The DNA Damage Response: Implications for Tumor Responses to Radiation and Chemotherapy

Michael Goldstein and Michael B. Kastan

Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, North Carolina 27710; email: michael.kastan@duke.edu, michael.goldstein@duke.edu

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Abstract
Cellular responses to DNA damage are important determinants of both cancer development and cancer outcome following radiation therapy and chemotherapy. Identification of molecular pathways governing DNA damage signaling and DNA repair in response to different types of DNA lesions allows for a better understanding of the effects of radiation and chemotherapy on normal and tumor cells. Although dysregulation of the DNA damage response (DDR) is associated with predisposition to cancer development, it can also result in hypersensitivity or resistance of tumors to therapy and can be exploited for improvement of cancer treatment. We highlight the DDR pathways that are activated after treatment with radiation and different classes of chemotherapeutic drugs and describe mechanisms determining tumor sensitivity and resistance to these agents. Further, we discuss approaches to enhance tumor sensitivity to radiation and chemotherapy by modulating the DDR with a goal of enhancing the effectiveness of cancer therapies.
THE DNA DAMAGE RESPONSE AND CANCER

Cells are constantly dealing with damage to their DNA due to replication stress, telomere shortening, and a variety of exogenous and endogenous DNA targeting exposures, such as UV light, chemical toxins, and reactive oxygen species (ROS) that are generated during general metabolism and inflammation. An intricate network of signaling pathways and repair mechanisms has evolved to help mammalian cells cope with a variety of DNA lesions in order to protect genomic stability. Much of our understanding of the DNA damage response (DDR) stems from studying human diseases caused by hereditary defects in DNA damage signaling and repair pathways. In these patients, an inability to properly detect, repair, or respond to DNA lesions results in a cancer-prone phenotype. For example, xeroderma pigmentosum is caused by mutations in the XP family of genes and is characterized by a predisposition to skin cancer due to an inability to effectively repair UV-light-induced DNA lesions by nucleotide excision repair (NER). Inherited mutations in the ATM or NBS1 genes, the products of which are involved in detecting and signaling DNA double-strand breaks (DSBs), result in the cancer-prone conditions ataxia telangiectasia and Nijmegen breakage syndrome, respectively, with a predisposition to lymphoid malignancies (1).

Mutations in the Brca1 and Brca2 genes result in defective repair of DSBs by homologous recombination (HR) and are associated with genomic instability and predisposition to breast and ovarian cancer (2). The hereditary nonpolyposis colon cancer (HNPCC) genes are involved in DNA mismatch repair, and their dysfunction predisposes individuals to colon and uterine tumors (3). Although such inherited mutations predispose to development of cancer, they can also create specific sensitivities of the consequent tumor cells to therapeutic agents, such as the extraordinary sensitivity of Brca1-null tumors to inhibitors of base excision repair (PARP inhibitors) and the hypersensitivity of ATM-null tumors to ionizing radiation and radiomimetic drugs. Further, clearly established links between certain environmental exposures to DNA damaging agents and cancer development also demonstrate the importance of the DDR in tumor development, even in the setting of nonhereditary malignancies (4).

The DDR has several distinct components that determine the outcome of the damaged cells, including (a) initial detection of the lesion resulting in activation of signaling networks and cell cycle checkpoint induction, (b) DNA repair, and (c) induction of cell death through activation of programmed cell death pathways. All parts of the DDR need to be properly coordinated to maintain genomic stability, and all can affect the outcome of cancer treatment. Thus, they are attractive targets for radio- and chemosensitization during cancer treatment. Knowing the DDR defects that are present in a tumor can also allow for selection of optimal treatments that can efficiently kill the tumor cells. This review explores the effects of dysregulation of DDR pathways on the response of tumors to radiation and chemotherapy and discusses strategies of targeting these pathways in order to sensitize tumors to genotoxic treatment (Figure 1).

THE DNA DAMAGE RESPONSE AND DNA REPAIR PATHWAYS

DNA Damage Signaling and Checkpoint Induction

Following induction of DNA breaks, initiation of signaling pathways is facilitated by members of the phosphatidylinositol 3-kinase (PI3K)-like kinase (PIKK) family, ATM, ATR (ataxia telangiectasia and Rad3-related protein), and DNA-PK (DNA-dependent kinase). ATM plays a critical role in DNA damage signaling originating at DSBs, whereas ATR responds to single-stranded DNA (ssDNA) regions. DNA-PK is directly involved in DNA repair by promoting DSB religation through nonhomologous end joining (NHEJ). An early event in DSB signaling is binding of the MRN complex to double-stranded DNA ends (5). MRN consists of the MRE11, RAD50,
Figure 1
DNA lesions induced by radiation and chemotherapy and their repair. The figure illustrates the specific DNA lesions induced by radiation and different classes of chemotherapeutic agents, the molecular pathways repairing these lesions, and the DNA damage response factors that can be targeted in order to improve the efficacy of the anticancer agents. Each color represents a repair machinery or multiple repair machineries involved in repair of a specific DNA lesion.
Abbreviations: BER, base excision repair; HR, homologous recombination; DSB, DNA double-strand break; ICL, DNA interstrand cross-link; IR, ionizing radiation; MGMT, methylguanine methyltransferase; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, nonhomologous end joining; SSB, DNA single-strand break.
Nonhomologous end joining (NHEJ): directly religates DNA double-strand breaks

MRN: complex of MRE11, RAD50, and NBS1 proteins, which detects DNA double-strand breaks

Interstrand cross-link (ICL): a chemical adduct that covalently cross-links both DNA strands

Minichromosome maintenance (MCM) helicase: DNA helicase that unwinds DNA and separates annealed DNA strands

Ionizing radiation (IR): radiation that releases electrons from molecules and atoms, thereby ionizing them

Single-strand break (SSB): DNA break affecting a single strand of DNA

DNA Double-Strand Break Repair

Double-strand DNA breaks are among the most toxic DNA lesions. Therefore, agents that induce DSBs, such as ionizing radiation (IR) and topoisomerase inhibitors, are widely used for cancer treatment. DSB formation can arise directly or indirectly from other DNA lesions, for instance, when a replication fork collides with a single-strand break (SSB) or an ICL during replication. This mechanism plays an important role in cancer therapy because toxicity of many chemotherapeutic agents depends on the conversion of primary DNA lesions induced by these drugs into DSBs. The two major DSB repair pathways are NHEJ and homologous recombination (HR). NHEJ is an error-prone repair pathway that can occur throughout all cell cycle phases, whereas HR is an error-free pathway that can be used only in the late S and G2 phases of the cell cycle as it requires a homologous sequence located on the sister chromatid. HR is the major pathway repairing DSBs in lower eukaryotes, and NHEJ predominates in mammalian cells (12). However, despite its minor role in repair of directly induced DSBs in human cells, HR is specifically required for repair of DSBs that are formed at collapsed replication forks in the S phase of the cell cycle. Further, HR is involved in repair of ICLs, where it collaborates with NER.

The initial step in NHEJ is the binding of the Ku70/Ku80 complex to the DSB, followed by recruitment and activation of the catalytic subunit DNA-PKcs (5). Active DNA-PK phosphorylates a variety of targets including XRCC4 (13). Finally, DNA ends are religated by the XRCC4-ligase
Base Excision Repair

Base excision repair (BER) is responsible for removal of damaged bases such as N-alkylated purines and 8-oxo-7,8-dihydroguanine (8-OxoG). A damaged base is recognized and removed by specific glycosylases, resulting in an apurinic/apyrimidinic (AP) site, followed by a cleavage of the AP site by either the glycosylase itself or AP endonuclease 1 (APE1). This DNA “nick,” along with directly induced SSBs, is a substrate for further steps of BER. In the next step, a displacement of either a single nucleotide (short-patch BER) or up to 13 nucleotides (long-patch BER) occurs at the cleaved DNA strand, followed by DNA resynthesis. Ligation is then performed by ligase III, XRCC1, and PARP1 in the case of short-patch BER or by ligase I and proliferating cell nuclear antigen (PCNA) in long-patch BER (14).

Nucleotide Excision Repair

Nucleotide excision repair (NER) serves to repair bulky DNA adducts such as UV-light-induced lesions and intrastrand cross-links. Also, it performs the first step of ICL repair, which is then completed by HR. NER is divided into transcription-coupled repair that removes DNA lesions blocking RNA polymerase progression along the DNA strand and global genomic repair that is independent of transcription. The NER pathway consists of recognition of the DNA lesion by members of the XP protein family, DNA unwinding, excision of the lesion by XPG and ERCC1-XPF, filling of the DNA gap, and sealing of DNA by ligase I (14).

Mismatch Repair

Mismatch repair (MMR) removes base mismatches caused by replication errors and by spontaneous or induced base modifications such as methylation and oxidation. The mismatch is recognized by the MutSα complex, which consists of MSH2 and MSH6 proteins that bind to the lesion and associate with the MutLα complex composed of MLH1 and PMS2. Then DNA excision at the daughter strand containing the incorrect base is performed by Exo1, and the gap is filled by Polε (14).

THE DNA DAMAGE RESPONSE IN TUMOR THERAPY

Ionizing Radiation

Ionizing radiation (IR), a common modality used to treat malignancies, particularly solid tumors, generates ROS that cause a variety of lesions in DNA. Most IR-induced DNA lesions are base...
modifications such as 8-OxoG (17). Additionally, IR causes DNA breaks; 1 Gy IR induces approximately 1,000 SSBs and 35 DSBs per cell (18, 19). Although DSBs constitute a minority of DNA lesions induced by IR, they play a central role in IR-induced cytotoxicity. Therefore, pathways involved in signaling and repair of DSBs are critical for the outcome of radiation therapy.

Alterations of DSB repair pathways that occur in tumors due to genetic or epigenetic changes affect the sensitivity of cancer cells to IR and can be exploited for an effective radiation therapy. Willems et al. identified several single-nucleotide polymorphisms (SNPs) within the Ku70 and Ku80 genes that are associated with an increased sensitivity of tumors to radiation (20). Furthermore, decreased Brca1 expression due to hypermethylation of the Brca1 promoter is a common event in multiple nonhereditary cancer types (21, 22), and a loss of functional Brca1 was reported to cause radiosensitization in tumors (23, 24), suggesting that the methylation status of the Brca1 promoter can potentially be used as a marker to identify tumors that are responsive to radiation.

As described above, the ATM kinase is activated following DSB induction, and ATM signaling contributes to DSB repair via HR by promoting DNA end-processing and Brca1 recruitment (2, 25). A protective role of ATM after exposure to IR is mirrored by the profound radiosensitivity observed in ataxia telangiectasia patients (1), suggesting that ATM is a suitable target for radiosensitization. Accordingly, small-molecule inhibitors of ATM were demonstrated to sensitize cancer cells to IR in preclinical models (26–28). It is worth noting that ATM loss results in radiosensitization independent of the p53 status (29), and chemical ATM inhibition efficiently sensitizes p53-mutant glioblastoma cells to IR (27). The ability of ATM inhibitors to sensitize p53-deficient cancer cells to radiation is highly important in light of the tumor resistance to therapy associated with p53 mutations and the high frequency of p53 mutations in malignant tumors.

Another cornerstone of radiosensitization is the inhibition of NHEJ, which plays a major role in repair of DSBs in human cells. Indeed, DNA-PK inhibitors exhibit a strong radiosensitizing effect in cancer cell lines (30). Because a partial redundancy between NHEJ and HR exists in repair of IR-induced DSBs (31), a simultaneous inhibition of DNA-PK and ATM appears to be an optimal approach to radiosensitization. Interestingly, the small-molecule inhibitor NVP-BEZ235, initially developed as an mTOR inhibitor, was found to inhibit both PIKKs, ATM and DNA-PK, and proved to be a potent radiosensitizer in preclinical experiments (32, 33). However, a potential drawback of NVP-BEZ235 is its ability to inhibit ATR (34). Because ATR is crucial in resolving stalled replication forks, it is generally required for survival, even in the absence of exposure to genotoxic stress. Consequently, disruption of ATR function results in lack of viability at both cellular and organism levels (10, 11). These findings suggest that an optimally designed radiosensitizing PIKK inhibitor might target both ATM and DNA-PK, but not affect ATR activity, in order to avoid systemic toxicity.

Another approach to radiosensitization is the inhibition of checkpoint kinase signaling. Specific inhibitors of Chk1 were shown to potentiate the toxicity of DSB-inducing agents, including IR (35, 36), whereas a loss of Chk2 appears to have an opposite effect, causing radioresistance in vivo (37). Thus, most research has focused on the development of Chk1 inhibitors. It is not clear, however, whether the abrogation of the cell cycle arrest is, indeed, responsible for radiosensitization by Chk1 inhibitors. In addition to checkpoint activation, Chk1 is involved in HR (5), and a recent study suggested that radiosensitization caused by a Chk1 inhibitor is mediated through its inhibitory effect on HR activity rather than checkpoint signaling (38).

Importantly, IR-induced lesions such as 8-OxoG and SSBs that have a low cytotoxic potential per se can indirectly induce toxic DSBs by blocking replication forks. Both 8-OxoG and SSBs are dealt with by BER. Consistently, a high expression level of the BER factor APE1 is associated with radioresistance in cervical cancer (39) and germ cell tumors (40). These findings suggest that inhibition of BER may be a suitable approach to radiosensitization. So far, methoxyamine has
Methylguanine methyl-transferase (MGMT): directly repairs DNA alkylations at O6-guanine

DNA Methylating Agents

The chemical simplicity of methyl adducts in DNA is in contrast to a surprisingly complicated mechanism of cytotoxicity caused by these DNA lesions. The main products of methylating agents such as temozolomide (TMZ) and procarbazine are N7- and N3-methylguanine (N7MeG, N3MeG) and N3-methyladenine (N3MeA). O6-methylguanine (O6MeG) is a minor product, but it possesses a high potential to induce cytotoxicity. O6MeG does not induce cell death directly but rather by converting to a DSB in an MMR- (45) and replication- (46) dependent manner. Mechanistically, it mispairs with cytosine or thymine during DNA synthesis in the S phase, and repetitive, futile attempts to remove the mismatch by MMR result in formation of DSBs that induce cell death (46, 47). Thus, efficient MMR is required for tumor sensitivity to TMZ (48), and loss of expression of MLH1, a member of the MMR pathway, is associated with resistance of gliomas (49) and medulloblastomas (50) to TMZ.

The O6MeG lesion is reversed in a stoichiometric manner by methylguanine methyl-transferase (MGMT) (51). Therefore, MGMT expression is an important determinant of cellular responses to methylating agents, and high MGMT expression levels in cancer were shown to correlate with resistance to TMZ (52, 53). However, a silencing of MGMT expression due to MGMT promoter hypermethylation was found in several cancer types (54). This epigenetic mark correlates with hypersensitivity of gliomas to TMZ (55), suggesting that MGMT promoter methylation can be used as a biomarker predictive of tumor response to methylating agents. It should be noted that in addition to removing methyl residues, MGMT can reverse other DNA alkylations, such as chlorethyl adducts induced by nitrosourea drugs, e.g., bis(2-chloroethyl)nitrosourea (BCNU), that are later converted into ICLs. Therefore, MGMT expression levels affect the tumor response to this class of agents as well.

Because of its critical role in resistance to alkylating drugs, MGMT was considered a promising target for inhibition. In fact, chemical inhibitors of MGMT highly potentiate the toxicity of TMZ and other alkylating agents in cancer cells (56) and entered clinical trials more than a decade ago (57). Unfortunately, clinical benefits of MGMT inhibition were limited owing to enhanced adverse side effects, mainly myelotoxicity, when administered in combination with TMZ and BCNU (58), which required a reduction of the chemotherapy dosage. This effect was attributed to MGMT inhibition in healthy tissues as the inhibitors lack specificity for tumor cells. Therefore, coupling MGMT inhibitors to molecules that can be used for targeted delivery, such as DNA or RNA aptamers (59), could be used in the future to avoid systemic side effects.

Unlike O6MeG, N3MeA and N3MeG cannot be repaired by MGMT but instead are substrates of BER. Notably, the toxicity of the N-methylations is dependent on the formation of BER intermediates such as AP sites and SSBs that can block replication forks during the S phase, resulting in replication fork collapse and DSB formation. Therefore, changes in protein activities that participate in early and late steps of BER generating and repairing these intermediates, respectively, have opposite effects on the cytotoxicity induced by methylating agents. For instance, an overexpression of N-methylpurine DNA glycosylase (MPG), which facilitates the initial step of BER, correlates with an increased formation of AP sites, resulting in hypersensitivity of cancer cells to TMZ (60). Importantly, increased expression levels of MPG were found in breast cancer
Topoisomerases (TOPs): relax supercoiled DNA structures by cleaving and religating DNA.

Topoisomerases (TOPs) are proteins that relax supercoiled DNA structures by cleaving either one (TOP I) or both (TOP II) DNA strands followed by unwinding of the supercoils and religation of DNA by TOPs. TOP I inhibitors, such as camptothecin and topotecan, and TOP II inhibitors, such as etoposide and anthracyclines, block the final religation step, resulting in accumulation of SSBs and DSBs, respectively. DNA breaks induced by TOP inhibitors differ from chemically induced DNA breaks because the inactive TOP remains covalently bound to the DNA at the break site and has to be removed during break repair. SSBs induced by TOP I inhibitors are repaired by a complex consisting of tyrosyl-DNA-phosphodiesterase 1 (Tdp1), which hydrolyzes the bond between TOP I and the 3′ DNA end at the break, and BER machinery (72). Consequently, PARP inhibitors, which blunt BER, sensitize cells to TOP I inhibitors (73). A dual PARP1/2 inhibitor has entered a clinical trial in combination with topotecan (74).

Whereas TOP II inhibitors induce DSBs independent of proliferation (75), TOP I inhibitors induce SSBs that can cause stalled replication forks during the S phase, resulting in their conversion into DSBs (76). Thus, the cytotoxicity induced by TOP I poisons is proliferation dependent (75). As discussed above, HR is involved in repair of DSBs that are generated from SSBs in the S phase. Therefore, alterations in HR affect sensitivity to TOP I poisons. For instance, Brca1 loss results in hypersensitivity to camptothecin (77), which could be exploited for treatment of Brca1-deficient tumors. Further, inhibition of ATM may sensitize cells to camptothecin and etoposide (28), suggesting a potential benefit of ATM inhibitors in combination with TOP I and TOP II inhibitors. Ultimately, because TOP I-induced cytotoxicity is mainly mediated by DSBs, targeting the NHEJ pathway by DNA-PK inhibitors is another approach to sensitize cells to TOP I poisons and was shown to be effective in combination with irinotecan (78).

Inhibition of the checkpoint kinase Chk1 also potentiates the toxicity induced by TOP poisons in preclinical settings (36). However, a phase II clinical trial investigating the efficacy of the Chk1 inhibitor UCN-01 in combination with irinotecan reported aggravation of chemotherapy side effects and showed little benefit of UCN-01 (79).

In contrast to TOP I poisons, DSBs are the primary lesion induced by TOP II inhibitors. Consequently, cells can be sensitized to etoposide by inhibitors of DNA-PK (80) and ATM (28). A recent study showed that ATM regulates TOP II expression, and ATM loss results in increased TOP II levels and enhances sensitivity to TOP II inhibition (81). This finding is in accordance with the notion that ATM and TOP II are involved in the processing of DSBs. In addition, the PARP1 inhibitor KU-0059332 was shown to sensitize cells to topotecan (82), suggesting a potential benefit of combining PARP1 and TOP I inhibitors. However, the clinical relevance of these findings remains to be tested.

In contrast, an overexpression of proteins that are involved in late steps of BER can cause resistance to methylating agents due to an enhanced repair of toxic BER intermediates. High levels of APE1 and PARP1, which are involved in processing of AP sites and ligation of SSBs, respectively, were found to be a common trait in cancer and can result in resistance to chemotherapy (63–65). Accordingly, high nuclear APE1 expression correlates with a shorter overall survival in patients with ovarian and gastroesophageal cancer treated with alkylating drugs (64). On the other hand, a defect in SSB religation due to low expression of XRCC1 and ligase III results in accumulation of DNA breaks and hypersensitivity to TMZ (66).

On the basis of these findings, PARP1 and APE1 appear to be attractive targets for inhibition, which could overcome the resistance of cancer cells to methylating agents caused by an overexpression of these repair factors. In fact, inhibition of PARP1 (67) and APE1 (68) was shown to sensitize cancer cell lines to TMZ in preclinical settings. Currently, APE1 inhibitors (69, 70) and PARP1 inhibitors (71) are undergoing clinical trials in combination with TMZ.
with the concept that TOP expression levels correlate with the number of DNA breaks induced by TOP inhibitors. Thus, ATM inhibitors may cause sensitization to TOP II inhibitors not only by affecting the cellular response to DSBs but also by enhancing TOP II expression and elevating the level of the breaks induced by TOP II poisons.

**DNA Cross-Linking Agents**

DNA cross-linking agents were among the first drugs used for cancer treatment. Cyclophosphamide was introduced into the clinic in 1958. This agent belongs to the group of nitrogen mustard (NM) compounds, which are bifunctional alkylating agents and preferentially target N7-GO on both DNA strands, thus inducing DNA ICLs. NM-induced toxicity is dependent on replication and has been mainly attributed to replication perturbations during the S phase and inhibition of transcriptional activity (82). Another group of agents that induce ICLs are nitrosourea drugs; BCNU, for example, conjugates a chlorethyl residue to O6 of guanine, which is then converted into an N1-guanine-N3-cytosine ICL (83). Finally, cisplatin, which covalently binds to guanine and adenine, generates DNA intra- and interstrand cross-links (84).

Whereas DNA intrastrand cross-links are repaired by NER alone, ICL repair involves parts of NER, HR, and translesion synthesis. Consequently, NER defects due to mutations of ERCC1 and xeroderma pigmentosum (XP) family proteins result in hypersensitivity to cisplatin in cultured cells (85). Consistent with these observations, low ERCC1 expression was found to cause sensitivity of testicular tumors to cisplatin (86), potentially explaining the high responsiveness of testicular cancer to cisplatin-based chemotherapy (87). Although no specific NER inhibitors are currently available, several drugs initially designed for other purposes, such as cyclosporine A (88), cetuximab (89), and spironolactone (90), were shown to inhibit NER by downregulating expression of NER factors and to increase sensitivity to platinum agents.

An important example of sensitivity to cross-linking agents due to HR deficiency is the loss of functional Brca1 in breast cancer, which results in high responsiveness to cisplatin (91, 92). Because the Fanconi anemia (FANC) pathway plays an important role in promoting HR during ICL repair, a loss of members of this pathway increases sensitivity to agents that induce ICLs (93). Interestingly, an inactivation of the FANC pathway due to epigenetic modification of various FANC genes was shown to be a common event in ovarian cancer (94), head and neck squamous cell carcinoma, and non–small cell lung cancer (95). This finding suggests that screening tumors for genetic and epigenetic alterations affecting either Brca1 or the FANC pathway may be useful in predicting tumor response to ICL-inducing agents.

**SYNTHETIC LETHALITY**

The concept of synthetic lethality has gained increasing popularity in the field of oncology. Synthetic lethality describes a condition where a disruption of two redundant DDR pathways results in accumulation of DNA damage leading to cell death, whereas abrogation of only one pathway is tolerated by the cell. This can be exploited therapeutically if cancer cells lack one of the pathways due to a genetic defect and another pathway is inhibited by a targeted drug. Ideally, this approach will kill cancer cells while sparing healthy tissues, in which both pathways are functional. A proof of principle was demonstrated using cancer cell xenograft models that were deficient in HR due to Brca1 or Brca2 mutations. These cancer cells are specifically sensitive to PARP inhibitors at concentrations that are nontoxic to healthy tissues (96, 97). The suggested mechanism behind this phenomenon is based on the accumulation of naturally occurring SSBs due to BER inhibition by PARP inhibitors resulting in conversion of these SSBs into DSBs at stalled replication forks.
during the S phase. In noncancerous cells these DSBs can be repaired by HR, but cancer cells lacking HR due to Brca1/2 mutations accumulate DSBs that induce cell death.

However, the idea of treating nonhereditary forms of Brca1/2-deficient tumors with a PARP inhibitor alone bears some caveats. These tumors appear to develop resistance to PARP inhibitors owing to a restoration of Brca1 and Brca2 functions by genetic reversion (92, 98). Another mechanism of resistance is pathway rewiring due to the loss of 53BP1 or DNA-PK, which restores HR activity by blunting NHEJ (99, 100). These findings suggest that treatment of Brca1/2-deficient tumors with a PARP inhibitor monotherapy may not be the optimal strategy. Notably, loss of functional Brca1 results in tumor sensitivity to IR (23) and to chemotherapeutic drugs such as TOP I inhibitors (77) and cisplatin (91, 92). Given that PARP inhibition also increases sensitivity to IR and multiple chemotherapeutic agents, as described above, a combination of IR and/or chemotherapy with PARP inhibitors in patients with Brca1/2-deficient tumors appears to be a superior strategy. By exploiting the tumor sensitivity caused by Brca1/2 deficiency in multiple ways, it would be more efficient than PARP inhibitors alone and could potentially impede resistance development.

CONCLUDING REMARKS

Since the introduction of radiation and chemotherapy, oncologic treatment regimens have been largely developed by trial and error and validated through clinical trials. Detailed characterization of DDR pathways over the past two decades has revealed many details about the cellular response to radiation and chemotherapeutic agents, and this knowledge is ready to be exploited for cancer treatment. Analysis of biomarkers such as MGMT promoter methylation and Brca1 mutations has potential to become an important tool for predicting tumor response to specific types of chemotherapeutic drugs and assigning an appropriate therapy regimen. Designing an individual tumor therapy based on the molecular phenotype of the cancer rather than on its histologic appearance will increase the efficacy of treatment and reduce systemic toxicity by avoiding drugs that the tumor is resistant to.

Alteration of DDR pathways by small-molecule inhibitors is another promising approach to improve the efficacy of radiation and chemotherapy. However, the use of these drugs as chemosensitizers requires caution because a systemic application of DDR inhibitors and chemotherapeutic agents not only potentiates the killing of cancer cells but also results in an increased toxicity of DNA-damaging agents in healthy tissues. During initial clinical trials including DDR inhibitors, an aggravation of side effects frequently forced a decrease in the dosage of chemotherapy, thus limiting the benefits of DDR modulators. The use of specific delivery methods such as nanoparticles or nucleic acid aptamers coupled to DDR inhibitors could improve their specificity for cancer cells and reduce the side effects when combined with chemotherapy. Importantly, inhibition of DDR in noncancerous tissues by small-molecule inhibitors is a lesser issue during radiation therapy. Unlike chemotherapy, the radiation beam is delivered specifically to the tumor, so systemic toxicity should be avoided if chemical DDR inhibitors are combined with radiation therapy. Therefore, the currently available DDR modulating agents appear to have better clinical prospects as radiosensitizers than as chemosensitizers.

An ideal cancer therapy would specifically target cancer cells while avoiding toxicities to normal tissues. The concept of synthetic lethality promised such a possibility. However, the enthusiasm about synthetic lethality aiming to specifically kill cancer cells by nontoxic doses of a DDR inhibitor has been challenged by reports showing an acquired resistance of tumors to synthetically lethal therapeutics due to genetic reversion of DDR defects and rewiring of DDR pathways. Nonetheless, exploiting a defective DDR pathway in cancer by targeting the redundant repair
pathway has clinical potential. It is conceivable that it is easier for cancer cells to adapt to a relatively low level of DNA damage that is indirectly induced by synthetically lethal DDR inhibitors and accumulates over a period of time than to high levels of DNA damage that are rapidly induced by chemotherapy and radiation. Therefore, a combination of a synthetically lethal drug with radiation and chemotherapeutic agents that the cancer cells are specifically sensitive to due to the loss of a DDR pathway appears to be a superior approach, as it would more broadly exploit the DDR dysregulation and might hinder the development of resistance.

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