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Review Article

DNA damaging agents and DNA repair: From carcinogenesis to cancer therapy

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ABSTRACT

Cancer genome instability arises from diverse defects in DNA-repair machinery, which make cancer cells more susceptible to DNA targeting agents. The interrelation between DNA repair deficiency and the increased effect of DNA targeting agents highlights the double-strand break (DSB) repair, which comprises the homologous recombination (HR) and non-homologous end joining (NHEJ) pathways. The DNA targeting agents are classified into two major groups: non-covalent DNA binding agents and covalent DNA-reactive agents. Although these agents have well-known limitations, such as resistance and secondary carcinogenesis risk, they are extremely important in today's real-life cancer therapy in combination with targeted therapy and immunotherapy. Indeed, DNA targeting drugs are promising therapeutics with a precise application through the background of cancer-specific DNA repair failure. In the current review, the mechanisms of action of diversified DNA-targeting agents, as well as the modulation of DNA repair pathways to increase the DNA-damaging drugs efficacy are presented. Finally, DNA-targeting-based therapies are discussed considering risks, resistance and its uses in the medicine precision era.

Abbreviations: 11q, chromosome no 11; 5-FU, 5, fluorouracil; ADCs, Antibody-Drug Conjugates;; ADP, Adenosine Diphosphate; AG, Adenine-Guanine; AGC, Adenine-Guanine-Cytosine; ALL, Acute Lymphoblastic Leukemia; ALTs, Alkyl transferases; AML, Acute Myeloid Leukemia; ATM, Ataxia Telangiectasia Mutated; ATP, Adenosine Triphosphate; *ATR*, Ataxia Telangiectasia and *RAD3* Related; BER, Base Excision Repair; BLM, Bloom Syndrome Protein; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *BRCA1*, Breast Cancer 1; *BRCA2*, Breast Cancer 2; BRIP1, BRCA1-Interacting Protein; CD22, Cluster of Differentiation -22; Cdc25A, Cell Division Cycle 25A; CDK, Cyclin-Dependent Kinase; CGC, Cytosine-Guanine-Cytosine; CHK 1 /2, Checkpoint Kinase 1 /2; CTLA4, Cytotoxic T Lymphocyte, Associated Antigen 4; DDB1, DNA Damage Specific Binding Protein 1; DDB2, DNA Damage Specific Binding Protein 2; DDR, DNA Damage Repair; DNA, Deoxyribonucleic Acid; DNA-PK, DNA-Dependent Protein Kinase; DNA-PKcs, DNA, Dependent Protein Kinases Catalytic Subunits; DSB, Double Strand Break; EGFR, Epidermal Growth Factor Receptor; *ERCC1*, Excision Repair Cross Complementing Group 1; Exo1, Exonuclease 1; FA, Fanconi Anaemia; *FAN1*, FANCD2/FANC1 Associated Nuclease 1; *FANCA*, Fanconi Anemia Complementation Group A; *FANCD2*, Fanconi Anemia Complementation Group D2; FANCG, Fanconi Anemia Complementation Group G; *FANCI*, Fanconi Anemia Complementation Group I; *FANCM*, Fanconi Anemia Complementation Group M; G/T, Guanine/Thymine; G_0/G_1, Gap0/Gap1 Cell Cycle Phase; G_2, Gap2 Cell Cycle Phase; GC, Guanine-Cytosine; GG, Guanine-Guanine; GGC, Guanine-Guanine-Cytosine; GxG, Guanine x Guanine; HDAC, Histone Deacetylase; HDACi, Histone Deacetylase Inhibitor; HER 2, Human Epidermal Growth Factor Receptor-Type 2; HIC, High-Income Countries; HL, Hodgkin Lymphoma; HR, Homologous Recombination; ICLs, Interstrand DNA Crosslinks; Ku70-Ku80, protein complex encoded by *XRCC6-XRCC5* genes; LIG4, DNA Ligase IV; LMIC, Low and Medium Income Countries;; M, Mitosis Cell Cycle Phase;; MAPK, Mitogen Activated Protein Kinases;; MDS, Myelodysplastic Syndrome; MEK, Mitogen-Activated Protein Kinase Kinase; MGMT, O^6-alkylguanine DNA alkyltransferase; *MLH1*, Human Mutl Homolog 1; *MLH3*, MutL Homolog 3; *MLL3*, Mixed-Lineage Leukemia Protein 3; MMR, Mismatch Repair; *MSH2*, MutS Homolog 2; *MSH3*, MutS Homolog 3; *MSH6*, MutS Homolog 6; N2, Nitrogen 2; N7, Nitrogen 7; NBS1, Nibrin; NER, Nucleotide Excision Repair; NHEJ, Non-homologous End Joining; NHL, Non-Hodgkin Lymphoma; O6, Oxygen 6; p21, wild-type activating factor-1/cyclin-dependent kinase inhibitory protein-1 or waf1/cip1; p53, Tumor Protein 53; *PARP1*, Poly (ADP-Ribose) Polymerase-1; *PCNA*, Proliferating Cell Nuclear Antigen; PD1, Programmed Cell Death Protein; PDL1, Programmed Cell Death Protein Ligand; PI3K, Phosphatidylinositol 3-Kinases; *PMS2*, Mismatch Repair Endonuclease; Pol δ, DNA Polymerase δ; Pol ε, DNA Polymerase ε; Pol κ, DNA Polymerase κ; RNA, Ribonucleic Acid; RPA, Replication Protein A; S, Synthesis Phase; SCC, Cutaneous Squamous Cell Carcinoma;; ssDNA, Single-Stranded DNA; TCG, Thymidine-Cytosine-Guanine; t-MDS/AML, Therapy, Related Myelosysplastic syndromes/Acute Myeloid Leukemia; Topo-II, Topoisomerase II; TS, Thymidylate Synthetase; TSL, Translesion Synthesis; TTPs, Thymidine Triphosphates;; VEGF, Vascular Endothelial Growth Factor; VEGFR, Vascular Endothelial Growth Factor Receptor; WEE-1, Nuclease Kinase; *XPA*, *Xeroderma pigmentosum* Complementation Group A; *XPC*, *Xeroderma pigmentosum* Complementation Group C; XPD, or ERCC2,is a protein involved in transcription-coupled nucleotide excision repair; *XPV*, gene encoding DNA polymerase eta also known as *POLH*; *XRCC1*, X-Ray Repair Cross Complementing 1; *XRCC3*, X-Ray Repair Cross Complementing 3; *XRCC4*, X-Ray Repair Cross Complementing 4; *XRCC6-XRCC5*, X-Ray Repair Cross Complementing 6- X-Ray Repair Cross Complementing 5 (Ku70-Ku80).

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Introduction

Cancer is a worldwide public health problem - one of the deadliest diseases with increasing incidence worldwide. Its number of cases increases with population growth, aging, and exposure to risk factors, such as tobacco use, physical inactivity, excess body weight, and reproductive patterns. It has been reduced in high-income countries (HIC) due to the amplification of screening and early detection. However, in low- and medium-income countries (LMIC), the incidence of cancer, for instance lung, breast, and colorectal cancers, has expanded due to increased exposure to risk factors. The cancer care includes surgical resection, radiation, chemotherapy, and specific therapies. Indeed, great efforts have been applied to overcome cancer therapy challenges, such as understanding molecular indicators of cancer for a personalized cancer genomic treatment [1,2,3].

The hallmarks of cancer are categorized in a variety of biological capabilities, which are distinctive from non-tumor cells. These abilities include sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, evading immune destruction, tumor-promoting inflammation, and genome instability and mutation [4]. The three first hallmarks are related to uncontrolled proliferation; thus, intrinsically related to DNA replication, turning cancer cells more susceptible to DNA targeting agents. Additionally, genome instability and mutation arise from diverse DNA-maintenance machinery defects. For instance, this deficiency may be on the detection of DNA damage and activation of DNA repair systems, and loss of telomeric DNA with dysfunction of telomerase, which is also cited as a hallmark for enabling replicative immortality [5,6]. From the ten hallmarks enumerated by Hanahan and Weinberg, 2011, four of them indicates that cancer cells are more sensitive to DNA targeting agents than non-cancer cells [4].

This review discusses the mechanism of action of diversified DNA-targeting agents, classifying them into two major groups: non-covalent DNA binding agents and covalent DNA-reactive agents. Hence, the main DNA repair pathways responsive to these agents are pondered, as well as the modulation of these pathways to increase the DNA-damaging drugs' efficacy. The cons and pros of this type of therapy are further discussed, in particular secondary carcinogenesis risk and its importance in cancer therapy in the medicine precision era.

Non-covalent DNA binding agents and DNA repair pathways

Compounds can bind to DNA through covalent or non-covalent molecular interactions, which may cause several different outcomes. The most common non-covalently DNA agents are known as DNA intercalators, which present a non-covalent interaction within the nucleic acid base pairs as the mechanism of action. These agents are commonly characterized by a planar polycyclic aromatic molecular structure [7] (**Fig. 1A**). Besides intercalative binding, there are two other major non-covalent interactions, which include electrostatic interaction and groove binding. The electrostatic binding consists of the interaction between the positively charged ends of small molecules and the negatively charged phosphate backbone of DNA. Valrubicin, a second-generation anthracycline, is an example of an anticancer drug that binds to DNA via intercalation and electrostatic modes [8]. Additionally, the groove binding is related to hydrogen bonds and hydrophobic interactions of the small molecule and functional groups of the nucleic acid bases (major groove) or structural recognition of a DNA binding site (minor groove) [9–,10,11,12] (**Fig. 1B**). Trabectedin is a groove binding agent useful in the treatment of Ewing's sarcoma and advanced ovarian cancer [13,14].

Similarly, to groove-binders and electrostatic agents, intercalating agents may have hydrophobic and polar interactions, as well as electrostatic binding of cationic intercalators with polyanionic bases, respectively. Therefore, significant π-π stacking may especially occur between the flat polycyclic aromatic rings present in the molecules and the heterocyclic rings of the base pairs, preferably in GC-rich regions. In contrast to groove binding, intercalation distorts the sugar-phosphate torsional angles, to accommodate the aromatic compound, which causes lengthening, stiffening and unwinding of the DNA helix [7,15–,16,17] (**Fig. 1A**). The intercalating compounds are classified according to their quantity of intercalating units: monofunctional, bifunctional, and polyfunctional; bifunctional intercalator contains double intercalation, usually cationic, such as dactinomycin. Finally, DNA intercalators inhibit DNA-related proteins, inhibiting the process of transcription, replication, and DNA repair systems [18,19].

The antineoplastic intercalator agents are classified as anthracycline antibiotics and non-anthracycline antibiotics (such as bleomycin) (American Cancer Society [20]). Anthracycline antibiotics are also classified as topoisomerase poisons [21–,22,23].

Topoisomerases are important targets of many antineoplastic drugs. These enzymes are responsible for the topological maintenance of the chromosomes; they are also known as DNA gyrase and play an important role in DNA replication, transcription, and chromosome segregation. Topoisomerases contain a tyrosine residue, which nucleophilic attacks the phosphodiester backbone, creating an enzyme-DNA adduct. The topoisomerases are primal classified in types I and II, according to the cleavage of single- or double-stranded breaks, respectively. Besides the four major domains (including the cleavage domain) found in topoisomerase I structure, topoisomerase II has an additional ATPase domain [24,25]. Inhibiting topoisomerase II function is an effective anticancer strategy. The two major mechanisms are its catalytic inhibition and the stabilization of the topoisomerase-drug-DNA ternary complex. Etoposide is an example of topoisomerase II catalytic inhibitor. Anthracyclines, for instance, inhibit the topoisomerases through interaction with the enzyme and DNA as a ternary complex [26–,27,28] (**Fig. 1C**).

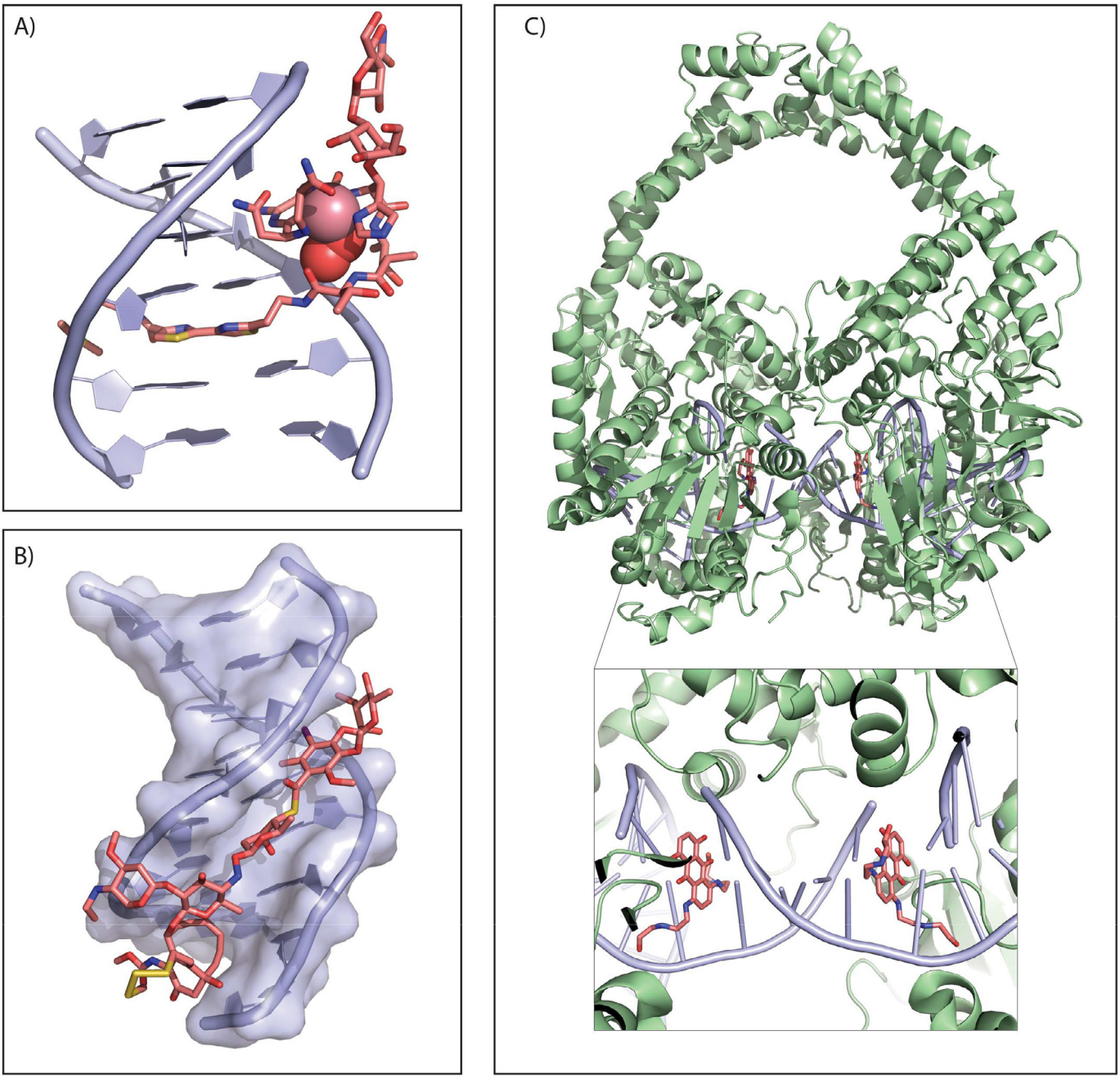

Fig. 1. Molecular representation of non-covalent DNA binding agents. (A) Bleomycin as a DNA intercalating agent. The bithiazole moiety in HO(2)-Co(III)bleomycin intercalates between DNA base pairs, with its tail on the major groove where the positively charged R group associates with the negatively charged DNA backbone (electrostatic interaction) [165]. HO(2)-Co(III) complex is shown in spheres. **(B)** Groove binding of calicheamicin to DNA. Calicheamicin gamma 1I binds to the minor groove of the DNA duplex and it positions the enediyne ring to abstract hydrogen atoms from partner strands, leading to the formation of DNA double-strand breaks [166]. **(C)** Mitoxantrone as a topoisomerase poison. Mitoxantrone uses its polycyclic aromatic dihydroxy-anthraquinone moiety to intercalate into the DNA cleavage sites inhibiting human Top2 (shown in pale green) [167]. DNA is shown in cartoon and light blue, electrostatic surface is also shown in B. Ligands (DNA binding agents) are shown in deep salmon. The PDBIDs 1MTG, 2PIK, and 4G0V were extracted from the Protein Data Bank (PDB) and Pymol was used to visualize and create the Fig..

The general anthracycline molecular structure is characterized by a planar naphthoquinone with a phenolic group, constituting three unsaturated rings (A-C), and one additional saturated ring (D) with mono- or polysaccharide substitutions [29,30]. Besides the topoisomerase-drug-DNA ternary complex formation, the anthracyclines have other mechanisms of action. Anthracyclines chromophore moiety intercalates between adjacent DNA base pairs, which inhibits topo-II and DNA and RNA synthesis as well. The quinone in anthracyclines molecular structure is responsible for reactive oxygen species and subsequent cytotoxicity. In addition, anthracyclines are also able to form drug-DNA adducts, blocking specific transcription factors [31–,32,33]. Among the anthracyclines in clinical use, the first-generation ones are daunorubicin and doxorubicin.

Doxorubicin and daunorubicin have similar molecular structures, differing only in a substitutive group in the side chain, which impact on their cytotoxic spectrum. Daunorubicin, with primary alcohol in the side chain, is active against acute lymphoblastic or myeloid leukemia. Meanwhile, doxorubicin, with a methyl group in the side chain, is an important drug in the treatment of breast cancer, solid tumors, and aggressive lymphomas. However, these drugs are limited by their major side effect – cardiotoxicity [30,34]. Besides the cardiotoxicity, another limitation is the development of resistance; some mechanisms of resistance related to topoisomerase poisons are the high drug efflux rate, down-regulation or amplification of topo-II, and alterations in DNA repair systems [35].

The DNA repair machinery plays an important role in the resistance to chemotherapy, removing the DNA lesions and avoiding toxicity to cells. The DNA repair pathways in response to anthracyclines DNA damage are nonhomologous end joining (NHEJ), homologous recombination (HR), translesion synthesis (TSL), and nucleotide excision repair (NER) [36]. The doxorubicin DNA-damaging mechanisms lead to NHEJ and HR, the more likely responses to double strand break (DSB). Studies show the increased cytotoxicity of doxorubicin to HR-deficient cells and in synergism with NHEJ inhibitor (SCR-7) [37,38]. Additionally, TSL occurs during the replication with the substitution of a standard DNA polymerase to a specialized DNA polymerase capable of synthesizing across base damage on the template strand. This DNA repair mechanism increases drug resistance and mutagenesis. Then, as a DNA-damage response to doxorubicin, its inhibition induces the cytotoxic potential of this drug [39].

NER is a multifaceted pathway activated by structural distortions in the DNA-double helix for the removal of lesions (**Fig. 2A**). The *Xeroderma pigmentosum* complementation group C (XPC) protein initiates the NER pathway by detecting DNA damage, along with damage specific DNA binding protein 1 (DDB1) and damage specific DNA binding protein 2 (DDB2). Replication protein A (RPA) and *Xeroderma pigmentosum* complementation group A (XPA) are recruited to relax the double helix and the XPF-ERCC1 nuclease complex cleaves the damage, releasing the DNA fragment. The initiation of repair synthesis is carried out by DNA polymerase δ (Polδ), DNA polymerase ε (Polε) and DNA polymerase κ (Polκ) and the completion of repair and sealing synthesis is promoted by DNA ligase IIIa / XRCC1 or DNA ligase I with the contribution of proliferating cell nuclear antigen (PCNA) [40,41,42]. NER-deficient cells, for instance, *XPC, XPA*, or *XPV* (polymerase eta, involved in TLS) deficient cells [43,44] are highly sensitive to doxorubicin. Furthermore, the induction of the *XPC* transcription after doxorubicin treatment has also been shown [45]. In addition, the high expression of *ERCC1* is intimately correlated to the anthracycline resistance [46]. As a versatile DNA repair pathway, NER is also a DNA damage response for others DNA damaging agents with different mechanisms of action, such as the alkylating agents, *i.e.* methylating agents that form adducts [47].

Regarding the non-anthracycline antibiotics, bleomycin is a glycopeptide used in the treatment of testicular and ovarian cancers, head and neck squamous cell carcinoma, Hodgkin, and non-Hodgkin lymphomas. The combination of bleomycin, etoposide, and cisplatin is effective to cure 90% of patients with testicular cancer. However, bleomycin leads to the development of lung fibrosis as its major side effect. Its molecular structure induces diverse DNA-damaging mechanisms; the terminal amine electrostatic interaction, DNA intercalation of bithiazole rings, and the simultaneous complex to DNA and redox-active transition metal ions, such as Fe^{2+}, promoting the oxidation of the metal and nucleophilic attack at the DNA deoxyribose C4' position. Bleomycin cleaves the DNA GC base pairs, producing up to 8 to 10 DNA breaks; it may also be considered an endonuclease [48–,49,50,51,52].

The double-strand breaks (DSBs) induced by bleomycin is also well known, and some studies show the induction of γH2AX, a DSB marker, by this drug. Therefore, the major pathways of DSB repair, for the maintenance of genomic stability, NHEJ and HR (**Fig. 2A**). NHEJ is characterized by the reattachment of the two ends of a double-strand break, without sequence homology between ends, while HR copies a DNA sequence from an intact DNA molecule. The repair of DSBs during G_0/G_1 cell cycle phase is primarily mediated by NHEJ. On the other hand, when the damage progress through S phase, HR plays an important role processing it in late S/G_2 phase [53]; bleomycin induces G_2/M arrest, but may also induce replication-independent DSBs that may kill non-replicating cells [54].

The bleomycin treatment increases *PCNA* transcription and its protein expression; this gene is related in several DNA repair pathways, including NHEJ [55,56]. The DSB repaired by NHEJ is initiated by the binding of Ku heterodimer (Ku70-Ku80, also known as *XRCC6-XRCC5*), which recruits DNA-dependent protein kinases catalytic subunits (DNA-PKcs), DNA ligase IV(LIG4) and the associated scaffolding factors, such as XRCC4 (**Fig. 2B**). Furthermore, RAD51 and Ataxia-telangiectasia mutated (ATM) regulate DSB through HR. RAD51 regulates strand invasion of the ssDNA into a homologous DNA region. The loss of function of RAD51 increases the sensitivity to bleomycin as well as bleomycin may activate ATM, indicating that DSBs promoted by this agent is repaired by HR [57–,58,59,60]. The DSB repair and its diverse pathways are involved in bleomycin DNA-damage response.

The incomplete or inefficient repair of DSB causes telomere shortening - a desired effect against cancer, which may reduce replicative immortality. A study shows increased levels of chromatid breaks, aberrant cells, and increased sensitivity in peripheral blood of colorectal cancer patients to bleomycin treatment, indicating a DSB defective repair in colorectal cancer [61]. Therefore, bleomycin is able to induce fibrosarcomas and renal tumors (adenomas, adenocarcinomas, and sarcomas) in rats [62]. Simple intercalating agents do not seem to have major mutagenic effects; however, most of them have additional DNA-damaging effects, such as bleomycin with radiomimetics and redox potential, and the topoisomerases poisons with inhibition of DNA-related proteins. Amsacrine is an aminoacridine that binds to DNA by intercalation and inhibits the topoisomerase II protein; it was shown that this agent induces small intestinal adenocarcinomas in rats [63].

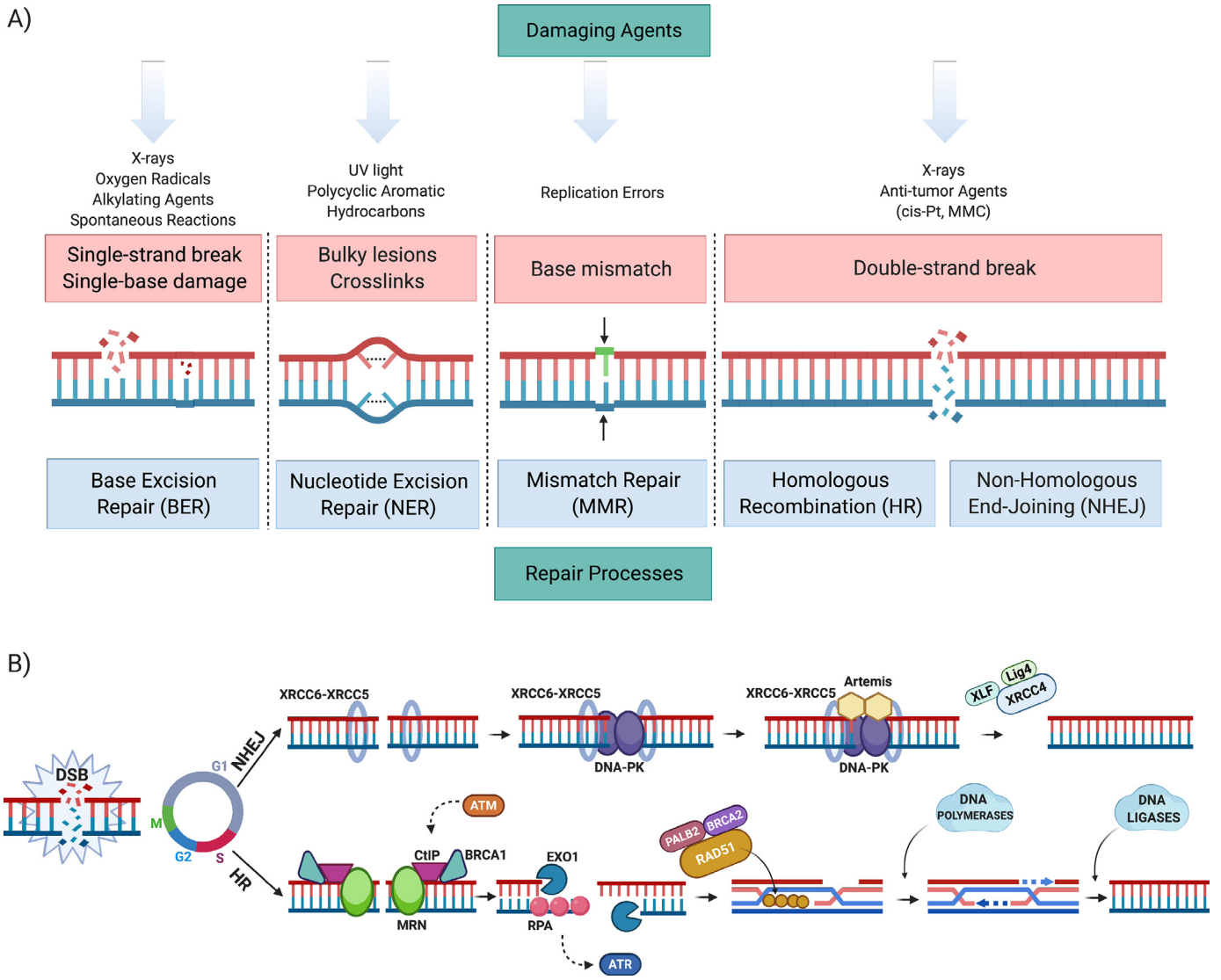

Fig. 2. DNA Damage and DNA repair. (A) Basic overview of which common DNA damaging agents (on top), creates different DNA lesions (middle) and their corresponding DNA repair processes responsible for the removal of such lesions (bottom). **(B)** DSB Repair: the induced DSBs during G_1- cell cycle phase is mostly repaired by NHEJ. *XRCC6/XRCC5* (Ku70/Ku80) binds to the ends of the broken DNA, serving as a scaffold to the recruitment of other proteins, such as DNA-PKs and the nuclease Artemis. The DNA-PKs and Artemis are related to the cleavage and release of the DSB. The ligation of the DNA ends occurs via LIG4, XRCC4, and XLF. HR is present only in S- or G_2-cell cycle phase. It is initiated through DNA end-resection by MRN complex and other accessory factors, such as CtIP, BRCA1, ATM, and EXO1; ATM phosphorylates histone H2AX and several DNA repair proteins and checkpoint signaling. Single-stranded DNA resulted from DNA end-resection is bound by RPA, which promotes ATR activation. RPA is replaced by RAD51 with contribution of PALB2 and BRCA2, leading to novel DNA synthesis and repair. ATM Ataxia Telangiectasia Mutated; ATR Ataxia Telangiectasia and Rad3 related; BRCA1 Breast Cancer 1; BRCA2 Breast Cancer 2; CtIP C-terminal binding protein 1 (CtBP1) interacting protein; DNA-PK DNA Protein Kinase; DSB Double-Strand Break; EXO1 Exonuclease 1; HR Homologous Recombination; LIG 4 DNA Ligase IV; MRE11 Meiotic Recombination 11 Homolog; MRN The complex of MRE11, RAD50 E NBS1; NBN Nibrin; NBS1 protein encoded by NBN gene; NHEJ Non-homologous End Joining; PALB2 Partner and Localizer of BRCA2; RAD50 DSB Repair Protein; RPA Replication Protein A; XLF XRCC4-like Factor; XRCC4 X-Ray Repair Cross Complementing 4; *XRCC6/XRCC5* X-Ray Repair Cross Complementing 5(KU70)/ X-Ray Repair Cross Complementing 5(KU80).

Covalent DNA-reactive agents and DNA repair pathways

Regarding the covalent DNA-reactive agents, the alkylation is a usual mechanism of anticancer DNA targeting drugs. The mechanism of action of alkylating agents along with platinum antitumor compounds are known as covalent interaction with DNA. The alkylating agents are classified by their binding profile and molecular structure: monofunctional alkylating agents (hydrazines, triazines, and isoquinoline alkaloids), and bifunctional alkylating agents (nitrogens mustards, aziridines, hexitol epoxides, alkyl sulfonates, and nitrosoureas). For a more detailed mechanism of action of each molecular structure, consult the reference Siddik, 2017 [64]. Herein, we are briefly discussing the general information of monofunctional and bifunctional alkylating agents, and platinum compounds.

Alkylating agents, in general, have highly reactive molecular groups, which strongly chemical binds to the nucleophilic centers (nitrogen or oxygen) of the DNA bases. The monofunctional alkylating agents promote single alkylation; hydrazines and triazines induce *O6*- and *N7*-methyl-guanine adducts formation, generating single-strand breaks [65,66]. Trabectedin, an example of isoquinoline alkaloid, alkylates the unusual N2-site of guanine of one strand and interacts noncovalently with the sequences TCG, CGG, AGC and GGC on the other strand [67]. This drug is clinically used to treat unresectable or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) that has been resistant to prior anthracycline-containing treatment [68].

The bifunctional alkylating agents' mechanism of action occurs through covalent bonds in the nucleophilic center of two different bases on DNA, inducing crosslinks or adducts. They are able to alkylate the four different bases, at different nucleophilic centers, however, the *N7*-guanine remains the preferential target [69–,70,71,72] (**Fig. 3A**). Cyclophosphamide, a nitrogen mustard, is a successful and widely used bifunctional alkylating agent. It is used against numerous types of cancer, such as breast adenocarcinoma, lymphocytic leukemia, lymphomas, soft tissue and osteogenic sarcoma, and solid tumors [73].

Considering the platinum compounds, they were firstly inspired on cisplatin, in order to reduce its toxicity profile and broader its spectrum [74]. Cisplatin is a metallic (platinum) coordination compound with a square planar geometry, two labile chloro, and two stable amine ligands in a *cis*-configuration [75]. For activity, the neutral cisplatin releases the chloride atoms inside the nucleus and transforms itself into a potent electrophile that can react with any nucleophile [76]. As well as the bifunctional alkylating agents, the platinum compounds attack preferentially the *N7*-site of guanines. Mostly of cisplatin binding is *1,2*-intrastrand AG and GG crosslinks, with *1,3*-intrastrand GXG crosslinks (X= any nucleotide), interstrand GG-crosslinks, and minority monofunctional adducts. The cisplatin DNA-damaging activity is very potent, widely used for the treatment of bladder, head and neck, lung, ovarian, and testicular cancers [77]; its binding to DNA is able to inhibit the transcriptional activity of DNA-dependent RNA polymerases and cause cytotoxicity [78] (**Fig. 3B**).

The alteration of DNA conformation induced by adducts formation is recognized by DNA repair proteins. The DNA damage sensor proteins for platinum-DNA adducts are related to mismatch repair (MMR) (**Fig. 2A**), DSB - NHEJ and HR, ATM/ATR pathways, NER, and Fanconi anemia (FA). Besides those, the DNA repair in response to alkylating agents may also involve base excision repair (BER) proteins and alkyl transferases (ALTs). Furthermore, MMR recognizes post replicative mispairing, mainly involving G/T. Additionally, MMR proteins (e.g. MSH2 and MSH6) detect GG crosslinks; however, MMR is not able to repair the damage, leading to the formation of DSBs and activation of ATM/ATR pathway. MMR proficiency is essential for DNA cross-linking agents activity, and its impairment leads to resistance of these drugs and is highly associated with carcinogenesis, especially in colorectal cancer [79–,80,81].

Regarding the ATM/ATR pathway, ATM and ATR kinases are activated by double-strand breaks and single-strand breaks (DNA replication stress), respectively. ATM phosphorylates p53, which induces p21, promoting G_1/S arrest. ATM is also responsible for CHK2 phosphorylation; CHK2, when activated, inhibits Cdc25A phosphatases and their function of regulating the activity of cyclin-CDK complexes and S/G_2 cell cycle progression. ATR mediates CHK1 phosphorylation, which has the similar functions to CHK2 by the inhibition of Cdc25A phosphatases, leading to S/G_2 arrest, and inhibition of Cdc25C phosphatases, leading to G_2/M arrest [82]. Therefore, inhibition of ATM/ATR and/or CHK1/2 is a strategy to enhance alkylating agents and platinum compounds cytotoxicity [83–,84,85].

The innate recognition and early processing stages of interstrand crosslinks (ICLs) are also resolved by FA proteins and the NER pathway. An important step of FA is the formation of the ID complex by the monoubiquitination of FANCI and FANCD2. Some studies show that the depletion of *FANCD2* increases the sensibility to cisplatin [86,87]. *FANCD2* may also induce topoisomerase poisons resistance [88]. Therefore, the FA pathway coordinates nucleolytic incision, recruiting, and regulating different nucleases, such as XPF-ERCC1 (NER related) and FAN1 [89,90]. Both nucleases, XPF-ERCC1 and FAN1, increase the resistance to ICLs agents [91,92].

BER, also responsive to alkylating agents and platinum compounds DNA damage, is a coordinated signaling cascade in order to exchange a DNA damaged base with the correct base; the DNA damage base may arise from hydrolysis, oxidation, deamination, and alkylation (**Fig. 2A**). BER is initiated by DNA glycosylases, which recognize and excise the damaged DNA base. Besides DNA glycosylases, poly(ADP-ribose) polymerase (PARP)1 plays an important role in recruiting DNA repair proteins to the DNA damage site. For instance, X-ray repair cross-complementing gene 1 (XRCC1) - a molecular scaffold protein, is recruited by PARP1, providing a platform for the interaction of several BER proteins. The absence of XRCC1 leads to potential formation of DSBs due to the accumulation of single-strand breaks. Both *PARP1* and *XRCC1* are anticancer targets of interest to amplify the alkylating agents' effect [93–,94,95]. In addition to BER proteins, another potential target to reduce resistance to alkylating agents are the ALTs – DNA repair proteins that remove alkylating damage in DNA [96,97].

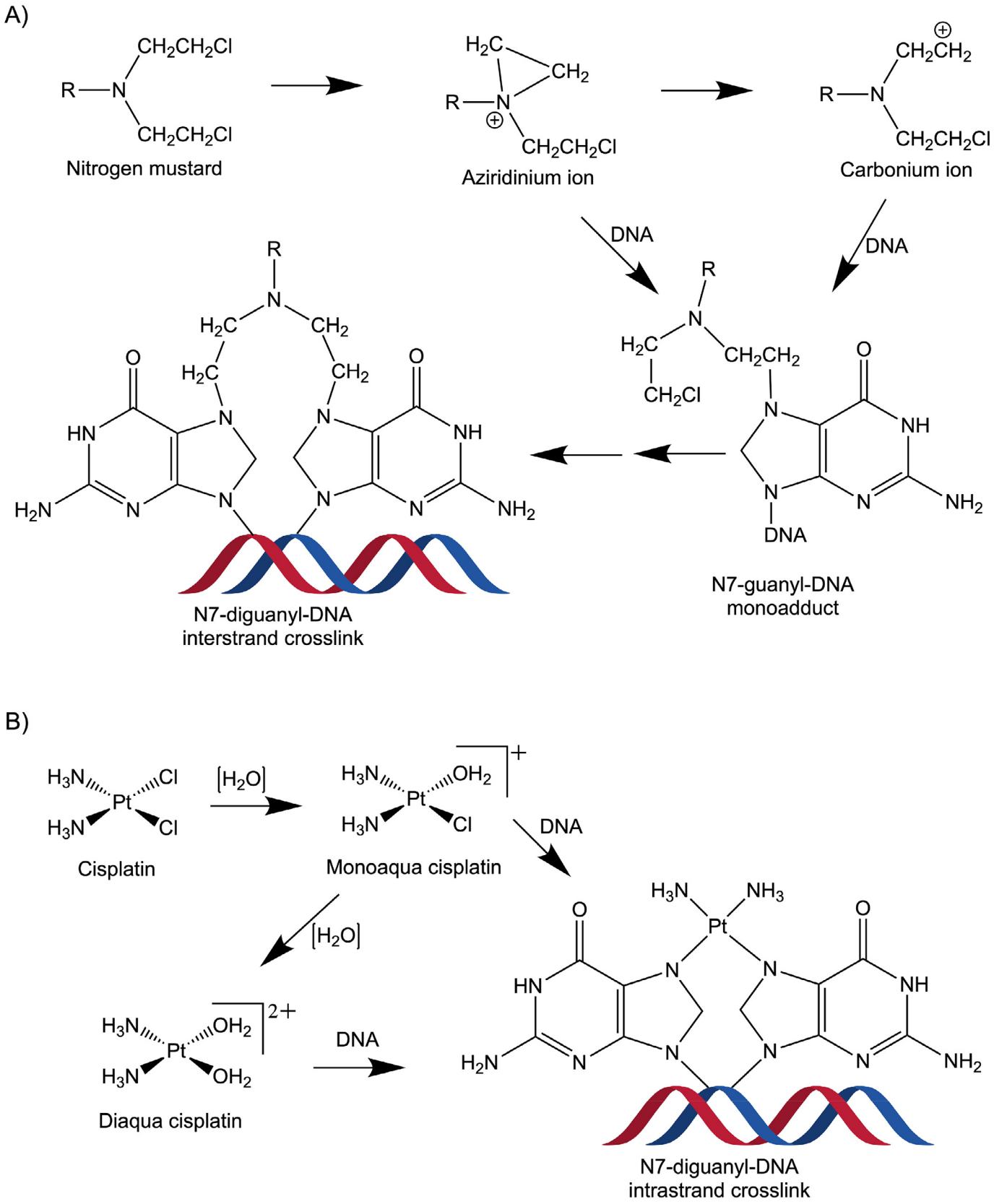

Fig. 3. DNA alkylation as an anticancer mechanism of action. **(A)** Nitrogen mustards interstrand crosslink representation. They start by forming aziridinium or carbonium ions by displacement of the chloride. These groups then alkylate DNA when attacked by the N7-nucleophilic site on the guanine base. The formation of interstrand crosslinks occurs when the displacement of the second chlorine happens, followed by a second attack and ligation. **(B)** Cisplatin intrastrand crosslink representation. The compound is linked to DNA when water displacement of one or both of its chloride groups happens, allowing N7-nucleophilic sites from adjacent guanines to attack cisplatin and form monoadducts and intrastrand DNA crosslinks.

Secondary carcinogenesis risk upon DNA targeting therapies

The DNA repair failure and the treatment with interstrand crosslinking agents and topoisomerase inhibitors are closely related to secondary leukemia. The term secondary leukemia describes the acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) due to hematotoxins or radiation exposure [98]. Therapy-related leukemia (t-MDS/AML) is derived from the treatment of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), sarcoma, and ovarian and testicular cancer with alkylating agent/radiation and/or topoisomerase II inhibitor. Its pathogenesis is associated with the repair of chromosomal damage promoted by these agents leading to chromosomal translocation and leukemogenesis [99]. Specific cytogenetic abnormalities on chromosomes 5 or 7 are linked to alkylating agents-related leukemia, while 11q abnormalities indicate topoisomerase II inhibitors-related leukemia [100,101]. MMR defects predispose t-MDS/AML, such as *MLH1* methylation [102] and defective *MSH2* expression [103,104]. Additionally, the DSBs promote loss of genetic material, inducing chromosomal aberration. Since NHEJ and HR are the main DNA repair pathways in response to DSBs, the polymorphism of *RAD51* and *XRCC3* (both HR related) is highly represented in patients with t-AML [105]. NER is another DNA repair pathway t-MDS/AML related. Polymorphic *XPD* is associated with these diseases [106].

Clinically, the median latency time of t-MDS/AML after exposure to therapy is 2 to 3 years, with incidence rates ranging from 0.8% to 6.3% over 20 years, and has a dismal prognosis (median survival of 6 months) [99].

DNA repair as a target to enhance DNA damaging agents' efficacy

Besides the secondary cancer induction, the DNA-reactive agents have a bad reputation because of their high toxicity and further resistance. Since they have the DNA as their target, most of the cells may be damaged by them, especially those with a high replicative rate, causing diverse side effects. Additionally, the resistance and secondary carcinogenesis to these drugs are also related to deletions or mutation in proteins associated with several DNA repair pathways, as well as some cancers have their own particular DNA repair alterations that might be used as a target to improve the selectivity of DNA damaging agents. Indeed, these limitations may be minimized by DNA repair modulation in combination with DNA damaging agents (**Table 1**).

DNA repair failure is present in most of the frequent cancer types, for instance, colon, breast, ovarian, and prostate cancers. Colon cancer DNA repair deficit is known especially by the loss of MMR and HR genes. An example of genetic instability, the MMR deficiency is observed in approximately 15-20% of colon cancers. Heterodimers such as *MLH1/MLH3* and *PMS2*, and *MSH2/MSH3* and *MSH6*, and the exonuclease 1 (*EXO1*) lose their functions by genomic alteration in colon cancers [80,107]. Concerning the lack of HR function in colon cancer, there is a loss of function on *ATM* and *RAD51* genes; however, the gene encoding helicase RecQ (*BLM*) is overexpressed [108,109]. The fluoropyrimidine 5-fluorouracil (5-FU) is the standard chemotherapy for patients with advanced-stage colorectal cancer. The 5-FU promotes DNA damage by inhibiting thymidylate synthetase (TS), depleting thymidine triphosphates (TTPs) available for DNA synthesis. Although MMR loss is prevailing in colon cancer, the MMR-proficiency augments the 5-FU cytotoxicity and patient survival [110,111]. In addition, HR repair failure, such as inhibition of *RAD51*, sensitizes cells to DNA damaging agents [112]. Interestingly, the *BLM* is overexpressed in colon cancer and 5-FU treatment also upregulates the *BLM* mRNA levels; recently, it has been developed novel *BLM* inhibitors as a potential anticancer strategy [113].

Breast cancer is frequently associated with hereditary mutations of the DNA repair genes *BRCA1* and *BRCA2*, with about 25% of family risk. *BRCA2* allele increases the lifetime risk of breast cancer to almost 50%, as well as 15% to ovarian cancer [114]. *BRCA1* and *BRCA2* are tumor suppressor genes that play important roles in HR repair, complexing with RAD51. Additionally, BRCA1 is able to activate p53 and control cell proliferation; the loss of function of *BRCA1* and *BRCA2* is characteristic of carcinogenesis [115]. Besides these *BRCA1/2*, breast cancer has function loss of *NSB1, ATM, RAD51, BRIP1, MLL3, CHEK2* genes; all related to HR [116]. In addition to HR, *PALB2* mutations are associated to breast cancer. PALB2 works as a partner and localizer of BRCA2, preventing cells from accumulating DNA damage [117]. Since breast cancer has DSB repair deficiency, the chemotherapy used to treat this type of cancer requires some DSB inductors such as anthracyclines, and cyclophosphamide [118]. In the same context, poly(ADP-ribose) polymerases (PARP) inhibitors may cause DBS formation, during attempted DNA formation; *BRCA*-deficient cells are unable to repair the accumulating DSBs, which makes the PARP inhibitors selective to induce cell death in *BRCA1/2* mutated cells [119].

Besides HR mutated genes, breast cancer may be hereditary due to FA pathway disorders, as well as ovarian cancer. The frequency of somatic mutations in the FA pathway in diverse types of cancer, such as cutaneous squamous cell carcinoma (SCC), bladder, pancreatic, breast cancer, prostate, lung SCC, stomach and ovarian cancers, is higher than 40%, which makes them more susceptible to crosslinking agents [120]. Ovarian cancer, for example, generally has function loss of the following FA genes: *FANCI, FANCD2, FANCA, FANCG*, and *FANCM* [116,121–,122,123,124]. Indeed, the treatment of ovarian cancer includes crosslinking agents - platinum compounds and cyclophosphamide [125].

Prostate cancer, as another example of cancer with DNA repair deficiency, has gene mutations and deletions of different DNA repair pathways, for instance, HR, and MMR. The clinical approach already has included DNA-damaging agents - mitoxantrone (topoisomerase poison) and platinum compounds, in prostate cancer treatment. Additionally, relevant studies corroborate the development of PARP inhibitors and DNA-damaging agents to improve prostate cancer treatment with personalized therapeutic strategies [126,127].

Some examples of cancer types with disruption of DNA repair pathways and their treatment with DNA-damaging agents support the idea that DNA repair-deficiency prompt the cancer cells to accumulate DNA damage, which greatly influences the response to DNA damaging agents. Therefore, understanding the particular DNA repair dysregulations in cancers is very important to turn these mechanisms against tumor cells with DNA targeting agents and specific DNA damage repair (DDR) inhibitors. The novel DDR inhibitors are classified in three groups according to their target: DDR sensor proteins (PARP); DDR signaling proteins (DNA-PK, ATM, ATR), and DDR effectors - cell cycle checkpoints (WEE-1, CHK1/2) [128–,129,130,131].

Among the DDR inhibitors cited, the PARP inhibitors are approved for treating particularly *BRCA* mutated patients, such as olaparib against breast and ovarian cancer [132]. The other classes of DDR inhibitor have shown promising effects in clinical trials. For instance, clinical trials with DNA-PK inhibitors show sensitized tumors to chemotherapy and radiation; the studies has tested these inhibitors against myeloma, advanced solid tumors, non-Hodgkin's lymphoma, and glioblastoma [133]. ATM or ATR inhibitors are also in clinical trial as a monotherapy or in combination with chemotherapy [134,135], as well as WEE inhibitor has been tested in clinical trials against pancreatic cancer in combination with Gemcitabine or radiation [136]. Most of DDR inhibitors

Table 1
Cancer-specific defects in DNA repair pathways and possible therapeutic strategies with DNA damaging agents and DNA damage repair pharmacological inhibitors.

Cancer	DR Pathway	Affected Component	DD Therapeutics	Mechanism	DDR Therapeutics	Mechanism	Ref.
Bladder	NHEJ FA NER MMR	*RB1* *FANCC* *XPD, XPA* *MLH1, MLH3*	Cisplatin, mitomycin C, and doxorubicin	Platinum compound/alkylating agent; alkylating agent and topoisomerase II inhibitor, respectively	-	-	[168,169,170,171, 172,173,174]
	Non-specific	*ATM, DNMT1, DAB2IP, TP53*			KU55933 CM-272	ATM inhibitor DNMT1 inhibitor	
Breast	HR	*BRCA1/2, NBS1, PALB2, RAD51, BRIP1*	Doxorubicin, cyclophosphamide, and carboplatin.	DSBs inductors: topoisomerase II inhibitor; alkylating agent, platinum compound, respectively.	Talazoparib, niraparib, olaparib, and iniparib	PARP inhibitor	[114,116,118,119,175, 176,177]
	Non-specific	*ATM, CHEK1/2, TP53*			AZD0156 LY2606368	ATM inhibitor CHK1/2 inhibitor	Clinical Trial NCT02203513
Colon	HR MMR	*RAD51, BLM* *MLH3, PMS2,MSH2,MSH3, MSH6, EXO1*	5-fluorouracil Irinotecan Oxaliplatin	DSBs inductor: TS inhibitor Topoisomerase I inhibitor Platinum compound/ alkylating agent	Compound 29 -	BLM inhibitor -	[178,107,80,108– ,109,110,111,179,180, 181,182,113]
	Non-specific	*ATM, TP53*	-	-	Olaparib KU55933, KU59403	PARP inhibitor ATM inhibitor	
Glioblastoma	Non-specific	*MGMT, TP53*	Temozolomide	Alkylating agent	-	-	[97,183,184]
Kidney	HR NHEJ Non-specific	*NBS1, VHL* *XRCC4* *TP53*	-	-	Olaparib -	PARP inhibitor -	[185,186,187]
Leukemia	HR	*BRCA1/2, RAD51, MRE11A*	Doxorubicin	DSBs inductors topoisomerase II inhibitor	-	-	[128,188– ,189,190,191,192,193, 194,130,129,195]
	NHEJ	*DNA-PK, XRCC6/XRCC5, LIG4*, Artemis, *MRE11A, SIRT1*	Doxorubicin Vorinostat, ACY957, ACY1035, ACY1071	DSBs inductors topoisomerase II inhibitor HDAC inhibitors	NU7026	DNA-PK inhibitor	
	FA	*FANCA, FANCC*	-	-			
	BER	*PARP1/2, LIG3*			BMN673	PARP inhibitor	
	Non-specific	*ATM, CHEK2, TP53*			AZD6738 Prexasertib	ATR inhibitor CHK1/2 inhibitor	

(*continued on next page*)

Table 1 (*continued*)

Cancer	DR Pathway	Affected Component	DD Therapeutics	Mechanism	DDR Therapeutics	Mechanism	Ref.
Liver	HR	*BRCA1/2*	Cisplatin, doxorubicin, 5- fluorouracil, capacitabine, mitoxantrone	Alkylating agent, topoisomerase II inhibitor, TS inhibitor, pro-drug of 5-fluorouracil/TS inhibitor, topoisomerase II inhibitor, respectively	ABT-888	PARP inhibitor	[196–,197,198,199,200,201,202,196,203,204,205,206]
	NHEJ	*XRCC6* (KU70)			-	-	
	NER	*XPC, ERCC1*					
	BER	*OGG1, XRCC1*					
	MMR	*MSH2, MLH1*					
	Non-specific	*ATM, MGMT, TP53*			Palbociclib	ATM inhibitor	
Lung	HR	*BRCA2*	-	-	Alazoparib and olaparib	PARP inhibitor	[207–,208,209,210,211,212,213]
	NER	*ERCC1*	Cisplatin	Platinum compound/ alkylating agent			
	Non-specific	*ATM, CHEK2, TP53*	-	-	CP466722, VE-821	ATM inhibitor	
Melanoma	HR	*BRCA2*	Dacarbazine, temozolomide, and cisplatin	Alkylating agents	-	-	[214–,215,216,217,218,219]
	NER	*XPD, XPC, DDB1* and *DDB2*					
	FA	*FANCA*					
	Non-specific	*ATM, ATR, TP53*					
Non-Hodgkin Lymphoma	HR	*BLM, RAD50, RAD51, BRCA1, NBS1, WRN*	Cyclophosphamide and doxorubicin	Alkylating agent and topoisomerase inhibitor/intercalating agent (athracycline), respectively.	Olaparib	PARP inhibitor	[220–,221,222,223,224], Clinical trial NCT03233204
	NHEJ	*MRE11A, XRCC4*			-	-	
	NER	*ERCC3, ERCC5*					
	Non-specific	*ATM, TP53*					
Oral	NHEJ	*MRE11A*	Cisplatin	Platinum compound/alkylating agent	-	-	[225–,226,227,228,229]
	NER	*ERCC1*					
	BER	*XRCC1*					
	Mismatch Repair	*MLH1, MLH3, MSH2, MSH6, PMS2*					
	Non-specific	*ATM*, Wip1, *TP53*					

(*continued on next page*)

Table 1 (*continued*)

Cancer	DR Pathway	Affected Component	DD Therapeutics	Mechanism	DDR Therapeutics	Mechanism	Ref.
Ovarian	HR	*BRCA1/2, PALB2, BLM*	Cyclophosphamide and cisplatin	Crosslinking agents	Olaparib	PARP inhibitor	[116,125,230,123, 122,121,124,177]
	FA	*FANCI, FANCD2, FANCA, FANCG, FANCM*			-	-	
	Non-specific	*TP53*					
Pancreas	HR	*BRCA1/2, PALB2, BARD1, NBN*	5-fluorouracil	DSBs inductor; thymidylate synthetase (TS) inhibitor.	Olaparib	PARP inhibitor	[231,232,233,234, 131,235]
	FA	*FANCC, FANCG*	Oxaliplatine	Platinum compound/ alkylating agent	-	-	
	MMR	*MSH2, MLH1, PMS2*	Irinotecan	Topoisomerase I inhibitor			
	Non-specific	*ATM, CHEK2, TP53*	-	-	AZD1774 AZD0156	WEE1 inhibitor ATM inhibitor	
Prostate	HR	*BRCA1/2*	Carboplatin, cisplatin, and satraplatin	Platinum compounds/ alkylating agents	Olaparib and rucaparib	PARP inhibitors	[127,126,236]
	FA	*BRIP1, FANCD2*			-	-	
	MMR	*MLH1, MSH2, MSH6*, and *PMS2*					
	Non-specific	*TP53*					
Thyroid	HR	*XRCC3*	Dacarbazine and cyclophosphamide	Alkylating agents	-	-	[237,238,239,240, 241]
	NER	*XPC, ERCC5, CCNH*					
	MMR	*MSH6*					
	Non-specific	*MGMT, TP53*					

Abbreviations: *ATM* ataxia telangiectasia mutated; *ATR* Ataxia telangiectasia and Rad3 related; *BARD1* BRCA1 Associated RING Domain 1;BER Base Excision Repair; *BLM* Bloom Syndrome RecQ like helicase; *BRCA1/2* breast cancer 1 and 2; *BRIP1* BRCA1 interacting protein C-terminal helicase 1; *CCNH* Cyclin H; *CHEK1/2* checkpoint kinase 1 and 2; *DAB2IP* DAB2 interacting protein; DD DNA Damage; *DDB1* damage specific DNA binding protein 1; DDR DNA Damage Repair; DNA-PK DNA protein kinase; *DNMT1* DNA methyltransferase 1; DSB double strand break; *ERCC1* Excision Repair Cross Complementing Group 1; *ERCC2* Excision Repair Cross Complementing Group 2; *ERCC5* Excision Repair Cross-Complementary Group 5; *EXO1* Exonuclease 1; FA Fanconi Anaemia; *FANCA* Fanconi Anemia Complementation Group A; *FANCC* Fanconi Anemia Complementation Group C; *FANCD2* Fanconi Anemia Complementation Group D2; *FANCG* Fanconi Anemia Complementation Group G; *FANCI* Fanconi Anemia Complementation Group I; FANCM Fanconi Anemia Complementation Group M; HR Homologous Recombination; LIG 3 DNA ligase III; LIG 4 DNA ligase IV; *MGMT* O-6-Methylguanine-DNA Methyltransferase; *MLH1* MutL homolog 1; *MLH3* MutL homolog 3; MMR Mismatch Repair; *MRE11A* Meiotic Recombination 11 Homolog A; *MSH2* MutS Homolog 2; *MSH3* MutS Homolog 3; *MSH6* MutS homolog 6; NBS1 protein encoded by *NBN* gene; NER Nucleotide Excision Repair; *NHEJ* Non-homologous End Joining; *NBN* Nibrin; *OGG1* 8-oxoguanine DNA glycosylase-1; *PALB2* partner and localizer of BRCA2; *PARP 1/2* poly(ADP-ribose) polymerase 1 and 2; *PMS2* PMS1 Homolog 2, Mismatch Repair System Component; *RAD50* DSB repair protein; *RAD51* recombinase; *RB1* RB Transcriptional Corepressor 1; *SIRT1* Sirtuin 1; *TP53* Tumor Protein p53; TS thymidylate synthetase; *VHL* Von Hippel-Lindau Tumor Supressor; *WRN* Werner Syndrome RecQ DNA Helicase; *XPA* Xeroderma Pigmentosum, Complementation Group A; *XPC* Xeroderma Pigmentosum, Complementation Group C; *XPD* Xeroderma Pigmentosum, Complementation Group D/protein encoded by *ERCC2* gene; *XRCC1* X-Ray Repair Cross Complementing 1; *XRCC3* X-Ray Repair Cross Complementing 3; *XRCC4* X-Ray Repair Cross Complementing 4; *XRCC6/XRCC5* X-Ray Repair Cross Complementing 5(Ku70)/ X-Ray Repair Cross Complementing 5(Ku80).

have been studied in clinical trials, only PARP inhibitors have already been in clinical use.

DNA targeting agents in precision medicine era

Current chemotherapy schemes are based on the ability to block tumor cell division and induce tumor cell death through the blockage of DNA replication (e.g. DNA targeting agent – cisplatin, cyclophosphamide and anthracyclines), cellular metabolism (*e.g.* thymidylate synthase inhibitor – 5FU), and microtubules assembly (*e.g.* taxanes). Due to side effects and resistance, it was necessary for the development of targeted therapy to improve the cancer treatment efficacy. However, chemotherapy has not been substituted by the novel targeted therapy and/or immunotherapy. Indeed, DNA-targeting agents are high clinically used, being included in about half of the cancer treatment regimens [137], besides the high cost of the immunotherapeutic agents reaching 250,000 USD per patient, which is unaffordable for developing countries [138]. Additionally, the combination of DNA-targeting agents with specific targeted drugs has resulted in considerable improvement outcomes, such as reduced side effects due to the lower doses of drugs in combination than in monotherapy [139–,140,141,142].

The targeted therapies are related to specific gene mutations in cancer. The overexpression of human epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), and the mutation of *BRAF* – protein downstream to EGFR - which leads to hyperactivation of the proliferative MAPK pathway, drive tumorigenesis. It has been developed specific inhibitors for each of these genes, for instance, the therapies targeting EGFR approved or under development include monoclonal antibodies, tyrosine kinase inhibitors, PI3K inhibitors, and antisense gene therapy. Another example of targeted therapy is the antagonism of vascular endothelial growth factor receptor (VEGFR), leading to angiogenesis inhibition. These therapies are indicated according to the tumor mutation status; further, trastuzumab (monoclonal antibody HER2 inhibitor) is approved for HER2-positive breast cancer in combination with cisplatin and 5FU, as well as EGFR inhibitors for head and neck carcinomas, and BRAF inhibitors for metastatic melanoma [143–,144,145].

Regarding immunotherapy, the most widely effective immune-based therapies are the antagonists of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and antagonists of programmed cell death protein (PD1) - PD1 ligand (PDL1) pathways. CTLA4 is a protein receptor that plays an immunosuppressive role; it may be expressed in regulatory T cells, conventional T cells, as well as cancer cells. Although the relation between CTLA4 expression and survival is controversial, neutralizing antibodies targeting this immune checkpoint are being particularly successful, for instance, ipilimumab plus dacarbazine (alkylating agents) against melanoma [146–,147,148].

PD1 is also an inhibitory receptor upregulated in chronic immune activation; it is expressed in tumor-specific T cells and tumor-infiltrating lymphocytes. Studies of PD1 inhibitors have been developed against different types of cancer, such as melanoma, head and neck cancer, and colorectal cancer [149]. The colon cancer treatment includes the immunotherapy with a PD-1 inhibitor (*e.g.* pembrolizumab), as well as targeted therapy, such as VEGF inhibitors (*e.g.* bevacizumab), EGFR inhibitors (e.g. cetuximab and panitumumab), BRAF, and MEK inhibitors (under clinical trials). Although there are other strategies besides chemotherapy, the DNA damaging agents 5FU, capecitabine (5FU pro-drug), oxaliplatin and irinotecan (topoisomerase I inhibitor) are required in combination with most of the targeted therapy and immunotherapy options [150]. Despite the advances in targeted therapy, DNA targeting agents along with other chemotherapeutic agents play a key role in cancer treatment, in combination with targeted therapy or immunotherapy or as single-agent chemotherapy.

Perspectives and conclusion remarks

The idea of DNA damaging agents being less appropriate than targeted therapy for cancer treatment is overly erroneous. Besides the development of novel targeted and immune therapies, the DNA-targeting agents still are widely applied in cancer treatment. Indeed, their cost is more accessible than those of newer treatments are. However, the toxicity effects of DNA damaging agents continue to be a problem due to its low selectivity. Precision in the clinical application of DNA targeting agents is both promising and challenging. Understanding the relation between DNA damage repair deficiency and DNA targeting agents, modulating of DNA repair pathways to enhance DNA-targeting agents' efficacy, and developing new formulation of DNA targeting agents may be strategies to improve the selectivity of these traditional pharmaceuticals.

Defective DNA repair contribute to cancer progression and may have therapeutics implications. For instance, the DNA damaged induced by 5-fluorouracil is repaired by BER and MMER; the MMR deficiency promote resistance to 5-fluorouracil (5-FU) adjuvant chemotherapy, as well as chemosensitivity to platinum compounds in colon cancer tumors [151,152]. On the other hand, MMR proficiency enhances 5FU and temozolomide (alkylating agent) activity. Additionally, methylguanine methyltransferase (MGMT; an enzyme that removes *O6*-methylguanine lesions) deficiency sensitizes cancer cells to the DNA lesions mediated by temozolomide [153].

The DNA targeting agents' primary molecular targets and mechanisms of action are well established: intercalation, electrostatic interaction, groove binding, topoisomerase I and/II inhibition, alkylation (crosslinks and/or adducts), DNA-strand breaks induction, and DNA synthesis impairment by enzymatic inhibition [137]. However, further research to investigate defects in DNA repair and their relation to chemosensitivity may provide suitable biomarkers for more precise application of DNA targeted drugs. Database studies should be more explored, since they correlate DNA damage repair genes and DNA damage repair drug resistance, inferring candidate targets for the choice of suitable oncotherapy [154,155].

Besides the possibility of a personalized treatment base on the patient's tumor mutational status for DNA repair, it is also a strategy the combination of DNA targeting agents with DNA repair inhibitors, such as PARP inhibitor; tumors with BRCA1/2 mutations

are well responded to PARP inhibitors, topoisomerase poisons, and cisplatin [156]. In addition, the fusion molecules may also be a strategy, which consists of a synergic mode of action from one hybrid molecule or from the combination of chemotherapeutics with targeted compounds. An interesting combination is bendamustine, a strong alkylating agent, with vorinostat, a histone deacetylase inhibitor (HDACi). HDAC inhibitors are able to improve the efficacy of DNA-damaging agents by the relaxation of chromatin, due to the increased histone acetylation, and by the impairment of DSB repair. HDACi may downregulate signaling NHEJ and HR proteins. Vorinostat, for example, reduces the expression of NHEJ related genes *XRCC6* and *XRCC5*, as well as HR-related genes, such *BRCA1* and *RAD51* [157–,158,159]. In addition, it has been developed a hybrid molecule that the side chain of bendamustine was replaced with the hydroxamic acid of vorinostat; this molecule contemplates both mechanisms of DNA alkylation and HDAC inhibition [160].

Regarding the development of formulations to DNA damaging toxicity, there are new formulations of liposomal doxorubicin, for example, that have shown less toxicity and increased efficacy [161,162]. Additionally, antibody-drug conjugates (ADCs) and fusion molecules are examples of improved selectivity of chemotherapy [163]. The ADCs consist of an antibody (or target) linked to a cytotoxic drug. For instance, ado-trastuzumab emtansine is an immunoconjugate with an antibody targeting HER2 tethered and a maytansine derivative (microtubule-targeting compound, which is indicated to HER2-positive breast cancer). Moreover, inotuzumab ozogamicin targets CD22 – protein with expression restricted to B-cell lineage – is associated with a calicheamicin derivative (minor groove DNA-binding agent). Inotuzumab ozogamicin is used against B-cell precursor acute lymphoblastic leukemia [164].

The DNA damaging agents are far from being excluded from cancer therapy. The new perspectives regarding these pharmaceuticals are focused on improve their clinical application. To sum up, some strategies were discussed in this review, such as modulation of DNA repair, synergism, and new formulations. Indeed, the main idea is to understand how we may use DNA repair proficiency and/or DNA repair deficiency in favor of DNA damaging agents' mechanism of action to advance oncotherapy.

Declaration of Competing Interest

The authors declare no competing financial interests.

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