1471-2407-7-152.
56. Ahmed M, Li L, Pinnix C, Dabaja B, Nomie K, Lam L, Wang M. ATM mutation and radiosensitivity: An opportunity in the therapy of mantle cell lymphoma. Crit Rev Oncol Hematol. 2016;107:14–9. https://doi.org/10.1016/j.critrevonc.2016.08.008.
57. Topka S, Steinsnyder Z, Ravichandran V, Tkachuk K, Kemel Y, Bandlamudi C, Winkel Madsen M, Furberg H, Ouerfelli O, Rudin CM, et al. Targeting Germline- and Tumor-Associated Nucleotide Excision Repair Defects in Cancer. Clin Cancer Res. 2021;27:1997–2010. https://doi.org/10.1158/1078-0432.CCR-20-3322.
58. Qi Z, Tan H. Association between MGMT status and response to alkylating agents in patients with neuroendocrine neoplasms: a systematic review and meta-analysis. Biosci Rep. 2020;40:BSR20194127. https://doi.org/10.1042/BSR20194127.
59. Rivera AL, Pelloski CE, Gilbert MR, Colman H, De La Cruz C, Sulman EP, Bekele BN, Aldape KD. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant

alkylating chemotherapy for glioblastoma. Neuro Oncol. 2010;12:116–21. https://doi.org/10.1093/neuonc/nop020.
60. Rosas-Alonso R, Colmenarejo-Fernandez J, Pernia O, Rodriguez-Antolín C, Esteban I, Ghanem I, Sanchez-Cabrero D, Losantos-Garcia I, Palacios-Zambrano S, Moreno-Bueno G, et al. Clinical validation of a novel quantitative assay for the detection of MGMT methylation in glioblastoma patients. Clin Epigenetics. 2021;13:52. https://doi.org/10.1186/s13148-021-01044-2.
61. Yamamoto H, Imai K, Perucho M. Gastrointestinal cancer of the microsatellite mutator phenotype pathway. J Gastroenterol. 2002;37:153–63. https://doi.org/10.1007/s005350200015.
62. Kato M, Takano M, Miyamoto M, Sasaki N, Goto T, Tsuda H, Furuya K. DNA mismatch repair-related protein loss as a prognostic factor in endometrial cancers. J Gynecol Oncol. 2015;26:40–5. https://doi.org/10.3802/jgo.2015.26.1.40.
63. Germano G, Amirouchene-Angelozzi N, Rospo G, Bardelli A. The Clinical Impact of the Genomic Landscape of Mismatch Repair-Deficient Cancers. Cancer Discov. 2018;8:1518–28. https://doi.org/10.1158/2159-8290.CD-18-0150.
64. López-Correa PE, Lino-Silva LS, Gamboa-Domínguez A, Zepeda-Najar C, Salcedo-Hernández RA. Frequency of Defective Mismatch Repair System in a Series of Consecutive Cases of Colorectal Cancer in a National Cancer Center. J Gastrointest Cancer. 2018;49:379–84. https://doi.org/10.1007/s12029-018-0132-1.
65. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003;349:247–57. https://doi.org/10.1056/NEJMoa022289.
66. Lukish JR, Muro K, DeNobile J, Katz R, Williams J, Cruess DF, Drucker W, Kirsch I, Hamilton SR. Prognostic significance of DNA replication errors in young patients with colorectal cancer. Ann Surg. 1998;227:51–6. https://doi.org/10.1097/00000658-199801000-00008.
67. Elsaleh H, Joseph D, Grieu F, Zeps N, Spry N, Iacopetta B. Association of tumour site and sex with survival benefit from adjuvant chemotherapy in colorectal cancer. Lancet. 2000;355:1745–50. https://doi.org/10.1016/S0140-6736(00)02261-3.
68. Karran P, Hampson R. Genomic instability and tolerance to alkylating agents. Cancer Surv. 1996;28:69–85.
69. Colella G, Marchini S, D'Incalci M, Brown R, Broggini M. Mismatch repair deficiency is associated with resistance to DNA minor groove alkylating agents. Br J Cancer. 1999;80:338–43. https://doi.org/10.1038/sj.bjc.6690360.
70. Borrego-Soto G, Ortiz-López R, Rojas-Martínez A. Ionizing radiation-induced DNA injury and damage detection in patients with breast cancer. Genet Mol Biol. 2015;38:420–32. https://doi.org/10.1590/S1415-475738420150019.
71. Sriramulu S, Thoidingjam S, Brown SL, Siddiqui F, Movsas B, Nyati S. Molecular targets that sensitize cancer to radiation killing: From the bench to the bedside. Biomed Pharmacother. 2023;158:114126. https://doi.org/10.1016/j.biopha.2022.114126.
72. Nickoloff JA. Targeting replication stress response pathways to enhance genotoxic chemo- and radiotherapy. Molecules. 2022;27:4736. https://doi.org/10.3390/molecules27154736.
73. Shelton J, Lu X, Hollenbaugh JA, Cho JH, Amblard F, Schinazi RF. Metabolism, biochemical actions, and chemical synthesis of anticancer nucleosides, nucleotides, and base analogs. Chem Rev. 2016;116:14379–455. https://doi.org/10.1021/acs.chemrev.6b00209.
74. Ewald B, Sampath D, Plunkett W. Nucleoside analogs: molecular mechanisms signaling cell death. Oncogene. 2008;27:6522–37. https://doi.org/10.1038/onc.2008.316.
75. van den Boogaard WMC, Komninos DSJ, Vermeij WP. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. Cancers (Basel). 2022:14. https://doi.org/10.3390/cancers14030627.
76. Cybulla E, Vindigni A. Leveraging the replication stress response to optimize cancer therapy. Nat Rev Cancer. 2023;23:6–24. https://doi.org/10.1038/s41568-022-00518-6.
77. Kondo N, Takahashi A, Ono K, Ohnishi T. DNA damage induced by alkylating agents and repair pathways. J Nucleic Acids. 2010;2010:543531. https://doi.org/10.4061/2010/543531.
78. Ryan AJ, Squires S, Strutt HL, Johnson RT. Camptothecin cytotoxicity in mammalian cells is associated with the induction of persistent double strand breaks in replicating DNA. Nucleic Acids Res. 1991;19:3295–300. https://doi.org/10.1093/nar/19.12.3295.
79. Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chem Biol. 2010;17:421–33. https://doi.org/10.1016/j.chembiol.2010.04.012.
80. Wakefield MJ, Nesic K, Kondrashova O, Scott CL. Diverse mechanisms of PARP inhibitor resistance in ovarian cancer. Biochim Biophys Acta Rev Cancer. 2019;1872:188307. https://doi.org/10.1016/j.bbcan.2019.08.002.
81. Cong K, Peng M, Kousholt AN, Lee WTC, Lee S, Nayak S, Krais J, Vander-Vere-Carozza PS, Pawelczak KS, Calvo J, et al. Replication gaps are a key determinant of PARP inhibitor synthetic lethality with BRCA deficiency. Mol Cell. 2021;81:3128-3144.e3127. https://doi.org/10.1016/j.molcel.2021.06.011.
82. Simoneau A, Xiong R, Zou L. The *trans* cell cycle effects of PARP inhibitors underlie their selectivity toward BRCA1/2-deficient cells. Genes Dev. 2021;35:1271–89. https://doi.org/10.1101/gad.348479.121.
83. Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, Ji J, Takeda S, Pommier Y. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res. 2012;72:5588–99. https://doi.org/10.1158/0008-5472.CAN-12-2753.
84. Quinet A, Tirman S, Jackson J, Šviković S, Lemaçon D, Carvajal-Maldonado D, González-Acosta D, Vessoni AT, Cybulla E, Wood M, et al. PRIMPOL-mediated adaptive response suppresses replication fork reversal in BRCA-deficient cells. Mol Cell. 2020;77:461-474.e469. https://doi.org/10.1016/j.molcel.2019.10.008.
85. Stanzione M, Zhong J, Wong E, LaSalle TJ, Wise JF, Simoneau A, Myers DT, Phat S, Sade-Feldman M, Lawrence MS, et al. Translesion DNA synthesis mediates acquired resistance to olaparib plus temozolomide in small cell lung cancer. Sci Adv. 2022;8:eabn1229. https://doi.org/10.1126/sciadv.abn1229.
86. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst). 2018;71:172–6. https://doi.org/10.1016/j.dnarep.2018.08.021.
87. Casale J, Patel P. Fluorouracil. [Updated 2024 Feb 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549808/.
88. Burchenal JH, Murphy ML, Ellison RR, Sykes MP, Tan TC, Leone LA, Karnofsky DA, Craver LF, Dargeon HW, Rhoads CP. Clinical evaluation of a new antimetabolite, 6-mercaptopurine, in the treatment of leukemia and allied diseases. Blood. 1953;8:965–99.
89. Triguero A, Xicoy B, Zamora L, Jiménez MJ, García O, Calabuig M, Díaz-Beyá M, Arzuaga J, Ramos F, Medina A, et al. Response to azacitidine in patients with chronic myelomonocytic leukemia according to overlap myelodysplastic/myeloproliferative neoplasms criteria. Leuk Res. 2022;116:106836. https://doi.org/10.1016/j.leukres.2022.106836.
90. Moreno Vanegas Y, Badar T. Clinical Utility of Azacitidine in the Management of Acute Myeloid Leukemia: Update on Patient Selection and Reported Outcomes. Cancer Manag Res. 2022;14:3527–38. https://doi.org/10.2147/CMAR.S271442.
91. Siddiqui NS, Godara A, Byrne MM, Saif MW. Capecitabine for the treatment of pancreatic cancer. Expert Opin Pharmacother. 2019;20:399–409. https://doi.org/10.1080/14656566.2018.1560422.
92. Norman G, Soares M, Peura P, Rice S, Suh D, Wright K, Sculpher M, Eastwood A. Capecitabine for the treatment of advanced gastric cancer. Health Technol Assess. 2010;14:11–7. https://doi.org/10.3310/hta14suppl2/02.
93. Popa EC, Shah MA. Capecitabine in the treatment of esophageal and gastric cancers. Expert Opin Investig Drugs. 2013;22:1645–57. https://doi.org/10.1517/13543784.2013.842974.
94. Johnston JB. Mechanism of action of pentostatin and cladribine in hairy cell leukemia. Leuk Lymphoma. 2011;52(Suppl 2):43–5. https://doi.org/10.3109/10428194.2011.570394.
95. Faruqi A, Tadi P. Cytarabine. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557680/.
96. Santini V, Allione B, Zini G, Gioia D, Lunghi M, Poloni A, Cilloni D, Sanna A, Masiera E, Ceccarelli M, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. Leukemia. 2018;32:413–8. https://doi.org/10.1038/leu.2017.186.

97. Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. Mol Cancer Ther. 2009;8:1015–25. https://doi.org/10.1158/1535-7163.MCT-08-0709.
98. Toschi L, Finocchiaro G, Bartolini S, Gioia V, Cappuzzo F. Role of gemcitabine in cancer therapy. Future Oncol. 2005;1:7–17. https://doi.org/10.1517/14796694.1.1.7.
99. Jinna S, Khandhar PB. Hydroxyurea Toxicity. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537209/.
100. Shariatifar H, Ranjbarian F, Hajiahmadi F, Farasat A. A comprehensive review on methotrexate containing nanoparticles; an appropriate tool for cancer treatment. Mol Biol Rep. 2022;49:11049–60. https://doi.org/10.1007/s11033-022-07782-7.
101. Rollins KD, Lindley C. Pemetrexed: a multitargeted antifolate. Clin Ther. 2005;27:1343–82. https://doi.org/10.1016/j.clinthera.2005.09.010.
102. O'Connor OA, Amengual J, Colbourn D, Deng C, Sawas A. Pralatrexate: a comprehensive update on pharmacology, clinical activity and strategies to optimize use. Leuk Lymphoma. 2017;58:2548–57. https://doi.org/10.1080/10428194.2017.1306642.
103. Fostea RM, Arkenau HT. Trifluridine/tipiracil in the treatment of gastric cancer. Future Oncol. 2022;18:1511–7. https://doi.org/10.2217/fon-2021-0754.
104. Voutsadakis IA. Biomarkers of Trifluridine-Tipiracil Efficacy. J Clin Med. 2021;10:5568. https://doi.org/10.3390/jcm10235568.
105. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer. 2005;104:1129–37. https://doi.org/10.1002/cncr.21324.
106. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer. 2011;11:239–53. https://doi.org/10.1038/nrc3007.
107. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnet NG. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer. 2009;9:134–42. https://doi.org/10.1038/nrc2587.
108. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90. https://doi.org/10.3322/caac.20107.
109. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9:193–9. https://doi.org/10.7150/ijms.3635.
110. Masuda Y, Kamiya K. Molecular nature of radiation injury and DNA repair disorders associated with radiosensitivity. Int J Hematol. 2012;95:239–45. https://doi.org/10.1007/s12185-012-1008-y.
111. Biau J, Chautard E, Verrelle P, Dutreix M. Altering DNA Repair to Improve Radiation Therapy: Specific and Multiple Pathway Targeting. Front Oncol. 2019;9:1009. https://doi.org/10.3389/fonc.2019.01009.
112. Kuzminov A. Single-strand interruptions in replicating chromosomes cause double-strand breaks. Proc Natl Acad Sci U S A. 2001;98:8241–6. https://doi.org/10.1073/pnas.131009198.
113. Kumar S, Singh RK, Meena R. Emerging targets for radioprotection and radiosensitization in radiotherapy. Tumour Biol. 2016;37:11589–609. https://doi.org/10.1007/s13277-016-5117-8.
114. Morgan MA, Lawrence TS. Molecular Pathways: Overcoming Radiation Resistance by Targeting DNA Damage Response Pathways. Clin Cancer Res. 2015;21:2898–904. https://doi.org/10.1158/1078-0432.CCR-13-3229.
115. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461:1071–8. https://doi.org/10.1038/nature08467.
116. Banerjee R, Russo N, Liu M, Basrur V, Bellile E, Palanisamy N, Scanlon CS, van Tubergen E, Inglehart RC, Metwally T, et al. TRIP13 promotes error-prone nonhomologous end joining and induces chemoresistance in head and neck cancer. Nat Commun. 2014;5:4527. https://doi.org/10.1038/ncomms5527.
117. Goodman LS, Wintrobe MM. Nitrogen mustard therapy; use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. J Am Med Assoc. 1946;132:126–32. https://doi.org/10.1001/jama.1946.02870380008004.
118. Huang D, Savage SR, Calinawan AP, Lin C, Zhang B, Wang P, Starr TK, Birrer MJ, Paulovich AG. A highly annotated database of genes associated with platinum resistance in cancer. Oncogene. 2021;40:6395–405. https://doi.org/10.1038/s41388-021-02055-2.
119. Dilruba S, Kalayda GV. Platinum-based drugs: past, present and future. Cancer Chemother Pharmacol. 2016;77:1103–24. https://doi.org/10.1007/s00280-016-2976-z.
120. Eastman A. The formation, isolation and characterization of DNA adducts produced by anticancer platinum complexes. Pharmacol Ther. 1987;34:155–66. https://doi.org/10.1016/0163-7258(87)90009-x.
121. Kasparková J, Brabec V. Recognition of DNA interstrand cross-links of cis-diamminedichloroplatinum(II) and its trans isomer by DNA-binding proteins. Biochemistry. 1995;34:12379–87. https://doi.org/10.1021/bi00038a035.
122. Lemaire MA, Schwartz A, Rahmouni AR, Leng M. Interstrand cross-links are preferentially formed at the d(GC) sites in the reaction between cis-diamminedichloroplatinum (II) and DNA. Proc Natl Acad Sci U S A. 1991;88:1982–5. https://doi.org/10.1073/pnas.88.5.1982.
123. Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anaemia pathway: new players and new functions. Nat Rev Mol Cell Biol. 2016;17:337–49. https://doi.org/10.1038/nrm.2016.48.
124. Garutti M, Pelizzari G, Bartoletti M, Malfatti MC, Gerratana L, Tell G, Puglisi F. Platinum Salts in Patients with Breast Cancer: A Focus on Predictive Factors. Int J Mol Sci. 2019;20:3390. https://doi.org/10.3390/ijms20143390.
125. Newlands ES, Stevens MF, Wedge SR, Wheelhouse RT, Brock C. Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. Cancer Treat Rev. 1997;23:35–61. https://doi.org/10.1016/s0305-7372(97)90019-0.
126. Margison GP, Santibáñez Koref MF, Povey AC. Mechanisms of carcinogenicity/chemotherapy by O6-methylguanine. Mutagenesis. 2002;17:483–7. https://doi.org/10.1093/mutage/17.6.483.
127. York SJ, Modrich P. Mismatch repair-dependent iterative excision at irreparable O6-methylguanine lesions in human nuclear extracts. J Biol Chem. 2006;281:22674–83. https://doi.org/10.1074/jbc.M603667200.
128. Christman JK. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene. 2002;21:5483–95. https://doi.org/10.1038/sj.onc.1205699.
129. Stresemann C, Lyko F. Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine. Int J Cancer. 2008;123:8–13. https://doi.org/10.1002/ijc.23607.
130. Marinello J, Delcuratolo M, Capranico G. Anthracyclines as Topoisomerase II Poisons: From Early Studies to New Perspectives. Int J Mol Sci. 2018;19:3480. https://doi.org/10.3390/ijms19113480.
131. Montecucco A, Zanetta F, Biamonti G. Molecular mechanisms of etoposide. EXCLI J. 2015;14:95–108. https://doi.org/10.17179/excli2015-561.
132. Inoue N, Terabayashi T, Takiguchi-Kawashima Y, Fujinami D, Matsuoka S, Kawano M, Tanaka K, Tsumura H, Ishizaki T, Narahara H, et al. The benzylisoquinoline alkaloids, berberine and coptisine, act against camptothecin-resistant topoisomerase I mutants. Sci Rep. 2021;11:7718. https://doi.org/10.1038/s41598-021-87344-2.
133. Kumar S, Sherman MY. Resistance to TOP-1 Inhibitors: Good Old Drugs Still Can Surprise Us. Int J Mol Sci. 2023;24:7233. https://doi.org/10.3390/ijms24087233.
134. Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol. 2017;18:610–21. https://doi.org/10.1038/nrm.2017.53.
135. Vaitsiankova A, Burdova K, Sobol M, Gautam A, Benada O, Hanzlikova H, Caldecott KW. PARP inhibition impedes the maturation of nascent DNA strands during DNA replication. Nat Struct Mol Biol. 2022;29:329–38. https://doi.org/10.1038/s41594-022-00747-1.
136. Muoio D, Laspata N, Dannenberg RL, Curry C, Darkoa-Larbi S, Hedglin M, Uttam S, Fouquerel E. PARP2 promotes Break Induced Replication-mediated telomere fragility in response to replication stress. Nat Commun. 2024;15:2857. https://doi.org/10.1038/s41467-024-47222-7.
137. Lheureux S, Lai Z, Dougherty BA, Runswick S, Hodgson DR, Timms KM, Lanchbury JS, Kaye S, Gourley C, Bowtell D, et al. Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clin Cancer Res. 2017;23:4086–94. https://doi.org/10.1158/1078-0432.CCR-16-2615.
138. Banerjee S, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, et al. Maintenance

olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22:1721–31. https://doi.org/10.1016/S1470-2045(21)00531-3.
139. Cong K, Peng M, Kousholt AN, Lee WTC, Lee S, Nayak S, Krais J, VanderVere-Carozza PS, Pawelczak KS, Calvo J, et al. Replication gaps are a key determinant of PARP inhibitor synthetic lethality with BRCA deficiency. Mol Cell. 2021;81:3227. https://doi.org/10.1016/j.molcel.2021.07.015.
140. Seppa IM, Ceppi I, Tennakoon M, Reginato G, Jackson J, Rouault CD, Agashe S, Sviderskiy VO, Limbu M, Lantelme E, et al. MRN-CtIP, EXO1, and DNA2-WRN/BLM act bidirectionally to process DNA gaps in PARPi-treated cells without strand cleavage. Genes Dev. 2025. https://doi.org/10.1101/gad.352421.124.
141. Taglialatela A, Leuzzi G, Sannino V, Cuella-Martin R, Huang JW, Wu-Baer F, Baer R, Costanzo V, Ciccia A. REV1-Polζ maintains the viability of homologous recombination-deficient cancer cells through mutagenic repair of PRIMPOL-dependent ssDNA gaps. Mol Cell. 2021;81:4008-4025.e4007. https://doi.org/10.1016/j.molcel.2021.08.016.
142. Hale A, Dhoonmoon A, Straka J, Nicolae CM, Moldovan GL. Multi-step processing of replication stress-derived nascent strand DNA gaps by MRE11 and EXO1 nucleases. Nat Commun. 2023;14:6265. https://doi.org/10.1038/s41467-023-42011-0.
143. Panzarino NJ, Krais JJ, Cong K, Peng M, Mosqueda M, Nayak SU, Bond SM, Calvo JA, Doshi MB, Bere M, et al. Replication Gaps Underlie BRCA Deficiency and Therapy Response. Cancer Res. 2021;81:1388–97. https://doi.org/10.1158/0008-5472.CAN-20-1602.
144. Tirman S, Quinet A, Wood M, Meroni A, Cybulla E, Jackson J, Pegoraro S, Simoneau A, Zou L, Vindigni A. Temporally distinct post-replicative repair mechanisms fill PRIMPOL-dependent ssDNA gaps in human cells. Mol Cell. 2021;81:4026-4040.e4028. https://doi.org/10.1016/j.molcel.2021.09.013.
145. Mao Q, Unadkat JD. Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport–an update. AAPS J. 2015;17:65–82. https://doi.org/10.1208/s12248-014-9668-6.
146. Robey RW, Pluchino KM, Hall MD, Fojo AT, Bates SE, Gottesman MM. Revisiting the role of ABC transporters in multidrug-resistant cancer. Nat Rev Cancer. 2018;18:452–64. https://doi.org/10.1038/s41568-018-0005-8.
147. Pettitt SJ, Krastev DB, Brandsma I, Dréan A, Song F, Aleksandrov R, Harrell MI, Menon M, Brough R, Campbell J, et al. Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. Nat Commun. 2018;9:1849. https://doi.org/10.1038/s41467-018-03917-2.
148. Gongora C, Vezzio-Vie N, Tuduri S, Denis V, Causse A, Auzanneau C, Collod-Beroud G, Coquelle A, Pasero P, Pourquier P, et al. New Topoisomerase I mutations are associated with resistance to camptothecin. Mol Cancer. 2011;10:64. https://doi.org/10.1186/1476-4598-10-64.
149. Wang LF, Ting CY, Lo CK, Su JS, Mickley LA, Fojo AT, Whang-Peng J, Hwang J. Identification of mutations at DNA topoisomerase I responsible for camptothecin resistance. Cancer Res. 1997;57:1516–22.
150. Chrencik JE, Staker BL, Burgin AB, Pourquier P, Pommier Y, Stewart L, Redinbo MR. Mechanisms of camptothecin resistance by human topoisomerase I mutations. J Mol Biol. 2004;339:773–84. https://doi.org/10.1016/j.jmb.2004.03.077.
151. Arakawa Y, Suzuki H, Saito S, Yamada H. Novel missense mutation of the DNA topoisomerase I gene in SN-38-resistant DLD-1 cells. Mol Cancer Ther. 2006;5:502–8. https://doi.org/10.1158/1535-7163.MCT-05-0246.
152. van der Merwe M, Bjornsti MA. Mutation of Gly721 alters DNA topoisomerase I active site architecture and sensitivity to camptothecin. J Biol Chem. 2008;283:3305–15. https://doi.org/10.1074/jbc.M705781200.
153. Losasso C, Cretaio E, Fiorani P, D'Annessa I, Chillemi G, Benedetti P. A single mutation in the 729 residue modulates human DNA topoisomerase IB DNA binding and drug resistance. Nucleic Acids Res. 2008;36:5635–44. https://doi.org/10.1093/nar/gkn557.
154. Jensen NF, Agama K, Roy A, Smith DH, Pfister TD, Rømer MU, Zhang HL, Doroshow JH, Knudsen BR, Stenvang J, et al. Characterization of DNA topoisomerase I in three SN-38 resistant human colon cancer cell lines reveals a new pair of resistance-associated mutations. J Exp Clin Cancer Res. 2016;35:56. https://doi.org/10.1186/s13046-016-0335-x.
155. D'Alessandro G, Morales-Juarez DA, Richards SL, Nitiss KC, Serrano-Benitez A, Wang J, Thomas JC, Gupta V, Voigt A, Belotserkovskaya R, et al. RAD54L2 counters TOP2-DNA adducts to promote genome stability. Sci Adv. 2023;9:eadl2108. https://doi.org/10.1126/sciadv.adl2108.
156. Zhang H, Xiong Y, Sun Y, Park JM, Su D, Feng X, Keast S, Tang M, Huang M, Wang C, et al. RAD54L2-mediated DNA damage avoidance pathway specifically preserves genome integrity in response to topoisomerase 2 poisons. Sci Adv. 2023;9:eadi6681. https://doi.org/10.1126/sciadv.adi6681.
157. Gutierrez R, O'Connor TR. DNA direct reversal repair and alkylating agent drug resistance. Cancer Drug Resist. 2021;4:414–23. https://doi.org/10.20517/cdr.2020.113.
158. Chen X, Zhang M, Gan H, Wang H, Lee JH, Fang D, Kitange GJ, He L, Hu Z, Parney IF, et al. A novel enhancer regulates MGMT expression and promotes temozolomide resistance in glioblastoma. Nat Commun. 2018;9:2949. https://doi.org/10.1038/s41467-018-05373-4.
159. van Nifterik KA, van den Berg J, van der Meide WF, Ameziane N, Wedekind LE, Steenbergen RD, Leenstra S, Lafleur MV, Slotman BJ, Stalpers LJ, Sminia P. Absence of the MGMT protein as well as methylation of the MGMT promoter predict the sensitivity for temozolomide. Br J Cancer. 2010;103:29–35. https://doi.org/10.1038/sj.bjc.6605712.
160. Happold C, Roth P, Wick W, Schmidt N, Florea AM, Silginer M, Reifenberger G, Weller M. Distinct molecular mechanisms of acquired resistance to temozolomide in glioblastoma cells. J Neurochem. 2012;122:444–55. https://doi.org/10.1111/j.1471-4159.2012.07781.x.
161. Kohsaka S, Wang L, Yachi K, Mahabir R, Narita T, Itoh T, Tanino M, Kimura T, Nishihara H, Tanaka S. STAT3 inhibition overcomes temozolomide resistance in glioblastoma by downregulating MGMT expression. Mol Cancer Ther. 2012;11:1289–99. https://doi.org/10.1158/1535-7163.MCT-11-0801.
162. Oldrini B, Vaquero-Siguero N, Mu Q, Kroon P, Zhang Y, Galán-Ganga M, Bao Z, Wang Z, Liu H, Sa JK, et al. MGMT genomic rearrangements contribute to chemotherapy resistance in gliomas. Nat Commun. 2020;11:3883. https://doi.org/10.1038/s41467-020-17717-0.
163. Zhao Y, Majid MC, Soll JM, Brickner JR, Dango S, Mosammaparast N. Noncanonical regulation of alkylation damage resistance by the OTUD4 deubiquitinase. EMBO J. 2015;34:1687–703. https://doi.org/10.15252/embj.201490497.
164. Konishi N, Nakamura M, Ishida E, Shimada K, Mitsui E, Yoshikawa R, Yamamoto H, Tsujikawa K. High expression of a new marker PCA-1 in human prostate carcinoma. Clin Cancer Res. 2005;11:5090–7. https://doi.org/10.1158/1078-0432.CCR-05-0195.
165. Dango S, Mosammaparast N, Sowa ME, Xiong LJ, Wu F, Park K, Rubin M, Gygi S, Harper JW, Shi Y. DNA unwinding by ASCC3 helicase is coupled to ALKBH3-dependent DNA alkylation repair and cancer cell proliferation. Mol Cell. 2011;44:373–84. https://doi.org/10.1016/j.molcel.2011.08.039.
166. Wang D, Xiang DB, Yang XQ, Chen LS, Li MX, Zhong ZY, Zhang YS. APE1 overexpression is associated with cisplatin resistance in non-small cell lung cancer and targeted inhibition of APE1 enhances the activity of cisplatin in A549 cells. Lung Cancer. 2009;66:298–304. https://doi.org/10.1016/j.lungcan.2009.02.019.
167. Shah F, Logsdon D, Messmann RA, Fehrenbacher JC, Fishel ML, Kelley MR. Exploiting the Ref-1-APE1 node in cancer signaling and other diseases: from bench to clinic. NPJ Precis Oncol. 2017;1. https://doi.org/10.1038/s41698-017-0023-0.
168. Li Z, Qing Y, Guan W, Li M, Peng Y, Zhang S, Xiong Y, Wang D. Predictive value of APE1, BRCA1, ERCC1 and TUBB3 expression in patients with advanced non-small cell lung cancer (NSCLC) receiving first-line platinum-paclitaxel chemotherapy. Cancer Chemother Pharmacol. 2014;74:777–86. https://doi.org/10.1007/s00280-014-2562-1.
169. Zhang S, He L, Dai N, Guan W, Shan J, Yang X, Zhong Z, Qing Y, Jin F, Chen C, et al. Serum APE1 as a predictive marker for platinum-based chemotherapy of non-small cell lung cancer patients. Oncotarget. 2016;7:77482–94. https://doi.org/10.18632/oncotarget.13030.
170. Fink D, Aebi S, Howell SB. The role of DNA mismatch repair in drug resistance. Clin Cancer Res. 1998;4:1–6.
171. Kat A, Thilly WG, Fang WH, Longley MJ, Li GM, Modrich P. An alkylation-tolerant, mutator human cell line is deficient in strand-specific mismatch repair. Proc Natl Acad Sci U S A. 1993;90:6424–8. https://doi.org/10.1073/pnas.90.14.6424.
172. Koi M, Umar A, Chauhan DP, Cherian SP, Carethers JM, Kunkel TA, Boland CR. Human chromosome 3 corrects mismatch repair deficiency and

microsatellite instability and reduces N-methyl-N′-nitro-N-nitrosoguanidine tolerance in colon tumor cells with homozygous hMLH1 mutation. Cancer Res. 1994;54:4308–12.
173. Fink D, Nebel S, Norris PS, Aebi S, Kim HK, Haas M, Howell SB. The effect of different chemotherapeutic agents on the enrichment of DNA mismatch repair-deficient tumour cells. Br J Cancer. 1998;77:703–8. https://doi.org/10.1038/bjc.1998.116.
174. Diouf B, Cheng Q, Krynetskaia NF, Yang W, Cheok M, Pei D, Fan Y, Cheng C, Krynetskiy EY, Geng H, et al. Somatic deletions of genes regulating MSH2 protein stability cause DNA mismatch repair deficiency and drug resistance in human leukemia cells. Nat Med. 2011;17:1298–303. https://doi.org/10.1038/nm.2430.
175. Swann PF, Waters TR, Moulton DC, Xu YZ, Zheng Q, Edwards M, Mace R. Role of postreplicative DNA mismatch repair in the cytotoxic action of thioguanine. Science. 1996;273:1109–11. https://doi.org/10.1126/science.273.5278.1109.
176. Nowosielska A, Marinus MG. DNA mismatch repair-induced double-strand breaks. DNA Repair (Amst). 2008;7:48–56. https://doi.org/10.1016/j.dnarep.2007.07.015.
177. Saxena S, Zou L. Hallmarks of DNA replication stress. Mol Cell. 2022;82:2298–314. https://doi.org/10.1016/j.molcel.2022.05.004.
178. Kimble MT, Sane A, Reid RJD, Johnson MJ, Rothstein R, Symington LS. Repair of replication-dependent double-strand breaks differs between the leading and lagging strands. Mol Cell. 2025;85:61-77.e66. https://doi.org/10.1016/j.molcel.2024.10.032.
179. Feng W, Dean DC, Hornicek FJ, Wang J, Jia Y, Duan Z, Shi H. ATR and p-ATR are emerging prognostic biomarkers and DNA damage response targets in ovarian cancer. Ther Adv Med Oncol. 2020;12:1758835920982853. https://doi.org/10.1177/1758835920982853.
180. Deriano L, Guipaud O, Merle-Béral H, Binet JL, Ricoul M, Potocki-Veronese G, Favaudon V, Maciorowski Z, Muller C, Salles B, et al. Human chronic lymphocytic leukemia B cells can escape DNA damage-induced apoptosis through the nonhomologous end-joining DNA repair pathway. Blood. 2005;105:4776–83. https://doi.org/10.1182/blood-2004-07-2888.
181. Beskow C, Skikuniene J, Holgersson A, Nilsson B, Lewensohn R, Kanter L, Viktorsson K. Radioresistant cervical cancer shows upregulation of the NHEJ proteins DNA-PKcs, Ku70 and Ku86. Br J Cancer. 2009;101:816–21. https://doi.org/10.1038/sj.bjc.6605201.
182. Mir SE, De Witt Hamer PC, Krawczyk PM, Balaj L, Claes A, Niers JM, Van Tilborg AA, Zwinderman AH, Geerts D, Kaspers GJ, et al. In silico analysis of kinase expression identifies WEE1 as a gatekeeper against mitotic catastrophe in glioblastoma. Cancer Cell. 2010;18:244–57. https://doi.org/10.1016/j.ccr.2010.08.011.
183. Wen Y, Hou Y, Yi X, Sun S, Guo J, He X, Li T, Cai J, Wang Z. EZH2 activates CHK1 signaling to promote ovarian cancer chemoresistance by maintaining the properties of cancer stem cells. Theranostics. 2021;11:1795–813. https://doi.org/10.7150/thno.48101.
184. Wang WJ, Wu SP, Liu JB, Shi YS, Huang X, Zhang QB, Yao KT. MYC regulation of CHK1 and CHK2 promotes radioresistance in a stem cell-like population of nasopharyngeal carcinoma cells. Cancer Res. 2013;73:1219–31. https://doi.org/10.1158/0008-5472.CAN-12-1408.
185. Sarmento LM, Póvoa V, Nascimento R, Real G, Antunes I, Martins LR, Moita C, Alves PM, Abecasis M, Moita LF, et al. CHK1 overexpression in T-cell acute lymphoblastic leukemia is essential for proliferation and survival by preventing excessive replication stress. Oncogene. 2015;34:2978–90. https://doi.org/10.1038/onc.2014.248.
186. Hsieh CC, Hsu SH, Lin CY, Liaw HJ, Li TW, Jiang KY, Chiang NJ, Chen SH, Lin BW, Chen PC, et al. CHK2 activation contributes to the development of oxaliplatin resistance in colorectal cancer. Br J Cancer. 2022;127:1615–28. https://doi.org/10.1038/s41416-022-01946-9.
187. Xu Y, Hu Y, Xu T, Yan K, Zhang T, Li Q, Chang F, Guo X, Peng J, Li M, et al. RNF8-mediated regulation of Akt promotes lung cancer cell survival and resistance to DNA damage. Cell Rep. 2021;37:109854. https://doi.org/10.1016/j.celrep.2021.109854.
188. Chroma K, Mistrik M, Moudry P, Gursky J, Liptay M, Strauss R, Skrott Z, Vrtel R, Bartkova J, Kramara J, Bartek J. Tumors overexpressing RNF168 show altered DNA repair and responses to genotoxic treatments, genomic instability and resistance to proteotoxic stress. Oncogene. 2017;36:2405–22. https://doi.org/10.1038/onc.2016.392.
189. Bian L, Meng Y, Zhang M, Guo Z, Liu F, Zhang W, Ke X, Su Y, Wang M, Yao Y, et al. ATM Expression Is Elevated in Established Radiation-Resistant Breast Cancer Cells and Improves DNA Repair Efficiency. Int J Biol Sci. 2020;16:1096–106. https://doi.org/10.7150/ijbs.41246.
190. Palmieri D, Valentino T, D'Angelo D, De Martino I, Postiglione I, Pacelli R, Croce CM, Fedele M, Fusco A. HMGA proteins promote ATM expression and enhance cancer cell resistance to genotoxic agents. Oncogene. 2011;30:3024–35. https://doi.org/10.1038/onc.2011.21.
191. Lee JH. Targeting the ATM pathway in cancer: Opportunities, challenges and personalized therapeutic strategies. Cancer Treat Rev. 2024;129:102808. https://doi.org/10.1016/j.ctrv.2024.102808.
192. Kim YM, Lee YM, Park SY, Pyo H. Ataxia telangiectasia and Rad3-related overexpressing cancer cells induce prolonged G_2 arrest and develop resistance to ionizing radiation. DNA Cell Biol. 2011;30:219–27. https://doi.org/10.1089/dna.2010.1141.
193. Wang F, Gouttia OG, Wang L, Peng A. PARP1 Upregulation in Recurrent Oral Cancer and Treatment Resistance. Front Cell Dev Biol. 2021;9:804962. https://doi.org/10.3389/fcell.2021.804962.
194. Michels J, Vitale I, Galluzzi L, Adam J, Olaussen KA, Kepp O, Senovilla L, Talhaoui I, Guegan J, Enot DP, et al. Cisplatin resistance associated with PARP hyperactivation. Cancer Res. 2013;73:2271–80. https://doi.org/10.1158/0008-5472.CAN-12-3000.
195. Maya-Mendoza A, Moudry P, Merchut-Maya JM, Lee M, Strauss R, Bartek J. High speed of fork progression induces DNA replication stress and genomic instability. Nature. 2018;559:279–84. https://doi.org/10.1038/s41586-018-0261-5.
196. Wang S, Zou Z, Luo X, Mi Y, Chang H, Xing D. LRH1 enhances cell resistance to chemotherapy by transcriptionally activating MDC1 expression and attenuating DNA damage in human breast cancer. Oncogene. 2018;37:3243–59. https://doi.org/10.1038/s41388-018-0193-4.
197. Hurley RM, Wahner Hendrickson AE, Visscher DW, Ansell P, Harrell MI, Wagner JM, Negron V, Goergen KM, Maurer MJ, Oberg AL, et al. 53BP1 as a potential predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. Gynecol Oncol. 2019;153:127–34. https://doi.org/10.1016/j.ygyno.2019.01.015.
198. Bouwman P, Aly A, Escandell JM, Pieterse M, Bartkova J, van der Gulden H, Hiddingh S, Thanasoula M, Kulkarni A, Yang Q, et al. 53BP1 loss rescues BRCA1 deficiency and is associated with triple-negative and BRCA-mutated breast cancers. Nat Struct Mol Biol. 2010;17:688–95. https://doi.org/10.1038/nsmb.1831.
199. Bunting SF, Callén E, Wong N, Chen HT, Polato F, Gunn A, Bothmer A, Feldhahn N, Fernandez-Capetillo O, Cao L, et al. 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell. 2010;141:243–54. https://doi.org/10.1016/j.cell.2010.03.012.
200. Gupta R, Somyajit K, Narita T, Maskey E, Stanlie A, Kremer M, Typas D, Lammers M, Mailand N, Nussenzweig A, et al. DNA repair network analysis reveals shieldin as a key regulator of NHEJ and PARP inhibitor sensitivity. Cell. 2018;173:972-988.e923. https://doi.org/10.1016/j.cell.2018.03.050.
201. Dev H, Chiang TW, Lescale C, de Krijger I, Martin AG, Pilger D, Coates J, Sczaniecka-Clift M, Wei W, Ostermaier M, et al. Shieldin complex promotes DNA end-joining and counters homologous recombination in BRCA1-null cells. Nat Cell Biol. 2018;20:954–65. https://doi.org/10.1038/s41556-018-0140-1.
202. Jaspers JE, Kersbergen A, Boon U, Sol W, van Deemter L, Zander SA, Drost R, Wientjens E, Ji J, Aly A, et al. Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov. 2013;3:68–81. https://doi.org/10.1158/2159-8290.CD-12-0049.
203. Yao J, Huang A, Zheng X, Liu T, Lin Z, Zhang S, Yang Q, Zhang T, Ma H. 53BP1 loss induces chemoresistance of colorectal cancer cells to 5-fluorouracil by inhibiting the ATM-CHK2-P53 pathway. J Cancer Res Clin Oncol. 2017;143:419–31. https://doi.org/10.1007/s00432-016-2302-5.
204. Alblihy A, Ali R, Algethami M, Shoqafi A, Toss MS, Brownlie J, Tatum NJ, Hickson I, Moran PO, Grabowska A, et al. Targeting Mre11 overcomes platinum resistance and induces synthetic lethality in XRCC1 deficient epithelial ovarian cancers. NPJ Precis Oncol. 2022;6:51. https://doi.org/10.1038/s41698-022-00298-0.
205. Altan B, Yokobori T, Ide M, Bai T, Yanoma T, Kimura A, Kogure N, Suzuki M, Bao P, Mochiki E, et al. High Expression of MRE11-RAD50-NBS1 Is Associated with Poor Prognosis and Chemoresistance in Gastric Cancer.

Anticancer Res. 2016;36:5237–47. https://doi.org/10.21873/anticanres.11094.
206. Ho V, Chung L, Singh A, Lea V, Abubakar A, Lim SH, Ng W, Lee M, de Souza P, Shin JS, Lee CS. Overexpression of the MRE11-RAD50-NBS1 (MRN) complex in rectal cancer correlates with poor response to neoadjuvant radiotherapy and prognosis. BMC Cancer. 2018;18:869. https://doi.org/10.1186/s12885-018-4776-9.
207. Söderlund K, Stål O, Skoog L, Rutqvist LE, Nordenskjöld B, Askmalm MS. Intact Mre11/Rad50/Nbs1 complex predicts good response to radiotherapy in early breast cancer. Int J Radiat Oncol Biol Phys. 2007;68:50–8. https://doi.org/10.1016/j.ijrobp.2006.12.005.
208. Laurberg JR, Brems-Eskildsen AS, Nordentoft I, Fristrup N, Schepeler T, Ulhøi BP, Agerbaek M, Hartmann A, Bertz S, Wittlinger M, et al. Expression of TIP60 (tat-interactive protein) and MRE11 (meiotic recombination 11 homolog) predict treatment-specific outcome of localised invasive bladder cancer. BJU Int. 2012;110:E1228-1236. https://doi.org/10.1111/j.1464-410X.2012.11564.x.
209. Choudhury A, Nelson LD, Teo MT, Chilka S, Bhattarai S, Johnston CF, Elliott F, Lowery J, Taylor CF, Churchman M, et al. MRE11 expression is predictive of cause-specific survival following radical radiotherapy for muscle-invasive bladder cancer. Cancer Res. 2010;70:7017–26. https://doi.org/10.1158/0008-5472.CAN-10-1202.
210. Bian L, Meng Y, Zhang M, Li D. MRE11-RAD50-NBS1 complex alterations and DNA damage response: implications for cancer treatment. Mol Cancer. 2019;18:169. https://doi.org/10.1186/s12943-019-1100-5.
211. Chen H, Li Y, Li H, Chen X, Fu H, Mao D, Chen W, Lan L, Wang C, Hu K, et al. NBS1 lactylation is required for efficient DNA repair and chemotherapy resistance. Nature. 2024;631:663–9. https://doi.org/10.1038/s41586-024-07620-9.
212. Soria-Bretones I, Sáez C, Ruíz-Borrego M, Japón MA, Huertas P. Prognostic value of CtIP/RBBP8 expression in breast cancer. Cancer Med. 2013;2:774–83. https://doi.org/10.1002/cam4.141.
213. Wu M, Soler DR, Abba MC, Nunez MI, Baer R, Hatzis C, Llombart-Cussac A, Llombart-Bosch A, Aldaz CM. CtIP silencing as a novel mechanism of tamoxifen resistance in breast cancer. Mol Cancer Res. 2007;5:1285–95. https://doi.org/10.1158/1541-7786.MCR-07-0126.
214. Mozaffari NL, Pagliarulo F, Sartori AA. Human CtIP: a 'double agent' in DNA repair and tumorigenesis. Semin Cell Dev Biol. 2021;113:47–56. https://doi.org/10.1016/j.semcdb.2020.09.001.
215. Zhou CS, Feng MT, Chen X, Gao Y, Chen L, Li LD, Li DH, Cao YQ. Exonuclease 1 (EXO1) is a Potential Prognostic Biomarker and Correlates with Immune Infiltrates in Lung Adenocarcinoma. Onco Targets Ther. 2021;14:1033–48. https://doi.org/10.2147/OTT.S286274.
216. Dai Y, Tang Z, Yang Z, Zhang L, Deng Q, Zhang X, Yu Y, Liu X, Zhu J. EXO1 overexpression is associated with poor prognosis of hepatocellular carcinoma patients. Cell Cycle. 2018;17:2386–97. https://doi.org/10.1080/15384101.2018.1534511.
217. Liu J, Zhang J. Elevated EXO1 expression is associated with breast carcinogenesis and poor prognosis. Ann Transl Med. 2021;9:135. https://doi.org/10.21037/atm-20-7922.
218. Keijzers G, Bakula D, Petr MA, Madsen NGK, Teklu A, Mkrtchyan G, Osborne B, Scheibye-Knudsen M. Human Exonuclease 1 (EXO1) Regulatory Functions in DNA Replication with Putative Roles in Cancer. Int J Mol Sci. 2018;20:74. https://doi.org/10.3390/ijms20010074.
219. Peng G, Dai H, Zhang W, Hsieh HJ, Pan MR, Park YY, Tsai RY, Bedrosian I, Lee JS, Ira G, Lin SY. Human nuclease/helicase DNA2 alleviates replication stress by promoting DNA end resection. Cancer Res. 2012;72:2802–13. https://doi.org/10.1158/0008-5472.CAN-11-3152.
220. Han Y, Zhang Z, Wang Z, Sun S. Increased Expression of DNA2 Was Linked to Poor Prognosis in Breast Cancer. Dis Markers. 2021;2021:8860728. https://doi.org/10.1155/2021/8860728.
221. Folly-Kossi H, Graves JD, Garan LAW, Lin FT, Lin WC. DNA2 Nuclease Inhibition Confers Synthetic Lethality in Cancers with Mutant p53 and Synergizes with PARP Inhibitors. Cancer Res Commun. 2023;3:2096–112. https://doi.org/10.1158/2767-9764.CRC-23-0166.
222. Thakkar MK, Lee J, Meyer S, Chang VY. RecQ Helicase Somatic Alterations in Cancer. Front Mol Biosci. 2022;9:887758. https://doi.org/10.3389/fmolb.2022.887758.
223. Ovejero S, Viziteu E, Dutrieux L, Devin J, Lin YL, Alaterre E, Jourdan M, Basbous J, Requirand G, Robert N, et al. The BLM helicase is a new therapeutic target in multiple myeloma involved in replication stress survival and drug resistance. Front Immunol. 2022;13:983181. https://doi.org/10.3389/fimmu.2022.983181.
224. Wojnicki K, Kaczmarczyk A, Wojtas B, Kaminska B. BLM helicase overexpressed in human gliomas contributes to diverse responses of human glioma cells to chemotherapy. Cell Death Discov. 2023;9:157. https://doi.org/10.1038/s41420-023-01451-9.
225. Birkbak NJ, Li Y, Pathania S, Greene-Colozzi A, Dreze M, Bowman-Colin C, Sztupinszki Z, Krzystanek M, Diossy M, Tung N, et al. Overexpression of BLM promotes DNA damage and increased sensitivity to platinum salts in triple-negative breast and serous ovarian cancers. Ann Oncol. 2018;29:903–9. https://doi.org/10.1093/annonc/mdy049.
226. Votino C, Laudanna C, Parcesepe P, Giordano G, Remo A, Manfrin E, Pancione M. Aberrant BLM cytoplasmic expression associates with DNA damage stress and hypersensitivity to DNA-damaging agents in colorectal cancer. J Gastroenterol. 2017;52:327–40. https://doi.org/10.1007/s00535-016-1222-0.
227. Gupta N, Huang TT, Nair JR, An D, Zurcher G, Lampert EJ, McCoy A, Cimino-Mathews A, Swisher EM, Radke MR, et al. BLM overexpression as a predictive biomarker for CHK1 inhibitor response in PARP inhibitor-resistant. Sci Transl Med. 2023;15:eadd7872. https://doi.org/10.1126/scitranslmed.add7872.
228. Savva C, Sadiq M, Sheikh O, Karim S, Trivedi S, Green AR, Rakha EA, Madhusudan S, Arora A. Werner Syndrome Protein Expression in Breast Cancer. Clin Breast Cancer. 2021;21:57-73.e57. https://doi.org/10.1016/j.clbc.2020.07.013.
229. Bernstein KA, Gangloff S, Rothstein R. The RecQ DNA helicases in DNA repair. Annu Rev Genet. 2010;44:393–417. https://doi.org/10.1146/annurev-genet-102209-163602.
230. Patel DS, Misenko SM, Her J, Bunting SF. BLM helicase regulates DNA repair by counteracting RAD51 loading at DNA double-strand break sites. J Cell Biol. 2017;216:3521–34. https://doi.org/10.1083/jcb.201703144.
231. Tripathi V, Agarwal H, Priya S, Batra H, Modi P, Pandey M, Saha D, Raghavan SC, Sengupta S. MRN complex-dependent recruitment of ubiquitylated BLM helicase to DSBs negatively regulates DNA repair pathways. Nat Commun. 2018;9:1016. https://doi.org/10.1038/s41467-018-03393-8.
232. Pedersen H, Anne Adanma Obara E, Elbæk KJ, Vitting-Serup K, Hamerlik P. Replication protein A (RPA) mediates radio-resistance of glioblastoma cancer stem-like cells. Int J Mol Sci 2020;21. https://doi.org/10.3390/ijms21051588.
233. Velegzhaninov IO, Belykh ES, Rasova EE, Pylina YI, Shadrin DM, Klokov DY. Radioresistance, DNA Damage and DNA Repair in Cells With Moderate Overexpression of RPA1. Front Genet. 2020;11:855. https://doi.org/10.3389/fgene.2020.00855.
234. Dueva R, Iliakis G. Replication protein A: a multifunctional protein with roles in DNA replication, repair and beyond. NAR Cancer. 2020;2:zcaa022. https://doi.org/10.1093/narcan/zcaa022.
235. Zhu Y, Liu Y, Zhang C, Chu J, Wu Y, Li Y, Liu J, Li Q, Li S, Shi Q, et al. Tamoxifen-resistant breast cancer cells are resistant to DNA-damaging chemotherapy because of upregulated BARD1 and BRCA1. Nat Commun. 2018;9:1595. https://doi.org/10.1038/s41467-018-03951-0.
236. Taron M, Rosell R, Felip E, Mendez P, Souglakos J, Ronco MS, Queralt C, Majo J, Sanchez JM, Sanchez JJ, Maestre J. BRCA1 mRNA expression levels as an indicator of chemoresistance in lung cancer. Hum Mol Genet. 2004;13:2443–9. https://doi.org/10.1093/hmg/ddh260.
237. Swisher EM, Sakai W, Karlan BY, Wurz K, Urban N, Taniguchi T. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res. 2008;68:2581–6. https://doi.org/10.1158/0008-5472.CAN-08-0088.
238. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, Villegas E, Jacquemont C, Farrugia DJ, Couch FJ, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature. 2008;451:1116–20. https://doi.org/10.1038/nature06633.
239. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, Boyd J, Reis-Filho JS, Ashworth A. Resistance to therapy caused by intragenic deletion in BRCA2. Nature. 2008;451:1111–5. https://doi.org/10.1038/nature06548.
240. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, Nones K, Cowin P, Alsop K, Bailey PJ, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015;521:489–94. https://doi.org/10.1038/nature14410.

241. Sakai W, Swisher EM, Jacquemont C, Chandramohan KV, Couch FJ, Langdon SP, Wurz K, Higgins J, Villegas E, Taniguchi T. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. Cancer Res. 2009;69:6381–6. https://doi.org/10.1158/0008-5472.CAN-09-1178.
242. Pettitt SJ, Frankum JR, Punta M, Lise S, Alexander J, Chen Y, Yap TA, Haider S, Tutt ANJ, Lord CJ. Clinical BRCA1/2 Reversion Analysis Identifies Hotspot Mutations and Predicted Neoantigens Associated with Therapy Resistance. Cancer Discov. 2020;10:1475–88. https://doi.org/10.1158/2159-8290.CD-19-1485.
243. Murciano-Goroff YR, Schram AM, Rosen EY, Won H, Gong Y, Noronha AM, Janjigian YY, Stadler ZK, Chang JC, Yang SR, et al. Reversion mutations in germline BRCA1/2-mutant tumors reveal a BRCA-mediated phenotype in non-canonical histologies. Nat Commun. 2022;13:7182. https://doi.org/10.1038/s41467-022-34109-8.
244. Johnson N, Johnson SF, Yao W, Li YC, Choi YE, Bernhardy AJ, Wang Y, Capelletti M, Sarosiek KA, Moreau LA, et al. Stabilization of mutant BRCA1 protein confers PARP inhibitor and platinum resistance. Proc Natl Acad Sci U S A. 2013;110:17041–6. https://doi.org/10.1073/pnas.1305170110.
245. Wang Y, Krais JJ, Bernhardy AJ, Nicolas E, Cai KQ, Harrell MI, Kim HH, George E, Swisher EM, Simpkins F, Johnson N. RING domain-deficient BRCA1 promotes PARP inhibitor and platinum resistance. J Clin Invest. 2016;126:3145–57. https://doi.org/10.1172/JCI87033.
246. Wang Y, Bernhardy AJ, Cruz C, Krais JJ, Nacson J, Nicolas E, Peri S, van der Gulden H, van der Heijden I, O'Brien SW, et al. The BRCA1-Δ11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin. Cancer Res. 2016;76:2778–90. https://doi.org/10.1158/0008-5472.CAN-16-0186.
247. Wang Y, Bernhardy AJ, Nacson J, Krais JJ, Tan YF, Nicolas E, Radke MR, Handorf E, Llop-Guevara A, Balmaña J, et al. BRCA1 intronic Alu elements drive gene rearrangements and PARP inhibitor resistance. Nat Commun. 2019;10:5661. https://doi.org/10.1038/s41467-019-13530-6.
248. Drost R, Dhillon KK, van der Gulden H, van der Heijden I, Brandsma I, Cruz C, Chondronasiou D, Castroviejo-Bermejo M, Boon U, Schut E, et al. BRCA1185delAG tumors may acquire therapy resistance through expression of RING-less BRCA1. J Clin Invest. 2016;126:2903–18. https://doi.org/10.1172/JCI70196.
249. Nesic K, Krais JJ, Wang Y, Vandenberg CJ, Patel P, Cai KQ, Kwan T, Lieschke E, Ho GY, Barker HE, et al. BRCA1 secondary splice-site mutations drive exon-skipping and PARP inhibitor resistance. Mol Cancer. 2024;23:158. https://doi.org/10.1186/s12943-024-02048-1.
250. Nacson J, Di Marcantonio D, Wang Y, Bernhardy AJ, Clausen E, Hua X, Cai KQ, Martinez E, Feng W, Callén E, et al. BRCA1 mutational complementation induces synthetic viability. Mol Cell. 2020;78:951-959.e956. https://doi.org/10.1016/j.molcel.2020.04.006.
251. Maacke H, Jost K, Opitz S, Miska S, Yuan Y, Hasselbach L, Lüttges J, Kalthoff H, Stürzbecher HW. DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma. Oncogene. 2000;19:2791–5. https://doi.org/10.1038/sj.onc.1203578.
252. Maacke H, Opitz S, Jost K, Hamdorf W, Henning W, Krüger S, Feller AC, Lopens A, Diedrich K, Schwinger E, Stürzbecher HW. Over-expression of wild-type Rad51 correlates with histological grading of invasive ductal breast cancer. Int J Cancer. 2000;88:907–13. https://doi.org/10.1002/1097-0215(20001215)88:6%3c907::aid-ijc11%3e3.0.co;2-4.
253. Feng Y, Wang D, Xiong L, Zhen G, Tan J. Predictive value of RAD51 on the survival and drug responsiveness of ovarian cancer. Cancer Cell Int. 2021;21:249. https://doi.org/10.1186/s12935-021-01953-5.
254. Liao C, Talluri S, Zhao J, Mu S, Kumar S, Shi J, Buon L, Munshi NC, Shammas MA. RAD51 Is Implicated in DNA Damage, Chemoresistance and Immune Dysregulation in Solid Tumors. Cancers (Basel). 2022;14. https://doi.org/10.3390/cancers14225697.
255. Pellegrino B, Herencia-Ropero A, Llop-Guevara A, Pedretti F, Moles-Fernández A, Viaplana C, Villacampa G, Guzmán M, Rodríguez O, Grueso J, et al. Preclinical In Vivo Validation of the RAD51 Test for Identification of Homologous Recombination-Deficient Tumors and Patient Stratification. Cancer Res. 2022;82:1646–57. https://doi.org/10.1158/0008-5472.CAN-21-2409.
256. Guffanti F, Alvisi MF, Anastasia A, Ricci F, Chiappa M, Llop-Guevara A, Serra V, Fruscio R, Degasperi A, Nik-Zainal S, et al. Basal expression of RAD51 foci predicts olaparib response in patient-derived ovarian cancer xenografts. Br J Cancer. 2022;126:120–8. https://doi.org/10.1038/s41416-021-01609-1.
257. Klein HL. The consequences of Rad51 overexpression for normal and tumor cells. DNA Repair (Amst). 2008;7:686–93. https://doi.org/10.1016/j.dnarep.2007.12.008.
258. Kim PM, Allen C, Wagener BM, Shen Z, Nickoloff JA. Overexpression of human RAD51 and RAD52 reduces double-strand break-induced homologous recombination in mammalian cells. Nucleic Acids Res. 2001;29:4352–60. https://doi.org/10.1093/nar/29.21.4352.
259. Wu JY, Vlastos AT, Pelte MF, Caligo MA, Bianco A, Krause KH, Laurent GJ, Irminger-Finger I. Aberrant expression of BARD1 in breast and ovarian cancers with poor prognosis. Int J Cancer. 2006;118:1215–26. https://doi.org/10.1002/ijc.21428.
260. Krais JJ, Wang Y, Patel P, Basu J, Bernhardy AJ, Johnson N. RNF168-mediated localization of BARD1 recruits the BRCA1-PALB2 complex to DNA damage. Nat Commun. 2021;12:5016. https://doi.org/10.1038/s41467-021-25346-4.
261. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell. 2001;7:263–72. https://doi.org/10.1016/s1097-2765(01)00174-5.
262. Ali R, Alabdullah M, Algethami M, Alblihy A, Miligy I, Shoqafi A, Mesquita KA, Abdel-Fatah T, Chan SY, Chiang PW, et al. Ligase 1 is a predictor of platinum resistance and its blockade is synthetically lethal in XRCC1 deficient epithelial ovarian cancers. Theranostics. 2021;11:8350–61. https://doi.org/10.7150/thno.51456.
263. Xu L, Ma X, Zhang X, Zhang C, Zhang Y, Gong S, Wu N, Zhang P, Feng X, Guo J, et al. hsa_circ_0007919 induces LIG1 transcription by binding to FOXA1/TET1 to enhance the DNA damage response and promote gemcitabine resistance in pancreatic ductal adenocarcinoma. Mol Cancer. 2023;22:195. https://doi.org/10.1186/s12943-023-01887-8.
264. Goetz JD, Motycka TA, Han M, Jasin M, Tomkinson AE. Reduced repair of DNA double-strand breaks by homologous recombination in a DNA ligase I-deficient human cell line. DNA Repair (Amst). 2005;4:649–54. https://doi.org/10.1016/j.dnarep.2005.02.004.
265. Sonego M, Pellarin I, Costa A, Vinciguerra GLR, Coan M, Kraut A, D'Andrea S, Dall'Acqua A, Castillo-Tong DC, Califano D, et al. USP1 links platinum resistance to cancer cell dissemination by regulating Snail stability. Sci Adv. 2019;5:eaav3235. https://doi.org/10.1126/sciadv.aav3235.
266. Meng D, Li D. Ubiquitin-specific protease 1 overexpression indicates poor prognosis and promotes proliferation, migration, and invasion of gastric cancer cells. Tissue Cell. 2022;74:101723. https://doi.org/10.1016/j.tice.2021.101723.
267. Murai J, Yang K, Dejsuphong D, Hirota K, Takeda S, D'Andrea AD. The USP1/UAF1 complex promotes double-strand break repair through homologous recombination. Mol Cell Biol. 2011;31:2462–9. https://doi.org/10.1128/MCB.05058-11.
268. Cukras S, Lee E, Palumbo E, Benavidez P, Moldovan GL, Kee Y. The USP1-UAF1 complex interacts with RAD51AP1 to promote homologous recombination repair. Cell Cycle. 2016;15:2636–46. https://doi.org/10.1080/15384101.2016.1209613.
269. Nishi R, Wijnhoven P, le Sage C, Tjeertes J, Galanty Y, Forment JV, Clague MJ, Urbé S, Jackson SP. Systematic characterization of deubiquitylating enzymes for roles in maintaining genome integrity. Nat Cell Biol. 2014;16(1016–1026):1011–8. https://doi.org/10.1038/ncb3028.
270. Xie Y, Liu YK, Guo ZP, Guan H, Liu XD, Xie DF, Jiang YG, Ma T, Zhou PK. RBX1 prompts degradation of EXO1 to limit the homologous recombination pathway of DNA double-strand break repair in G1 phase. Cell Death Differ. 2020;27:1383–97. https://doi.org/10.1038/s41418-019-0424-4.
271. Kasten U, Borgmann K, Burgmann P, Li G, Dikomey E. Overexpression of human Ku70/Ku80 in rat cells resulting in reduced DSB repair capacity with appropriate increase in cell radiosensitivity but with no effect on cell recovery. Radiat Res. 1999;151:532–9.
272. Yang S, Wang XQ. XLF-mediated NHEJ activity in hepatocellular carcinoma therapy resistance. BMC Cancer. 2017;17:344. https://doi.org/10.1186/s12885-017-3345-y.
273. Liu Z, Yu M, Fei B, Sun J, Wang D. Nonhomologous end joining key factor XLF enhances both 5-florouracil and oxaliplatin resistance in colorectal cancer. Onco Targets Ther. 2019;12:2095–104. https://doi.org/10.2147/OTT.S192923.

274. Robb R, Yang L, Shen C, Wolfe AR, Webb A, Zhang X, Vedaie M, Saji M, Jhiang S, Ringel MD, Williams TM. Inhibiting BRAF Oncogene-Mediated Radioresistance Effectively Radiosensitizes BRAF. Clin Cancer Res. 2019;25:4749–60. https://doi.org/10.1158/1078-0432.CCR-18-3625.
275. Takada Y, Someya M, Matsumoto Y, Satoh M, Nakata K, Hori M, Saito M, Hirokawa N, Tateoka K, Teramoto M, et al. Influence of Ku86 and XRCC4 expression in uterine cervical cancer on the response to preoperative radiotherapy. Med Mol Morphol. 2016;49:210–6. https://doi.org/10.1007/s00795-016-0136-5.
276. Xu M, Huang X, Zheng C, Long J, Dai Q, Chen Y, Lu J, Pan C, Yao S, Li J. Platinum-Resistant Ovarian Cancer Is Vulnerable to the cJUN-XRCC4 Pathway Inhibition. Cancers (Basel). 2022:14. https://doi.org/10.3390/cancers14246068.
277. Hori M, Someya M, Matsumoto Y, Nakata K, Kitagawa M, Hasegawa T, Tsuchiya T, Fukushima Y, Gocho T, Sato Y, et al. Influence of XRCC4 expression in esophageal cancer cells on the response to radiotherapy. Med Mol Morphol. 2017;50:25–33. https://doi.org/10.1007/s00795-016-0144-5.
278. Guirouilh-Barbat J, Rass E, Plo I, Bertrand P, Lopez BS. Defects in XRCC4 and KU80 differentially affect the joining of distal nonhomologous ends. Proc Natl Acad Sci U S A. 2007;104:20902–7. https://doi.org/10.1073/pnas.0708541104.
279. Li Z, Zhang W, Chen Y, Guo W, Zhang J, Tang H, Xu Z, Zhang H, Tao Y, Wang F, et al. Impaired DNA double-strand break repair contributes to the age-associated rise of genomic instability in humans. Cell Death Differ. 2016;23:1765–77. https://doi.org/10.1038/cdd.2016.65.
280. Jun S, Jung YS, Suh HN, Wang W, Kim MJ, Oh YS, Lien EM, Shen X, Matsumoto Y, McCrea PD, et al. LIG4 mediates Wnt signalling-induced radioresistance. Nat Commun. 2016;7:10994. https://doi.org/10.1038/ncomms10994.
281. Kumari N, Antil H, Kumari S, Raghavan SC. Deficiency of ligase IV leads to reduced NHEJ, accumulation of DNA damage, and can sensitize cells to cancer therapeutics. Genomics. 2023;115:110731. https://doi.org/10.1016/j.ygeno.2023.110731.
282. Liu H, Huang R, Shan J, Xie X, Wang C, Hu P, Sun X. Artemis as predictive biomarker of responsiveness to preoperative chemoradiotherapy in patients with locally advanced rectal cancer. Curr Oncol. 2024;31:535–46. https://doi.org/10.3390/curroncol31010037.
283. Sridharan DM, Whalen MK, Almendrala D, Cucinotta FA, Kawahara M, Yannone SM, Pluth JM. Increased Artemis levels confer radioresistance to both high and low LET radiation exposures. Radiat Oncol. 2012;7:96. https://doi.org/10.1186/1748-717X-7-96.
284. Frye CC, Tennant L, Yeager A, Azimzadeh P, Bhardwaj P, Xu Y, Liu J, Othoum G, Maher CA, Chernock R, et al. Overexpression of human DNA polymerase theta is a biomarker of aggressive and DNA repair-deficient papillary thyroid cancers. Surgery. 2024;176:1380–7. https://doi.org/10.1016/j.surg.2024.05.006.
285. Higgins GS, Harris AL, Prevo R, Helleday T, McKenna WG, Buffa FM. Overexpression of POLQ confers a poor prognosis in early breast cancer patients. Oncotarget. 2010;1:175–84. https://doi.org/10.18632/oncotarget.124.
286. Lemée F, Bergoglio V, Fernandez-Vidal A, Machado-Silva A, Pillaire MJ, Bieth A, Gentil C, Baker L, Martin AL, Leduc C, et al. DNA polymerase theta up-regulation is associated with poor survival in breast cancer, perturbs DNA replication, and promotes genetic instability. Proc Natl Acad Sci U S A. 2010;107:13390–5. https://doi.org/10.1073/pnas.0910759107.
287. Shinmura K, Kato H, Kawanishi Y, Yoshimura K, Tsuchiya K, Takahara Y, Hosokawa S, Kawase A, Funai K, Sugimura H. POLQ Overexpression is associated with an increased somatic mutation load and PLK4 overexpression in lung adenocarcinoma. Cancers (Basel). 2019;11. https://doi.org/10.3390/cancers11050722.
288. Allera-Moreau C, Rouquette I, Lepage B, Oumouhou N, Walschaerts M, Leconte E, Schilling V, Gordien K, Brouchet L, Delisle MB, et al. DNA replication stress response involving PLK1, CDC6, POLQ, RAD51 and CLASPIN upregulation prognoses the outcome of early/mid-stage non-small cell lung cancer patients. Oncogenesis. 2012;1:e30. https://doi.org/10.1038/oncsis.2012.29.
289. Goullet de Rugy T, Bashkurov M, Datti A, Betous R, Guitton-Sert L, Cazaux C, Durocher D, Hoffmann JS. Excess Polθ functions in response to replicative stress in homologous recombination-proficient cancer cells. Biol Open. 2016;5:1485–92. https://doi.org/10.1242/bio.018028.
290. Li Q, Ma C, Zuo L, Xu A, Zhao F, Hu Y, Sun C. Polymerase Theta Inhibition Impairs Tumor Growth and Enhances Melphalan-Induced DNA Damage in Multiple Myeloma. Blood. 2024;144(Supplement 1):4659. https://doi.org/10.1182/blood-2024-201184.
291. Wood RD, Doublié S. DNA polymerase θ (POLQ), double-strand break repair, and cancer. DNA Repair (Amst). 2016;44:22–32. https://doi.org/10.1016/j.dnarep.2016.05.003.
292. Sfeir A, Symington LS. Microhomology-Mediated End Joining: A Back-up Survival Mechanism or Dedicated Pathway? Trends Biochem Sci. 2015;40:701–14. https://doi.org/10.1016/j.tibs.2015.08.006.
293. Ho V, Chung L, Singh A, Lea V, Abubakar A, Lim SH, Chua W, Ng W, Lee M, Roberts TL, et al. Aberrant Expression of RAD52, Its Prognostic Impact in Rectal Cancer and Association with Poor Survival of Patients. Int J Mol Sci. 2020;21:1768. https://doi.org/10.3390/ijms21051768.
294. Shi TY, Yang G, Tu XY, Yang JM, Qian J, Wu XH, Zhou XY, Cheng X, Wei Q. RAD52 variants predict platinum resistance and prognosis of cervical cancer. PLoS ONE. 2012;7:e50461. https://doi.org/10.1371/journal.pone.0050461.
295. Cao X, Hou J, An Q, Assaraf YG, Wang X. Towards the overcoming of anticancer drug resistance mediated by p53 mutations. Drug Resist Updat. 2020;49:100671. https://doi.org/10.1016/j.drup.2019.100671.
296. Magnussen GI, Holm R, Emilsen E, Rosnes AK, Slipicevic A, Florenes VA. High expression of Wee1 is associated with poor disease-free survival in malignant melanoma: potential for targeted therapy. PLoS ONE. 2012;7:e38254. https://doi.org/10.1371/journal.pone.0038254.
297. Luserna G, di Rorà A, Cerchione C, Martinelli G, Simonetti G. A WEE1 family business: regulation of mitosis, cancer progression, and therapeutic target. J Hematol Oncol. 2020;13:126. https://doi.org/10.1186/s13045-020-00959-2.
298. Zhang Q, Zhao X, Zhang C, Wang W, Li F, Liu D, Wu K, Zhu D, Liu S, Shen C, et al. Overexpressed PKMYT1 promotes tumor progression and associates with poor survival in esophageal squamous cell carcinoma. Cancer Manag Res. 2019;11:7813–24. https://doi.org/10.2147/CMAR.S214243.
299. Sun QS, Luo M, Zhao HM, Sun H. Overexpression of PKMYT1 indicates the poor prognosis and enhances proliferation and tumorigenesis in non-small cell lung cancer via activation of Notch signal pathway. Eur Rev Med Pharmacol Sci. 2019;23:4210–9. https://doi.org/10.26355/eurrev_201905_17925.
300. Liu Y, Qi J, Dou Z, Hu J, Lu L, Dai H, Wang H, Yang W. Systematic expression analysis of WEE family kinases reveals the importance of PKMYT1 in breast carcinogenesis. Cell Prolif. 2020;53:e12741. https://doi.org/10.1111/cpr.12741.
301. Zhang QY, Chen XQ, Liu XC, Wu DM. PKMYT1 Promotes Gastric Cancer Cell Proliferation and Apoptosis Resistance. Onco Targets Ther. 2020;13:7747–57. https://doi.org/10.2147/OTT.S255746.
302. Xuan ZH, Wang HP, Zhang XN, Chen ZX, Zhang HY, Gu MM. PKMYT1 aggravates the progression of ovarian cancer by targeting SIRT3. Eur Rev Med Pharmacol Sci. 2020;24:5259–66. https://doi.org/10.26355/eurrev_202005_21308.
303. Liu L, Wu J, Wang S, Luo X, Du Y, Huang D, Gu D, Zhang F. PKMYT1 promoted the growth and motility of hepatocellular carcinoma cells by activating beta-catenin/TCF signaling. Exp Cell Res. 2017;358:209–16. https://doi.org/10.1016/j.yexcr.2017.06.014.
304. Chen P, Zhang Z, Chen X. Overexpression of PKMYT1 facilitates tumor development and is correlated with poor prognosis in clear cell renal cell carcinoma. Med Sci Monit. 2020;26:e926755. https://doi.org/10.12659/MSM.926755.
305. Sokhi S, Lewis CW, Bukhari AB, Hadfield J, Xiao EJ, Fung J, Yoon YJ, Hsu WH, Gamper AM, Chan GK. Myt1 overexpression mediates resistance to cell cycle and DNA damage checkpoint kinase inhibitors. Front Cell Dev Biol. 2023;11:1270542. https://doi.org/10.3389/fcell.2023.1270542.
306. Bargiela-Iparraguirre J, Prado-Marchal L, Fernandez-Fuente M, Gutierrez-González A, Moreno-Rubio J, Muñoz-Fernandez M, Sereno M, Sanchez-Prieto R, Perona R, Sanchez-Perez I. CHK1 expression in Gastric Cancer is modulated by p53 and RB1/E2F1: implications in chemo/radiotherapy response. Sci Rep. 2016;6:21519. https://doi.org/10.1038/srep21519.
307. López-Contreras AJ, Gutierrez-Martinez P, Specks J, Rodrigo-Perez S, Fernandez-Capetillo O. An extra allele of Chk1 limits oncogene-induced

replicative stress and promotes transformation. J Exp Med. 2012;209:455–61. https://doi.org/10.1084/jem.20112147.
308. Patil M, Pabla N, Dong Z. Checkpoint kinase 1 in DNA damage response and cell cycle regulation. Cell Mol Life Sci. 2013;70:4009–21. https://doi.org/10.1007/s00018-013-1307-3.
309. Zannini L, Delia D, Buscemi G. CHK2 kinase in the DNA damage response and beyond. J Mol Cell Biol. 2014;6:442–57. https://doi.org/10.1093/jmcb/mju045.
310. Alikarami F, Safa M, Faranoush M, Hayat P, Kazemi A. Inhibition of DNA-PK enhances chemosensitivity of B-cell precursor acute lymphoblastic leukemia cells to doxorubicin. Biomed Pharmacother. 2017;94:1077–93. https://doi.org/10.1016/j.biopha.2017.08.022.
311. Stefanski CD, Keffler K, McClintock S, Milac L, Prosperi JR. APC loss affects DNA damage repair causing doxorubicin resistance in breast cancer cells. Neoplasia. 2019;21:1143–50. https://doi.org/10.1016/j.neo.2019.09.002.
312. O'Connor MJ, Forment JV. Mechanisms of PARP Inhibitor Resistance. Cancer Treat Res. 2023;186:25–42. https://doi.org/10.1007/978-3-031-30065-3_3.
313. Collet L, Hanvic B, Turinetto M, Treilleux I, Chopin N, Le Saux O, Ray-Coquard I. BRCA1/2 alterations and reversion mutations in the area of PARP inhibitors in high grade ovarian cancer: state of the art and forthcoming challenges. Front Oncol. 2024;14:1354427. https://doi.org/10.3389/fonc.2024.1354427.
314. Geissler F, Nesic K, Kondrashova O, Dobrovic A, Swisher EM, Scott CL, J Wakefield M. The role of aberrant DNA methylation in cancer initiation and clinical impacts. Ther Adv Med Oncol. 2024;16:17588359231220512. https://doi.org/10.1177/17588359231220511.
315. Laurini E, Marson D, Fermeglia A, Aulic S, Fermeglia M, Pricl S. Role of Rad51 and DNA repair in cancer: A molecular perspective. Pharmacol Ther. 2020;208:107492. https://doi.org/10.1016/j.pharmthera.2020.107492.
316. Grundy MK, Buckanovich RJ, Bernstein KA. Regulation and pharmacological targeting of RAD51 in cancer. NAR Cancer. 2020;2:zcaa024. https://doi.org/10.1093/narcan/zcaa024.
317. Zhang S, Cao M, Yan S, Liu Y, Fan W, Cui Y, Tian F, Gu R, Zhan Y, Sun Y, et al. TRIM44 promotes BRCA1 functions in HR repair to induce Cisplatin Chemoresistance in Lung Adenocarcinoma by Deubiquitinating FLNA. Int J Biol Sci. 2022;18:2962–79. https://doi.org/10.7150/ijbs.71283.
318. Nacson J, Krais JJ, Bernhardy AJ, Clausen E, Feng W, Wang Y, Nicolas E, Cai KQ, Tricarico R, Hua X, et al. BRCA1 Mutation-Specific Responses to 53BP1 Loss-Induced Homologous Recombination and PARP Inhibitor Resistance. Cell Rep. 2018;25:1384. https://doi.org/10.1016/j.celrep.2018.10.009.
319. Chen J, Li P, Song L, Bai L, Huen MSY, Liu Y, Lu LY. 53BP1 loss rescues embryonic lethality but not genomic instability of BRCA1 total knockout mice. Cell Death Differ. 2020;27:2552–67. https://doi.org/10.1038/s41418-020-0521-4.
320. Belotserkovskaya R, Raga Gil E, Lawrence N, Butler R, Clifford G, Wilson MD, Jackson SP. PALB2 chromatin recruitment restores homologous recombination in BRCA1-deficient cells depleted of 53BP1. Nat Commun. 2020;11:819. https://doi.org/10.1038/s41467-020-14563-y.
321. Zong D, Adam S, Wang Y, Sasanuma H, Callén E, Murga M, Day A, Kruhlak MJ, Wong N, Munro M, et al. BRCA1 haploinsufficiency is masked by RNF168-mediated chromatin ubiquitylation. Mol Cell. 2019;73:1267-1281.e1267. https://doi.org/10.1016/j.molcel.2018.12.010.
322. Luijsterburg MS, Typas D, Caron MC, Wiegant WW, van den Heuvel D, Boonen RA, Couturier AM, Mullenders LH, Masson JY, van Attikum H. A PALB2-interacting domain in RNF168 couples homologous recombination to DNA break-induced chromatin ubiquitylation. Elife. 2017;6:e20922. https://doi.org/10.7554/eLife.20922.
323. Mateos-Gomez PA, Gong F, Nair N, Miller KM, Lazzerini-Denchi E, Sfeir A. Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination. Nature. 2015;518:254–7. https://doi.org/10.1038/nature14157.
324. Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin MI, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ, et al. Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair. Nature. 2015;518:258–62. https://doi.org/10.1038/nature14184.
325. Feng W, Simpson DA, Carvajal-Garcia J, Price BA, Kumar RJ, Mose LE, Wood RD, Rashid N, Purvis JE, Parker JS, et al. Genetic determinants of cellular addiction to DNA polymerase theta. Nat Commun. 2019;10:4286. https://doi.org/10.1038/s41467-019-12234-1.
326. Landau DA, Carter SL, Stojanov P, McKenna A, Stevenson K, Lawrence MS, Sougnez C, Stewart C, Sivachenko A, Wang L, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell. 2013;152:714–26. https://doi.org/10.1016/j.cell.2013.01.019.
327. Anderson K, Lutz C, van Delft FW, Bateman CM, Guo Y, Colman SM, Kempski H, Moorman AV, Titley I, Swansbury J, et al. Genetic variegation of clonal architecture and propagating cells in leukaemia. Nature. 2011;469:356–61. https://doi.org/10.1038/nature09650.
328. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, Fouse SD, Yamamoto S, Ueda H, Tatsuno K, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343:189–93. https://doi.org/10.1126/science.1239947.
329. Gerlinger M, Horswell S, Larkin J, Rowan AJ, Salm MP, Varela I, Fisher R, McGranahan N, Matthews N, Santos CR, et al. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. Nat Genet. 2014;46:225–33. https://doi.org/10.1038/ng.2891.
330. Walter MJ, Shen D, Ding L, Shao J, Koboldt DC, Chen K, Larson DE, McLellan MD, Dooling D, Abbott R, et al. Clonal architecture of secondary acute myeloid leukemia. N Engl J Med. 2012;366:1090–8. https://doi.org/10.1056/NEJMoa1106968.
331. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, Ritchey JK, Young MA, Lamprecht T, McLellan MD, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature. 2012;481:506–10. https://doi.org/10.1038/nature10738.
332. Zhang J, Fujimoto J, Wedge DC, Song X, Seth S, Chow CW, Cao Y, Gumbs C, Gold KA, Kalhor N, et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. Science. 2014;346:256–9. https://doi.org/10.1126/science.1256930.
333. de Bruin EC, McGranahan N, Mitter R, Salm M, Wedge DC, Yates L, Jamal-Hanjani M, Shafi S, Murugaesu N, Rowan AJ, et al. Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. Science. 2014;346:251–6. https://doi.org/10.1126/science.1253462.
334. Hiley C, de Bruin EC, McGranahan N, Swanton C. Deciphering intratumor heterogeneity and temporal acquisition of driver events to refine precision medicine. Genome Biol. 2014;15:453. https://doi.org/10.1186/s13059-014-0453-8.
335. Nakamura K, Hayashi H, Kawano R, Ishikawa M, Aimono E, Mizuno T, Kuroda H, Kojima Y, Niikura N, Kawanishi A, et al. BRCA1/2 reversion mutations in a pan-cancer cohort. Cancer Sci. 2024;115:635–47. https://doi.org/10.1111/cas.16033.
336. Germano G, Lamba S, Rospo G, Barault L, Magrì A, Maione F, Russo M, Crisafulli G, Bartolini A, Lerda G, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature. 2017;552:116–20. https://doi.org/10.1038/nature24673.
337. Harding SM, Benci JL, Irianto J, Discher DE, Minn AJ, Greenberg RA. Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature. 2017;548:466–70. https://doi.org/10.1038/nature23470.
338. Bakhoum SF, Ngo B, Laughney AM, Cavallo JA, Murphy CJ, Ly P, Shah P, Sriram RK, Watkins TBK, Taunk NK, et al. Chromosomal instability drives metastasis through a cytosolic DNA response. Nature. 2018;553:467–72. https://doi.org/10.1038/nature25432.
339. Ley TJ, Mardis ER, Ding L, Fulton B, McLellan MD, Chen K, Dooling D, Dunford-Shore BH, McGrath S, Hickenbotham M, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. Nature. 2008;456:66–72. https://doi.org/10.1038/nature07485.
340. Dulbecco R. A turning point in cancer research: sequencing the human genome. Science. 1986;231:1055–6. https://doi.org/10.1126/science.3945817.
341. Govindan R. Cancer. Attack of the clones. Science. 2014;346:169–70. https://doi.org/10.1126/science.1259926.
342. Ding L, Bailey MH, Porta-Pardo E, Thorsson V, Colaprico A, Bertrand D, Gibbs DL, Weerasinghe A, Huang KL, Tokheim C, et al. Perspective on oncogenic processes at the end of the beginning of cancer genomics. Cell. 2018;173:305-320.e310. https://doi.org/10.1016/j.cell.2018.03.033.

343. Knijnenburg TA, Wang L, Zimmermann MT, Chambwe N, Gao GF, Cherniack AD, Fan H, Shen H, Way GP, Greene CS, et al. Genomic and molecular landscape of DNA damage repair deficiency across the cancer genome atlas. Cell Rep. 2018;23:239-254.e236. https://doi.org/10.1016/j.celrep.2018.03.076.
344. Kreth S, Thon N, Eigenbrod S, Lutz J, Ledderose C, Egensperger R, Tonn JC, Kretzschmar HA, Hinske LC, Kreth FW. O-methylguanine-DNA methyltransferase (MGMT) mRNA expression predicts outcome in malignant glioma independent of MGMT promoter methylation. PLoS ONE. 2011;6:e17156. https://doi.org/10.1371/journal.pone.0017156.
345. Krais JJ, Johnson N. BRCA1 Mutations in Cancer: Coordinating Deficiencies in Homologous Recombination with Tumorigenesis. Cancer Res. 2020;80:4601–9. https://doi.org/10.1158/0008-5472.CAN-20-1830.
346. van de Kooij B, van Attikum H. Genomic Reporter Constructs to Monitor Pathway-Specific Repair of DNA Double-Strand Breaks. Front Genet. 2021;12:809832. https://doi.org/10.3389/fgene.2021.809832.
347. Figueroa-González G, Pérez-Plasencia C. Strategies for the evaluation of DNA damage and repair mechanisms in cancer. Oncol Lett. 2017;13:3982–8. https://doi.org/10.3892/ol.2017.6002.
348. Feng W, Simpson DA, Cho JE, Carvajal-Garcia J, Smith CM, Headley KM, Hathaway N, Ramsden DA, Gupta GP. Marker-free quantification of repair pathway utilization at Cas9-induced double-strand breaks. Nucleic Acids Res. 2021;49:5095–105. https://doi.org/10.1093/nar/gkab299.
349. Rajendra E, Grande D, Mason B, Di Marcantonio D, Armstrong L, Hewitt G, Elinati E, Galbiati A, Boulton SJ, Heald RA, et al. Quantitative, titratable and high-throughput reporter assays to measure DNA double strand break repair activity in cells. Nucleic Acids Res. 2023. https://doi.org/10.1093/nar/gkad1196.
350. Compadre AJ, van Biljon LN, Valentine MC, Llop-Guevara A, Graham E, Fashemi B, Herencia-Ropero A, Kotnik EN, Cooper I, Harrington SP, et al. RAD51 Foci as a Biomarker Predictive of Platinum Chemotherapy Response in Ovarian Cancer. Clin Cancer Res. 2023;29:2466–79. https://doi.org/10.1158/1078-0432.CCR-22-3335.
351. Kim K, Kim SH, Lee JY, Kim YN, Lee ST, Park E. RAD51/geminin/γH2AX immunohistochemical expression predicts platinum-based chemotherapy response in ovarian high-grade serous carcinoma. J Gynecol Oncol. 2023;34:e45. https://doi.org/10.3802/jgo.2023.34.e45.
352. Yoshida GJ. Applications of patient-derived tumor xenograft models and tumor organoids. J Hematol Oncol. 2020;13:4. https://doi.org/10.1186/s13045-019-0829-z.
353. Hengel SR, Spies MA, Spies M. Small-Molecule Inhibitors Targeting DNA Repair and DNA Repair Deficiency in Research and Cancer Therapy. Cell Chem Biol. 2017;24:1101–19. https://doi.org/10.1016/j.chembiol.2017.08.027.
354. Yap TA, Plummer R, Azad NS, Helleday T. The DNA Damaging Revolution: PARP Inhibitors and Beyond. Am Soc Clin Oncol Educ Book. 2019;39:185–95. https://doi.org/10.1200/EDBK_238473.
355. Groelly FJ, Fawkes M, Dagg RA, Blackford AN, Tarsounas M. Targeting DNA damage response pathways in cancer. Nat Rev Cancer. 2023;23:78–94. https://doi.org/10.1038/s41568-022-00535-5.
356. Illuzzi G, Staniszewska AD, Gill SJ, Pike A, McWilliams L, Critchlow SE, Cronin A, Fawell S, Hawthorne G, Jamal K, et al. Preclinical Characterization of AZD5305, A Next-Generation, Highly Selective PARP1 Inhibitor and Trapper. Clin Cancer Res. 2022;28:4724–36. https://doi.org/10.1158/1078-0432.CCR-22-0301.
357. Herencia-Ropero A, Llop-Guevara A, Staniszewska AD, Domènech-Vivó J, García-Galea E, Moles-Fernández A, Pedretti F, Domènech H, Rodríguez O, Guzmán M, et al. The PARP1 selective inhibitor saruparib (AZD5305) elicits potent and durable antitumor activity in patient-derived BRCA1/2-associated cancer models. Genome Med. 2024;16:107. https://doi.org/10.1186/s13073-024-01370-z.
358. Dellavedova G, Decio A, Formenti L, Albertella MR, Wilson J, Staniszewska AD, Leo E, Giavazzi R, Ghilardi C, Bani MR. The PARP1 Inhibitor AZD5305 Impairs Ovarian Adenocarcinoma Progression and Visceral Metastases in Patient-derived Xenografts Alone and in Combination with Carboplatin. Cancer Res Commun. 2023;3:489–500. https://doi.org/10.1158/2767-9764.CRC-22-0423.
359. AZD5305 More Tolerable than Earlier PARP Agents. Cancer Discov. 2022;12:1602. https://doi.org/10.1158/2159-8290.CD-NB2022-0039.
360. Houl JH, Ye Z, Brosey CA, Balapiti-Modarage LPF, Namjoshi S, Bacolla A, Laverty D, Walker BL, Pourfarjam Y, Warden LS, et al. Selective small molecule PARG inhibitor causes replication fork stalling and cancer cell death. Nat Commun. 2019;10:5654. https://doi.org/10.1038/s41467-019-13508-4.
361. Zatreanu D, Robinson HMR, Alkhatib O, Boursier M, Finch H, Geo L, Grande D, Grinkevich V, Heald RA, Langdon S, et al. Polθ inhibitors elicit BRCA-gene synthetic lethality and target PARP inhibitor resistance. Nat Commun. 2021;12:3636. https://doi.org/10.1038/s41467-021-23463-8.
362. Zhou J, Gelot C, Pantelidou C, Li A, Yücel H, Davis RE, Färkkilä A, Kochupurakkal B, Syed A, Shapiro GI, et al. A first-in-class Polymerase Theta Inhibitor selectively targets Homologous-Recombination-Deficient Tumors. Nat Cancer. 2021;2:598–610. https://doi.org/10.1038/s43018-021-00203-x.
363. Qiu Z, Oleinick NL, Zhang J. ATR/CHK1 inhibitors and cancer therapy. Radiother Oncol. 2018;126:450–64. https://doi.org/10.1016/j.radonc.2017.09.043.
364. Lavin MF, Yeo AJ. Clinical potential of ATM inhibitors. Mutat Res. 2020;821:111695. https://doi.org/10.1016/j.mrfmmm.2020.111695.
365. Zenke FT, Zimmermann A, Sirrenberg C, Dahmen H, Kirkin V, Pehl U, Grombacher T, Wilm C, Fuchss T, Amendt C, et al. Pharmacologic Inhibitor of DNA-PK, M3814, Potentiates Radiotherapy and Regresses Human Tumors in Mouse Models. Mol Cancer Ther. 2020;19:1091–101. https://doi.org/10.1158/1535-7163.MCT-19-0734.
366. van Bussel MTJ, Awada A, de Jonge MJA, Mau-Sørensen M, Nielsen D, Schöffski P, Verheul HMW, Sarholz B, Berghoff K, El Bawab S, et al. A first-in-man phase 1 study of the DNA-dependent protein kinase inhibitor peposertib (formerly M3814) in patients with advanced solid tumours. Br J Cancer. 2021;124:728–35. https://doi.org/10.1038/s41416-020-01151-6.
367. Matheson CJ, Backos DS, Reigan P. Targeting WEE1 Kinase in Cancer. Trends Pharmacol Sci. 2016;37:872–81. https://doi.org/10.1016/j.tips.2016.06.006.
368. Szychowski J, Papp R, Dietrich E, Liu B, Vallée F, Leclaire ME, Fourtounis J, Martino G, Perryman AL, Pau V, et al. Discovery of an Orally Bioavailable and Selective PKMYT1 Inhibitor, RP-6306. J Med Chem. 2022;65:10251–84. https://doi.org/10.1021/acs.jmedchem.2c00552.
369. Giudice E, Huang TT, Nair JR, Zurcher G, McCoy A, Nousome D, Radke MR, Swisher EM, Lipkowitz S, Ibanez K, et al. The CHK1 inhibitor prexasertib in BRCA wild-type platinum-resistant recurrent high-grade serous ovarian carcinoma: a phase 2 trial. Nat Commun. 2024;15:2805. https://doi.org/10.1038/s41467-024-47215-6.
370. Cadzow L, Brenneman J, Tobin E, Sullivan P, Nayak S, Ali JA, Shenker S, Griffith J, McGuire M, Grasberger P, et al. The USP1 Inhibitor KSQ-4279 Overcomes PARP Inhibitor Resistance in Homologous Recombination-Deficient Tumors. Cancer Res. 2024;84:3419–34. https://doi.org/10.1158/0008-5472.CAN-24-0293.
371. Cavalu S, Abdelhamid AM, Saber S, Elmorsy EA, Hamad RS, Abdel-Reheim MA, Yahya G, Salama MM. Cell cycle machinery in oncology: A comprehensive review of therapeutic targets. FASEB J. 2024;38:e23734. https://doi.org/10.1096/fj.202400769R.
372. Li Q, Qian W, Zhang Y, Hu L, Chen S, Xia Y. A new wave of innovations within the DNA damage response. Signal Transduct Target Ther. 2023;8:338. https://doi.org/10.1038/s41392-023-01548-8.
373. Farrés J, Martín-Caballero J, Martínez C, Lozano JJ, Llacuna L, Ampurdanés C, Ruiz-Herguido C, Dantzer F, Schreiber V, Villunger A, et al. Parp-2 is required to maintain hematopoiesis following sublethal γ-irradiation in mice. Blood. 2013;122:44–54. https://doi.org/10.1182/blood-2012-12-472845.
374. Farrés J, Llacuna L, Martin-Caballero J, Martínez C, Lozano JJ, Ampurdanés C, López-Contreras AJ, Florensa L, Navarro J, Ottina E, et al. PARP-2 sustains erythropoiesis in mice by limiting replicative stress in erythroid progenitors. Cell Death Differ. 2015;22:1144–57. https://doi.org/10.1038/cdd.2014.202.
375. Lin X, Gupta D, Vaitsiankova A, Bhandari SK, Leung KSK, Menolfi D, Lee BJ, Russell HR, Gershik S, Huang X, et al. Inactive Parp2 causes Tp53-dependent lethal anemia by blocking replication-associated nick ligation in erythroblasts. Mol Cell. 2024;84:3916-3931.e3917. https://doi.org/10.1016/j.molcel.2024.09.020.
376. Staniszewska AD, Pilger D, Gill SJ, Jamal K, Bohin N, Guzzetti S, Gordon J, Hamm G, Mundin G, Illuzzi G, et al. Preclinical Characterization of AZD9574, a Blood-Brain Barrier Penetrant Inhibitor of PARP1. Clin Cancer Res. 2024;30:1338–51. https://doi.org/10.1158/1078-0432.CCR-23-2094.

377. Ravindranathan R, Somuncu O, da Costa AABA, Mukkavalli S, Lamarre BP, Nguyen H, Grochala C, Jiao Y, Liu J, Kochupurakkal B, et al. PARG inhibitor sensitivity correlates with accumulation of single-stranded DNA gaps in preclinical models of ovarian cancer. Proc Natl Acad Sci U S A. 2024;121:e2413954121. https://doi.org/10.1073/pnas.2413954121.
378. Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, de Bruijn R, James DI, Guerrero Llobet S, Vis DJ, Annunziato S, et al. Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality. Cancer Cell. 2018;33:1078-1093.e1012. https://doi.org/10.1016/j.ccell.2018.05.008.
379. Gelot C, Kovacs MT, Miron S, Mylne E, Haan A, Boeffard-Dosierre L, Ghouil R, Popova T, Dingli F, Loew D, et al. Polθ is phosphorylated by PLK1 to repair double-strand breaks in mitosis. Nature. 2023;621:415–22. https://doi.org/10.1038/s41586-023-06506-6.
380. Fried W, Tyagi M, Minakhin L, Chandramouly G, Tredinnick T, Ramanjulu M, Auerbacher W, Calbert M, Rusanov T, Hoang T, et al. Discovery of a small-molecule inhibitor that traps Polθ on DNA and synergizes with PARP inhibitors. Nat Commun. 2024;15:2862. https://doi.org/10.1038/s41467-024-46593-1.
381. Tobalina L, Armenia J, Irving E, O'Connor MJ, Forment JV. A meta-analysis of reversion mutations in BRCA genes identifies signatures of DNA end-joining repair mechanisms driving therapy resistance. Ann Oncol. 2021;32:103–12. https://doi.org/10.1016/j.annonc.2020.10.470.
382. Luedeman ME, Stroik S, Feng W, Luthman AJ, Gupta GP, Ramsden DA. Poly(ADP) ribose polymerase promotes DNA polymerase theta-mediated end joining by activation of end resection. Nat Commun. 2022;13:4547. https://doi.org/10.1038/s41467-022-32166-7.
383. Kim H, Xu H, George E, Hallberg D, Kumar S, Jagannathan V, Medvedev S, Kinose Y, Devins K, Verma P, et al. Combining PARP with ATR inhibition overcomes PARP inhibitor and platinum resistance in ovarian cancer models. Nat Commun. 2020;11:3726. https://doi.org/10.1038/s41467-020-17127-2.
384. Zimmermann M, Bernier C, Kaiser B, Fournier S, Li L, Desjardins J, Skeldon A, Rimkunas V, Veloso A, Young JTF, et al. Guiding ATR and PARP inhibitor combinationswith chemogenomic screens. Cell Rep. 2022;40:111081. https://doi.org/10.1016/j.celrep.2022.111081.
385. Wethington SL, Shah PD, Martin L, Tanyi JL, Latif N, Morgan M, Torigian DA, Rodriguez D, Smith SA, Dean E, et al. Combination ATR (ceralasertib) and PARP (olaparib) Inhibitor (CAPRI) Trial in Acquired PARP Inhibitor-Resistant Homologous Recombination-Deficient Ovarian Cancer. Clin Cancer Res. 2023;29:2800–7. https://doi.org/10.1158/1078-0432.CCR-22-2444.
386. Lloyd RL, Wijnhoven PWG, Ramos-Montoya A, Wilson Z, Illuzzi G, Falenta K, Jones GN, James N, Chabbert CD, Stott J, et al. Combined PARP and ATR inhibition potentiates genome instability and cell death in ATM-deficient cancer cells. Oncogene. 2020;39:4869–83. https://doi.org/10.1038/s41388-020-1328-y.
387. Turchick A, Zimmermann A, Chiu LY, Dahmen H, Elenbaas B, Zenke FT, Blaukat A, Vassilev LT. Selective Inhibition of ATM-dependent Double-strand break repair and checkpoint control synergistically enhances the efficacy of ATR inhibitors. Mol Cancer Ther. 2023;22:859–72. https://doi.org/10.1158/1535-7163.MCT-22-0685.
388. Gallo D, Young JTF, Fourtounis J, Martino G, Álvarez-Quilón A, Bernier C, Duffy NM, Papp R, Roulston A, Stocco R, et al. CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition. Nature. 2022;604:749–56. https://doi.org/10.1038/s41586-022-04638-9.
389. Seligmann JF, Fisher DJ, Brown LC, Adams RA, Graham J, Quirke P, Richman SD, Butler R, Domingo E, Blake A, et al. Inhibition of WEE1 Is Effective in. J Clin Oncol. 2021;39:3705–15. https://doi.org/10.1200/JCO.21.01435.

Publisher's Note